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ON FICTIONS AND REALITIES IN DRUG DEVELOPMENT - AN ACCOUNT ON RATIONALITY IN DRUG DEVELOPMENT

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An Account on Rationality in Drug Development

Martin René Boyer: *On fictions and realities in drug development,* An Account on Rationality in Drug Development, © November 2012

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Dedicated to the loving memory of my mother Suzana Boyer

1946 – 1997

ABSTRACT

The development of useful, curing, specific and safe drugs is a laborious, delicate and cost intense underpinning taking place within a complex framework of as much political, social, as scientific and biological constraints. The complexity of biology is faced by an ever increasing amount of knowledge and sets of technologies and models enabling ever more structured approaches and allowing for even more specific interactions to treat manyfold diseases. To models, technologies and biological knowledge at hand a certain degree of rationality is ascribed in drug development. Taken together, this possibilities permit the description of diseases in molecular terms and enable goal-oriented procedures to take place. Even though the technological and scientific advances in the domain of drug development are striking and highly valuable, the pharmaceutical industry is facing decreasing rates of new drug launches and likewise a diminishing productivity. Hence, continually larger amounts of money have to be invested to bring new products to the market. The ambition of the present work is to scrutinise the state-of-the-art of contemporary pharmacological research and drug development, and also to elucidate some potential reasons explaining the shrinking overall productivity of the pharmaceutical industry. Specially considered will be the imputed rationality of processes and technologies employed in present-day drug development, where and when rational strategies emerged and how they are assessed.

The origins of rational drug development is retraced along the scientific career of Paul Ehrlich who first succeeded developing, in rational terms, a synthesised, specific chemotherapeutic: the syphilis drug Salvarsan. The development of Sunitinib has proven a genuine example illuminating present-day drug development and raising many questions concerning the validity of the employed and allegedly rational methods and technologies. An introspection into present-day industry based drug development as it is perceived by research and development experts at a single research division of a global pharmaceutical company shows that, behind the cover, a rather different story of drug development can be narrated. Besides trying to elucidate the reasons for the drop of productivity, the questionnaire at-

tempted to clarify the role of the rationality ascribed to many development processes. Moreover, models, technologies, strategies and key concepts applied are evaluated concerning their usability in the day by day drug development processes for the creation of new products. Among those figure technologies as omics, strategies as repositioning and key concepts as personalised health care. The three accounts are bracketed and merged by a detailed introduction and a comprehensive conclusion.

ZUSAMMENFASSUNG

Die Entwicklung von nützlicher, heilender, spezifischer und sicherer Arzneimittel ist ein arbeits-, delikates- und kostenintensives Unterfangen, welches in einem komplexen Bezugssystem aus politischen, sozialen, wissenschaftlichen und biologischen Rahmenbedingungen stattfindet. Der Komplexität der Biologie wird mit einer ständig wachsenden Menge an Wissen und einer Reihe von Technologien und Modelle begegnet, die immer strukturiertere Ansätze ermöglichen und hierdurch erlauben spezifischere Wechselwirkungen aufzudecken, so dass eine Vielzahl von Krankheiten behandelt werden können. Den verwendeten Modellen, den Technologien und dem biologischen Wissen wird in der Medikamentenentwicklung ein gewisses Mass an Rationalität zugeschrieben. Zusammengenommen, erlauben diese Möglichkeiten die Definition von Krankheiten auf molekularer Ebene und ermöglichen so eine zielgerichtete Herangehensweise. Auch wenn die technologischen und wissenschaftlichen Errungenschaften im Bereich der Entwicklung von Medikamenten auffällig und überaus wertvoll sind, sieht sich die pharmazeutische Industrie mit abnehmenden Raten neuer Medikamentenentwicklungen und einer abnehmenden Produktivität konfrontiert. Immer größere Geldbeträge müssen investiert werden, um neue Produkte auf den Markt zu bringen.

Das Ziel der vorliegenden Arbeit ist es, den aktuellen Stand der pharmakologischen Forschung und Entwicklung von Arzneimitteln eingehend zu hinterfragen und mögliche Gründe für die insgesamt schrumpfenden Produktivität der pharmazeutischen Industrie aufzuführen. Besondere Berücksichtigung erhält die in der heutigen Medikamentenentwicklung verwendeten Prozessen und Technologien unterstellte Rationalität, sowie, wo und wann diese rationalen Strategien entwickelt wurden und wie deren Wert heute einschätzt wird.

Die Ursprünge der rationalen Medikamentenentwicklung wird entlang der wissenschaftlichen Karriere von Paul Ehrlich nachgezeichnet, welchem es als erster gelang ein synthetisches und spezifisches Chemotherapeutikum nach einem rationalen Verfahren zu entwickeln: das Syphilis Medikament Salvarsan. Die Entwicklung vom Medikament Sunitinib erwies sich als eingängiges Beispiel, welches über die heutigen Medikamentenentwicklung Aufschluss gibt und hierdurch viele Fragen bezüglich der Gültigkeit der verwendeten und vorgeblich rationalen Methoden und Technologien aufwirft. Eine Innenansicht der heutige industriebasierten Medikamentenentwicklung, wie sie durch Forschungs- und Entwicklungsexperten an einem einzelnen Forschungsstandort eines weltweit tätigen Pharmaunternehmen wahrgenommen wird, zeigt, dass sich hinter dem blendenden Schirm, etwas andere Geschichten über die Entwicklung von Medikamenten erzählt werden können. Nebst der Bemühung Gründe für den Produktivitätsschwund aufzuführen, versucht der Fragenkatalog die Rolle die dem Medikamentenentwicklungsprozess zugeschriebene Rationalität nachzugehen. Darüber hinaus wird die Verwendbarkeit von Modellen, Technologien, Strategien und Schlüsselbegriffen hinsichtlich ihrer tagtäglichen Verwendbarkeit im Medikamentenentwicklungsprozess für die Herstellung neuer Produkte untersucht. Vorgestellt werden Technologien wie omics, Strategien wie Repositioning und Schlüsselbegriffe wie personalisierte Medizin. Eingeklammert und zusammengeführt werden die drei Teilanalysen durch eine ausführliche Einführung und eine umfassende Schlussfolgerung.

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With gratitude I will remember my time at the Collegium Helveticum for the persistent comradeship, the generous support, the enjoyed confidence accomplishing projects on my own responsibility, opening doors to the *créme de la créme* of today's scientific world, the allowed inspection into working mechanisms in place in the domain of science as well as in the corporate world, and last but not least for introducing me to the fascinating realm of pharmacology.

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Martin Boyer, Zurich, November 2012

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ACRONYMS

AMP	adenosine monophosphate
ATP	adenosine triphosphate
cAMP	cyclic adenosine monophosphate
CETP	cholesteryl ester transfer protein
cGMP	cyclic guanosine monophosphate
CNS	central nervous systems

CSF	cerebrospinal fluid
CT	x-ray computed tomography
DMSO	dimethyl sulfoxide
EGF-R	epidermal growth factor receptor
EMA	European Medicines Agency
FDA	US Federal Drug Administration
FGF-R	fibroblast growth factor receptor
Flk-1	fetal liver kinase 1
FN	false negative
FP	false positive
GAO	US Government Accountability Office
GDP	gross domestic product
GMP	guanosine monophosphate
HDL	high-density lipoprotein
hs-CRP	high-sensitivity C-reactive protein
HTS	high throughput screening
KIS	kinase insertion sequence
LDL	low-density lipoprotein
MRI	magnetic resonance imaging
NDA	new drug application
NHS	British National Health Institute
NME	new medical entity
PI	clinical trail phase 1
PII	clinical trail phase 2
PIII	clinical trail phase 3
PIV	clinical trail phase 4
PDE	phosphodiesterase

PDGF	plated-derived growth factor
PDGF-R	plated-derived growth factor receptor
PDGF-R2	plated-derived growth factor receptor 2
PE	penile erection
PET	positron emission tomography
PHC	personalised healthcare
PSA	prostate-specific antigen
RDD	rational drug design
ROC	receiver operating characteristics
RTK	receptor tyrosine kinase
SNP	single-nucleotide polymorphisms
snRNA	small nuclear ribonucleic acid
TKI	tyrosine kinase inhibitor
TP	true positive
VEGF	vascularendothelial growth factor
VEGF-R	vascularendothelial growth factor receptor
VEGF-R2	vascularendothelial growth factor receptor 2
VLDL	very low-density lipoprotein

1

INTRODUCTION

The pharmaceutical sciences and their industry scale implementation is a panoramic screen for all kinds of projections. The benevolent points to its achievements improving medicine and thereby increases general health, to the promises of salvation from neglected diseases by future breakthroughs, to the specific targeting of the disease's origin, to enrichment of the pharmacopeia by over and over new drugs, to the control and eradication of most infectious diseases, to the heroic and painstaking work for the diseased and to its economic and commercial impact for our societies. On the contrary, the malevolent may accentuate the fuzzy mode of action of certain drugs, the variety of off-target side-effects, the grim reported devilish pact of the pharmaceutical industry and medical practitioners interested just in their own profit, the ill-put prerequisites for the clinical trails proofing the effectiveness of new drugs, to the inability to meet up with given promises or raised hopes for cure.

The list of arguments for both points of view could be easily extended endlessly. In a nutshell, the framework of development, production, distribution and consumption of drugs is an emotionally highly charged one: Demurs, hopes, disappointments, beliefs, illusions, etc. clash upon the topic in question. Those conceptions of what pharmacology could be, should be, allegedly is or is not will be in part discussed at length in the following.

Whatever the interpretation of its consequences might be, the state of art of developing successful and purposeful drugs is a delicate, long-lasting, risky and expensive endeavour. It, too, relies on a broad field of interdisciplinary expertises reaching from the "most subtle" chemistry to the practice of marketing.

Since the advent of the industrial expansion of chemistry, pharmacology has been able to *play* with an ever increasing number of new chemical entities. This has led to a gargantuan number of available drugs for an equally increased number of *new* disease patterns. Especially the foundation of synthetic dye chemistry on an industrial level gave birth to an additional and completely different method of drug development. Based on the variety of available dyes, biological

tissues, cell types and microorganisms could be discriminated. This, together with more refined microscopes available led to an in-depth insight into the relation of biological materials. The detection and discrimination of specific microorganisms, in particular, enabled the more precise attribution of certain diseases to the presence of certain microorganisms in bodily tissues and fluids.

The availability of specific pathogen detection through staining led to the conception that, besides specific staining, specific interaction with the physiology of the pathogen is practicable. Hence, the dyes were chemically altered in such a way as to expand the binding properties of the dye with a physiological effect hindering the pathogen from reproducing or from living at all. This gave birth to a new way of dealing with infectious diseases, what is known today under the label of antibiotics. The German chemist Paul Ehrlich was the first who succeeded applying this new drug development technology in the synthesis of Salvarsan, the first efficacious treatment of the worldwide rampant disease syphilis. The developments leading to this early success in the treatment of an infectious disease will be discussed at length later on.

The development and application of disease specific antibiotics was successful and established a novel type of method for drug development. It was delineated as *rational*, as the developed drug targeted the supposed origin of a particular disease. It is also intended the drug does not to affect, or at least, spare the treated organism, and that it interacts solely with its target; the disease provoking microorganism.

What has proven prosperous with infectious diseases has been applied in other therapeutic fields in the following and has grown to the predominant mode of drug development in present day pharmacology. Whereas in infectious diseases the pathogen is made responsible, in analogy, in other therapeutic fields (e.g., chronic diseases or cancer), particular bodily structures, as cellular receptors, are thought of as being implicated in the disease. Here, as well, the structure implicated is aimed at working in a specific manner, that is to say, the drug preferably should interact exclusively with the predefined structure.

This approach has been supported by the growing number of available pharmaceutical tools up to computer assisted design media and an ever growing amount of understanding of the biological interrelations. It is this combination, which has been made accountable for the growing number of chemical therapeutics available. Notwithstanding, the indisputable success to deliver new therapeutic possibilities

for medical applications, the pharmaceutical industry has witnessed a decline in output rates in the last two decades. Not only that the annual drug releases to the market has declined in recent years, also the overall productivity considering the invested sums needed to bring a new therapeutic product to the market has been in sharp decline. This circumstance is, if not alarming, at least distressing for the pharmaceutical industry and has also implications for patients, assurances, economies and the natioal state, in short for the whole society.

1.1 OBJECTIVES OF THE THESIS

This thesis was initiated and embedded within the transdisciplinary research project "Tracking the Human: Technologies of Collecting, Ordering and Comparing, or the Problem of Relevant Knowledge"[1] of the Collegium Helveticum, running for three years from 2007 until 2010. The project scrutinised the scientific construction of ideas of man suitable for the four scientific fields in question and compared their characteristics, applications and implications.

The overall ambition of the thesis was to investigate how the human is represented in pharmaceutical sciences concerning drug development. Especial emphasis was given to what is often referred to as *rational* in drug development and medical therapy.

1.2 OUTLINE OF THE THESIS

The thesis is tripartite: The first chapter deals with an historical perspective on the emergence and evolution of the *rational* paradigm in drug development. Its history is retraced along the scientific career of the eminent German chemist Paul Ehrlich, who was the first to achieve the rational development of a chemotherapeutic drug. The final product, Salvarsan, was the first drug curing syphilis and was the first synthesised antibiotic.

The second chapter encompasses an present day example of *rational drug design*. It recapitulates the developmental history of the anti-angiogenic cancer drug Sunitnib. Upon its release Sunitinib was hailed as a prime example of a straightforward product from the very conception of the idea about the mode of action, through its development to its approval and release to the market. The history of the

1 Detailed descriptions about the project can be found here: *http://www.trackingthehuman.ch/*

development of Sunitinib retraced here is a case study illustrating potentials and drawbacks of present day's modes of drug development. The recapitulation of the development process shows clearly that the initial idea was realised in the final product. The way, however, leading to the successful outcome was a rather anfractuous one and deviated manifold from the *rectified* official account found in the literature. The story of the development of Sunitinib raises a number of questions concerning the practicability of *rational* approaches in developing drugs. The story gives an account on how the initial idea of a drug, cutting down blood vessel growth, was successfully accomplished. It illustrates which methods and premises have been in place and points out how the development process was right for the wrong reason producing a useful and successful medical product.

The third chapter encompasses an introspection into the current state of the art of industrial drug development by means of expert interviews with leading scientists working at one of the world's market leaders in drug development, fabrication, marketing and distribution. This key part gives insights into the applied conceptions of the human biological body and its interaction with drugs, employed *rational* models and technologies as well as their relevance for a fruitful development outcome leading to a beneficial therapeutic product. In addition, it gives a rough evaluation of the current state of the pharmaceutical industry.

2

PAUL EHRLICH'S CHEMOTHERAPY

2.1 INTRODUCTION

The present work[1] examines how the method of specific molecular exertion of influence upon particular diseases emerged in pharmaceutical research and development. The narrative thread follows the development of the exploratory focus of the physician and chemist Paul Ehrlich (1854 - 1915). It was Ehrlich, who by elaborating his "experimental" or "specific chemotherapy" established the fundaments for *rational* approaches in drug development. Furthermore, it was again Ehrlich's merit to develop the syphilis drug Salvarsan and thereby to reach a first practical implementation of a "rational" development. Ehrlich is therefore considered to be the father of new pharmacology aiming at specific molecular targets.

The emergence of the chemotherapy and its development history is relevant here mainly for two reasons: First, the introduction of chemotherapy established a new paradigm, which in its basic structure is valid for the pharmacy of present days. On the basis of biochemical function relationships, macroscopic disease symptoms are attributed – wherever possible – as one distinct, molecularly defined cause of disease. This cause in turn can be influenced by an equally distinct drug. In contemporary pharmacy, the rational drug development approach is known as rational drug design (RDD). The postulated rationality of this approach is based on the fact that a causal chain can be assembled: A symptom is attributed to a measurable cause of disease, which in turn can be influenced by a specifically developed drug.

Secondly, through the introduction of chemotherapy a further stage of reduction has been introduced into pharmacy: A physical disease state should be ascribed to a single, measurable molecular component and likewise treated by the chemical manipulation of this molecular

1 The paper was first published in German in the volume "Model Mensch - Konturierung des Menschlichen in den Wissenschaften": Martin Boyer: Paul Ehrlichs Chemotherapie, in: Rainer Egloff/Priska Gisler/Beatrix Rubin (eds.): Modell Mensch: Konturierungen des Menschlichen in den Wissenschaften 2011, pp. 181–197. All quotes are cited in their respective languages. Translation by the author of German quotes can be found in the corresponding footnotes.

cause of disease. Following this rational consistently, not only the external circumstances of a patient for the description and treatment of a disease is negligible, but also, except for the cause of disease, the body of the patient itself. This paradigm shift reveals a significant change of the idea of man, which conceives the human in principle as an at all levels chemically manipulable *machine*.[2] This does not only suggest an in principle interchangeability of corporal components, but also the manipulability, as a matter of principle of the human body, under the condition of the specific influence upon targeted molecular components. Increasingly, pharmacy has been oriented along the ideal of *chemical engineering*.

To trace this paradigm shift and its far-reaching influences, not primarily the vita and the concrete scientific achievements of Ehrlich are of concern. Of interest is rather what conceptual changes took place, what explanation patterns were used and how the new "rational" process of drug development could be consolidated to allow its influence distinctive until the present days. This paper discusses in detail how explanatory models and techniques from different scientific disciplines - including histology, immunology, microbiology and chemistry - left their mark on the conceptualisation and implementation of chemotherapy. In particular, the accomplished transition to increasingly identify causes of disease in molecular dimensions is of key interest in the present work.

The analysis presented here embarks on a discussion of the concept of Ehrlich's chemotherapy and upon its integration into the pharmacy of his time, which extends over the first two sections of this work. These sections provide an introduction to the chemotherapy and the contemplated possibilities and limits ascribed to the new working methods and their potential to treat especially infectious diseases. The following sections describe the emergence of the definition of disease-specific causes and their visualisation. It will be shown how the visualisation enabled by dyes led to the first therapy trials and ultimately to the first practical and specific implementation of chemotherapy in the treatment of syphilis. The last section tracks down the harnessing of the immunological concept of *side-chains* as receptor for the explanation of the effect of drugs.

The amount of works dedicated to Ehrlich's work and vita are in accordance with the eminence of his work for the establishment of

2 Fritz Kahn represented this conception in his lithographs in pointed style: e.g., Der Mensch als Industriepalast, 1926 (Man as Industrial Palace). *http://www.nlm.nih.gov/dreamanatomy/da_g_IV-A-01.html*, 29.11.2010.

the new molecularly oriented pharmacy. Especially Ehrlich's 150th birthday in 2004 and the 100th anniversary of the awarding of the Nobel Prize for the achievements in immunology in 2008 were the occasion of numerous publications.[3] The disciplinary background of contributions ranges from life sciences over history of medicine to science research. Common to many of these works is their heroic writing style to describe life and work of Ehrlich to whom they attribute the genius of an innovator.[4] In contrast, the present work elucidates Ehrlich's contribution to the integration of various ideas, which led to the conceptualisation of chemotherapy. This is of interest because chemotherapy is still in the foundations of contemporary drug development, something which is further emphasised by the current trend to collectively sell diagnostic and therapeutic techniques as a medical strategy by the pharmaceutical industry.

2.2 INTRODUCTION TO THE CONCEPT OF CHEMOTHERAPY

Both, in the memory of the life sciences as well as in medical science and the history of medicine the introduction of the term "chemotherapy" is attributed to the medical chemist Paul Ehrlich.[5] The term was first mentioned in a newspaper article written by him on the occasion of the opening of the Georg-Speyer-Haus built for his research in Frankfurt a. M. in 1906. In this feuilleton article, he described his idea

3 Among others: J. Drews: Paul Ehrlich: magister mundi, in: Nature Reviews Drug Discovery 3.9 (2004), pp. 797–801; Christoph Friedrich: Paul Ehrlich - Von der Immunologie bis zu Salvarsan, in: Pharmazeutische Zeitung 2004, pp. 16–22; F. Sörgel et al.: Vom Farbstoff zum Rezeptor: Paul Ehrlich und die Chemie, in: Nachrichten aus der Chemie 52.7-8 (2004), pp. 777–782; F. Stern: Paul Ehrlich: the founder of chemotherapy, in: Angewandte Chemie International Edition 43.33 (2004), pp. 4254–4261; K. Strebhardt/A. Ullrich: Paul Ehrlich's magic bullet concept: 100 years of progress, in: Nature Reviews Cancer 8.6 (2008), pp. 473–480.

4 These tributes are citing almost entirely from Ehrlich's posthumously published collected works, which were first published in 1956: Paul Ehrlich/F. Himmelweit: The collected papers of Paul Ehrlich... Vol. 1, 1956. In this edition significant linguistic adjustments and harmonisations has been accomplished. Among others terms initially used by Ehrlich as "Chemiotherapie" were consequently replaced by the latter common term "Chemotherapie". Wherever possible the present work drew on to the Ehrlich's original published work to remain faithful to the former wording. It should be mentioned here that the almost complete and freely accessible collection of Ehrlich's original work can be found on the website of the German Paul-Ehrlich-Institut (PEI): *http://www.pei.de/cln_236/nn_157280/DE/institut/paul-ehrlich/publikationen/paul-ehrlich-publikationen.html?__nnn=true*, accessed 15.08.2010.

5 John Parascandola: The theoretical basis of Paul Ehrlich's chemotherapy, in: Journal of the History of Medicine and Allied Sciences 36.1 (1981), pp. 19–43, here p. 19;H. H. Dale: The collected papers of Paul Ehrlich, in: ed. by Paul Ehrlich et al., vol. 3, 1960, chap. Introduction, pp. 1–18, here: p. 6.

of the"duties of chemotherapy," which should be the focus of the research of the new institute:

> "The main task of the new Institute will now be to find chemical substances and groups who have a particular affinity for certain organs (organotropic substances). Of particular importance will now be, however, to supply chemical substances acting alike trucks with chemical groups having pharmacological or toxicological effects, so that they carry the same load entrusted to them efficiently to the appropriate places." (Own translation.)[6]

The article reveals that according to Ehrlich drugs should be looked for, which seek priorly defined specific tissue in order to exert their effects. Depending on the target of the drug, the "trucks" are changed chemically such that they promote an endogenous function, restrict it or even block it. In the case of the chemotherapeutic treatment of diseases caused by microorganisms that would mean finding a drug that specifically binds to a pathogen and also affect its viability.

Ehrlich's attention was focused on the development of chemotherapeutic agents for infectious diseases. In principle, he considered the possibility to extend this form of therapy to other areas of disease such as cancer, but he remained with theoretical considerations in this respect. The further development of the concept of chemotherapy, as it is used now mostly, in cancer therapy, will not be considered here.

Ehrlich does not deny that various substances were already part of the chemotherapeutic drug vocabulary: "From the very first beginnings of therapeutics chemiotherapy has, indeed, been in existence, as all the remedies which we employ are chemicals ..." But he delimits the term sometimes referred to as "specific" or "experimental chemotherapy" and points to its historical context: "... experimental chemiotherapy could only develop in modern times in a fruitful manner as a result of all this pioneer work."[7] Ehrlich expected from the

6 German original: "Die wesentliche Aufgabe des neuen Instituts wird es nun sein, Substanzen und chemische Gruppierungen aufzufinden, welche eine besondere Verwandtschaft zu bestimmten Organen besitzen (organotrope Stoffe). Von besonderer Wichtigkeit wird es nun aber sein, solche gewissermaßen als Lastwagen fungierende Substanzen mit chemischen Gruppierungen von pharmakologischer oder toxikologischer Wirkung zu versehen, so dass sie gleichzeitig die ihnen anvertraute wirksame Last an die geeigneten Stellen befördern." In: Paul Ehrlich: Die Aufgaben der Chemotherapie. In: Frankfurter Zeitung und Handelsblatt: Zweites Morgenblatt 51 1906

7 P. Ehrlich: Address In Pathology, On Chemiotherapy, in: The British Medical Journal 1913, pp. 353–359, here p. 535.

development of specific chemotherapeutic agents for the treatment of infectious diseases not only ways to a "disinfection from within"[8] and thus a better understanding of the underlying physiology, but the establishment of a new branch of medical research. This clearly differed from the pharmacology of the 19th century, which emerged with the participation of eminent protagonists such as Rudolf Buchheim (1820-1879) and Oswald Schmiedeberg (1838-1912).[9] Furthermore, this can be taken as an abandonment of Virchow's cellular pathology, according to which diseases are based on disturbance of functions of body cells. The objective to define the pathology on a molecular level was new.

Ehrlich wanted to extend the existing and successful treatments that largely focused on symptom control – such as pain relievers, antipyretics and narcotics – with specific drugs; that is to say, drugs targeting directly the cause of disease:

> "Although the benefits of this type of pharmacological research is evident and the beautiful successes, which pharmacology has produced are of great practical importance, one can not but fail to recognise that the majority of substances entered in the pharmacopoeia are pure symptomatics, that favourably influence certain symptoms but are not directed against the disease itself or its cause. It will be the aim now to attain real medicinal substances, organotropic or aetiotropic active substances." (Own translation.)[10]

For Ehrlich "true" drugs should be therefore only be effective in specific tissues, i.e., be "organotropic" or they should directly address the cause of disease and therefore be "aetiotrop". Ehrlich did not

8 H. Bechhold/P. Ehrlich: Beziehungen zwischen chemischer Konstitution und Desinfektionswirkung, in: Z. physiol. Chem 47 (1906), pp. 173–199, here p. 174

9 S. Scheindlin: A brief history of pharmacology, in: Modern Drug Discovery 4 (2001), pp. 87–88. About the development of pharmacy into an academic discipline consult Gerd Folkers: Modell Mensch: Konturierungen des Menschlichen in den Wissenschaften, in: ed. by Rainer Egloff/Priska Gisler/Beatrix Rubin, 2011, chap. Von der Umkehrung der Pyramide, pp. 199–218.

10 Original German quote: "Wenn auch der Nutzen dieser Art pharmakologischer Forschung evident ist und die schönen Erfolge, welche die Pharmakologie gezeitigt hat, von größter praktischer Bedeutung sind, so läßt sich doch nicht verkennen, daß die Mehrzahl der in den Arzneischatz übergegangen Substanzen reine Symptomatika sind, die gewisse Krankheitssymptome günstig beeinflussen aber nicht gegen die Krankheit selbst oder ihre Ursache gerichtet sind. Es wird sich aber jetzt darum handeln, wirkliche Heilstoffe, organotrope oder ätiotrope wirksame Substanzen zu gewinnen." Ehrlich: Die Aufgaben der Chemotherapie. (See n. 6), here p. 1.

discriminate these terms strictly and used "organotropic" often with the meaning of "aetiotrop".

2.3 CHEMOTHERAPY CONCEPT

The introduction of chemotherapy as a concept meant a shift in point of view. The aim was any longer the search for more or less specific influences on the organism with respect to macroscopic factors (fever reducing, etc.), but the one for a singular and differentiable disease cause (e.g., a microorganism), which could be neutralised by a specific agent alike the above described "disinfection from within". As a consequence, several important methodological innovations were introduced in the pharmaceutical drug development process:

(1) According to Ehrlich, chemotherapy should be based on the principle of selective affinity, which requires a highly selective interaction of the drug with the cause of the disease:

> "The whole area is governed by a simple – I might even say natural – principle. If the law is true in chemistry that Corpora non agunt nisi liquida, then for chemiotherapy the principle is true that Corpora non agunt nisi fixata. When applied to the special case in point this means that parasites are only killed by those materials to which they have a certain relationship, by means of which they are fixed by them. I call such substances 'parasitotropic'."[11]

Here, Ehrlich transferred the chemical maxim, according to which substances can react with each other only when they are dissolved in a solvent into pharmacology. Derived from this, he postulated that substances, or in this case, drugs act only if they are bound on the surface of their target structure, for example a microorganism. As will be clarified below, this concept of drug action through selective binding is of paramount importance in the development of Ehrlich's chemotherapy.

(2) The new method was based no longer on healthy laboratory animals as before, but on ones artificially infected with pathogens. Through techniques of microbiology significantly influenced by Louis Pasteur (1822-1895) and Robert Koch (1843-1910), it became possible to purify, identify and cultivate microorganisms in vitro and to infect laboratory animals specifically and at will. This method transfer

11 Ehrlich: Address In Pathology, On Chemiotherapy (see n. 7), here p. 353.

opened up a number of options: A potential drug could be first tested *in vitro* for efficacy against specific pathogens. If successful, the drug efficacy could be tested under controlled laboratory conditions in animals infected with specific pathogens. These results shed light on the dose necessary for treatment, the toxicity, the course of healing as well as on any unwanted side effect. The studies on laboratory animals were regarded as a starting point for evaluating the efficacy and safety of a potential drug for humans.[12]

(3) However, Ehrlich was also aware that the specificity of immunisation or a serum therapy[13] could not easily be reproduced by the administration of different, foreign and small synthetic molecules. In addition, he pointed out that it should also be expected that they do not only influence the wanted target, but that they also could damage the body at the same time:

> "Such 'central shots', as allowed by the bacterial antiproducts are no longer possible, but we will need to be aware that all these agents can hit always, and always besides the bacteria also other parts of the body and cause harm."[14] (Own translation.)

Thus, for Ehrlich, the specificity of immunological antibodies is aimed as a maxim, which is to be achieved as possible even in chemotherapy. But by the same token, he also indicated the limits concerning the specificity of such a therapy, and accordingly, he anticipated the occurrence of side effects associated with the specific mode of action. Correspondingly, the properties of a drug should be therefore possible set so that it affects pathogens, either by killing them or at

12 Paul Ehrlich: Chemotherapie, in: Soziale Kultur und Volkswohlfahrt während der ersten 25 Regierungsjahre Kaiser Wilhelm 2 (1913), pp. 345–356, here p. 556.; Silvia Berger: Bakterien in Krieg Und Frieden Eine Geschichte Der Medizinischen Bakteriologie in Deutschland, 1890-1933, Göttingen 2009, here p. 425; J. Lederberg: Infectious history, in: Science 288.5464 (2000), pp. 287–293, here p. 288.

13 The serum therapy is a method in which animals are infected with a pathogen, whereupon the resulting serum containing the antibodies is purified *in vitro* and then applied for the treatment of infections of the same pathogen in humans. This method of passive immunisation was introduced by Emil von Behring (1854-1917), a colleague of Ehrlich at Robert Koch's Berlin Institute for infectious diseases. B. Lohff: Serumtherapie-Emil von Behring und die Anfaenge der Immunitaetsforschung, in: Deutsche Medizinische Wochenschrift 124 (1999), pp. 1321–1322, here p. 1321-1322.

14 Original German quote: "Solche 'Zentralschüsse', wie sie die bakteriellen Antiprodukte gestatten, sind hier nicht mehr möglich, sondern wir werden uns bewusst sein müssen, daß alle diese Mittel immer und immer außer den Bakterien auch andere Teile des Körpers treffen und schädigen können." P. Ehrlich: Über moderne Chemotherapie. In: Beiträge zur Experimentellen Pathologie und Chemotherapie, Leipzig: Akademische Verlagsgesellschaft mbh 1909, pp. 167–202, here p. 171.

least by hindering them reproducing. This however, without producing unacceptable side effects in the treated body, or having undesirable "organotropic" effects in Ehrlich's terminology.[15]

(4) According to Ehrlich, a further prevention of the harmful side effects could be achieved by the application of several drugs active in a particular pathogen in lower dosages, which will minimise the adverse impact on the human body by the fact that the burden is distributed on several organs.[16]

Nonetheless, as defined by Ehrlich, immunological products are considered as ideal models for the vision of a specific chemotherapy:

> "These antibodies are exclusively 'parasitotrop' and not 'organotrop', and hence it can be no surprise that they find their target as a kind of magic bullet. In this way, I also explain some of the marvellous cures of that [therapeutic] direction. It is therefore eo ipso self-evident, that the serum method must be ceteris paribus superior to every other type of therapy precisely through the pure parasitotropy of theses medical substances."[17] (Own translation.)

Indeed Ehrlich was aware, that his most important contribution to the specific chemotherapy, the drug Salvarsan for the treatment of the syphilis, fell short of the high requirements of harmlessness for the body and could thus not be entitled as "magic bullet",[18], "truck"[19] or "bewitched bullet".[20] But he considered himself closer to the goal of a specific therapy than it was the case with Salvarsan: The arsenic contained in the drug accumulates during prolonged therapy to toxic doses in the bodily tissues. The effect is thus also "organotropic" and can have serious side-effects. Ehrlich led the side effects he got to know of back to the already poor state of health of those

15 P. Ehrlich/R. Gonder: Experimentelle Chemotherapie, in: Prowazes Haridb. Patholog. Protozoen 2, 752 3 (1920), here p. 754.

16 ibid., here p. 772.

17 Original German quote: "Es sind diese Antikörper ausschließlich 'parasitotrop', nicht 'organotrop', und so kann es nicht wundernehmen, daß sie nach Art von Zauberkugeln ihr Ziel selbst aufsuchen. Auf diese Weise erkläre ich auch die zum Teil wunderbaren Heilerfolge dieser Richtung. Es ist daher eo ipso selbstverständlich, daß die Serummethode ceteris paribus eben durch die reine Parasitotropie der Heilstoffe jedem anderen Heilmodus überlegen sein muß."Ehrlich: Über moderne Chemotherapie. (See n. 14), here p. 170.

18 ibid. here p. 170; also referred to as "Freikugel des Freischütz" in Paul Ehrlich: Biologische Therapie, in: Internationale Wochenschrift fuer Wissenschaft, Kunst und Technik 1 (1907), pp. 125–132, here p. 131.

19 idem: Die Aufgaben der Chemotherapie. (See n. 6), here p. 1.

20 Ehrlich: Address In Pathology, On Chemiotherapy (see n. 7), here p. 355.

syphilis patients.[21] Yet he was confident that the chemotherapy will bear fruits. Also, in his opinion, the number of developed chemotherapeutic agents is in simple proportion to the number of scientists working on a particular problem:

> "But the chances in favor of finding a real cure, and so of winning the big prize, will naturally increase with the number of those who occupy themselves with their problem."[22]

Despite all reservations, Ehrlich was confident that chemotherapy will be a major successes in the future. He made the success solely dependent on the technical and human resources invested: The more research will be operated, the more successful drugs would be developed. Ehrlich suggested a purely linear relationship between effort and success.

In order to discuss the main features of Ehrlich's chemotherapy in detail, two further concepts should be addressed. Firstly, the "therapia sterilisans magna", which aimed at eliminating parasites by a single dose of the drug, in order to withdraw the parasite the ability to develop resistances and escape the treatment. Ehrlich referred here to the old therapeutic axiom "frapper fort et frapper vite" and added:

> "And, fortunately, it has been shown that in a number of diseases already the compliance of the second part of the claim: 'frapper vite', was completely enough."[23] (Own translation.)

Ehrlich, however, was not able to exemplify his idea with his own development of the syphilis therapy – the Salvarsan.[24]

21 "Zwar sind 4 Todesfälle nach Anwendung des Mittels beschrieben worden, es handelt sich jedoch hier um Todeskandidaten mit schwersten Degenerationen des Zentralnervensystems, bei denen die Anwendung des Mittels von vornherein eine Gefahr bedeuten mußte und wohl nur noch als Ultimum refugium erfolgte." idem: Die Chemotherapie der Spirillosen, in: Zeitschrift f. Immunitätsforschung 1911, here p. 1135. English: "Although four deaths after therapy with the drug have been described, it is to say that these were candidates for death with severe degeneration of the central nervous system, where the use of the drug posed a priori a threat and probably only occurred as ultimum refugium." (Own translation.)

22 idem: Address In Pathology, On Chemiotherapy (see n. 7), here p. 359.

23 Original German quote: "Und glücklicherweise hat sich herausgestellt, daß bei einer Reihe von Krankheiten schon die Befolgung des zweiten Teils der Forderung: 'frapper vite', vollkommen genügt." Paul Ehrlich/Richard Gonder: Chemotherapie, in: Handbuch der pathogenen Mikroorganismen, 1913, here p. 361.

24 Ehrlich: Address In Pathology, On Chemiotherapy (see n. 7), here p. 356; Paul Ehrlich/S. Hata: Die experimentelle Chemotherapie der Spirillosen: Syphilis, Rückfallfieber, Hühnerspirillosen, Frambösie, in: 1910, chap. Schlussbemerkungen, pp. 114–163, here p. 160.

Secondly, it is the"combination therapy", for which was proposed to administer at least two drugs in combination each having a different mechanisms of action to get hold of a parasite – or in Ehrlich's words: "march separately, beat united."[25] Each of the drugs administered together should target to another receptor:

> "Above all, it must be noted here that for the combination therapy the healing substances have to target diverse chemoceptors on the parasites. [...] Two different types of medicinal substances may possibly be administered to the organism in very small quantities without harming it, but without losing their parasiticidal properties. On the contrary, often the ratio of the medicinal dose, dose curativa, and the toxic dose, dose toxica, is extremely favourable and by far smaller than when each medicinal substances would enter into action individually."[26] (Own translation.)

Therefore, Ehrlich suggests this combination therapy for two reasons. The effectiveness of the therapy should be enhanced by the intervention on several receptors. At the same time the harm for the body should be minimised by the fact that the employed drugs affect the body in various tissues and also find application in smaller doses. This type of approach also reduces the likelihood of developing resistance.

2.4 EMERGENCE OF CHEMTHERAPY

In the following sections the early history of chemotherapy will be traced along Ehrlich's scientific career. With the development of the syphilis drug Salvarsan, Ehrlich was able to successfully implement his theoretical considerations into practice. Here, the examined period runs over three decades, from the 1880's to the 1910's.

At beginning of the 19th century it was generally believed that drugs work mainly on and through the nerves. Later on, it was as-

25 Own translation. German original quote: "getrennt marschieren, vereint schlagen."

26 Original German quote: "Vor allem muß hier bemerkt werden, daß man für die Kombinationstherapie solche Heilstoffe wählen muß, die im Parasiten verschiedenartige Chemozeptoren finden. [...] Zwei verschiedenartige Heilstoffe können eventuell in sehr kleinen Mengen dem Organismus zugeführt werden, ohne ihn dabei zu schädigen, ohne aber auch ihre parasitiziden Eigenschaften einzubüßen. Im Gegenteil wird häufig das Verhältnis der Heildosis, Dosis curativa, und der toxischen Dosis, Dosis toxica, äußerst günstig und weit kleiner als wenn die einzelnen Heilstoffe ein jeder für sich in Aktion treten würden."Ehrlich/Gonder: Chemotherapie (see n. 23), here p. 361.

sumed that specific organs are addressed by drugs.[27] Furthermore, it was assumed that the specific binding at the respective organs was determined by their chemical constitution.

Already as a student, Ehrlich was interested in the selective distribution and the mode of action of drugs and toxins.[28] In particular the work of Emil Heubel (1839-1912) was groundbreaking for him:

> "Reading the work of Heubel on lead poisoning in my third semester I got to the idea that the way in which drugs are distributed in the body must be of greatest importance for a rational implementation of therapy."[29] (Own translation.)

Through his cousin, Carl Weigert (1845-1904), a pioneer of histological staining, Ehrlich was animated to investigate the distribution of colouring substances in living tissue. Already in his doctoral thesis from 1878 he was occupied with the theory and practice of histological staining, in which he dealt with the selectivity of certain dyes. He stressed that, in his opinion, chemical bonds are more important for the coloration and rejected the idea of colouring caused by physical bonds. Due to the lack of alternatives, a chemical interaction between molecules could only be explained via covalent or ionic bonds, which were difficult to reconcile with the available experimental results. Thus the drug action in distinct organs were commonly explained by physical parameters such as different solubilities.[30]

In his habilitation, submitted in 1885, he continued his work on dyes and examined in particular the chemical reactivity of certain tissues with dyes. The work describes concepts, which later developed into the"side-chain theory of immunisation" and was formative for his future thinking about chemotherapy. Based on the idea

27 M. P. Earles: Early theories of the mode of action of drugs and poisons, in: Annals of Science 17.2 (1961), p. 97, here p. 110;A. H. Maehle/C. R. Prüll/R. F. Halliwell: The emergence of the drug receptor theory, in: Nature Reviews Drug Discovery 1.8 (2002), pp. 637–641, here p. 637.

28 Parascandola: The theoretical basis of Paul Ehrlich's chemotherapy (see n. 5), p. 22.

29 Original German quote: "In meinem dritten Semester kam ich durch die Lektüre der Arbeit von Heubel über Bleivergiftung auf die Idee, daß die Art und Weise, in der sich die Arzneimittel im Körper verteilen, von der größten Bedeutung für die rationelle Ausbildung der Therapie sein müsse." Ehrlich/Hata: Die experimentelle Chemotherapie der Spirillosen (see n. 24), here p. 114. Ehrlich is referring to the following paper by Heubel: E. Heubel: Pathogenese und Symptome der chronischen Bleivergiftung: experimentelle Untersuchungen, 1871

30 P. Ehrlich: Ueber die Beziehungen von chemischer Constitution, Verteilung und pharmakologischer Wirkung, in: Gesammelte Arbeiten zur Immunitaetsforschung 574 (1904), here p. 574; J. Parascandola: The controversy over structure activity relationships in the early twentieth century. In: Pharmacy in history 16 (1974), p. 54, here p. 57.

at that time, the protoplasm of cells consisted of a giant molecule, which, depending on cell type had specific side-chains carring out the functions of the cells.[31] These side-chains are responsible for the vital cellular processes such as cellular respiration and nutrient uptake. Through random similarities of naturally binding agents and certain dyes, the latter reacts with these side-chains and staines them. The specific staining of tissues could be explained by these means.[32]

Ehrlich assumed that colourless derivatives of dyes have similar binding properties as these dyes.[33] This is significant in the following, because through the chemical alteration of dyes – often enabling a physiological effect –, frequently, molecules were produced that had no staining properties.

Based on his writings on the action of iodine,[34] thallium,[35] methylene blue,[36] and cocaine[37] in the period from 1885 to 1894 it become clear that Ehrlich acquired concepts and methods for dealing with the problem of affinity and distribution of drugs in the body. These were of eminent usefulness for his later work on the treatment of syphilis and diseases caused by trypanosomes.[38] These works, especially his studies of the clinical treatment of complications caused by nerve pain (neuralgia) by methylene blue, reinforced his belief that

31 H. J. Rheinberger: Von der Zelle zum Gen. Repräsentationen der Molekularbiologie, in: Rheinberger, H.-J., Hagner, M. and Wahrig-Schmidt, B., Räume des Wissens. Repräsentation, Codierung, Spur, Berlin: Akademie Verlag 1997, here p. 270; Paolo Mazzarello: A unifying concept: the history of cell theory, in: Nat Cell Biol 1.1 (1999), E13–E15, here p. E14.

32 P. Ehrlich: Das Sauerstoff-Bedürfniss des Organismus: eine farbenanalytische Studie. 1885, here p. 4.

33 Idem: Beiträge zur Theorie und Praxis der histologischen Färbung, 1878.

34 Idem: Ueber Wesen und Behandlung des Jodismus. In: Charité-Annalen 10 (1885), pp. 129–135.

35 Paul Ehrlich: Beobachtungen über Thallinwirkung. In: Berliner klinische Wochenschrift 163 (1886).

36 P. Guttmann/P. Ehrlich: Über die Wirkung des Methylenblau bei Malaria, in: Berliner Klinische Wochenschrift 39 (1891), pp. 953–956.

37 Cocaine is mentioned here as the only non-staining substance, since it was a well studied substance which applied as local anesthetic "caused most characteristic alterations of organs, inasmuch as it provided the opportunity to study the potential relationship between chemical constitution, local damage and anesthetic effect." (Own translation) Original German quote: "... specifische und höchst charakteristische Organveränderungen hervorrief, insofern als sich so die Möglichkeit bot, eventuelle Beziehungen zwischen der chemischen Constitution, localer Schädigungen und anästhetischer Wirkung aufzufinden." Paul Ehrlich: Studien in der Cocainreihe. In: Deutsche medizinische Wochenschrift 1890, pp. 717–719, here p. 717; Paul Ehrlich/Alfred Einhorn: Ueber die physiologische Wirkung der Verbindungen der Cocainreihe. In: Berichte der Deutschen Chemischen Gesellschaft 27 (1894), pp. 1870–1873, here p. 1871.

38 The diseases are caused by flagellates, which is mostly insectborn and infect vertebrates. The flagelates cause diseases as the Changas disease and afrikan sleeping sickness as well as animal plages as Nagana and Surra.

active substances have to be bound by the cells to exert their effect. This, since methylene blue stains nerves specifically in living tissue.[39] Ehrlich suggested the same methylene blue also for the treatment of malaria, because the pathogen plasmodium is also dyed by this substance.[40] This specific visualisation by means of dyeing enabled the possibility to narrow down the site of action of a potential drug, which was derived from a specific dye, and hence reaches the desired specificity. Previously, just the macroscopic effects of a drug could be observed, but where and how drugs unfold their effects remained in the dark. Since Ehrlich was based in Berlin at that time, and thus worked outside the malaria zone, he could, despite promising results, carry out just two trials of malaria treatment by methylene blue in humans. These experiments were Ehrlich's first entry into the specific chemotherapy for the treatment of infectious diseases. Furthermore, these studies aroused his interest for the relationship of pharmacological action and chemical constitution; a question that has been discussed since 1840.[41]

2.5 SIDE-CHAIN THEORY OF IMMUNISATION

From the year 1890 onwards, Ehrlich turned his attention increasingly to the emerging field of immunology. He only temporarily left his research on dye-derived therapeutic substances. Through his work in the field of immunology, he developed his previously mentioned, already famous and widely quoted "side-chain theory of immunisation",[42] which was of importance for the following research on chemotherapeutics and for which he was awarded the Nobel Prize in medicine in 1909.

To explain the process of immunisation, he took up the previously conceived concept explaining the cellular respiration at side-chains, which has been relevant for the explanation of tetanus poisoning.

39 P. Ehrlich/A. Leppmann: Über schmerzstillende Wirkung des Methylenblau, in: Dtsch med Wochenschr 16 (1890), pp. 493–494, here p. 493.

40 Guttmann/Ehrlich: Über die Wirkung des Methylenblau bei Malaria (see n. 36), here p. 953.

41 W. F. Bynum: Chemical structure and pharmacological action: a chapter in the history of 19th century molecular pharmacology. In: Bulletin of the History of Medicine 44.6 (1970), p. 518, here p. 521.

42 Paul Ehrlich/C. Bolduan: A general review of the recent work in immunity, 1906; P. Ehrlich/J. Morgenroth: Die Seitenkettentheorie der Immunität, in: Anleitung zu hygienischen Untersuchungen: nach den im Hygienischen Institut der königl. Ludwig-Maximilians-Universität zu München üblichen Methoden zusammengestellt 3 (1902), pp. 381–394

The side-chains responsible for cell respiration have by any chance the same chemical constitution, that they, do not only bind the predetermined nutrient molecules, but that also exhibit a high affinity for tetanus toxin. By the binding of the toxin the side-chain loses its function, whereupon the cell forms more side-chains to counteract the loss of function. Usually, this leads to the overproduction of these specific side-chains, with the excess dissolving from the cell into the bloodstream, where they intercept the free toxins and, hence, render them harmless.[43]

Ehrlich distinguished between toxic – "toxophore' – and binding – "haptophore' – groups of a toxin. Again, he let himself be inspired by dyes, where the staining and the groups binding to the material could be distinguished. In spite of his reflection on immunisation against tetanus toxin he did not transferred the concept immediately into the practical application of chemotherapy. The known differences in behaviour of toxins and drugs might have been the reason: (1) Drugs could be dissolved again from the bound tissue by a solvent. (2) Their observable effects were usually only of limited duration. (3) No immunisation could be established against drugs. Thereof, it was concluded that the binding properties of drugs and toxins must be different. It had to be concluded that the bond could be neither of chemical nor of ionic nature, which are difficult to dissolve, but that they rather could be explained by the physical properties of the molecule. Whether chemical or physical properties were to be considered responsible for the characteristic effects and the precise distribution of a substance was a discussion present throughout the 19th century.[44] This is relevant because the binding, which mediates the effect of a drug, was not explainable with the concepts of chemical bindings used at that time.

2.6 FROM DYES TO CHEMOTHERAPEUTIC DRUGS

From 1898, Ehrlich devoted himself again intensively to the study of dyes for chemotherapy, in particular for infectious diseases. First, Ehrlich dealt with trypanosome infections, which could be produced

43 P. Ehrlich: Die Wertbestimmung des Diphterieheilserums und deren theoretische Grundlagen, in: Klinische Jahrbucher 6 (1897), pp. 299–326, here p. 311.

44 Bynum: Chemical structure and pharmacological action: a chapter in the history of 19th century molecular pharmacology. (See n. 41), here p. 522; J. Parascandola: Structure-activity relationships–the early mirage. In: Pharmacy in history 13 (1971), p. 3, here p. 55ff.

experimentally in laboratory animals. He tried to treat them with the benzoate purpurin dyes and their derivatives. He came across a red dye – trypan red – which cured the infection in a mouse model, but not in the other laboratory animals such as rats.[45]

Furthermore, he tried his hand on arsenic compounds. These had already found use before in the treatment of disease symptoms that could be attributed to infections caused by trypanosomes. Ehrlich tested atoxyl,[46] a synthetic arsenic compound, successful *in vitro*, but he could not reproduce the proven disinfectant action in a sequence of animal model experiments. To complicate matters further, for successful treatment doses of atoxyl were required, which damaged the optic nerve. Ehrlich aimed at reducing this effect on the optic nerve, while improving the therapeutic properties by systematically varying the functional groups of the molecule.[47]

2.7 SALVARSAN: FIRST SUCCESS IN CHEMOTHERAPY

When in 1905 *spirochete pallida* finally was identified as the causative agent of syphilis, which is similar to trypanosomes, arsenic compounds have been immediately considered as potential therapeutic agents for syphilis. Ehrlich left the testing of arsenic compounds for syphilis therapy at first to his friend Albert Neisser (1855-1916). In 1909 he entrusted his new assistant Sahachiro Hata (1873-1938) with the tests.[48] Hata tested a series of molecules and found a substance which previously had been declared to be ineffective: The afterwards famous compound number 606, the arsenic amine.[49] The effectiveness of this substance was first demonstrated in animals and then in experiments in patients.[50] In April 1910, Ehrlich was able to introduce his achievements on a medical conference to the public. The

45 P. Ehrlich/K. Shiga: Farbentherapeutische Versuche bei Trypanosomenerkrankung, in: Berlin Klin Wochenschrift 12 (1904), pp. 329–362, here p. 234.

46 Now know as arsanilic acid. The substance inventor Antoine Béchamp optimistically designated it as atoxy, referring to its lower toxicity compared to arsenic.

47 P. Ehrlich/A. Bertheim: Über p-Aminophenylarsinsäure, in: Berichte der deutschen chemischen Gesellschaft 40.3 (1907), pp. 3292–3297.

48 Ehrlich/Hata: Die experimentelle Chemotherapie der Spirillosen (see n. 24), here p. 110.

49 Axel C. Hüntelmann: Arzneimittel des 20. Jahrhunderts: historische Skizzen von Lebertran bis Contergan, in: ed. by Nicholas Eschenbruch et al., Sept. 2009, chap. 1910. Transformationen eines Arz nei stoffes – vom 606 zum Salvarsan.

50 P. Ehrlich: Chemotherapie von Infektionskrankheiten, in: Zeitschr. f. ärztliche Fortbildung 1909, here p. 730.

new syphilis treatment was received with great enthusiasm.[51] It did not take long untill the chemists at Ehrlich's research institute were no longer able to cover up the demand for arsenic amine. So, Ehrlich addressed the dye factory Farbwerke Höchst. Höchst was able to produce large quantities of the drug and marketed under the trade name Salvarsan. Significantly here is not only that a product for therapeutic purposes developed from a dye molecule was taken back into the large-scale production by the dye industry, but rather that the big medical and financial success of Salvarsan established a new research direction common to the present day.

2.8 FROM THE SIDE-CHAIN TO THE CHEMORECEPTOR

Ehrlich considered the understanding of the mechanism of drug action as a necessary foundation for "rationally" developed drugs. He distinguished therefore drugs discovered "experimentally" from drugs discovered purely empirically – that is, by pure trial and error.[52]

Through experiments demonstrating the development of resistance by repeated administration of the same substance in trypanosomes, Ehrlich was inspired to adapt his previously developed side-chain theory of immunisation to similar effects of drugs.[53] In addition, it was found that the resistance was not only limited to a single chemical compound, but that it also extends to molecules of the same class of substances. The effect of other drug classes, however, was not affected by the development of resistance:

> "If we want to consider this phenomenon more precisely, we shall have to imagine that the protoplasm of trypanosomes and in general of all cells have very different sites of interference, each of which corresponds to a special type of a medicinal substance and both share a [structural] relationship. In higher organisms where the organs are differentiated, such a conception is indeed obvious, but even amoeba or lower single-celled organisms have in their cytoplasm a large number of different groups,

51 Paul Ehrlich: Allgemeines über Chemotherapie, in: Verhandlungen des Deutschen Kongresses fuer Innere Medizin 27 (1910), pp. 226–234, here p. 227ff.
52 Ehrlich: Address In Pathology, On Chemiotherapy (see n. 7), here p. 353.
53 idem: Über moderne Chemotherapie. (See n. 14), here p. 189.

> which can be attacked for therapeutic purposes."[54] (Own translation.)

In the often quoted *Harben Lectures* at the Royal Institute of Public Health from 1907, Ehrlich explained for the first time his concept of "chemoreceptors", which he derived from his own *side-chain* theory of immunisation.[55] The chemoreceptors must be built simpler than the ones of the toxins, particularly since, in contrast to the latter, no immunisation could be found. These chemoreceptors, so the assumption, undertake the task of such important functions as cellular respiration and nutrient uptake on the cell surface and are inhibited in their function by the specific binding of a drug. Ehrlich assumed that these chemoreceptors are found in similar implementation on cells of the infected organism. Thus, it must be expected that drugs do not only controlled harm to the parasites, but that they also interfere with the treated human body. The aim was therefore to strengthen the "parasitotrope" effect and simultaneously reduce the "organotropic" effect - today we speak of side effects - to an acceptable minimum.[56]

The optimisation of the specificity of drug action should be accomplished by means of inserted, omitted, replaced or modified residues on the active molecule. Ehrlich suggested that the binding of the molecule at the chemoreceptor occurs in steps, and therefore he distinguish between primary and further secondary "haptophores":

> "Various groups of a drug are so to speak tied up successively by special side-chains of the protoplasm. This happens like a butterfly, whose individual parts are fixed with different needles. Exactly like the butterfly is first put up on the trunk and then gradually to the wings, this is also true for the complicated structure of drugs. Here again, we often can determine a group experimentally that mediates the primary anchor. I call such groups

54 Original German quote: "Wenn wir diese Erscheinung präziser fassen wollen, so werden wir uns vorstellen müssen, dass das Protoplasma der Trypanosomen und überhaupt aller Zellen ganz verschiedene Angriffsstellen hat, von denen jede einzelne einem besonderen Typus eines Heilstoffes entspricht und zu ihm Verwandtschaft hat. Beim höheren Organismus, bei dem die Organe differenziert sind, ist ja eine solche Vorstellung etwas selbstverständliches; aber auch bei einer Amöbe oder bei einem niederen einzelligen Wesen müssen im Protoplasma eine grosse Reihe verschiedener Gruppierungen von differenter therapeutischer Angriffsfähigkeit vorhanden sein."idem: Chemotherapeutische Trypanosomen-Studien, in: Berliner klinische Wochenschrift 11 (1907), pp. 310–314, here p. 342.

55 Sometimes one will find the German term"Chemoceptor":idem: Chemotherapie von Infektionskrankheiten (see n. 50), here p. 727.

56 Ehrlich/Gonder: Experimentelle Chemotherapie (see n. 15), here p. 754.

> the primary haptophore, the others the secondary haptophores."[57] (Own translation.)

In analogy to immunology, Ehrlich applied thus the haptophore-toxophor-concept for the description of the mode of drug action at the receptor. In order to enter into an effective interaction with a desired receptor a molecule need to consist of two distinct parts. The first condition is the chemical complementarity of drug and receptor, which ensures a strong bond. This part of the drug was designated by Ehrlich as "haptophore" and was regarded as an essential precondition for its effectiveness; especially since many substances bind to a pathogen without developing a visible effect. The second component was the toxic or "toxophore" group, which was responsible for the harmful effect of the substance. For complex synthesised compounds, Ehrlich assumed the two components to be spatially separated and connected via a chemical bridge similar to side-chains. The "poisoned arrow" is another catchy metaphor that can be found in the writings of Ehrlich, which describes the mode of drug action as he thought of it:

> "In this way we come naturally to this, that chemiotherapeutic agents, built up in a complicated manner, may be compared to a poisoned arrow; the fixing group of the drug which anchors itself to the chemioreceptor of the parasite corresponds to the point of the arrow, the binding member is the shaft, and the poisonous group is the poison smeared on the arrow's head. Corresponding to this scheme in the case of Salvarsan (dioxydiamidoarsenobenzol) the benzol group would correspond to the shaft, the orthoamidophenol group to the point, and the trivalent arsenic group would correspond to the toxophoric group on the head of the arrow."[58]

Through the introduction of the receptor concept the supposed ideal drug target shifted into the molecular dimensions. Whereas

57 Origninal German quote: "Der Arzneistoff wird gewissermaßen in seinen verschiedenen Gruppierungen sukzessive von besonderen Fangen des Protoplasmas gefesselt, gleich wie ein Schmetterling, dessen einzelne Teile mit verschiedenen Nadeln fixiert werden. Genau wie der Schmetterling erst am Rumpf und dann sukzessive an den Flügeln aufgespannt wird, gilt das auch von den komplizierter gebauten Arzneistoffen. Auch hier können wir häufig eine Gruppierung experimentell festlegen, die die primäre Verankerung vermittelt. Ich nenne eine solche Gruppe das primäre Haptophor, die anderen die sekundären Haptophore." Ehrlich: Chemotherapie von Infektionskrankheiten (see n. 50), here p. 726.

58 idem: Address In Pathology, On Chemiotherapy (see n. 7), here p. 354.

Ehrlich formerly suggested an"organotropic" orientation of drug molecules he now shifted these to the receptor as a key target. It was thus inevitable to investigate the receptors of microorganisms, and thereby, if possible, identify those, which occur only in a specific species and which can be addressed in a targeted manner. Ehrlich himself expressed his idea of an ideal drug with the following words:

> "A remedy provided with such a haptophoric group would be completely innocuous in itself, not being fixed by the organs. It would, however, strike the parasite with full intensity, and in this sense it would correspond to the immune productions, the antisubstances discovered by Behring that fly in search of the enemy after the manner of a bewitched bullet. Let us hope that it will be possible chemiotherapeutically to hit the bull's eye in this manner also."[59]

But even Ehrlich was aware that such specific drugs were difficult to implement and it was imperative, therefore, to delicately adjust the "dose toxica" and the "dosis tolerata" in order to produce valuable drugs:

> "I do not consider this all out of question, as it may be proved in certain diseases – spirillosis in hens, for example – that from the fiftieth to the hundredth part of the *dosis tolerata* of salvarsan entirely frees the animal from the parasite and leads to cure. [...] But such favorable conditions have only very rarely been discovered up to the present; we shall have to be satisfied if we can succeed in obtaining therapeutic results with the tenth or even fifth or sixth portion of the *dosis tolerata*."[60]

2.9 CONCLUSION

Ehrlich thought of this manner of the development of chemotherapeutic agents as novelty insofar as he considered it a rational or – compared to prior procedures – at least a more rational approach. This approach was thought of to be "rational" because the unique staining suggested the existence of a focus of disease. The same dye could

59 ibid., here p. 355.
60 ibid., here p. 355.

be modified in an iterative process in order to display the same or enhanced binding properties. If possible, the dye should even specifically affect the viability of a pathogen – and all this by minimising the harm caused to the human body.

The early practical success of chemotherapy in the treatment of infectious diseases triggered a wave of excitement. It was believed that the end of pharmaceutical development has been reached, since it was supposed that by means of chemotherapy all hostages of humanity causing illnesses could be erased:

> "Hardly at any time in the history of modern medicine has there existed a more intense excitement and a more absorbing interest among the medical fraternity than at present. One of the greatest scourges of humanity – perhaps the most insidious and cruel of all, since it so often places its victims beyond the pale of human sympathy, to be loathed rather than pitied – is on the point of being eradicated."[61]

Thus, a writer rejoiced in 1910 in the journal *Science* about the merits of Ehrlich's chemotherapy. Ehrlich himself expressed no less confidence about the possibilities of chemotherapy:

> "It cannot escape from any unprejudiced observer that this direction of pharmacological thinking and working allows to draw up problems and get their solution closer in ways, which could not be taken into account in previous research. Certainly, this is as yet pioneering work. However, it has already yielded promising results, which has received the recognition of numerous pharmacologists. And it is to be hoped that the adopted line of research will gradually wrestle its way to the prevailing doctrine of pharmacy." [62] (Own translation.)

61 H. Schweitzer: Ehrlich's Chemotherapy–A New Science, in: Science, New Series 32.832 (Dec. 1910), ArticleType: primary_article / Full publication date: Dec. 9, 1910 / Copyright © 1910 American Association for the Advancement of Science, pp. 809–823, here p. 809.

62 Original German quote: "Es kann keinem vorurteilsfreien Beobachter entgehen, daß diese Richtung des pharmakologischen Denkens und Arbeitens Probleme aufzustellen und ihrer Lösung näher zu bringen gestattet, welche die bisherige Forschung so gut wie gar nicht berücksichtigt hat. Gewiß handelt es sich vorläufig noch um eine Pionierarbeit. Sie hat jedoch bereits vielversprechende Resultate gezeitigt, die die Anerkennung zahlreicher Pharmakologen gefunden hat. Und es ist zu hoffen, daß die eingeschlagene Forschungsrichtung sich allmählich zu der in der Arzneimittellehre herrschenden emporringen wird." Ehrlich: Biologische Therapie (see n. 18), here p. 132.

The development of the specific synthetic chemotherapy has been moving between poles of different, mutually influencing conceptual and technological possibilities. To stake out the limits of relevant conditions, and to take the most important elements of a developing story in a linear narrative is always problematic.[63]

But it is possible, as set forth above, to emphasise in five points the decisive factors of the development history leading to the specific chemotherapy and bring them into a gross order:

(1) The development of the dye chemistry, which first developed into a major industry in Germany can be placed at the beginning of the history of chemotherapy. This enabled the production of large quantities of drugs, which were initially derived from drugs.

(2) Synthetic dyes had become the cornerstone of histology. Certain tissues could be stained with specific dyes. Not only differences in tissue could be worked out, but also certain microorganisms could be specifically stained and thus isolated and identified.

(3) Microbiological research made it possible to cultivate specific microorganisms *in vitro* to study them in detail and to describe their characteristics.

(4) The modulation of functional groups of dye molecules allowed the production of substances that bind not only specifically but also prevented the pathogens from reproducing, or even killing them immediately. In a first approximation, the efficacy of drugs could be tested on organisms cultured *in vitro*.

(5) The cultivation of pathogens *in vitro* made it possible to infect laboratory animals selectively in a controlled environment. This allowed to determine the amount of pathogen necessary for an infection to establish, as well as to study in detail both the course of infection and track the distribution of pathogens in the body. Substances proved to be efficient in *in vitro* tests could be tested in laboratory animals prior to be tested in humans.

63 The philosopher of science Ludwik Fleck brings this issue to the point as follows: "The continuity in time of the line of thought already mapped out must continually be interrupted to introduce other lines. The main line of development often must be held in abeyance to explicate connections. Moreover, a grate deal has to be omitted to preserve the idealized main lines. Instead of a description of dynamic inter-action, one is left with a more or less artificial scheme." L. Fleck: Genesis and development of a scientific fact, 1981, here p. 15. (Original German quote: "Wir müssen die zeitliche Stetigkeit der beschriebenen Gedankenlinien immer wieder unterbrechen, um andere Linien einzuführen; vieles weglassen, um die idealisierte Hauptlinie zu erhalten. Ein mehr oder weniger gekünsteltes Schema tritt dann an die Stelle der Darstellung lebendiger Wechselwirkungen." Ludwik Fleck: Entstehung und Entwicklung einer wissenschaftlichen Tatsache (1935), Neuauflage, 1994, here p. 23.)

These developments were significantly supported and mutually influenced by immunology and by models explaining staining. This led to the elaboration of the chemoreceptor concept, which in turn rendered the specific drug effects explainable.

The transformations of drug development illustrated here, which stretched from 1880 over three decades and which was decisively influenced by Paul Ehrlich, reflects the increasing localisation of the foci of disease from organs to the side-chains and finally to the receptors. Accordingly, the pharmaceutical focus moved from a systemic to a molecular level. Causes of disease were associated with the occurrence of particulate entities like microorganisms. This idea was subsequently expanded to the presence, absence or the functional state of certain biochemical structures such as specific receptors. Ehrlich described this in his Nobel Prize speech and pointed at the possibility of a new chemical orientated pharmacy:

> "Now, at this moment, the time has come to penetrate into the *most subtle* chemism of cell life and to break down the concept of the cell *as a unit* into that of a *great number* of individual specific *partial functions*. But since what happens in the cell is *chiefly* of a *chemical* nature and since the configuration of chemical structures lies beyond the limits of the eye's perception, we shall have to find other methods of investigation for this. This approach is not only of great importance for a *real* understanding of the life processes, but also the basis for a truly rational use of medicinal substances."[64]

Ehrlich emphasised here again, and in all clarity, the importance of immersion into "the most subtle chemism" and the rupturing of the cell concept in individual, specific single functions for a real comprehension of vital processes and as the foundation of a rational use of drugs.

Contemporary pharmacology has preserved this rational process of drug development as the central paradigm of research. Nevertheless, modern pharmacy does not help itself by starting drug development with dyes, as sophisticated imaging techniques in theory even permit a computer-based *de novo* drug design. Even if the visualisation media of past and present and the ideas of the biochemical

64 P. Ehrlich: Partial cell functions, in: Nobel Lectures, Physiology or Medicine 1921 (1908), here p. 304.

relationships may have little in common, the method in its basic features is still the same: an unambiguous focus of a disease is identified, which should preferably be influenced only by one highly selective drug. Furthermore, despite the present "rational" drug design methods, medications truly free of side effects are still not the norm in today's pharmaceutical treasury.

The present analysis set out to show that the development process of the "experimental chemotherapy" is not the result of a scientific revolution. This is particularly the case, since this idea has crystallised from an oscillating process between disciplines of what is thinkable and feasible. Concepts, having been borrowed from one discipline, have been extended and reintroduced to the scientific field from which they originated.

However, what has significantly changed with Ehrlich's introduction of chemotherapy is the perception of man from a pharmaceutical perspective. The single individual endowed with an individual body integrated into its living environment has lost importance in the evaluation of diseases, especially since the pathological can be determined at molecular resolutions and addressed specifically by chemical means. By postulating a cause of disease, which could be addressed specifically and with visible success, socio-cultural factors being considered insignificant for the therapy were therefore ignored. In the case of infectious diseases, the cause of the disease was henceforth considered to be both unambiguously diagnosable and specifically treatable.

After this historical perspective on the evolution and emergence of the rational paradigm, we will now give an account in following on how this paradigm is put into practice in contemporary drug development along the example of the cancer drug Sunitinib. The ensuing chapter elaborates, among others, on how this concept is considered today by experts from the pharmaceutical industry.

3

INNOVATION BY CHANCE: THE SUNITINIB CASE

3.1 INTRODUCTION

Nowadays, drug development can rely on an unprecedented amount of knowledge on systemic biochemical and molecular properties. In addition, advanced technologies such as screening methods or computer-based molecular design are also available. This means enable a targeted and, therefore, rational approach - at least in theory - in which first a molecular structure not behaving according to the norm is correlated with symptoms of a disease. This is used as a starting point for a causal understanding of diseases and can lead to their specific therapy. Based on such ideas, an often typical approach is to modulate the malfunction of the component by developing a so-called ligand – a molecule binding to the component in question. This procedure, which is only roughly outlined here is known as rational drug design (RDD) and is considered one of the key methods in contemporary drug development.

Despite these conceptual and practical achievements, the yield of new drugs only available on prescription from the pharmaceutical industry has decreased dramatically in recent decades. According to a study by the US Government Accountability Office (GAO), the annual number of new entries of drugs into the market diminished slightly in the period studied from 1993 to 2004. At the same time, the research and development costs rose by a factor of 2.5 during the same period of time.[1]

In the following, some potential reasons for that productivity decline should be discussed and the question raised as to how goal-oriented, and to what extent the celebrated method of drug development really turns out to be *rational*. Following the development history of the kidney cancer drug Sunitinib, we want to exemplify how drugs are currently developed. The assumptions made at the beginning of the drug development, the technologies applied in the development process and the key results stimulating the progression

1 GAO: NEW DRUG DEVELOPMENT Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts, 2006.

of the development will be reviewed. Firstly, however, the historical development of rational drug development and its intelectual underpinning will be traced briefly.

3.2 HISTORY OUTLINE OF RATIONAL DRUG DEVELOPMENT

Rational drug development is based, among others, on the idea that a structure-activity relationship of the ligand and its target exists. Accordingly, ligands are designed so that they have a high specificity for their target, which in turn guarantees the exclusive effect of the previously defined target structure. Hence, in an over-simplified manner, a congruent link is build up between the symptom of a particular disease, its supposed biochemical point of origin, the target, and the drug modulating this target in a favourable way.

The idea of such is already apparent in Lucretius, who, at the beginning of the Christian era, thought about the different viscosities of oil and wine, as well as about the differences in taste of honey and wormwood:

> "We see how quickly through a colander / The wines will flow; how, on the other hand, / The sluggish olive-oil delays: no doubt, / Because 'tis wrought of elements more large, / Or else more crook'd and intertangled. Thus / It comes that the primordials cannot be / So suddenly sundered one from other, and seep, / One through each several hole of anything. / And note, besides, that liquor of honey or milk / Yields in the mouth agreeable taste to tongue, / Whilst nauseous wormwood, pungent centaury, / With their foul flavour set the lips awry."[2]

Obviously, Lucretius leads the effect of a substance here back to its molecular composition. For practical use, and about two millennia later, these thoughts will be taken up in the rationalised drug development aiming at specific targets. Paul Ehrlich postulated in 1885 his side-chain hypothesis for the binding of antibodies on cells' surface, according to which the cell possess specific side-chains, which bind to the appropriate antibodies.[3] A little later, Emil Fischer in 1894 published his description of the binding of sugar molecules to enzymes by introducing the metaphor of complementarity of a small

2 T.L. Carus/W.E. Leonard: On the nature of things, 1952.

3 Ehrlich/Bolduan: A general review of the recent work in immunity (see n. 42); Ehrlich/Morgenroth: Die Seitenkettentheorie der Immunität (see n. 42)

key, which specifically binds to a lock of same dimensions or in a much larger lock.[4] Thus, Fischer coined the lock-and-key principle still present in the current paradigm of contemporary pharmacy. Ehrlich, then, took on Fischer's idea and expanded it to one of a drug as a magic bullet, which traverses the body up to a previously defined and required biochemical component without interaction, thereby excluding unwanted side effects. He first presented this idea during the famous Harben Lecture at the Royal Institute of Public Health in 1907.[5] This moment can be considered the initial conceptualisation of a specific chemotherapy.

With the advent of the dye chemistry at the turn of the 19th century and their possibilities for specific staining of biological tissues and, consequently, of microorganisms, it was attempted to change the structure of the dyes in order to get hold of specific pathogens dangerous to humans by affecting their viability.

With the development of "the magic bullet" arsenic amine under the aegis of Ehrlich succeeded not only the first ever chemotherapeutic treatment, but also the realisation of the first specific syphilis therapy. Arsenic amine reached the market in 1910 as Salvarsan and replaced the previously common, and extremely toxic, mercury containing ointments and lotions for syphilis therapy.[6] In spite of constituting a resounding success in drug development and its probably rightly consideration as a prime example of a *rational drug development*, the fact that Salvarsan is not a magic bullet free of risks cannot be hidden: When applied for prolonged time periods, toxic amounts of arsenic accumulates. This results from the degradation of the drug within the body so that at the very end the body is accidentally affected.[7]

Despite the theoretical tools and practical success of this approach, it is probably one of the peculiar characteristics of the history of science that rational drug development was really taken on at greater

4 Emil Fischer: Einfluss der Configuration auf die Wirkung der Enzyme, in: Ber. Dtsch. Chem. Ges 27 (1894), pp. 2985–2993.

5 Paul Ehrlich: Experimental Researches on Specific Therapy. On Immunity with special Reference to the Relationship between Distribution and Action of Antigens, in: Royal Institute of Public Health (ed.), London 1908, p. 107.

6 Fritz Kahn: Unser Geschlechtsleben: ein Führer und Berater für jedermann, 1937; Paul Ehrlich/Alfred Bertheim: Über das salzsaure 3.3'-prime-Diamino-4.4'-prime-dioxy-arsenobenzol und seine nächsten Verwandten, in: Berichte der deutschen chemischen Gesellschaft 45.1 (1912), pp. 756–766.

7 Ehrlich: Die Chemotherapie der Spirillosen (see n. 21).

scale in the late 1950's and early 1960's.[8] Two principal reasons can be found in Schueler's highly recommendable book *Chemobiodynamics and Drug Design* from 1960:

> "It may be conjectured that delays were inevitable: first, because the great complexity of medical sciences forced investigators, otherwise having much in common, to work in semi-isolation from one another, scattered as it were, among the various scientific fields that ranged from the consideration of molecules to men; and, second, because the desire to find, as rapid as possible, particular therapeutic agents for the treatment of particular ills has always been so acute that to take the time to build a unified science has seemed, to people with urgent practical ends in mind, somewhat visionary and dilettante. [...] Yet, and in recent years only, it does appear that a great many investigators are collecting their data in specific areas of drug study, a preliminary step which if sustained and increased, promises to give birth to drug design as a scientific speciality in its own rights."[9]

Moreover, technological advances and innovations in research on biochemistry and molecular biology lead to new tools for scientific explorations that enabled deeper insights into biological interconnections. These tools include isotopic labelling (1930's),[10] chromatographic methods (1940/50's),[11] x-ray crystallography (1940/50's),[12] and improved simulations of molecular dynamics in the wake of the proliferation of computers (1950's).[13]

Another reason may be that life sciences had increasingly to deal with more complex diseases. This, in particular, since with the advent of antibiotics and the availability of new vaccination techniques infectious diseases had become treatable. This was accomplished even

8 Matthias Adam: Integrating research and development: the emergence of rational drug design in the pharmaceutical industry, in: Studies in History and Philosophy of Biological and Biomedical Sciences 36.3 (Sept. 2005), PMID: 16137601, pp. 513–37.

9 Fred Warren Schueler: Chemobiodynamics and drug design, 1960, p. 33.

10 G. Hevesy: Application of radioactive indicators in biology, in: Annual Review of Biochemistry 9.1 (1940), pp. 641–662.

11 A.J.P. Martin: Partition chromatography, in: Annual review of biochemistry 19.1 (1950), pp. 517–542.

12 D. Crowfoot: X-ray crystallographic studies of compounds of biochemical interest, in: Annual review of biochemistry 17.1 (1948), pp. 115–146.

13 J.D. Bernal: The Bakerian lecture, 1962. The structure of liquids, in: Proceedings of the Royal Society of London. Series A, Mathematical and Physical Sciences 280.1382 (1964), pp. 299–322.

more easily, because the metabolism of infectious microorganisms differs significantly from that of humans by their evolutionary distance. Interestingly, it was at this time that a shift of approach took place: the cause of the disease was shifted from "outside" of the body (bacteria) to the "inside" the body (systemic diseases).[14]

3.3 ANGIOGENISIS RESEARCH

Since the 1980's the cell membrane bound receptor tyrosine kinases (RTKs) of the ErbB family were investigated regarding their role in blood vessel growth (angiogenesis), something which is essential for the growth of cancer.[15] Through a series of mutation experiments and by blocking the receptors' functions with antibodies it was possible to determine which receptors were the best candidates to serve as target structures. In the 1990's two receptors had been identified that are critical for angiogenesis. These receptors could therefore serve as targets in subsequent drug development: The plated-derived growth factor receptor (PDGF-R)[16] and vascularendothelial growth factor receptor (VEGF-R).[17]

3.4 POTENTIAL TARGETS: PDGF-R AND VEGF-R

Since the late 1980's it was known that the binding of plated-derived growth factor (PDGF) at the PDGF-R on the cell membrane on fibroblasts and on smooth muscle cells triggers a cascade of cell-internal processes, which ultimately leads to the initiation of cell division and blood vessel growth. This process follows the gradient of the messenger PDGF and is therefore directed so that the blood vessels grow

14 Emilie Martin: Flexible bodies: Tracking immunity in American culture from the days of polio to the age of AIDS, 1994.

15 William J. Gullick et al.: The structure and function of the epidermal growth factor receptor studied by using antisynthetic peptide antibodies, in: Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character. Royal Society (Great Britain) 226.1242 (Oct. 1985), PMID: 2866520, pp. 127–134.

16 Klaus Seedorf et al.: Analysis of platelet-derived growth factor receptor domain function using a novel chimeric receptor approach, in: J. Biol. Chem. 266.19 (July 1991), pp. 12424–12431; Klaus Seedorf et al.: Differential effects of carboxy-terminal sequence deletions on platelet-derived growth factor receptor signaling activities and interactions with cellular substrates, in: Molecular and Cellular Biology 12.10 (Oct. 1992), PMID: 1406626, pp. 4347–56.

17 Birgit Millauer et al.: High affinity VEGF binding and developmental expression suggest Flk-1 as a major regulator of vasculogenesis and angiogenesis, in: Cell 72.6 (Mar. 1993), PMID: 7681362, pp. 835–846; Laurie M. Strawn et al.: Flk-1 as a target for tumor growth inhibition, in: Cancer Research 56.15 (Aug. 1996), PMID: 8758924, pp. 3540–5.

towards the source of the messenger (see Fig. 1 on page 35). Dysfunction of this system has been associated with various diseases such as pulmonary fibrosis, glomerulonephritis, osteomyelofibrosis, keloid formation and cancer.[18] To further investigate the functions of the PDGF-R, several experiments were performed. Through the fabrication of chimeric receptors and by selective cutting of certain gene sequences such as the cytoplasmic kinase insertion sequence (KIS), to name just one example, the signalling function of the receptor could be examined.[19] In further studies, pieces of different lengths from the C-terminus of the receptor were cut off and it turned out that this selective deformation of the receptor structure reduced the cell division activity of the receptor and simultaneously inhibited the signals of the tutor.[20]

The vascularendothelial growth factor (VEGF) was discovered in 1983. Initially, it was associated with the control of the permeability of blood vessels[21] and later on it was described as the initiator of the blood vessel growth.[22] By *in situ* hybridisation experiments, the vascularendothelial growth factor receptor 2 (VEGF-R2) (formerly known as fetal liver kinase 1 (Flk-1)) was suspected as a possible receptor for VEGF.[23] Since then, numerous signalling cascades have been described, which initiated by the activated receptor control the process of blood vessel growth.[24] In 1993, by using monoclonal antibodies

18 Lewis T. Williams: Signal Transduction by the Platelet-Derived Growth Factor Receptor, in: Science, New Series 243.4898 (Mar. 1989), ArticleType: primary_article / Full publication date: Mar. 24, 1989 / Copyright © 1989 American Association for the Advancement of Science, pp. 1564–1570.

19 Seedorf et al.: Analysis of platelet-derived growth factor receptor domain function using a novel chimeric receptor approach (see n. 16).

20 Seedorf et al.: Differential effects of carboxy-terminal sequence deletions on platelet-derived growth factor receptor signaling activities and interactions with cellular substrates (see n. 16).

21 Donald R. Senger et al.: Tumor Cells Secrete a Vascular Permeability Factor that Promotes Accumulation of Ascites Fluid, in: Science, New Series 219.4587 (Feb. 1983), ArticleType: primary_article / Full publication date: Feb. 25, 1983 / Copyright © 1983 American Association for the Advancement of Science, pp. 983–985.

22 Pamela J. Keck et al.: Vascular Permeability Factor, an Endothelial Cell Mitogen Related to PDGF, in: Science, New Series 246.4935 (Dec. 1989), ArticleType: primary_article / Full publication date: Dec. 8, 1989 / Copyright © 1989 American Association for the Advancement of Science, pp. 1309–1312; David W. Leung et al.: Vascular Endothelial Growth Factor is a Secreted Angiogenic Mitogen, in: Science, New Series 246.4935 (Dec. 1989), ArticleType: primary_article / Full publication date: Dec. 8, 1989 / Copyright © 1989 American Association for the Advancement of Science, pp. 1306–1309.

23 Millauer et al.: High affinity VEGF binding and developmental expression suggest Flk-1 as a major regulator of vasculogenesis and angiogenesis (see n. 17).

24 Masabumi Shibuya/Lena Claesson-Welsh: Signal transduction by VEGF receptors in regulation of angiogenesis and lymphangiogenesis, in: Experimental Cell Research 312.5 (Mar. 2006), PMID: 16336962, pp. 549–560.

the messenger VEGF could be intercepted in mice, which blocked the growth of implanted tumours.[25] In following knock-out experiments in mouse models, in which the gene for VEGF-R was deleted, the inhibition of growth of implanted brain tumours could be confirmed for the first time.[26] Later on, in the year 1996, experiments confirmed the same results for several solid tumours.[27] Thus, the importance of this receptor for angiogenesis was abundantly sustained by facts.[28]

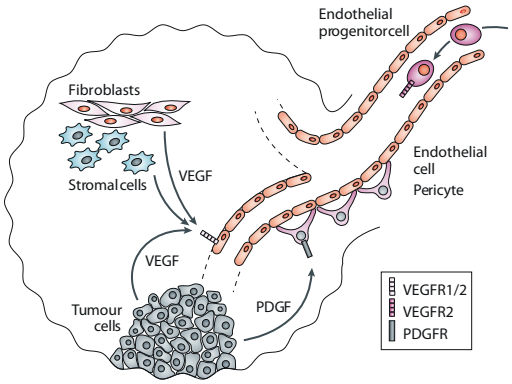

Figure 1: Receptors involved in the process of angiogenesis. Several cell types are implicated in the process of tumour driven agiogenisis such as tumour cells, endothelial progenitor cells, endothelial cells and pericytes. Directed endothelial cell growth is triggered by vascularendothelial growth factor receptors (VEGF-R/VEGF-R2) and platelet-derived growth factor receptors (PDGF-R). This process is sustained by the attraction of pericytes and progenitor endothelial cells. This enables the tumour cells' further growth by the supply with blood born nutrients and oxygen. (Illustration taken and adapted from: S. Faivre et al.: Molecular basis for sunitinib efficacy and future clinical development, in: Nature Reviews Drug Discovery 6.9 (2007), pp. 734–745.)

3.5 DEVELOPMENT OF SUNITINIB

In 1991, due to the identification of several specific angiogenesis initiating neurotransmitters and their corresponding RTK receptors, described above, two leading experts in this field, Axel Ullrich and

25 K. Jin Kim et al.: Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo, in: Nature 362.6423 (Apr. 1993), PMID: 7683111, pp. 841–844.

26 Birgit Millauer et al.: Glioblastoma growth inhibited in vivo by a dominant-negative Flk-1 mutant, in: Nature 367.6463 (Feb. 1994), PMID: 8107827, pp. 576–579.

27 Birgit Millauer et al.: Dominant-negative inhibition of Flk-1 suppresses the growth of many tumor types in vivo, in: Cancer Research 56.7 (Apr. 1996), PMID: 8603410, pp. 1615–1620.

28 Laura K. Shawver et al.: Receptor tyrosine kinases as targets for inhibition of angiogenesis, in: Drug Discovery Today 2.2 (Feb. 1997), pp. 50–63.

Joseph Schlessinger, decided to make these findings useful for the development of cancer drugs and established for this purpose the company SUGEN.[29] As a spin-off company of two large research institutes – namely the Max Planck Institute, Martinsried, and NYUMC, New York - SUGEN could not only rely on a lot of existing expertise, but could also draw on their patents relevant for angiogenesis.[30] One of the goals was to develop a drug that inhibits blood vessel growth - and thus cut off the tumour from its necessary supply, preventing in this way further growth.

Based on these findings at SUGEN, it was initially attempted to produce a small molecule binding, the VEGF-R, and thereby inhibiting its function. In 1996, in a so-called *in vitro* random screening of synthetic compounds divers molecules were tested for their binding properties for VEGF, and several appropriate classes of compounds were encountered.[31] In further experiments published in 1998, in which cell growth was measured in the presence of, among others, VEGF and PDGF, as well as the respective classes of substances, molecules based on indolones (see Fig. 2) were determined as the most suitable candidates for a potential drug.[32]

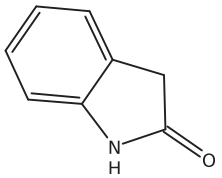

Figure 2: The chemical structure of indolon.

Although there were among the designated substances potent inhibitors of the VEGF-R2, a molecule was continued, which was described in the next year under the designation of SU5416 (see Fig. 3) and was already praised as a potential drug.[33] According to this publication from 1999 SU5416 has previously been tested in 1998 in clinical

29 MPI: Max-Planck-Innovation - Pressemitteilungen, 2006.

30 Joseph Schlessinger: SU 11248: Genesis of a new cancer drug, in: The Scientist (Philadelphia, PA) 19.7 (2005), pp. 17–18.

31 Strawn et al.: Flk-1 as a target for tumor growth inhibition (see n. 17).

32 Li Sun et al.: Synthesis and biological evaluations of 3-substituted indolin-2-ones: a novel class of tyrosine kinase inhibitors that exhibit selectivity toward particular receptor tyrosine kinases, in: Journal of Medicinal Chemistry 41.14 (July 1998), PMID: 9651163, pp. 2588–603.

33 T. Annie T. Fong et al.: SU5416 is a potent and selective inhibitor of the vascular endothelial growth factor receptor (Flk-1/KDR) that inhibits tyrosine kinase catalysis, tumor vascularization, and growth of multiple tumor types, in: Cancer Research 59.1 (Jan. 1999), PMID: 9892193, pp. 99–106.

trail phase 1 (PI), which in turn suggests that SU5416 had been determined quite some time earlier as a drug candidate.[34]

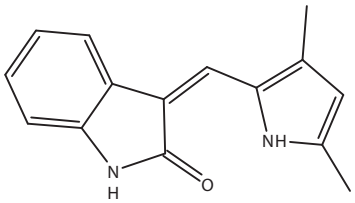

Figure 3: The chemical structure of SU5416.

Also in 1999, first results about potential blocking of PDGF-R, VEGF-R and fibroblast growth factor receptor (FGF-R) emerged.[35] Once again, substituted indolinones were at the focus of investigation. For the first time a substance was tested, which showed not only a high specificity for the PDGF-R, but also important binding properties for VEGF-R2 and FGF-R. SUGEN published the results of studies about this new substance in the following, where it was designated as SU6668 (see Fig. 4). The study indicated that SU6668 had good anti-agiogenic properties in the treatment of several tumours – this at least in animal models.[36]

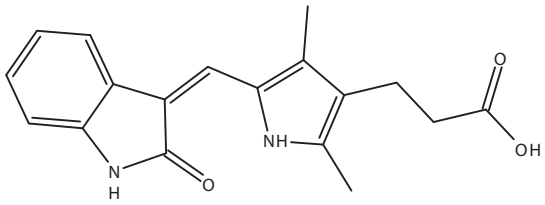

Figure 4: The chemical structure of SU6668.

These results led to the testing of this substance in the PI. Furthermore, through crystallographic methods, it was shown that SU6668 and derivatives thereof bind the adenosine triphosphate (ATP) binding site of the PDGF-R.[37] Since ATP acts throughout the body as an

34 Such delays, postponements and also partially transfigurations in publishing histories can be explained by marketing technical considerations, whereby keeping the caution over the competition, the baiting of own investors with promising news and legal reasons (patent application processes) are balanced.

35 L Sun et al.: Design, synthesis, and evaluations of substituted 3-[(3- or 4-carboxyethylpyrrol-2-yl)methylidenyl]indolin-2-ones as inhibitors of VEGF, FGF, and PDGF receptor tyrosine kinases, in: Journal of Medicinal Chemistry 42.25 (Dec. 1999), PMID: 10602697, pp. 5120–30.

36 A. Douglas Laird et al.: SU6668 is a potent antiangiogenic and antitumor agent that induces regression of established tumors, in: Cancer Research 60.15 (Aug. 2000), PMID: 10945623, pp. 4152–60.

37 Idem: SU6668 is a potent antiangiogenic and antitumor agent that induces regression of established tumors (see n. 36); Li Sun et al.: Identification of substituted

energy source within cells and is thus involved in numerous processes, it is nevertheless amazing that such a high specificity for a hand-picked number of receptors was reached. In the history of pharmacy it was almost a taboo to take a target such as ATP binding site into consideration for a drug target.

Despite the considerable number of promising preclinical and clinical studies on the effect of the specific VEGF-R2 inhibitor SU5416, SUGEN was forced to terminate clinical trail phase 3 (PIII) on colon cancer ahead of time in February 2002 due to poor poor performance of the substance.[38] First, SUGEN solely announced that SU5416 did not meet up with the expectations concerning clinical efficiency and safety. At the same time the company showed confidence that VEGF-R2 still served as a viable target for drug development, according to a SUGEN sponsored researcher.[39]

That this confidence was not totally unfounded, as well as the reason why SU5416 failed in clinical trials, became apparent in March 2003 with the first official mentioning of the potent angiogenesis inhibitor of the next generation, SU11248.[40] It is a potent inhibitor of RTK, which has similar binding properties as SU6668 by binding strongly to multiple receptors such as VEGF-R2 and plated-derived growth factor receptor 2 (PDGF-R2) and also exerts a weaker binding to FGF-R. In addition the new molecule distinguished itself with optimized pharmaceutical properties: water solubility, good receptor binding and good bioavailability.[41] It was also mentioned that the new substance was in the PI.

This publication is central in the course of the drug development not only because of the breakthrough regarding the pharmaceutical properties, but also because it is in many respects a rupture with previous methodological approaches:

(i) What has been described in this paper as improved bioavailability and thus improved solubility of the new inhibitor palliated the fact

3-[(4,5,6, 7-tetrahydro-1H-indol-2-yl)methylene]-1,3-dihydroindol-2-ones as growth factor receptor inhibitors for VEGF-R2 (Flk-1/KDR), FGF-R1, and PDGF-Rbeta tyrosine kinases, in: Journal of Medicinal Chemistry 43.14 (July 2000), PMID: 10893303, pp. 2655–2663.

38 Pharmacia's SU5416 not effective, in: Expert Review of Anticancer Therapy 2.1 (Feb. 2002), PMID: 12113066, p. 5.

39 Matthew Herper: Pharmacia Cancer Drug Halted, Aug. 2002.

40 Li Sun et al.: Discovery of 5-[5-fluoro-2-oxo-1, 2-dihydroindol-(3 Z)-ylidenemethyl]-2, 4-dimethyl-1 H-pyrrole-3-carboxylic acid (2-diethylaminoethyl) amide, a novel tyrosine kinase inhibitor targeting vascular endothelial and platelet-derived growth factor receptor tyrosine kinase, in: Journal of Medicinal Chemistry 46.7 (Mar. 2003), PMID: 12646019, pp. 1116–9.

41 Ibid.

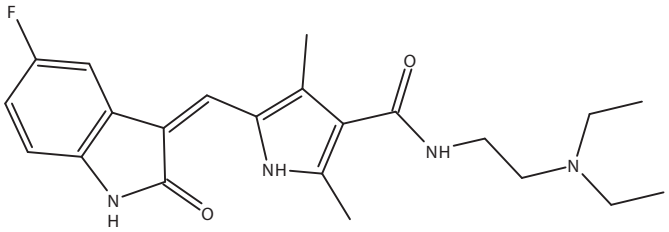

Figure 5: The chemical structure of SU11248.

that the previous two molecules were actually hardly water soluble. This was probably the real reason why SU5416 and SU6668 did not reach up with the expectations concerning efficiency in the clinical trials, which have been anticipated through the good results from the preclinical studies. The clinical trials for both molecules were therefore not pursued further.[42] While, as mentioned above, the end of the clinical study of SU5416 was published, the SU6668 studies have still not officially been terminated.[43] Too, solubility of the substances is in the above-cited literature not an issue until the publication of SU11248. This is quite surprising, since the water solubility of a drug is one of the most fundamental factors which ensures that the ligand can reach its target at all. About the reasons for this quite drastic miscalculation, one can only speculate. It is likely that different scientific practices and methods in preclinical and clinical research, which is divided sharply among biological and medical disciplines was of importance here.[44]

In all preclinical studies of SU5416 and SU6668 the molecules have been tested in the presence of the solvent dimethyl sulfoxide (DMSO), which is widely used in biochemical and cell biological research. This is also reflected in the literature: While DMSO is used, solubility is not an issue. With the announcement of SU11248 DMSO is not mentioned any more, however, detailed figures about the solubility even of the predecessor molecules SU5416 and SU6668 were published. In humans DMSO is only applied externally, e.g., as part of ointments used

42 Schlessinger: SU 11248: Genesis of a new cancer drug (see n. 30).
43 NCI: SU006668 in Treating Patients With Advanced Solid Tumors, Nov. 2008.
44 Fleck: Entstehung und Entwicklung einer wissenschaftlichen Tatsache (1935), Neuauflage (see n. 63).

for local anesthesia.[45] Furthermore, DMSO also has cytotoxic properties and is therefore not suitable for internal use in humans.[46]

Here we see that in a lengthy, labour and cost intensive process two highly specific and efficient compounds have been *rationally* designed. But out of lack of sufficient solubility both did not find application as drugs.

(ii) Another interesting point is that by the choice of a suitable inhibitor the original "dogma" of RDD was apparently not followed. This would, as described above, imply the maximisation of the specificity of an inhibitor so as to modulate just one single target structure and likewise to obviate the occurrence of side effects. One step in this direction has already been taken with the substance SU6668, which binds besides PDGF-R2 also VEGF-R2 and FGF-R. The binding properties of the both latter targets lays by a factor of 40 (VEGF-R2) respectively a factor of 50 (FGF-R) lower then at the main target. But these values still range in the bioactive spectrum of SU5416 for its main target (FGF-R). It is to say they lay by factors of 2, respectively, 3.5. The binding properties of SU11248 range by an order of magnitude higher and, whereby now the effect of all three of these receptors can be inhibited (see Table 1 on page 42).

This development reflects an emerging change of attitude concerning the specificity of the aimed at drug . Formerly, the principle of the *magic bullet* was central, where the modulation focuses on a target structure and where a drug with multiple effects will be pejoratively designated as *dirty drug*. Whereas, now the same drug may be designated as having a rich pharmacology. Also the term "polypharmacology" can be found in the literature.[47]

For one, this can probably be attributed to the fact that the previous approach has led to a rather "poor harvest". A finer analysis of a variety of approved drugs shows that the desired effect can be achieved just by binding to far more targets than intended. One of the most significant examples is aspirin, which would no longer be approved according to common practice, especially as it interacts with a barely manageable number of cellular components in order to exert its known effects. For another, the more accurate traced and under-

45 Wikipedia: Dimethylsulfoxid — Wikipedia, Die freie Enzyklopädie, [Online; Stand 6. Juli 2009], 2009.

46 Weidong Qi/Dalian Ding/Richard J Salvi: Cytotoxic effects of dimethyl sulphoxide (DMSO) on cochlear organotypic cultures, in: Hearing Research 236.1-2 (Feb. 2008), PMID: 18207679, pp. 52–60.

47 Simon Frantz: Drug discovery: playing dirty, in: Nature 437.7061 (Oct. 2005), PMID: 16222266, pp. 942–3.

stood systemic relationships that are willingly spread under the label of systems biology, are a driving force of "polypharmacology". The known complexity of biological systems is ever more taken into account in drug development.

Whilst in a review paper written by SUGEN in August 2000 SU5416 is described as being in PIII,[48] another review paper from 2006 pointed out that SU11248 has been tested in PI since December 2000 and in clinical trail phase 2 (PII) from April 2001 onwards.[49] It should be noted here that SU6668 was mentioned in the literature for the first time only four months prior to the entry of SU11248 into the clinical trials. It comes as no surprise that the poor pharmaceutical properties in terms of the solubility of the predecessor molecules must have had already become obvious before the year 2000. Nevertheless, these molecules have been further tested with the necessary high doses. In any case, as already mentioned, the clinical trials of SU5416 have not been stopped until February 2002.[50] It may be assumed, then, that SUGEN has tried, starting with SU5416 as initial structure, to produce a molecule that is characterized by a higher water solubility – and therefore being better bioavailabile - and yet having the corresponding binding properties at least for one of those receptors involved in the initiation of blood vessel growth.

Another important point was of great relevance for the actual development history and is of interest in the aftermath of the announcement of SU11248 and refers to the history of SUGEN. As already mentioned, SUGEN was founded in 1992. In 1999, the start-up has been completely taken over by the Swedish-American pharmaceutical company Pharmacia&Upjohn. SUGEN continued as largely independent company with only the top leadership exchanged. Just a month after the development of SU11248 has been published in March 2003, Pharmacia&Upjohn was taken over by pharmaceutical giant Pfizer. In succession Pfizer decided to incorporate SUGEN into their own division for cancer drug development and to dissolve SUGEN as a separate company. This brought with it that from this line of development only one drug candidate, SU11248, were pursued by Pfizer. In addition, the majority of employees of SUGEN left the company, because they did not want to be displaced from the region around the

48 Li Sun/Gerald McMahon: Inhibition of tumor angiogenesis by synthetic receptor tyrosine kinase inhibitors, in: Drug Discovery Today 5.8 (Aug. 2000), PMID: 10893547, pp. 344–353.

49 Isan Chen/Carlo Bello/Zuleima Aguilar: Clinical Development of Sunitinib Malate, http://dx.doi.org/10.1007/978-3-540-33177-3_38, 2008.

50 Pharmacia's SU5416 not effective (see n. 38).

bay from San Francisco to the research and development headquarters of Pfizer in Boston.

Nevertheless, Pfizer carried on the clinical trials successfully. Already in February 2005 the PIII could be completed, seven months earlier than planned. The good results prompted an independent expert panel to recommend to cancel the trail in order to allow patients who received placebo during the study to profit from the advantageous treatment by SU11248.

In January of the following year SU11248 was approved by the US Federal Drug Administration (FDA) in United States[51] and then in July by the European Medicines Agency (EMA). The approval of SU11248, which was subsequently marketed as Sutent™ became instantly described as a great innovation and promptly hailed as a prime example of rational drug design par excellence[52] - and not just in the relevant scientific literature.

Compound	*In vitro* kinase activity IC_{50} µM				*In vivo* kinase activity in 3T3 cells IC_{50} µM		cytotoxicity	solubility µg/mL	
	VEGF-R2	PDGF-R	FGF-R	EGF-R	VEGF	PDGF	LD_{50} µM	pH 2	pH 6
SU5416	1.23	22.9	>100	>100	1.04	20.3	>50	<1	<1
SU6668	2.4	0.060	3.00	>20	1-2	0.1-1.0	>50	>5	18
SU11248	0.080	0.0020	2.90	>20	0.005-0.05	0.01	48.9	2582	364

Table 1: The table lists the main activity of discussed compounds for the targeted receptors, cytotoxic activity and solubility parameters. The compiled data indicates two important points discussed above: For once, both, SU5516 and SU6668, are rather selective for either of the targeted receptors VEGF-R2 and PDGF-R, respectively, while SU11248 shows strong binding properties for both. For another, the solubility in water of the later developed SU11248 is orders of magnitude larger then of the previous drug candidates SU5516 and SU6668. (Data taken from: Li Sun et al.: Discovery of 5-[5-fluoro-2-oxo-1,2- dihydroindol-(3Z)-ylidenemethyl]-2,4- dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide, a novel tyrosine kinase inhibitor targeting vascular endothelial and platelet-derived growth factor receptor tyrosine kinase, in: Journal of Medicinal Chemistry 46.7 (2003), PMID: 12646019, pp. 1116–9.)

51 FDA: FDA Approves New Treatment for Gastrointestinal and Kidney Cancer, Jan. 2006.

52 Chen/Bello/Aguilar: Clinical Development of Sunitinib Malate (see n. 49); Laura Q. M. Chow/S. Gail Eckhardt: Sunitinib: from rational design to clinical efficacy, in: Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 25.7 (Mar. 2007), PMID: 17327610, pp. 884–96.

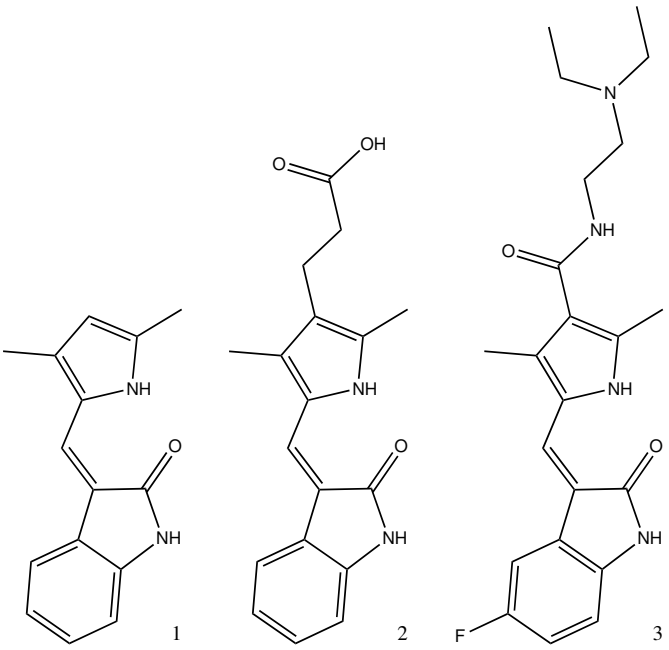

Figure 6: The chemical structures of SU5416 (1), SU6668 (2) and SU11248/Sunitinib (3).

3.6 MINI-REVIEW OF ANTIAGIOGENENIC DRUGS IN CANCER THERAPY

The idea to modulate blood vessel growth (angiogenesis) to control tumour growth in cancer therapy was first set forth by Dr Judah Folkman in 1971.[53] Only in 1994 the humanized anti-VEGF antibody bevacizumab (marketed by Roche/Genentech as Avastin) in combination with chemotherapy was approved by the US FDA for clinical application in human metastatic colorectal cancer patients.[54] Bevacizumab's application has been broadened and is now applied as first-line treatment in a variety of human cancers such as non-small-cell lung cancer, metastatic breast cancer and others.[55] Consecutively, tyrosine kinase inhibitor (TKI) drugs, as the above described sunitinib and a further one, sorafenib (marketed by Bayer and Onyx Pharmaceuticals as Nexavar), have been approved in cancer therapy in combination

53 L.M. Sherwood/E.E. Parris/J. Folkman: Tumor angiogenesis: therapeutic implications, in: New England Journal of Medicine 285.21 (1971), pp. 1182–1186.

54 H. Hurwitz et al.: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer, in: New England Journal of Medicine 350.23 (2004), pp. 2335–2342.

55 Y. Cao: Angiogenesis: What can it offer for future medicine?, in: Experimental cell research 316.8 (2010), pp. 1304–1308.

with chemotherapy.[56] Both drugs are orally applicable small molecule drugs targeting VEGF-R and PDGF-R signalling pathways, which have proven to prolong survival in certain cancer types, as renal cell carcinoma.[57] Still, the accumulated experience with antiangiogenic drugs has not been able to satisfactorily deal with mechanistically unexplainable realities:[58]

- Different types of tumour respond differently to anitangiogenic therapy. A small fraction of solid tumours as colorectal, lung and breast cancers respond to therapy, while other types of cancer as pancreatic cancer have shown to be resistant. Renal cell carcinoma and ovarian cancer respond best the antiangiogenic therapy.

- Patients with the same type of cancer respond differently to the same antiangiogenic drug. Survival improvements of cancer patients by these drugs remain modest. In a minority of patients (ca 30%), addition of the antiangiogenic component to the classical chemotherapy may extend the average lifespan of a few weeks to several months. In contrast, a majority of cancer patients remain unbeneficial to these costly drugs.

- Low response rates and high costs of antiangiogenic drugs urges the discrimination of responsive and non-responsive patient. Nevertheless, at least as for now, any biomarker has reached reliable levels of predictivness of clinical outcome of antiangiogenic therapy.

- Currently applied antiangiogenic drugs loose their initial effectiveness during therapy and cancer patients develop resistance towards the drugs. An feasible explanation is that the cancers switch to other angiogenic factors.

- Most adverse antiangiogenic drug-induced side effects are clinically manageable. Although, severe cardiovascular incidences and lethal cardiovascular thrombosis cases have been reported in subpopulations.

56 S. Wilhelm et al.: Discovery and development of sorafenib: a multikinase inhibitor for treating cancer, in: Nature Reviews Drug Discovery 5.10 (2006), pp. 835–844.

57 J. Brugarolas: Renal-cell carcinoma-molecular pathways and therapies, in: New England Journal of Medicine 356.2 (2007), pp. 185–187.

58 The following list has been borrowed adapted from Cao: Angiogenesis: What can it offer for future medicine? (See n. 55). Please consult this paper for references.

- Most angiogenic drugs are applied in combination with chemotherapy. Due to the number of possible choices it remains an open question which chemotherapy should be applied with which antiangiogenic drug.
- Following the model of tumour angiogenesis, antiangiogenic drug should be prescribed livelong for cancer patients. Discontinuation of drug application is followed by renewed blood vessel growth, and tumour expansion and invasion. The therapeutic window of best antiangiogenic drug application remains an open issue.
- Optimal and maximal dosing antiangiogenic drugs remain an unresolved issue.

As was shown here many clinically related problem will be addressed in the future to guaranty better therapeutic outcomes for cancer patients and to learn more about the molecular mechanisms involved in modulating angiogenic processes.

3.7 CONCLUSION

> "As a rule, detailed knowledge about the biological system has been lacking. It was thus not surprising that the working hypotheses were wrong and the results differed from expectations. Over the years random finding moved over more and more into the background. Today the random findings made way for a focused but tenacious struggle. An exception is only testing of largest possible numbers of chemically diverse compounds, microbial extracts or plant ingredients to obtain entirely new chemical structures. Here chance is desirable in order to yield the widest possible range of lead compounds [...], which are then further optimized specifically [...]."[59]

59 Own translation from H. J. Böhm/G. Klebe/H. Kubinyi: Wirkstoffdesign: Der Weg zum Arzneimittel, 1996. Original: "In aller Regel fehlten detaillierte Kenntnisse über das biologische System. So erstaunt es nicht, dass die Arbeitshypothesen falsch waren und die Ergebnisse von den Erwartungen abwichen. Mit den Jahren rückte der Zufall mehr und mehr in den Hintergrund. Heute hat er einem gezielten und zähen Ringen Platz gemacht. Ausgenommen davon ist nur die Testung einer möglichst grossen Anzahl chemisch diverser Verbindungen, mikrobieller Extrakte oder Pflanzeninhaltsstoffe, um vollkommen neue chemische Strukturen zu erhalten. Hier ist der Zufall erwünscht um zu einer möglichst breiten Palette von Leitstrukturen [...] zu gelangen, die dann gezielt weiter optimiert werden [...]."

It is to hope that it could be demonstrated above how specifically targeted the tenacious struggle of the development of new drugs really still is. In the development presented above, chance – others may call it serendipity[60] – has a share hardly be underestimated in contributing to the ultimate effectiveness of the blood growth inhibitor and, therefore, on its innovation for the pharmaceutical market. Moreover, one should not be mislead by very vague, but often used flowery phrases like "innovation". Such affirmations generally settle for the description of the success of a new product on the market. It remains matter of speculation to what extent the *a priori* proposed assumption and the deduced approach had influenced the eventual achievement. Through a single case study, this problem can hardly be detected unambiguously. However, structures can be worked out, which illustrate the problems to which drug development is subject to. For example, a random screening, which is now known mostly by the massive parallel processing as high-throughput screening, can only test a finite number of compounds in a fixed experiment. Thus, the question that emerges is twofold. For once it is the question how to select the substances to be tested from a large library. Secondly, the question is how to formulate the criteria leading to the selection, and this without abstracting away from potentially valuable compounds. This is even more important, since these selections prepare only starting points, which allow for further transformations of the chemical structure of the compounds to increase their specificity and affinity.

It was also shown how imponderabilities, e.g., the compounds' insolubility in water – influence the course of development processes. Furthermore, it was exemplified how the predefined parameters were ever readjusted – first binding at single and then at multiple receptors. In this respect, one could hardly resent the involved parties that by the success, or rather, by the success attributed to the marketed drug, such a development process is straightened, or more appropriately termed here, "rationalised" in retrospect.

The following chapter will scrutinise in more detail the question raised here. It carefully inspects the present day implementation of *rationality* in several core aspects of present day drug development. Experts from various branches of industry based drug development were interrogated concerning their assessment of *rational* tools employed to day, as well as their general perception of the current state of the pharmaceutical industry.

60 For a more in-depth discussion of serendipity please see footnote15 on page 60.

4

EXPERT INTERVIEWS

4.1 OBJECTIVES

This chapter deals with questions risen in the case study on the development history of the cancer drug Sunitinib. It is partly concerned with the applicability rational procedures in drug development, whose evolution and emergence have been laid out in the previous chapter on the scientific career of Paul Ehrlich and his achievement to produce the first rationally developed chemotherapeutic drug.

In more detail, the aim of this series of interviews was to elucidate general concepts, premisses and working strategies applied in contemporary drug development processes and to evaluate their productivity in the framework of a big multinational pharmaceutical company. Too, the interviews scrutinise chances, advantages and disadvantages of currently employed theoretical frameworks, as well as how they are implemented in technology. Hence, this work involves an introspection of professionals into theoretical and practical aspects of their daily work concerning drug development. The introspection includes various instances along the drug development process from preclinical laboratory testing to clinical trails in humans to evaluate the efficacy of new compounds.

The goal of the interviews was to tackle chances, advantages and disadvantages of currently employed theoretical frameworks, as well as their implementation in technology, as mentioned above.

The investigated theme complexes can be grouped loosely in theoretical and practical issues. Theoretical issues include the following questions:

- If there is a thing like a central paradigm in drug development, what is its content and its scope?
- Which are the crucial steps in the drug development process?
- Can a drug development process be considered linear?

- What is the role of accidental findings – commonly named as serendipity[1] – in the process of drug development?
- In what sense are rational approaches – e.g., rational drug design (RDD) – used in drug development projects?
- How can the discrepancy between diminished productivity and cost explosion in drug development be explained and what are the circumstances producing it?

The second complex of themes was concerned with the relevance of currently much discussed and often used technology in the drug development process. The questions were the following:

- What is the pertinence of the usage of *omics* technologies (genomics, proteomics, etc.) and where were they successfully applied?
- What is the value and the function of *biologics* as drugs?
- What is the potential of biomarkers in therapy?
- How is the prospect of personalised healthcare as seen by professionals in the field?

4.2 STUDY DESIGN

4.2.1 *Target group*

The target group was composed of nine industry-employed experts, all of which in leading positions from various basic research units as well as clinical trail specialists. Three of the experts were *biomarker and experimental medicine leaders*, concerned with late stage biomarker and drug development: e.g., conducting clinical trails. All others had various positions in basic research units: one *head for metabolic diseases*, one was *head of diagnostics laboratory*, one was *head of protein and metabolite biomarker technologies*, one was *head of preclinical central nervous systems research*, one was *group leader translational biomarkers* and one was *head of proteomics group*. All interviewees were either trained

1 There is a twofold definition of serendipity: (1) An unsought, unintended, and/or unexpected discovery and/or learning experience that happens by accident and sagacity. (2) A combination of events which are not individually beneficial, but occurring together produce a good or wonderful outcome. (*en.wiktionary.org/wiki/serendipity*, accessed: 2/8/2011.)

physicians or held a PhD in life sciences and have worked at a major pharmaceutical company for at least three years.

4.2.2 *Interviews*

Data acquisition was carried out by means of guided interviews lasting for 30-90 minutes each, according to the willingness of the experts to dig into details. All interviews took place at a campus of a major pharmaceutical company in Basel, Switzerland, between March and April 2010.

The composition of the questionnaire was discussed with several long-serving induviduals in pharmaceutical sciences, from the industry and from the academic world.

A copy of the questionnaire of the interview is reprinted in the appendix (see appendix A on page 117).

As the interrogations were conducted as open guided interviews, not all experts necessarily touched upon all the topics in the same depth.

4.2.3 *Analysis*

The analysis of the compiled material was carried out in five consecutive steps. (1) All interviews were digitally recorded on a voice recorder and then individually transliterated word by word using the software package *Transcriber*.[2] (2) The transcribed text was sorted according to the questions and summarised sentence by sentence. This again was carried out individually for each interview . (3) All answers across all interviews were coded to work out main lines of argumentation and to gain a semi-quantitative assessment of the spread of opinions. (4) The coded answers were rated according to their frequency of mention and grouped into arbitrarily defined sub-topics pertaining to the same field of interest. Both latter steps were carried out using an spread-sheet,[3] enabling semiautomatic sorting arguments according to their frequency and grouping into sub-topics. (5) finally, results were collected and ordered in text form with a separate section for each topic of questions. (See Fig. 7 on page 50.)

2 Transcriber is an open-source tool for segmenting, labeling and transcribing speech. It can be downloaded here: *http://trans.sourceforge.net* (accessed: 2/8/2011)

3 Microsoft Excel was used.

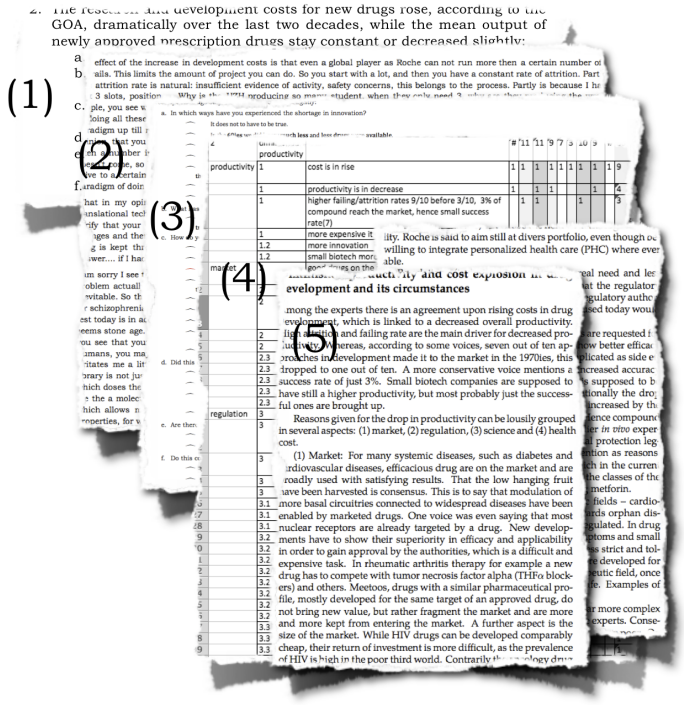

Figure 7: The analysis of the expert interviews was carried out in five consecutive steps: (1) Digital voice recording, (2) sentence-by-sentence transcription, (3) coding of answers, (4) sorting of answers according to mentioning frequency and sub-grouping, (5) writing of this report.

In each result section a discussion of the scope and relevance of the question can be found. The summarised answers of the experts are given in condensed form. Here, the ideas distilled from the interviews are embedded.

4.3 RESULTS AND DISCUSSION

4.3.1 *Central paradigms in drug development*

This question aimed at elucidating the central or common procedures applied in the development of drugs. In other words, what, in the view of the experts are the standard strategies to develop new drugs. The question roots from the clearly visible orientation in pharmaceutical research towards molecular targets.[4] This approach evolves over several consecutive steps and may be summarised as follows:

4 As immediately apparent, this molecular target centred approach dates back to the beginning of the 19th century when Paul Ehrlich succeeded to develop the first specific syphilis drug Salvarsan. More on this development towards a molecularly target

(1) The appearance of a disease is correlated with particular molecular aberration. The premiss that all biological processes can be explained in molecular terms allows for the determination of processes which deviate from the observed norm. This aberration may be the initial idea for a to be developed drug with the scope to modulate the aberrant process in a beneficial way. The aberration may be likewise quantitative, structural or both. The measurable deviation from the norm is the surrogate marker of a physical infirmity. (2) The aberration is identified and ascribed to a molecular entity, which is then defined as a target. Enzymes, receptors, ion channels, DNA/RNA sequences or membrane structures are examples of potential targets. To illustrate the circumstances of the case the example of the development of Salvarsan is illuminating: The specific corporal aberrations linked to syphilis are the surrogate markers, while the target is the syphilis inducing microorganism *Treponema pallidum pallidum*. (3) An chemical entity – an orally applicable small molecule with a molecular weight below 600 or an intravenously applicable biologic – is developed, which interacts agonistically, antagonistically or inhibitorally with the target. (4) An *in vitro* test is established, where the investigated target is extracted from the multitude of cellular interactions in order to investigate the target's interaction with a potential drug molecule, also termed as the target's ligand.

This comparatively recent procedure is contrasted by the phenotypical approach. Here, a compound is already manufactured and an appropriate medical field of application is searched for.

The experts were asked to comment from their perspective on how such a central paradigm could be framed.

Answers

The question about the central paradigm in drug development was interpreted in various ways. Three main lines of argumentation can be discerned: (1) the distinction between the causal and the phenotypical approach, (2) the science of drug development and (3) business processes.

(1) The causal approach was named to be currently the preferred approach in drug development, as it was said to be the most rational one. It aims at finding a molecular target being both "rate limiting in a complex network of biological events" and "functionally impli-

pharmacy can be found in chapter on the development of Ehrlich's chemotherapy on page 5.

cated in a disease". In most cases this molecular target is an enzyme, a receptor, or an ion-channel. For this molecular target a suitable modulator is searched, mostly taking the form of a small molecule, even though biologics – e.g., antibodies – gain terrain.

This approach is opposed by the phenotypical approach, which was considered to have preceded the causal one. Here, animal models of diseases are treated with a new substance and the observed changes in behaviour are interpreted as a consequence thereof. This paradigm still finds use in the drug development for psychiatric diseases, namely schizophrenia and depression, as was mentioned. The mechanisms of action of a drug along with its potential molecular causes are peripheral, as they are not elucidated with sufficient resolution. In behavioural screens of animal disease models, box screen set-ups are used, in which changes of chemical structure are correlated with behavioural changes. Results are then extrapolated to human behaviour as an estimate of the effect of a particular drug.

(2) Science of drug development: The procedural framework, including legal and regulatory commponents, guiding the development process of drugs from the conception of the idea for a new development project to its market entrance is a second line of argumentation termed as paradigm by some experts. The following example is coined for projects with a molecular orientation. Or as one expert put it: "In essence, it is pretty easy: all starts from the target."

Every new drug development starts with a project proposal. The proposal outlines the potential field of application, possible targets, their "rational" – the reasons why it is reasonable to target a certain biochemical structure – and a collection of available evidence supporting the idea of the project. A first generation of compounds – small molecules, antibodies, peptides and in the future potentially small nuclear ribonucleic acid (snRNA) – are produced and tested in preclinical *in vitro* cell cultures and then later in animal studies. After having shown that the compound is doing what it is supposed to in the animal model, toxicological studies are performed to evaluate the safety of the compound. With the safety proven, the much more expensive and delicate human studies – also called clinical trail phase 1 (PI) – start with the proof of concept mostly in healthy subjects. This is followed by trials in a small population of ill subjects (clinical trail phase 2 (PII)). Here the statistical data is said not to be so strong yet, but it is still supposed to indicate that the induced changes may be significant. In addition it proves that the drug is well tolerated. Finally, upon the

evaluation of the hereto accumulated data the continuation into the expensive trials including 1000-2000 test subjects (clinical trail phase 3 (PIII)) is performed. PIII trials are expensive even for big pharmaceutical companies, bearing in mind the experts estimate expenses of about 200-300 million dollars for this late state of drug development. The high costs of final development lead even the biggest multinational pharmaceutical companies to collaborate in order to share costs and to reduce the financial risk of abandoning development projects at late stages.

Most companies were said to work in this way. However, how the development process is regulated and monitored appears to make the difference. It is also here where there is room for improvement, as one expert explained:

> "The way the patients are chosen, how the trials are implemented, how the discovery of the drug is done, how hypothesis are generated, your support, the balanced degree of freedom and the originality of the monitoring systems differ among companies."

It was also stated that the applied paradigms differ depending on the type of field of indication such as oncology, metabolic diseases and virology, and they may hence diverge from the paradigm described above. Furthermore, one interviewee referred to the contemporary urge to implement the concept of biomarkers directly into every step of the process of development.

(3) Business processes: The third line of argumentation is linked to the prerequisites that there is a medical need, and that the will to pay for the medication exists. It was alleged to be obvious that project proposals always claim the eminence of diseases like , e.g., schizophrenia, depression and cancer, and that there is a market. Apparently the marketing people must be convinced that the project aimed at involves a desperate disease – e.g., an orphan disease[5] – with sufferers able and willing to pay for the therapy. Therefore, to make visible the potential for the return of investment is here of pivotal importance. A concrete example thereof was given:

5 Orphan disease are diseases which have not been tackled by the pharmaceutical industry because they are, or, at least, seem financial unprofitable to develop and market a drug for treatment and prevention. There are two criteria designating orphan diseases: (1) A low number of patients. In the USA this means a number lower then 200'000 people. (2) A disease is ignored because its prevalence lays in development countries, which renders return of investment unlikely. Examples are: cholera, typhoid, malaria, and tuberculosis.

> "If you have people with a trauma in the back and they remain paralysed. [...] I guess if we had a drug or else a system to re-establish connections, so that this people after six months of treatment can go back to work, the government will be willing to pay, and, a lot, because this means [paying] less pension of invalidity – go back to work and pay taxes again, as you are supposed to. There is a willingness of society to bring people back to the active, productive, manageable conformation."

To conclude, along the development line of drugs, experts weighted the paradigms differently depending on their kind of expertise. Three main lines of argumentation crystallised from the answers given by the experts. The orientation towards synthesised molecules[6] and the focus on at best specific targets were said to be paradigmatic in drug research. The process from preclinical research to the developed drug itself was also designated as a paradigm. Furthermore, the potential to ascribe the targeted disease a particular eminence with a potentially high market value were considered to be crucial parameters and were valued as being part of the paradigm.

4.3.2 *Crucial steps in the drug development process*

The scope of this question was to trace which steps have to be necessarily taken to permit the development of a new drug. The question was meant to elucidate in more detail what was said in response to the previous question. Drug development, as seen through the literature, seems a process based on milestones, which have to be taken to advance from the initial idea to the marketed drug. These milestones are based on either scientific or business reasons.

The consecutive milestones of drug development are grouped in preclinical and clinical phases. The preclinical phase encompasses the steps, which have been described in the section above: The correlation of disease symptoms with biological processes deviating from the norm, selecting a biologic component in involved in the process as drug target, finding a suitable molecule targeting the selected entity and establishing an *in vitro* test. The four steps following the preclinical phase of drug development are called the clinical trails: (1) The PI deals with the safety of the drug. The toxicological profile of the

6 For a in detail discussion of the difference of synthetic drugs and biologics please consult section 4.3.9 on page 80.

drug and its dosing, metabolisation and side effect range is assessed in small healthy population of 20-80 people. (2) The PII evaluates the treatment efficiency and further test the safety profile in a population of 100-300 patients. (3) In PIII the treatment's effectiveness is established, side effects are monitored, comparisons to already established treatments are made and the safest mode of application is established. In this phase larger populations of 1,000-3,000 subjects are tested. (4) The clinical trail phase 4 (PIV) are the post-approval studies, hence, the testing how the drug performs in daily clinical application. Here the risks and benefits of the treatment are continuously studied and the its use are further optimised.

The experts were asked to account on what they consider as crucial steps in the drug development process.

Answers

Almost all the steps in drug development named in the section from above were designated as being crucial by the interviewees. Nevertheless, there were differences in the weighting of the drug development milestones. Most of those differences are enlisted here for completeness: Target identification and validation, and optimisation concerning side effects. Thereafter, proof of concept in PI, as well as the following clinical trail phases PII and PIII.

With two exceptions, all experts put special emphasis on toxicology. This is the main reason to discuss it here so prominently. One expert drew attention to the problematic of the reliability of toxicological estimation for animal studies upon humans:

> "We do toxicology in different species ticking off boxes. But if you look at the science around it... Let's take one example: the liver. Here the liability is low because there are very few publications, because toxicologists from the pharmaceutical industry do not publish so much for obvious reasons. For some reasons, I tried to dig down how predictive our toxicology models in term of human toxicology really are. You can find funny things, if you dig deeper. [...] This is needed to bring anything forward to man, but you can never really cover all the potential surprises one can see later in all the drug models. [...] Especially in the numbers: for example Vioxx,[7] in which some

7 A nonsteroidal anti-inflammatory drug with the active agent rofecoxib, which was applied in the therapy of osteoarthritis, acute pain conditions, and dysmenorrhoea,

> of the idiosyncratic responses in coagulants came only up in very large patient populations in clinical trail phase 3 and clinical trail phase 4. So we cannot filter that out earlier."

Toxicology, hence, does just estimate the potential risk for a large population of individuals in testing in a comparably small population. Idiosyncratic reactions of individuals, however, can hardly ever be predicted and tend to get visible only during drug application in large populations.

The same expert elaborated more on the issue of toxicology broadening the theme to the question of the accuracy of scientific data coming from various sources and being incorporated into a model serving as a framework for drug development:

> "That are the two crucial steps for me: Is it a toxicology issue, can we solve that? I don't see an easy solution. And how to draw the right conclusions based on the many biological data, which come from academia, molecular biology, *in vivo* experiments, and then to pick from this large wells from outside data, and some that you generate inside: the proper pathway and the proper target. This is not a very structured process, the target selection and toxicology."

So, besides toxicological issues and the above-mentioned milestones in drug development, the integration and evaluation of the available information coming from divers sources[8] is seen as one of the critical steps. For obvious reasons, not all informations that frame the project idea for a new drug development can be double checked and verified. To a certain degree, the process starts relying on information, whose validity for any given development projects can only be verified at later stages.[9] This bears the risk of costly and dangerous misjudgements, but this seems as of now inevitable.

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but which was withdrawn from the market in 2004 for safety concerns. It has been originally marketed by Merck also as Ceoxx, and Ceeoxx.

8 Information from as divers sources as fundamental research in biology and chemistry, insights gained during the developmental process and results from clinical application has to be integrated, each of which is encoded in its idiosyncratic, specific language.

9 An insightful example is the lethal reactivation of an silent virus in clinical trails of the development of the VLA antibody for the treatment of multiple sclerosis. This example is elaborated in more detail below, see section 4.3.4 on page 63.

4.3.3 *Chances of linearity in drug development*

Once a drug has been successfully launched on the market its development history is often published in the pharmaceutical literature. Those descriptions narrate the development from the initial idea to the final product in a rather straight forward way: For a target implicated in the picture of a disease, a compound is developed, which has to run through all the necessary and predefined steps checking its safety and efficacy. This process happens at a steady pace and is usually just unidirectional.[10] But as the development of Sunitinib as shown, drug development may not enrol as straight forward as recounted thereafter. Consequently, the question arose whether these descriptions are not somewhat straightened *a posteriori*, as the chain of events seemed to good to be completely true.

The experts were then asked about their views on the potential linearity of the drug development processes.

Answers

All but one expert figured that drug development processes cannot be considered to be linear or undeciated: it is to say leading in a straight way from the primal idea to the drug ready for the market. Just one expert stated that the process is linear, "even if there are again and again surprises" and correcting himself in adding that "the aim is at least to keep it linear". It was often mentioned that rather then being linear, drug development is and it should be "circular" and "interactive". Circularity in drug development was described by one interviewee as follows:

> " ... we should do more of these cycles: going from research to clinic, and then from the clinic back to the research. I am not sure whether that was happening that much before, but I think it is happening more and more. So, first you have a track, then you put it into the patient. So, you do all the discovery steps and research steps: you put into the patients, you learn what happens in the patients, and you should go back to the bench and look what

10 Besides others, the development of sunitinib malate (marketed as Sutent by Pfizer) is one the recent success stories, which has been described as having resulted from a straight forward, undeviated and *rational* development process: Chen/Bello/Aguilar: Clinical Development of Sunitinib Malate (see n. 49); Chow/Eckhardt: Sunitinib (see n. 52) A more delicately drawn picture about the development leading to the approved cancer drug can be found in chapter 3 on page 29.

> you again see in your animal models or in your preclinical studies. So, it is not so linear and it shouldn't be."

Thus, the goal should be to test potential drugs, or rather lead compounds, much earlier direct in humans to prove their efficacy. Then, to take those substances back to the laboratory for another round of fine-tuning. Hence, process should be guided in a more iterative manner.

Another interviewee admitted that the process is being presented as if it were linear, but in reality this is not the case. He pointed out that "trail and error has still a big share" and in the same argument he cited a pharmaceutical saying: "every good project has to have died at least once." This points to the experience that drug developments may seem to lead nowhere, but then they are sometimes rescued by special coincidences, as new indications emerge or as potential side effects gain profile as main indication.

He also named a potential reason why the development process is hardly kept linear:

> "The more the drug development process advances, the more one learns about the target and the compound, the more difficult it gets. Not only good things are learned, but also things appear, which are not explainable, potential side effects, effects, which were not intended... The main path of development is often left on behalf of a potential more secure bypath. It is never as linear as it appears."

Quoting a head of research, he added to his last argument that the backup compound seems always better then the frontrunner, simply because less is known about it. Still nothing is known about former's drawbacks and just the advantages are known. Concluding he added the platitude:

> "The further one progresses, the more one knows ..."

Rofecoxib[11] was mentioned as an example of a deviated course of development. According to the expert raising this example, the development of rofecoxib was relocated geographically at least once, as it was bought by Pfizer. Actually, rofecoxib is a drug that was developed by Merck. But the expert's argument is still worth mentioning

11 See footnote 7 on page 56.

as he emphasised that the success of each development process is generally linked to a very small group knowing most about the project. The group constitutes an important driving force to strongly believe in the success of the product. These development experts are usually not easily transferred to a new location and would be, for that reason, lost moving the project across the globe.

Notabene, tocilizumab[12] was brought up by a further interviewee as an example of a *non-linear* drug development. Even though he did not go into any details, it is listed here for completeness.

The development history of sildenafil citrate[13] was also mentioned as an example of non-linear development.

Summing up the notions made by the experts leads to the conclusion that drug development is not to be considered to be generally linear, and as it was noted several times that it should not be so. Rather, the flipping back and forth between milestones is expected to be the way to go. In practice this would mean, as mentioned by some interviewees, that lead molecules from early development should be tested as early as possible in clinical setting, in order to estimate their performance under real world conditions. Early estimations of lead molecules' actions, side effects and toxicological shortcomings are thought to give beneficial inputs for optimisations of preclinical testing facilities and to increase the performance of the lead molecules themselves. As much as a more *circular* approach may be desired and may well be productive, it might for obvious reasons raise ethical concerns as untested molecules would have to be administered to healthy and diseased subjects. Certainly this approach would also bear the chance to establish tighter relations and firmer communication channels among the now mostly autonomously acting divisions of a pharmaceutical company involved in a drug development endeavours.

12 Tocilizumab is marketed by Hoffmann-La Roche and Chugai as Actemra and RoActemra.

13 Sildenafil citrate is marketed as Viagra, Revation and other labels by Pfizer. The drug was initially developed for the use in hypertension (high blood pressure) and angina pectoris, but was found to induce penile erection in male volunteers in clinical trails. N.K. Terrett et al.: Sildenafil (VIAGRATM), a potent and selective inhibitor of type 5 cGMP phosphodiesterase with utility for the treatment of male erectile dysfunction, in: Bioorganic & Medicinal Chemistry Letters 6.15 (1996), pp. 1819–1824

4.3.4 *The implication of serendipitous findings in drug development*

Serendipity means to find something beneficial by accident, or to state is clearer, to draw the right conclusion in an issue, but for the wrong reasons.[14] Many scientific discoveries have been attributed to it, an example being penicillin. The impact of serendipity on different scientific fields seems to vary, but pharmacology and chemistry are said to be specially vulnerable.[15] It might be speculated that the more complex the studied system is and the less is actually known about its mode of operation, the more the field of study is prone to make unexpected discoveries. So it is of interest here how the pharmaceutical experts evaluate the importance of serendipity for the development of new drugs.

Answers

With one exception all experts considered serendipity a crucial parameter in drug development. Statements reached from "serendipity is not the fundament of drug development processes, it happens seldom, but when it happens it is good" over "everything other we like, but there is always some serendipity" to "serendipity has been very big and I would like to believe that the importance of serendipity is decreasing" and "people forget this nowadays, but serendipity plays still a huge role".

One interviewee mentioned a succinct sentence, which, as a matter of fact, paraphrases Louis Pasteur: "Chance favours the prepared mind."[16]

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14 See footnote 1 on page 48 for definition.

15 For a general overview on descriptions of serendipity in science and technology please consult: R.K. Merton/E.G. Barber: The travels and adventures of serendipity: A study in sociological semantics and the sociology of science, 2004; R.M. Roberts: Se ren di pi ty: Accidental discoveries in science, in: Se ren di pi ty: Accidental Discoveries in Science, by Royston M. Roberts, pp. 288. ISBN 0-471-60203-5. Wiley-VCH, June 1989. 1 (1989); G. Shapiro: A skeleton in the darkroom: Stories of serendipity in science, 1986. Several works scrutinise the impact of serendipity on drug development and medical discoveries: H Kubinyi: Chance favors the prepared mind–from serendipity to rational drug design, in: Journal of Receptor and Signal Transduction Research 19.1-4 (1999), PMID: 10071748, pp. 15–39; T. Greiner: Why we rarely know about drugs, in: JAMA: The Journal of the American Medical Association 177.1 (1961), p. 42; T.A. Ban: The role of serendipity in drug discovery, in: Dialogues in clinical neuroscience 8.3 (2006), p. 335; M. Golin: Serendipity - big word in medical progress, in: Journal of the American Medical Association 165.16 (1957), p. 2084; M.A. Meyers: Happy accidents: Serendipity in modern medical breakthroughs, 2007

16 This refers to the following quote from a speach given by Pasteur in December 1854: "Dans les champs de l'observation le hasard ne favorise que les esprits préparés." L. Pasteur: Oeuvres de Pasteur, in: ed. by Pasteur Vallery-Radot, vol. 7, 1939, chap. Dis-

One expert commented hereupon that there is a need for someone, who is able to see the difference in behaviour and might recognise the unexpected advantageous effect of a drug. He also mentioned that physicians are particularly well suited to recognise the different drug actions. This for the case that new indications for an already marketed drug are spotted. Often, he continued, unexpected "things" are found, but they are not always associated with some potential different benefit. He also touched upon an explanation of the occurrence of serendipity and brought forward the example of the protein syncytin:[17]

> "... nature is using the same trick over and over again, same proteins do different jobs. There are surprising things, like the protein syncytin, which comes from a retrovirus. It is now used by the placenta to keep the fertilised egg attached. Why the retrovirus has used the syncytin, what it was doing in the virus, how did it happen that the virus infected some mammalian, found it useful and kept it in the DNA, though it is from viral origin, to me this remains a mystery."

The expert points to the fact that related or introduced proteins may have different functions within the new environment. Hence, targeting one protein one might influence other similar proteins with potentially unintended results.

Elsewhere the same expert referred to serendipity stating that it obstructs the planed drug development processes as different questions tend to be answered then the one intended:

> "The prize of the discoveries made by serendipity is that we do not know how to make another drug."

As a consequence, he argues apparently, that all pharmaceutical discoveries can be ascribed to the influence of serendipity. This would imply to reduce the pharmaceutical discovery methods to a mere constraint of the focus of analysis, and that discoveries are owed solely

cours prononcé à Douai, le 7 décembre 1854, à l'occasion de l'installation solennelle de la Faculté des lettres de Douai et de la Faculté des sciences de Lille (Speech delivered at Douai on December 7, 1854 on the occasion of his formal inauguration to the Faculty of Letters of Douai and the Faculty of Sciences of Lille), reprinted in: Pasteur Vallery-Radot, ed., Oeuvres de Pasteur

17 Syncytin is a protein encoded by the ERVWE1 gene, which is of endogenous retrovirus (HERV) origin and it is expressed on high levels in the placenta. It is referred to here as an example showing that proteins can take new function in the course of evolution and this even though they may emanate from a virus.

to the fact that the effect of the chemical exertion of influence on the treated body is subjected to attentive vigilance.

Another two reasons for the occurrence of serendipity were given by an additional interviewee:

> "... but is still, if you think of the size of the chemical space that you screen for molecules. I have seen already presentations, that show the unbelievable large number of compounds that can be generated with only a certain number of atoms of carbon, hydrogen, oxygen and nitrogen. Then serendipity plays still a big role, because the compound you are ending up is restricted to the chemical space that you have screened for. Second is that our knowledge of biology is still quite limited. You select your indications, even for the target with very limited information. Then you have to be lucky that you pick up the right target for the right indication, and treat it with the right compound."

According to the first argument serendipity comes into play because the potential variety of compounds is restricted to the chemical space that one applies in the test setting. Therefore, a restricted chemical space is paired with a restricted testing setting, resulting in a selection of candidate compounds, whose effects on a system-wide scale cannot be extrapolated from the test setting. This is also where the second argument apparently points at: Knowledge about a subsystem and the action of a compound upon it is necessarily restricted to the field of investigation. The compound's efficacy on a systemic level, however, cannot be deduced. Hence, finding the perfect match of compound, target and indication can be considered the result of pure luck rather then insightful, goal-oriented development.

Sildenafil citrate and many fibrates[18] were enlisted as examples, which resulted from serendipitous discoveries.

Just one of the experts maintained an opposing opinion asserting that there is less and less serendipity and that "drug development is not by chance". He, too, cited, besides others, the example of sildenafil citrate, but in favour of his argument he postulated that:

18 Fibrates are lipid-lowering drugs that are used to normalise altered blood fat levels. They lower elevated cholesterol and triglyceride levels. They act upon PPAR (peroxisome proliferator-activated receptors), an intracellular receptor modulating sugar and fat metabolism and adipose tissue differentiation.

> "They did not understand their target properly. It is amazing to get such a surprise. It was just ignorance. We try to keep the process of drug development fast and linear."

He is implying therefore, that there is no such thing as serendipity, because all accidental findings can be attributed to deficiency in knowledge. Would the researches have investigated the target of their drug properly, they should have known where the stimulation leads to. Seemingly, this expert uses the term serendipity in a different, but still in an unexplained manner.

Furthermore, he named the example of an antibody against VLA4 protein, natalizumab (developed and marketed by Biogen as Tysabri), for the treatment of multiple sclerosis, which in the clinical trails caused deaths due to the reactivation of the silent virus JC virus, which induce the deadly incidence of progressive multifocal leukoencephalopathy. After all, according to the experts, the antibody proved its efficiency in multiple sclerosis and Biogen would have had to do much more work to figure out the antibody's side effect. This is to say Biogen would have had to test their antibody in a much larger population. The expert added that it was just bad luck. Even thought the drug showed the deadly side effect it was withdrawn from the market just shortly and is now applied in a more restricted regime allowing its application as monotherapy only. It was found that the overall beneficial effect in multiple sclerosis justifies the increased risk of the reactivation of the JC virus.[19]

Concluding it can be stated that serendipity, deliberately or not, still plays a crucial role in drug development. It does so mostly for the obvious discrepancy of the systemic complexity and the scientific understanding thereof.

4.3.5 *The role of rational drug design in drug development*

Rational drug design (RDD) – also referred to as *drug design* or *structure based drug design* – is a development strategy for drugs centred on the available information about the biochemical target. Goal is the development of a mostly small compound complementary in structure and energy to the intended biochemical target. Thereby the com-

19 D.B. Clifford et al.: Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases, in: The Lancet Neurology 9.4 (2010), pp. 438–446.

pound and the target should bind each other with a high specificity and affinity: the compound should fit the target, in accordance to Emil Fischer's metaphor, like a "key in a lock".[20] Mostly, the target is a key modulator in a biochemical pathway, which is eminently implicated in a disease to be treated and whose action should be controlled through the binding of the compound. Crucial is the specificity of the binding to secure that no other pathway is tackled and hence no side effects occur. Central to the process is the information of the target's three-dimensional structure and the application of computer-assisted design tools.

Through the spread of computer technology in the late 1980's, RDD witnessed a boom and much hope was risen that it will be possible to plan drugs from scratch.[21] Many successful drug developments are described as having been enabled through the application of the RDD strategy. One of those examples previously described, is the cancer drug sunitinib.[22]. The inquired experts were asked to give their account on the possibilities of rationally based procedures, as the company-employed researches were not heard making use of the term, at least not during the industry internship. This sharply contrasts with the frequency of occurrence of the term within the scientific literature.

Answers

Generally, the experts considered RDD to be not without use, but it is not regarded as crucial. Estimations expressed by the experts about this concept were multiple: from "not very central", "not so common in basic research", "it is a buzz word and the literature is full of it", "not so common in basic research" to "sometimes it works, sometimes it does not".

20 For a description of Emil Fischer's key and lock metaphor see section 3.2 on page 30.

21 The following works give a rough overview on the development of *rational* methods from the establishment chemotherapy by Paul Ehrlich to present day implementation in pharmaceutical research: Schweitzer: Ehrlich's Chemotherapy–A New Science (see n. 61); Schueler: Chemobiodynamics and drug design (see n. 9); Leland J Gershell/Joshua H Atkins: A brief history of novel drug discovery technologies, in: Nature Reviews. Drug Discovery 2.4 (Apr. 2003), PMID: 12669031, pp. 321–7; Hugo Kubinyi: Drug research: myths, hype and reality, in: Nature Reviews. Drug Discovery 2.8 (Aug. 2003), PMID: 12904816, pp. 665–8; Chun Meng Song/Shen Jean Lim/Joo Chuan Tong: Recent advances in computer-aided drug design, in: Briefings in Bioinformatics 10.5 (Sept. 2009), PMID: 19433475, pp. 579–591

22 Chen/Bello/Aguilar: Clinical Development of Sunitinib Malate (see n. 49); Chow/Eckhardt: Sunitinib (see n. 52) More information about the real world application of RDD and its relation to serendipity can be found in this work in the case study on the development of the cancer drug sunitinib malete. See 3 on page 29.

One interviewee was referring to the particular problem of fitting the model to real life conditions as he explained that pure *in silico* design suffers from two major problems:

> "Even if we have the crystal, we know the binding site, we can design the molecule... But if the computer twists the molecule a little bit to much, so, in the end it fits. But then if you do the real experiment it doesn't. So, I guess the computer still doesn't know how to be discriminative, or just the information is missing. Although we have the 3D structure, the assumption whether it bind or not is still a bit weak."

Hence, the fitting of computational models with real world experiments is still a not adequately resolved goal, as nowadays the computational models do not represent real world circumstances accurately enough. The postulations made in the 1980's about the possibilities of drug design did not hold. Another expert was referring hereon saying, that looking at the three-dimensional images is nice, but that RDD "did not hold its promises, since it was established some 15 years back, when in silico pharmacology was said to be the way to develop drugs". He added that RDD is just one of the tools used in drug development. An additional voice supported the last statement in saying: "So, it is a complementation aiding in the development. We use it, but not purely. Starting from a crystal is very rare."

A third expert reviewed the problem of computational drug design in detail in enlisting the premises and shortcomings of this approach:

> "When I came to the company in 1989, we where very excited about rational drug design. We now know: It is simply not possible and that is why you did not hear it at the company. At that time I had some peptide derived growth factor and we made use of the tools and possibilities that were here. We made first an x-ray structure, which I didn't have had then. I said: you have the x-ray structure of the ligand, you have some idea of the x-ray structure of the receptor, so it should be very easy. Very naive thinking when you are coming from the outside. Completed from what we tried there, it is not possible. [...] We did a lot of things, deep pocket and enzymes, serine proteases, where you have needles which

> are diving into the pocket. But if you don't have a starting point, completely *de novo* is not possible. You generate hypotheses, the chemist makes a molecule and a crystal. Sometimes you have big surprises, you have a lot of hypotheses how it should be, but then it was completely different. RDD helps in the discussion; it gives you ideas on how to come up with the next molecule. But it will never be that here is my x-ray structure of my ligand here you have my receptor, I give you from *in silico* design a small molecular weight compound, which gives an affinity of one pica mole, or which blocks the interaction. We are still not there. I think we understand not enough. [...] The colleagues from molecular modelling are more enthusiastic. I am always impressed what you can do. But it does not give you a result."

Again, in the opinion of this interviewee RDD is a methodology hardly keeping up with the naive expectations raised three decades ago. RDD in the narrower sense – pure *de novo in silico* design – is supposed to be even altogether impossible. Still, he admitted that that technology is not entirely obsolete, as it may give suggestions on how to proceed further in the development process. He raised some hope for the future of rational approaches in drug development, when a better understanding of the systemic interrelationship will be in place.

The experts' view on rational approaches to develop drugs, as RDD, is a rather critical one. Clearly the expectation towards the computational method were exaggerated from its beginning in 1980's and have not yet seen their fulfilment in the practice of drug development. It is rather seen as a further tool giving insights into the properties of compounds and their target, which might give a hint on how to proceed further. The experts agreed that they would like the development process to be rational, but that still much rests on pure empiricism. The hope that rational procedures will gain ground was sum up by one expert:

> "Of course we cannot do to the perfection, but we try to make [drug development] as rational as a process that is so much empiric allows. I think it is getting more rational."

4.3.6 *Diminished productivity and cost explosion in drug development and their circumstances*

This question is referring to a study conducted by the US Government Accountability Office (GAO) evaluating the productivity of the national pharmaceutical industry.[23] Comparing the annual expenditures for research and development with the number of annual market approvals, the study revealed that over the investigated period from 1993 to 2004 the productivity dropped by a factor of 2.5. Within the time frame the annual investment in research and development increased from about 16 to nearly 40 billion US dollars, while the rate for new drug approvals stayed more or less constant, likewise for new compounds (new medical entity (NME)) as for the total new drug applications (NDAs). NDAs include both, the NMEs as well as already existing drugs being approved for a new indication. The downward trend of productivity described by the GAO in the 2006 study has been confirmed by further published papers.[24]. The study by Bain&Company calculated that the productivity factor (NMEs per Billion US $ spend) dropped from 2.6 in 1998 to 0.3 in 2007, which equals a productivity drop by a factor of 8.6. The interviewees were asked to give their account on this issue to discuss reasons for the drop in productivity in drug development.

Answers

Among the experts there was agreement that rising costs in drug development were linked to a decreased overall productivity. High attrition and failing rates are the main drivers for this scenario. Whereas, according to some voices, seven out of ten approaches in development made it to the market in the 1970's, this dropped now to one out of ten. A more conservative opinion postulated a success rate of just 3%. Small biotech companies are supposed to have still a higher productivity, but most probably just the successful ones are brought up and gain publicity, as one expert emphasised.

23 See Fig. 8 on page 104 for clarification. GAO: NEW DRUG DEVELOPMENT Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts (see n. 1)

24 J.P. Garnier: Rebuilding the R&D engine in big pharma. In: Harvard Business Review 86.5 (2008), p. 68; P. O'Hagan & C. Farkas: Bringing pharma R&D back to health. 2009; S.M. Paul et al.: How to improve R&D productivity: the pharmaceutical industry's grand challenge, in: Nature Reviews Drug Discovery 9.3 (2010), pp. 203–214

The reasons given for the drop in productivity can be grouped in several areas: (1) market, (2) regulation, (3) science and (4) health cost.

(1) Market: For many systemic diseases, such as diabetes and cardiovascular diseases, efficacious drugs are on the market and are broadly used with satisfying results. Likewise, among the experts there was consensus on the notion that the low hanging fruits have been harvested. This is to say that the modulation of more basal biochemical pathways connected to widespread diseases have been enabled by marketed drugs. One expert even stated that available drugs already target most nuclear receptors.

It was stated that new developments have to show their superiority in efficacy and applicability in order to gain approval by the authorities, something which is a difficult and expensive task. In rheumatic arthritis therapy for example, a new drug has to compete with tumour necrosis factor alpha (TNFα blockers) and others. Hence, a new drug has in many cases to compete with well-established therapies already applied with satisfying results.

Meetoos, thus, new drugs with a similar pharmaceutical profile to already approved ones – developed mostly to influence the same biochemical pathways – are not of new value, but rather fragment the market. *Meetoos* are said to be kept more and more from entering the market by the regulative authorities to prevent market fragmentation and to guide resources into development of drugs for *unmet medical needs*, or so called *orphan diseases*.

A further aspect is the size of the market, as was pointed out by one expert. While HIV drugs can be developed at comparably low costs, their pay off is more difficult, as the prevalence of HIV is high in the third world. It is not only the economic weakness of poor countries that renders financial benefits small, but also the deficits in infrastructure, which disables the distribution of the drug and hence hinders access to the market. On the contrary, drug development in the domain of oncology, while expensive, is also the field with the highest profitability. Hence, consideration about the return of investment is guiding the selection of disease areas. One interpretation might be that the available resources are bundled in expensive projects expected to yield high returns of investment.

Commenting on the statements from above, and contrarily to other companies, one expert described Roche as a company still aiming at a divers portfolio with the new emphasis of integrating personalised healthcare wherever possible.

(2) Regulation: A common view was that the regulatory standards have become more and more strict: Regulatory authorities act more conservatively in approving drugs and most drugs used today would not gain approval in the current regulatory framework.

To show better efficacy and safety, huge and costly morbidity and mortality trails are requested for already well treatable endemic diseases. The approval of drugs is further complicated as side effects are less and less tolerated. This is in part due to the increased accuracy of analytic methods available today. But society has also become accustomed to the qualities of existing drugs and is now demanding the reached level of safety for all new drugs, as one interviewee emphasised. One of the expected qualities of drugs is the exclusive specificity for a particular target.

Additionally, the drop out rate of compounds in the preclinical phase is increased by the earlier evaluation of efficacy and toxicology data. Hence, compounds are excluded based on biochemical essays and earlier *in vivo* experiments performed in cell cultures. Stronger animal protection legislations and public relation considerations were mentioned as reasons for omitting direct tests in animal models. This was given as one reason to increase the attrition rate.

Stated examples of drugs applied today, which in the current regulation regime would not anymore reach the market, are the classes of the statins and steroids, and the diabetes drug metformin.[25]

Stricter regulations for established therapeutic fields – e.g., cardiovascular disease – are said to drive industry projects towards less regulated and much smaller markets like the one of orphan diseases. In the case of drug development for deadly diseases with diverse symptoms and small patients populations, as in some types of cancer, regulations are less strict and tolerate more adverse side effects. In such cases, drugs are developed for specific diseases with the goal of widening the therapeutic field once the drug has proven to be efficacious and fairly safe. The experts named two examples of such cross indications: (i) imatinib[26] and (ii) rituximab:[27]

(i) Imatinib was developed for chronic myelogenous leukemia initially and was granted market approval by May 2001. By 2011 its use for at least nine additional cancers has been approved. At its release,

25 Metformin, formerly known as Glucophage sold by Bristol-Myers Squibb, is a drug mainly applied in the therapy of type 2 diabetes.

26 Marketed by Novartis as Gleevec (USA) and Glivec (Europe).

27 Marketed by Biogen, Genentech, Hoffmann-La Roche, Chugai Pharmaceuticals, Zenyaku Kogyo as MabThera and Rituxan.

imbatinib was celebrated as being a new *magic bullet* for the cure of cancer. Furthermore, it is rated among the examples of drugs having been developed using RDD, as the lead compound for the mutation was found by the help of high throughput screening and was then optimised to gain imatinib.[28]

(ii) Rituximab was initially developed for B-cell non-Hodgkin lymphomas resistant to other chemotherapies and was gained market approval in 1997. Its indication has been extended for the treatment of various other lymphomas. It was also shown to be effective in the autoimmune disease of rheumatoid arthritis and it has also found off-label application in kidney transplant patients.[29]

Both examples illustrate how the development of a drug for a niche market can be even financially successful, as safety and efficacy can be proven first in small patient populations, whereupon the indication can be enlarged to treat other diseases.

(3) Science: The biochemical functioning is by far more complex then thought of before, as was admitted by half of the experts. Consequently, the understanding of diseases is generally rather poor. On the one hand, this seems coupled to more difficult questions requesting more difficult answers. On the other hand, there is an apparent association to the rise of the "molecular revolution" that shifted the focus to molecular causes of diseases, demanding the search for a "single master switch" – a single molecular target –, which can be modulated to cure a disease. Not even brute force technologies, as high throughput screening (HTS) were said to have yielded better results:

> "Many people were expecting that high throughput screening would provide better lead molecules. I think, it is the complexity of the human biology and of the disease that leads us to have the gap in innovation in the sense of really being able to produce something in the end, right? I think to some extent, it is the complexity of the biology, that lies behind of many of this. Let's say it is the lack of the really concrete results from the several ways that pharmaceutical companies try to innovate."

28 B.J. Druker/N.B. Lydon, et al.: Lessons learned from the development of an ab1 tyrosine kinase inhibitor for chronic myelogenous leukemia, in: Journal of Clinical Investigation 105.1 (2000), pp. 3–8; Claudia Dreifus: A Conversation With Brian J. Druker, M.D., Researcher Behind the Drug Gleevec, in: The New York Times by Claudia Dreifus, , November 2,November 2 (2009).

29 MD Pescovitz: Rituximab, an Anti-CD20 Monoclonal Antibody: History and Mechanism of Action, in: American Journal of Transplantation 6.5p1 (2006), pp. 859–866.

According to this perception the complexity of the human biology, and hence of the diseases too, constricts the prospects of successful interference with the system. The advanced technologies used in the development of drugs are not of use, when the mapping of scientific models and methodologies with the reality is inadequate. The restrictions of HTS were said to be twofold: (i) The chemical space that is being tested is curtailed by the size and selection represented by the employed library. It consists of a limited number of compounds, which were selected, at least to a certain degree, arbitrarily. (ii) In addition, even the most sophisticated testing system for selection of potential lead compounds is lacking the representational power to fairly indicate the compound's action on a systemic level. Therefore HTS and other similar methodologies guides a development process by restricting the focus of attention on selections provided. This may or may not guide the development process to a lead compound suited for further optimisation.

The applied development paradigm it-self, is said to lead to suboptimal drugs: the emphasis lays to much on the understanding of molecular interaction of drugs and the "molecular master switches". This concept is supposed to be overcome and replaced by a more systemic and integrated thinking about diseases in order to allow taking into consideration the complex interconnectedness of living systems. None of the experts provided a concrete proposal of an approach to develop drugs with a systemic orientation, integrating the evolution dependent systemic connectedness. That is to say, a development approach yielding drugs able to interact on purpose with various "switches", hence with various pathways in order to reach a commutative and beneficial effect.[30]

(4) Health costs: The general opinion was that the national health systems are under high pressure concerning the economical outlay they produce, and that the gross domestic product (GDP) fraction societies are willing to pay for health is virtually reached. The British National Health Institute (NHS) was named to exemplify the refusal to fund certain expensive cancer drugs. This trend to selectivity by national health systems is reckoned to become more prevalent in the

30 This is in fact similar the concept of distributed targets expressed by Paul Ehrlich. He suggested applying several drugs having different targets in the treatment of infectious disease in order to increase efficiency, to prevent the emergence of resistances, and to decrease the harm of side effects of the suffering organism. For more detail see section 2.3 on page 12.

future and is an issue intensely debated in the pharmaceutical industry. This is so, because it threatens the returns in lucrative markets.

According to the experts, the situation is expected to be subject to further deterioration because the costs generated in drug research and development are said to rise further in the future. How society and the pharmaceutical industry will face with this problem has not been solved yet. Health economics was named as a useful tool for the pharmaceutical industry to illustrate the efficacy of their products. It is supposed to show that an overall cost reduction may be yielded in applying a certain drug, even though the price for the drug might be high. The cost reduction may be then reached by the way of fewer days of hospitalisation.

Some big pharmaceutical companies started collaborating on drug development projects. Either in "joint drug development", joining forces in the along the whole drug development process, or, on sharing risks of the costly and difficult to assessable stage of PIII reduces the financial burden for single companies.[31]

Summarising, what was said indicated clearly that the raising costs are a crucial issue for the pharmaceutical industry. In addition, the experts are conscious about the weight of this problem. It was stated that the pharmaceutical industry became partly victim of its own previous successes, as ubiquitous diseases have become well manageable. This renders it ever more difficult to develop better drugs. Then regulations for the approval of new drugs became more strict: Still less side effects are tolerated and higher quality standards concerning specificities are requested. Regarding the state of the pharmaceutical science, it was said that generally no satisfactory understanding of the underlying biology has been established to allow for a straightforward drug development. The molecular orientation toward a single master switch was mentioned as a potential reason to drive costs of development, as this orientation was considered to directly support the attrition rate of new development. Finally, the explosion of health costs and the limits of national health budgets were mentioned as a critical issue for the pharmaceutical industry. Both issues

31 Sharing risks among global pharmaceutical player was also discussed elsewhere. Please consult section 4.3.1 on page 53. Whether joining forces bears a real advantage for pharmaceutical companies is ambivalently debated in the literature. Whereas joining forces during the research and development phase was found be potentially beneficial, advantages for whole jointly held development projects could not be found. Too, joint projects were not found to have a higher likelihood for a successful outcome. For in-depth discussion see: R. Gulati/D. Lavie/H. Singh: The nature of partnering experience and the gains from alliances, in: Strategic Management Journal 30.11 (2009), pp. 1213–1233

threaten the return of investment for expensive drug development. Along the interviews it became clear that the lowered productivity of the pharmaceutical industry is grounded in multiple causes in a widespread, highly interdependent network of science, the various idiosyncratic languages of scientific disciplines, regulatory authorities, markets, public expectations, the very complexity of biology and probably many other factors not considered here.

4.3.7 *Value and usage of omics technologies in drug development processes*

Oimcs is a neologism referring as a general term, at least in the life sciences, to genomics and proteomics and others. Besides being a useful technology to uncover biochemical networks, much hope was raised that it might facilitate and speed up drug development processes.

In drug development, omics are used to assess the mechanism of action of drug candidates on various systemic levels. With the emergence of omics technologies much hope was raised in pharmaceutical research that drug development might require much less effort, and that drug development will speed up.

Genomics, for example, designates the study, on a large scale, which it-self comprise for the wholeness of all genes in an organism. Studying genomics implies evaluating qualitatively and quantitatively the interdependencies of a genome. Genomics is considered useful for example to detect individual genetic differences soliciting aberration in drug response. Likewise, proteomics, attempts to study the biggest share of present protein in an organism and to show how these entities work together on a systemic level. Besides the named examples there are many more omics fields applicable in drug development like: lipidomics, studying lipids; transcriptomics, studying mRNA transcrips; metabolomics, studying the networks of metabolites; and many others.[32]

32 For a general review on omics technologies and their implication in drug developmen see: J.A. Bilello: The agony and ecstasy of "OMIC" technologies in drug development, in: Current molecular medicine 5.1 (2005), pp. 39–52. For in-depth reviews on specialised omics subfields see: on genomics, A.D. Roses: Pharmacogenetics and drug development: the path to safer and more effective drugs, in: Nature Reviews Genetics 5.9 (2004), pp. 645–656; on proteomics, S. Hanash: Disease proteomics, in: Nature 422.6928 (2003), pp. 226–232; on lipidomics, M.R. Wenk: The emerging field of lipidomics, in: Nature Reviews Drug Discovery 4.7 (2005), pp. 594–610; on transcriptomics, P.S. Hegde/I.R. White/C. Debouck: Interplay of transcriptomics and proteomics, in: Current opinion in biotechnology 14.6 (2003), pp. 647–651; and on metabolomics, R. Kaddurah-Daouk/B.S. Kristal/R.M. Weinshilboum: Metabolomics: a global biochemical approach to drug response and disease, in: Annu. Rev. Pharmacol. Toxicol. 48 (2008), pp. 653–683; E.Y. Xu/W.H. Schaefer/Q. Xu: Metabolomics in

The experts were asked to comment on the value of this rather recent and promising technology for the development of new drugs.

Answers

Among the experts the value of omics technologies was evaluated controversially. About half of the experts favour this technology and considered it useful and of high value for the drug development process. Some of them used it on a daily basis and rated themselves explicitly as "fans" of it. They expressed the perception that the omics already helped to develop drugs, but no concrete examples were named. The technology is reckoned to be a discovery tool, which helps selecting lead candidates, elucidating targets and off-target drug interactions and uncovering of the mechanism of action of potential lead compounds. Omics was said to be promising for the implementation of the personalised healthcare (PHC): In the case of testing for the variety of possible drug responses, and to find pattern changes, signatures and downstream effects of compounds, which could also be made fruitful for the biomarker discovery. The latter were also thought of as being valuable for assessments in toxicology.

The other half of the experts were critical about the real value of omics and reckon their impact for drug development to be limited. Moderate notions claimed that omics technologies, by showing disease phenotype markers being down- and up-regulated, yield no picture of the pathophysiology and that there is no security that a target modulation will give the response hoped for on a systemic level. It was lamented that applying omics technologies alone neglects the overall complexity of biological functioning. More critical views complained that through the help of omics not a single drug has yet reached the market and that likewise omics have not yet brought the promised revolution in drug development. One expert considered omics technologies a "terrible disappointment". One of the reasons given why the technology has been dashing pharmacologists' hopes, is that it is still a rather recent achievement, which has been overestimated from the beginning. According to these experts, omics have to face further improvement and its fruits may eventually be collected in some 15 years from now.

Genomics was particularly criticised because particular genes would only rarely, in cases of "terrible" mutations, be considered predicable

pharmaceutical research and development: metabolites, mechanisms and pathways. In: Current opinion in drug discovery & development 12.1 (2009), p. 40.

for diseases. For the rest, genes are not thought of to be deterministic themselves, as they are just one level of organisation in a more complex ensemble. This was underlined by reference to epigenetics. Supplementary, the heterogeneity of individual genomes would require the genomes of all individuals to be screened to reach conclusions worth to be considered, which additionally limits the scope of genomics.

Similar opinions were found concerning the problem of dealing with the huge amount of information produced by all of the omics technologies. "Easily", as it was said, large lists of data are produced in biochemical essays, but their management and interpretation raises concerns. There are still no appropriated means to integrate the produced information in a productive manner, which, at least by now, leads to a multitude of possible answers. A further drawback would be the fact that data evaluation is not automatised yet, which requires much of the analysis to be performed manually by expensive experts. Furthermore, it was criticised that the various studies applying omics technologies do not follow up each other, leaving fragmented results encoded in idiosyncratic terminologies which can be hardly integrated into *holistic* systemic models. In this fragmented form, many results remain unemployable for drug development purposes.[33]

In summary, omics technologies, as seen by most experts, did not reach up with the expectations. The immaturity of the technologies and the mostly not manageable bulge of data generated, whose analysis is still laborious and hence expensive were seen as central problems. Nevertheless, omics are employed in various ways in drug development and are still considered as useful tools to evaluate a variety of factors in the drug development process. The potential of these technologies was considered to have not been exhausted and was expected to become more useful in the coming two decades.

33 A recent review paper suggests that the field of system biology is well aware of the shortcomings of unintegrated data sets and that a paradigm shift is taking place. The present technologies still fall short in what is described as "full coverage". Hence, many biochemical interactions are missed (false negatives) and calculating the false positives is still a challenging endeavour. Even thought, "pipelines to integrate large and diverse data sets and narrow them down to connected pathways that have prognostic value" are said to be emerging, their integration into research or clinical decision making awaits its implementation. Implementation is said to be deferred due to the interdisciplinary nature of these studies and due to the lack of easy to handle tools enabling scientist and clinicians to collaborate in a straight forward manner.G. Bebek et al.: Network biology methods integrating biological data for translational science, in: Briefings in bioinformatics 13.4 (2012), pp. 446–459

4.3.8 *Practice and implications of repositioning in drug development*

Repositioning, also known as *drug repositioning*, *drug reissuing* or *drug repurposing*, designates the use of already approved drugs for new indications. Repositioning is said to have gained importance over the last couple of years, as the development of new drug grew harder, which abets the depletion of the pipelines of the pharmaceutical companies.[34] To reposition a known drug for a new indication has several advantages that render their approval less expensive and faster at the same time. Toxicological studies have already been performed and the safety profile is known, evaluated in both clinical trails and medical practice. Furthermore, the efficacy of the former indication has been elucidated in detail, which might be of interest for new indications too.

One of the most eminent examples of repositioning is the erectile dysfunction drug sildenafil (marketed by Pfizer as Viagra), which was repositioned during development of the drug for heart related diseases as hypertension and angina pectoris, but which was then shown, in the PI, to induce penile erection (PE). Hence, the indication was changed before reaching the market from heart related disease to a drug used, besides potency problems, also for life style purposes. In the mid-1980's Pfizer did much research to find new vasodilators for the cardiovascular conditions as angina pectoris.[35] The scientist at Pfizer became interested in the possibility to modulate the conversion of cyclic guanosine monophosphate (cGMP) into its non-cyclic form GMP, which regulates the intracellular cascade leading to decreased calcium levels, whereby promoting the relaxation of smooth muscles and dilatation of veins and arteries. Among the family of phosphodiesterases (PDEs) (types 1–6), all catalysing either cGMP or cyclic adenosine monophosphate (cAMP) to their non-cyclic forms (guanosine monophosphate (GMP) and adenosine monophosphate (AMP), PDE type 5 was found to be present in smooth muscle cell and chosen as valuable target. A potent inhibitor was found in the novel synthesised pyrazolopyrimidine UK-92,480, which is now better know as sildenafil. During the clinical trails of sildenafil it was

34 T.T. Ashburn/K.B. Thor: Drug repositioning: identifying and developing new uses for existing drugs, in: Nature Reviews Drug Discovery 3.8 (2004), pp. 673–683; A. Louis/L.E. Babiss: REPOSITIONING's, in: Drug Discovery 7 (2006), p. 9; E.L. Tobinick: The value of drug repositioning in the current pharmaceutical market, in: Drug News Perspect 22.2 (2009), pp. 119–125

35 Angina pectoris is sever chest pain symptom due to atherosclerotic obstruction of the coronary arteries feeding the heart muscle.

found that, besides minor side effects as deteriorated vision due to its binding to PDE type 6 present in the eye, the drug was well tolerated. However, sildenafil was found having a short plasma half-life of about four hours, which would require its less practical administration at least three times daily for chronic treatment. Hence, by 1993 sildenafil looked less promising as a new treatment for angina pectoris. Some volunteers of clinical trails reported PE as side effect. The induction of PE was then further investigated in clinical trails in 1994. It was found that single doses of sildenafil enhance erectile responses to sexual stimulation, and furthermore a dose-response relationship could be observed. In the following six further types (6–11) of PDEs were identified, for all of which sildenafil was not particular selective. Except for PDE type 6, which sildenafil binds with a tenfold lower selectivity as compared with PDE type 5. This later binding property was shown to be responsible for the sildenafil induced visual impairments, as PDE type 6, a cGMP-metabolising enzyme, is exclusively present in photoreceptors. Sildenafil was approved in 1998 by the US Federal Drug Administration (FDA) and the European Medicines Agency (EMA) after having been tested in 4,500 individuals in 21 clinical trails and has been marketed as Viagra thereafter.[36]

The experts were asked to give their assessment about the advantages and chances of the deployment of repositioning strategies. Likewise, they were asked to give an account about how the potential of repositioning may be explained.

Answers

The experts were unanimous in their opinions about repositioning being an interesting and important concept in drug development, which is allegedly to gain in importance in future drug developments. The accumulated knowledge, at least knowing about the safety profile of a particular *repositionable* drug was named as the central advantage of this procedure. This makes the development less costly and new drugs can hence be sold at more competitive prizes on the market.

There was a variety of conceptions what repositioning actually means. One interpretation given involved the shifting or adding of an indication for a drug. Others implied the modulation of the chem-

36 This account on the development of sildenafil was taken and adapted from: H.A. Ghofrani/I.H. Osterloh/F. Grimminger: Sildenafil: from angina to erectile dysfunction to pulmonary hypertension and beyond, in: Nature Reviews Drug Discovery 5.8 (2006), pp. 689–702. Please consult this insightful review for a more detailed discussion and references.

ical structure of an existing drug yielding a new molecular entity. Or, as a variation thereof, taking a drug with a failed development history as point of departure to gain a new drug. Either by adjusting the drug actions for new indications, or by analysing and altering a before unwanted toxic side effect towards a new indication. This last point, however, was controversial, and some experts actually explicitly denied the possibility of repositioning side effects.

Most interviewees, however, agreed upon the idea that in order to enable repositioning an understanding of the mechanism of action of the old drug, of the pathways and the potential targets in the pathophysiology in the new indication has to be reached. Identification of new target effects might show new indications. This being said, it seems clear to all interviewees that not much is known neither about many drug targets, nor about the mode of action of many drugs.

A key aspect given an account of by several experts is that *drugable* compounds tend not to be solemnly selective for their assumed target. A drug developed against one target might – usually, "does", as was alleged – hit other targets as well, or if the hypothesis was wrong, it might hit another or other targets altogether. All these possibilities open the door for repositioning. Accordingly, on a systemic level, most processes tackled by drugs are so central that they may play a crucial role in various biochemical systems and, hence, in various diseases.

It is a trivial, but still well emphasised fact that not everything that is measurable is measured and that the knowledge, hence, draws back just on what is measured. Likewise it is plausible that even with the best will measurements might be mistaken. In spite of the "enormously" increased biological knowledge, it remains unknown how to make better drugs and how to produce them differently.[37]

One of the experts brought up the concept of "reverse pharmacology", which he understood as a potentially more successful way of repositioning: The idea is to analyse the mostly unknown mechanisms of action of older drugs from the "pre-biological, pre-clinical period of pharmacology". In this manner, the development of more specific and less side effects prone drugs would be possible. Still, as he added, the new drug may also be less efficacious in scope for the indication, because it is forced to be more specific, which implies having fewer targets.

37 Compare to the notion of one expert cited on page 61 claiming that the prize of serendipity was not knowing how to make another drug.

This last example shows clearly that some of the applied concepts work in opposite directions. There is a common goal to search for and target central *master switches* in particular pathologies with the aim for a unique specific interaction of the drug with its supposed target. This is supposed to guarantee an ideal toxicology profile and thus to obviate side effects. On the other hand, there is the opinion that targeting a variety of biochemical targets is not only indispensable, but also a necessary condition for a drug to be efficacious.

Throughout the interviews an array of concrete examples was named, which are discussed here. An impression repeatedly given was that most drugs used to treat central nervous systems (CNS) disorders were either discovered by chance – or, by serendipity[38] – or are repositioned drugs, which were used for different purposes before: Isoniazid,[39] a drug originally intended for the treatment of tuberculosis was given as an example. Isoniazid has an effect in tuberculosis therapy but leads quickly to resistance. So, people still died because of the infection, nevertheless they did so with a brighter mood, as was said by one of the experts. The "psychic energising" effect was discovered by these means and made isonazid one of the first antidepressant drugs on the market.

Another example mentioned was the statins, which were initially applied as an anti-infection treatment, until their potential for cardiovascular diseases treatment was revealed. One of the experts rated this repositioning as a much greater success as the one, which initially was developed for the treatment of hypertension and angina pectoris. The drugs heparin and metformin were other examples of repositioning. Heparin is still in use as an anticoagulant, but further indications such as cancer, asthma, as immunosuppressive drug to prevent transplant rejection and even other indications are either already in use or are being tested at various stages. The anti-diabetic drug metformin is used or is in evaluation for other indications such as polycystic ovary syndrome (PCOS), precocious puberty and others.

Finally, a rather unorthodox solution to the problem of drug development was given along the discussion of repositioning by one of the elder experts interviewed:

> "So, the thing would be to sell drugs even if they are not efficacious as long as they are safe. Physicians will use them as they want. One physician will be clever enough

38 Compare with what was said in section 4.3.4 on serentipity on page 60.
39 Marketed by Roche as Rimifon.

> to recognise a drug for schizophrenia but it does wonderfully in rheumatism. That may be one way. But I don't know whether this is ethic."

Recapitulating the experts' opinions, repositioning seems a gainful strategy, whose potential has not been fully exhausted yet. In addition, repositioning has strong implications for the understanding of biological functioning: Through structural similarities of divers central biological control modules and the mostly unintentional lack of specificity of drugs acting on them, a variety of effects potentially useful in various indications can be achieved by a single chemical entity. One interesting aspect of the potential of drug repositioning is apparently that the low specificity of drugs is responsible for both their efficacy and their applicability in divers indications. Most importantly, this also indicates that the specific structures targeted by the drugs are evolutionarily and, hence, structurally akin with other structures implicated in the regulation of a diversity of biochemical networks.

4.3.9 *Function and value of biologics, and how they differ from small molecular drugs*

Biologics are medical substances derived from biological processes, in contrast to small molecular drugs, mostly produced through synthesis. Many different entities have been designated as biologics. Some examples are (recombinant) therapeutic proteins, vaccines, somatic cells, gene therapy, tissue and many more, which are isolated from a variety of sources such as humans, animals, or microorganisms.[40]

Their importance for the pharmaceutical industry has increased over the past years.[41] The experts were requested to report on the potential of biologics as therapeutic agents, on the difference of applicability compared to small molecular drugs and their mechanism of action.

40 FDA Center for Biologics Evaluation/Research: FDA Basics - What is a biological product?, WebContent, FDA 101:Biological products, or biologics, are medical products.

41 D C Swinney/J Anthony: How were new medicines discovered?, in: Nat Rev Drug Discov 10.7 (2011), pp. 507–519; J Arrowsmith: A decade of change, in: Nat Rev Drug Discov 11.1 (2011), pp. 17–18; EMEA: Biotech medicines: first biosimilar drug on EU market, 2006.

Answers

Experts named several classes of biologics. Most eminently, the class of antibodies were discussed. But also references to therapeutic proteins such as interferon[42] and erythropoetin[43] and to peptides were given as well.

One of the main features, which set biologics apart from small molecules drugs was considered to be the route of application. Being limited to the intravenous, or as mentioned by one expert, since recently also intramuscular administration, this route cuts back the application range. For practical reasons, they are excluded from therapies that need repeated dosing in short intervals. So, for most indications, daily application is not feasible. According to one interviewee, even though making biologics orally available – in the form of a tablet rather then through injections – is a goal dreamt of for the last decades, which has remained without any success so far.

Biologics were also described as being logistically more difficult to handle, as they are sensitive to temperature and hence generate high costs. It was mentioned that having both a biologic and a small molecule at hand for the same target or pathway – e.g., for the same indication –, it is clear that the small molecule will be preferred because it is less cost intensive. Therefore, it appeared that manageability is one of the key differences.

The most mentioned characteristics of biologics were their high target specificity and their high affinity in binding. One expert drew attention to the fact that exactly the well praised characteristic of high specificity is a double-edged sword:

> "Antibodies, for example, are more specific then small molecules generally. But when one looks carefully, [small molecules] modulate a number of pathways, and that is why they are successful. So, it is questionable if specificity of biologics yields the better drug in the end. This works only if you believe in master switches. Nowadays, there is the tendency to regulate several modulators, not just on-off-switches. You want to modulate the stimulation and

42 Interferons are a class of proteins released by animal cells to trigger the protective defense of the immune system usually in response to the infection by a virus, bacteria, parasites or tumor cell. They belong to the large class of glycoproteins also designated as cytokines.

43 Erythropoetin, also known as EPO, is a glycoprotein hormone regulating red blood cell production (erythropoiesis). It belongs to the class of cytokines.

> not just block the process. This is done more easily with small molecules then with biologics."

According to that notion the lack of specificity of small molecular drugs drives their overall efficacy and sets them thereby apart from the high specificity and "lower" efficacy of biologics.

Other interviewees added to this point that although not being a mature technology yet, peptides are considered to be as good modulators as small molecules. Other interviewees added to this point that although not being a mature technology yet, peptides are considered to be as good modulators as small molecules. High specificity can also cause problems due to the heterogeneity of molecular targets across individuals. A biologic drug may show the wanted outcome just for a subpopulation, which would have to be selected for by special assays. The cancer drug trastuzumab[44] was mentioned as being one of the most eminent examples of a specific antibody targeting a particular over-expression. A comment on single-nucleotide polymorphisms (SNP) points into the same realm: This small aberrations in the DNA coding sequence are much less common in the somatic pocket – the binding place of the drug on its target – where small molecules bind. But SNPs might inhibit the binding of antibodies, as it was exemplified.

For biologics, new types of targets were said to be possible, and a whole new catalogue of potential targets were considered to be available through them. Biologics are, by their nature, well integrated in the biology of the organism. For example, their degradation does not tend to lead to harmful consequences, as it follows genuine cellular degradation processes. Whereas, small molecules are not metabolised uniformly. Therefore, this process is not easy to predict and may lead to unfavourable degradation products harming the treated organism.

Drug development projects for biologics tend to be stopped rather late in PIII of clinical trails when it becomes clear that the drug does not perform as expected. By contrast, and due to toxicology issues, small molecules tend to be stopped much earlier in the development process. In the interviews, it was pointed out that the attrition rate seems to be higher for small molecules developments, but as biologics fail later in development process, their developments are still supposed to be more expensive overall. Nevertheless, in general, the evaluation of biologics toxicity is not easy testable. Testing carried out in

44 Marketed by Genentech/Roche as Herceptin.

primates cannot be extrapolated to humans, as most biologics, antibodies in particular, are species specific, which renders it impossible using the same entity in various species for testing purposes.[45] Further on, biologics are limited mostly to extracellular targets, which compose mainly upstream elements of intracellular pathways. For the time being, bearing in mind these facts, aiming at intracellular targets, small molecules seem indispensable. Not even for stable peptides, which raised great expectations, penetration into, and therefore acting from within the cell is possible.

An interviewee mentioned in an example about Alzheimer's therapy another limitation for the applicability of biologics in the domain of CNS:

> "Like in Alzheimer disease, which is produced apparently by misprocessing and accumulation of the protein amyloid beta. So, that is your bad guy. Antibodies can bind to it and trigger the immune system to destroy it. You can measure this fragment in the cerebrospinal fluid now. So, you have a biomarker and an antibody. It is difficult though to get the antibody into the brain. But as amyloid is abundant and highly reactive, it works like a magnet in attracting antibody trough the blood brain barrier. But still just one in thousand will enter the brain. As long as there is no amyloid in the periphery it is no problem having high concentrations of antibodies. Otherwise, it is dangerous. But still bringing an antibody to the brain is a difficult task."

Accordingly, the problem lies in supplying the CNS with a high enough concentration of biologics, which requires comparatively high concentrations in the periphery in order to push an antibody for example across the rather impermeable blood brain barrier. This makes biologics ill-suited for treatment of brain related diseases.

One interviewee brought up a further important issue: The difference in susceptibility to be recognised by the immune system of the host. By their size and nature, biologics can be recognised by the immune system and have therefore be adapted appropriately for each species were they are applied. In the case of application of for example antibodies in humans, so called *humanised* versions have to be

45 The problem of species specificity of biomarkers is discussed in detail here: J.L. Bussiere: Species selection considerations for preclinical toxicology studies for biotherapeutics, in: 2008

developed. This is also another reason favouring small molecules, as they are not recognised by the immune system.

As the production of biologics is based on sophisticated biotechnology, generic producers need longer periods of time after the expiration of a drug patent to bring their biologicals to the market then it is the circumstance for small molecules. This is the case since not only the similarity to the drug on the market has to be proven, but also because for security reasons the complicated production facilities have to be built and verified. Mostly, the second producer is not able to use the same recipe for the production of a biologics – e.g., not having access to the same transgenic microorganism – that may lead to significant differences in the final product, which has to run again through all the costly approval steps. The latter was stated to be a real advantage for a producer of biological drugs over its competitors.

Summarising the given opinions, it becomes evident that biologics compared to drugs do not have a *per se* advantage in applicability as is the case for drugs over small molecules. Rather, biologics crystallised towards being a valuable additional option to interfere with the biology of the human body. Thus, the disease area, the temporal structure of application, the market situation and many more factors listed above influence the favourability of one drug form over another.

Reviewing the literature concerned with drawing an overall picture of the differences of biologics and small molecule drugs from the research bench to marketing and sales reveals a row of important points, which go beyond what was mentioned by the experts interviewed and tackle further important aspects, and which are given here for the sake of completeness:

- A major shift is observable in the pharmaceutical industry toward biopharmaceutical products, whose current momentum overtakes small molecule products research, developmental and market wise. Their share in top-selling products is already remarkable. Rituximab (Mabthera/Rituxan) and bevacizumab (Avastin) for example are among others Roche's products with the highest revenues and both are biologics.[46]

- Biologics are generally thought of as reaching specificity levels in their mode of action, which are unlikely realised with small molecule drugs. One drawback being, as was was mentioned above, that biological are limited to extracellular inter-

46 Annual Report 2011, 2011.

action. This however is also the reason why it might be advisable to think of combinatory therapies composed of biologics and small molecules. Antibody-drug conjugates for example are currently under development. A already marketed example is brentuximab vedotin (sold as Adcetris by Seattle Genetics) for the treatment of to treat anaplastic large cell lymphoma (ALCL) and Hodgkin lymphoma.[47]

- While biologics are not present in all therapeutic areas as of yet, their presence is expanding. Up to 40% of late stage developments are biologics according to the IMS R&D Focus. Biologics were also found to have higher probability in succeeding in technical and regulatory terms once they have reached PI.[48]

- Biologics and small molecule drugs are often thought as substantial different types of products. This might hold true from a scientific, regulatory and production point of view. From a commercial perspective however they show striking similarities and are likewise suitable in many therapeutic areas with the evident exception of vaccines, which are biologics.[49]

4.3.10 *Function and value of biomarkers in drug development and their application in drug therapy*

Biomarkers, also designated as biological markers, are substances, which quantitatively and qualitatively measured indicate biological states and are often used to evaluate disease states or pharmacologic responses to therapeutic interventions. Specific cells, molecules, genes, gene products, enzymes, hormones and other bodily characteristics are measured in blood, tissue samples and more accessible body fluid and structures. Besides the measurable endogenous markers, contrast agents and further substances making disease states visible through imaging techniques are also designated as biomarkers. Through the employment of omics technologies several biomarkers or even whole nets of pathways can be studied at once in order to gain a better insight into the disease state.

47 FDA: FDA approves Adcetris to treat two types of lymphoma.
48 J.A. DiMasi/H.G. Grabowski: The cost of biopharmaceutical R&D: Is biotech different?, in: Managerial and Decision Economics 28.4-5 (2007), pp. 469–479.
49 M. Trusheim/M.L. Aitken/E.R. Berndt: Characterizing Markets for Biopharmaceutical Innovations: Do Biologics Differ from Small Molecules?, tech. rep., National Bureau of Economic Research, 2010.

Biomarkers are a well-discussed issue in the pharmaceutical industry today, as more personalised approaches are intended to realise higher rates of success in the development and application of new therapies. This is summarised by the concept of PHC, in which a drug is bundled with one or several biomarker for multiple reasons. Screening for receptive population is one of the use domains, as many drugs work efficiently just in a fraction of the population. Progression markers are used to check the progression of specific diseases. And there are many more possibilities to make use of biomarkers.[50]

The experts were asked to give their account on the application and prospect of biomarkers in the field of medicine.

Answers

The discussion on the function of biomarkers, their development and applicability in today's medicine opened a vast field of often contradicting points of views. Whereas all interviewees agreed upon the eminence of the biomarker concept as the central goal of the whole industry, and particularly the suitable bundling of drugs with biomarkeras its role and potential future were discussed controversially.

Even though some voices mentioned that there couldn't be any future without biomarkers, some others considered the concept of biomarker as promising. In any case biomarkers were considered to be unable to "solve all problems". More critical were the statements that there are not many examples of useful diagnostic biomarkers, and that drug and biomarker packages are still a largely unmet goal. The reluctance of clinicians and physicians to use biomarkers without a clear readout was emphasised as a further drawback.

The wide spectrum of given answers are here grouped into the following two categories: (1) costs and (2) application of biomarkers.

(1) Costs: A majority of the interviewees indicated that a validation of a regulation authority, such as the FDA or the EMA, is required to launch a biomarker on the market. Additionally, it was stated that the development and validation of a biomarker – hence the correlation of a disease state and a biomarker – takes usually more than eight years. Therefore, it takes as long to develop as a new drug, or even longer,

50 For a indepth review on biomarkers consult: N. Bhogal/M. Balls: Translation of new technologies: from basic research to drug discovery and development, in: Current Drug Discovery Technologies 5.3 (2008), pp. 250–262; I. Antonijevic et al.: Perspectives for an Integrated Biomarker Approach to Drug Discovery and Development, in: Biomarkers for Psychiatric Disorders 2009, pp. 1–49; P. de Koning/J. Keirns: Clinical pharmacology, biomarkers and personalized medicine: education please, in: Biomarkers 3.6 (2009), pp. 685–700

and it is at least as expensive as developing a new drug. It was also stated that patents on the accompanying drug may expire until the biomarker is validated and available on the market. These circumstances are supposed to render the development of biomarkers rather uninteresting. In addition, these facts raised concerns about the applicability of the idea to sell product bundles of drug and biomarker. One expert stated that even though development costs, and hence drug and biomarker prizes are substantial, an overall cost reduction in therapy might be possible. This would be the case as specfic therapies would be applied just in susceptible patients selected by the biomarker accompanying a drug in a bundle. As discussed above, this last point was also one of the fields where health economics comes into play to demonstrate the overall cost reduction, even in the case of expensive therapies.[51]

(2) Application: The experts indicated a substantial number of potential applications of biomarkers. (i) One family were diagnostic biomarkers used to detect specific diseases. A special kind there of are biomarkers for the screening of genetic mutations, either in hereditary diseases or for spontaneous mutations as in the case of cancer. In the opinion of one interviewee, this kind of biomarker should be possible for any type of disease according to his definition:

> "Per definition, having a disease means to a have a dysfunction, which should be traceable."

This last utterance is probably emblematic for the whole enterprise of biomarker research and development. The principle of measurability of disease states is its fundament.

(ii) Another area of application that was mentioned by the experts is the monitoring of therapies. This variant tries to predict the response to a certain drug, to measure the progression of treatment, and to evaluate the effectiveness of a certain therapy. Verifying the target engagement of a drug is believed to be standardly applied as a drug development aid, as a decision instrument to evaluate the potential risks and also to stratify the risks.

(iii) A further promising domain of biomarker application, which is still mostly unrealised, is the domain of imaging techniques. Tissue damages and tumour growth have been mentioned to be assessable through imaging techniques such as positron emission tomography (PET), magnetic resonance imaging (MRI) , x-ray computed to-

51 Compare to the notion on health economics in section 4.3.6 on page 72.

mography (CT) and ultrasonography with or without specific contrast enhancing substances.

About three-thirds of the experts evaluated the combination of various biomarkers as useful. Specially the evaluation of patterns in accessible corporal fluids – e.g., blood and cerebrospinal fluid cerebrospinal fluid (CSF) – through multiplex assays seem not only feasible, but were considered as the eminent technology of the future. One expert pointed out that using a combination of biomarkers is already current praxis:

> "For instance, when a patient arrives with suspicion of a cardiovascular event, a myocardial infarction, in a hospital. You measure several things: You do an electro cardiogram, you can do some stress test in the patient, you measure several biochemical markers in the blood like troponin T. [...] In the end starting the treatment you exactly follow the blood pressure, you follow LDL [low-density lipoprotein] cholesterol, and hopefully in the future you will use compounds and follow HDL [high-density lipoprotein] cholesterol, hs-CRP [high-sensitivity C-reactive protein]. I think this is the right example and this tends to increase, I would say ... "

Another voice also brought up the example of high-sensitivity C-reactive protein (hs-CRP). hs-CRP was described as being the most advanced and broadly used biomarker in the USA. Nevertheless, it was also explained that it has still not been enlisted in the official guidelines and, hence, is still not validated.

In spite of the described value of the multiple biomarker usage, concerns were raised in mainly two directions: (i) One objection was that using several biomarkers might lead to false positive (FP) – or likewise false negative (FN) results –, because a multitude of answers is less critically evaluated compared to a single one. (ii) The other argument concerned the realizability of a multidimensional correlation of a biomarker with a disease phenotype. As one expert put it:

> "We were always dreaming of an approach, where you just use pattern recognition. So you take peripheral blood, you take immunocytes, circulating T-cells, or cells coming in contact with any regions of body have got imprinted, because stimulated by certain tissues, which were presented.

> There must be a possibility to link certain expression patterns with disease phenotypes. But to find this is a humongous effort, it is a multi dimensional correlation between transcriptase patterns and a large number of people with a disease phenotype. If we could go this way we may be able to correlate certain patterns with certain disease phenotypes, but nobody is willing to do that. It is a huge investment. We are still all thinking on a very small scale, having a small group of four or five people, and this should be the biomarker discovery team... Very small scale thinking, just to cover the bases. If you want to go after that you need a big effort."

So, the realisation of multiplexing approaches, which may draw back on omics technologies are, in theory, very appealing and are thought to give a good evaluation of the disease states. But in practice, to correlate several factors, to pin down a disease giving all particulars is a laborious enterprise involving large populations of patients and employing many scientists. This, of course, requires spending large sums of money. Furthermore, the expert pointed to the fact that the "intellectual" tools available enable just the coverage of the bases and need to be extended to deal with the complexity. All in all, it needs a tremendous effort to be made, something that has not been put in place yet.

A notion brought up by another expert follows the same line of argumentation: the interdependence of sensitivity and specificity of biomarkers, and their representations in the evaluation of the predictive power of biomarkers in the statistical analyses of the receiver operating characteristics (ROC) curves:[52]

> "There are two main problems of biomarkers: In order to detect as much sick persons as possible, high sensitivities are needed. Likewise, a high specificity is required to detect as few as possible healthy subjects, which still show the biomarker in question but are not sick. Though these parameters are somewhat opposed. Now, combining biomarkers renders it more difficult to get a meaningful results – as maximising both parameters in the ROC curves

52 ROC is a graphical plot used in signal detection theory and finds application in the evaluation of the predictiveness of biomarkers. See Fig. 9 on page 105 for more detailed discussion.

> is quite difficult. Hence, measuring more is not necessarily better."

Another aspect mentioned by one interviewee went into the same direction as the preceding one and tackles the problem of setting up normative thresholds. In treating everything lying outside of the predefined norm, more than the intended might be treated. This fact might result in negative consequences and hence further enhances healthcare costs. The prostate-specific antigen (PSA) marker was given as an example. PSA is normally present in healthy males and is elevated in cases of prostate cancer, but the marker also reacts to general inflammation and may lead to false positive results. So it is useful only as a primary indicator, whereupon other tests must follow.[53]

A further row of examples of biomarkers was given and is enlisted for the sake of completeness here: Four out of nine experts emphasised, as mentioned above, the solid multidimensional correlation of statin application, lowered low-density lipoprotein (LDL) cholesterol levels and reduced cardiovascular risk in metabolic disease.[54] Some of those experts considered cholesterol to be even the only validated biomarker.

Blood glucose level was named by several experts as a strong biomarker indicating diabetes. However, it has to be coupled to other measurements to uncover the source of diabetes. It was also in this context that the use of single versus multiple biomarkers – multiplexing – was brought up. In the same frame of reference, low levels of insulin were named as being strong indicators for diabetes.

Trastuzumab, which was brought up above in the context of biologics, was an often-heard instance for a successful combination of a drug and an accompanying biomarker for the selection of the treatable subgroup. The subgroup of breast cancer patients in question evidence a specific detectable genetic point mutation, which leads to the expression of the oncogenic Her-2 protein.[55]

To summarise the experts' opinions about the concept of biomarkers, it has to be stated that they were divers and in part contradict-

53 M.J. Barry: Prostate-specific–antigen testing for early diagnosis of prostate cancer, in: New England Journal of Medicine 344.18 (2001), pp. 1373–1377; J. Hernández/ I.M. Thompson: Prostate-specific antigen: A review of the validation of the most commonly used cancer biomarker, in: Cancer 101.5 (2004), pp. 894–904; T.A. Stamey et al.: The prostate specific antigen era in the United States is over for prostate cancer: what happened in the last 20 years?, in: The Journal of urology 172.4 (2004), pp. 1297–1301.

54 LDL was discussed above: see section 4.3.10 on page 88.

55 Trastuzumab was also deiscussed above, see section 4.3.9 on page 82.

ing. The concept itself was not questioned and was considered to be of major importance for contemporary medicine. The main goal of the pharmaceutical industry to sell bundles of drugs and biomarkers was evaluated as still not having been put in place and was considered to be a largely unmet goal. The demanded validation of biomarkers set forth by the regulatory authorities was described as a long lasting, and therefore expensive process, which was considered a major hurdle for the realisation of planed bundled products. Biomarker validation was said to be as resource consuming as the development of a new drug. It was also mentioned that patents may expire until the biomarker can be launched on the market, which renders the biomarker far less financially lucrative. Mainly three domains of biomarker application were mentioned: the detection and characterisation of diseases, the monitoring of therapies and their implementation in imaging techniques. The problem of read outs of disease states and therapy progression through the deployment of several biomarkers was discussed in detail. The difficulty was said to lay in the selection and the adjusting of threshold values in order to reach a beneficial ration of true positive and false positive test responses. Notwithstanding, in spite of all the potential drawbacks of contemporary approaches to the utilisation of biomarkers, it was also stated that various biomarker measurements are daily practice in clinical settings, aiding in the evaluation of patients' diseases states.

As a suitable example illuminating the difficulty of validating and applying biomarkers in an efficient way in clinical practice one may refer to development history of the cholesterol lowering drug torcetrapib. The biomarker cholesterol was mentioned above at several instances, of which an account is given here in more detail: From the 1950 onwards several influential studies have proven a correlation between elevated blood levels of LDL and increased risks of cardiovascular incidences. Likewise an elevated levels of high-density lipoprotein (HDL) was coupled to a decreased risk of cardinal infraction.[56] Hence those specific cholesterol levels were applied as surrogate marker – a measurable signal – for the likelihood of a cardiac infarction. Transferred to colloquial terms the types of cholesterol were described as "good" (HDL) and "bad" (LDL) and evolved into a kind of dogma und entered the daily vocabulary of physicians, pharmaceutical companies and patients evenhandedly. The metaphor

56 W.B. Kannel/W.P. Castelli/T. Gordon, et al.: Cholesterol in the prediction of atherosclerotic disease. New perspectives based on the Framingham study. In: Annals of Internal Medicine 90.1 (1979), p. 85.

that good cholesterol protects and bad cholesterol harms obscures the fact that a causal relation has as of yet not been given. Nevertheless, drugs were search for beneficially influence the blood cholesterol levels, which lead to the medical and financially successful drug family of the statins. Expiring patents led to the research and development of drugs of the next generation. One of the ideas, based on the above described metaphor, was to beneficially influence the ration of good and bad cholesterol. As a potential target the enzyme cholesteryl ester transfer protein (CETP) was chosen. The CETP is linked to HDL and mediates the transfer of cholesterol from HDL onto LDL and very low-density lipoprotein (VLDL). One reason for CETP as a target was that only animals having CETP – as conies, apes and humans in contrast to mice – tend to display arteriosclerosis when fed on cholesterol rich diet.[57] By 1994 the pharmaceutical multinational Pfizer had developed a ligand inhibiting the function of CETP: torcetrapib. Torcetrapib quickly and successfully passed PI and PII showing to be well tolerated and to strikingly elevate the "good" HDL.[58] In 2003 Pfizer started the huge PIII with the euphonious name ILLUMINATE, in which participated 15'067 patients with increased risk of cardiac infarction.[59] One particularity in this study was that the effect of the new substance torcetrapib was tested in combination with it's predecessor drug atorvastatin against atorvastatin alone. This was chosen for the obvious reason that ones approved the combination therapy could be sold justifying its higher prize, besides that the patents linked to atorvastatin could be prolonged. The results from PIII looked promising in showing an impressing increase of 72% of HDL and a notable decrease of 25% of LDL blood levels. That mean systolic blood pressure values showed an increase by 5.4 mm Hg was considered negligible in consideration of the "beneficial" shifts of HDL and LDL.[60] In late 2006 however it became evident that what was intended by the combination therapy, reducing deadly cardiac incidences, was not only not reached, but even aggravated: more patients died in the double therapy cohort than with atorvastatin. This misjudgment of the diagnostic findings was a disaster for Pfizer: the very the day the clinical

57 A. Tall: Plasma lipid transfer proteins, in: Annual review of biochemistry 64.1 (1995), pp. 235–257.

58 T. Joy/R.A. Hegele: Is raising HDL a futile strategy for atheroprotection?, in: Nature Reviews Drug Discovery 7.2 (2008), pp. 143–155.

59 M. Vergeer et al.: Cholesteryl Ester Transfer Protein Inhibitor Torcetrapib and Off-Target ToxicityCLINICAL PERSPECTIVE, in: Circulation 118.24 (2008), pp. 2515–2522.

60 P.J. Barter et al.: Effects of torcetrapib in patients at high risk for coronary events, in: New England journal of medicine 357.21 (2007), pp. 2109–2122.

were aborted trails were aborted, the value of Pfizer at the stock exchange halved.[61] The prognostic worth of HDL levels has been only poorly investigated so far, as sole and independent surrogate marker for arteriosclerosis and for cardiac incidence risk it has proven to be inappropriate. Furthermore, torcetrapib has been found inefficient in reducing the amount and the size of arteriosclerotic plaques. In defiance of all the prophecies of doom, the neat belief in the "good" HDL is alive.[62] Still, major pharmaceutical companies as Roche and Merck kept heavily investing in the paradigm in the hope to find future blockbusters. The clinical testing of Roche's dalcetrapib was halted in 2012 after initial beneficial results due to lack of clinical efficiency.[63] Merck's anacetrapib is still being tested in a second round PIII through till 2017.[64]

4.3.11 *Prospect and applicability of personalised healthcare strategies*

Personalised healthcare – also called *personalised medicine* – tries to take into consideration that drugs tend not to work in all patients with the same satisfying results. For this reason, it attempts to select the population most likely and best responding to the application of a particular drug. The concept of personalised healthcare (PHC) has been long in use in the practice of consulting a family physician, who considers the patient's family history and social, environmental and behavioural circumstances to shape an individual therapy. This approach has, partly, led to more rational, or rather more quantitative molecular procedures through the deployment of biomarkers. A multitude of assays have nowadays recourse on metabolic, genetic and proteomic evaluation, which allows the characterisation of both the patient profile as well as the disease to be treated.

Most international pharmaceutical companies now venture business models aiming at packaging drugs with therapy related biomarkers – also labelled *companion diagnostics*. The latter are expected

61 P. Diver: When the party's over. In: Surveyor 2005, pp. 20–21.

62 J. Couzin: Cholesterol veers off script, in: Science 322.5899 (2008), pp. 220–223; A. von Eckardstein: HDL–a difficult friend, in: Drug Discovery Today: Disease Mechanisms 5.3 (2009), e315–e324.

63 Naomi Kresge/Simeon Bennett: Roche Drops After Halting Cholesterol Drug Development, in: Bloomberg, May 2012.

64 Aug. 2012. For a more detailed discussion of HDL and LDL related drug development consult the work of Vivianne Otto, among other papers: V.I. Otto: Modell Mensch – Konturierungen des Menschlichen in den Wissenschaften, in: ed. by Beatrix Rubin Rainer Egloff Priska Gisler (Edition Collegium Helveticum), 2011, chap. Weniger "schlechtes" und mehr "gutes" Cholesterin = weniger Herzinfarkte?

to classify the disease status of the patient, adjusting the therapy and the dosage between others. The application of diagnostics to evaluate the patient's risk factors may induce preventive therapy. This also may lead to political pressure aiming at the reduction of the overall costs through the urge for preventive measures. Final goal might be to integrate all available information in order to reach a more systemic account on the individual disease state, hence drawing on the personal history, molecular tracers and information derived from imaging techniques.[65]

The experts were requested to explain their view on the releasability and efficacy of the concept of personalised healthcare and its prospect for the pharmaceutical industry.

Answers

The concept of personalised healthcare was not unequivocally defined among the experts. Some experts defined it as treatment according to the graveness of the disease: matching the dosage of a drug according to the degree of illness. In contrast, others argued that personalised healthcare does not aim at individual subjects, as it might be implied by tailor-made medicine, but rather directed towards better diagnostics and the selection of subpopulations susceptive to certain drugs. Yet others asserted that PHC implies bringing the drug to where is supposed to act in the individual body, hence, the development of a highly specific drug – a kind of personalised *magic bullet*.

Agreement among experts was reached on that the better diseases and their characteristic occurrence in individuals are understood the more PHC will be realised through the deployment of omics technology. However, more cautious opinions pointed out that the concept of PHC has not been implemented in many disease areas yet, and that there are reasons to doubt whether the possibility of its application in many fields will exist at all.

65 For a review on topic of personalised healthcare consult: R. Hapgood: The potential and limitations of personalised medicine in primary care. In: The British Journal of General Practice 53.497 (2003), p. 915; A. Smart/P. Martin/M. Parker: Tailored medicine: whom will it fit? The ethics of patient and disease stratification, in: Bioethics 18.4 (2004), pp. 322–343; T.A. Clayton et al.: Pharmaco-metabonomic phenotyping and personalized drug treatment, in: Nature 440.7087 (2006), pp. 1073–1077; P. Du et al.: 2009 and beyond: the decade of personalised medicine, in: International Journal of Computational Biology and Drug Design 1.4 (2008), pp. 329–333

The experts drew a line between two classes of disease with genetic and more diverse origins. Cancer was one example given for a genetically driven disease for which it would be feasible to be brought in line with PHC strategies, as the number of significant genetic aberrations seem "manageable":

> "If being adjusted to the individual, means employing a genome analysis, looking for activated mono genes have to be employed. In accordance with Vogelstein's evolutionary theory of cancer,[66] having four hits [detection of aberrant genes] in colon cancer and one [the phisician] waits for the fifth [hit]. If [gene] p53 is also mutated, specific drugs are given. But still we are not as far as this. The goal is to scan the patient and generate a clear cut genomic fingerprint. This, I can imagine in the case of cancer."

Hence, tumour classification is in the focus. In line with the quote from above, another expert put forward that the tumour classification has shifted from the "point of origin to [the] point of mutation". As it was said, this molecular gaze sets the field of oncology apart from others and makes it being "10 years ahead" of other therapy forms for other diseases. The most heard example for successful application of PHC is the above mentioned breast cancer drug trastuzumab.

Virology, and infectology in general, like oncology, is nowadays considered as being well equipped for the application of PHC strategies. Through the aid of omics technologies, infecting agents – e.g., viruses and bacteria – can be detected and phenotyped. This in turn enables the application of appropriate therapies. On the other hand, not all diseases can be strictly defined in genetic terms – e.g., obesity and cardiovascular disease. The inoperable amount of different factors such as life style, diet, personal history and other environmental effects in disease alike were said by the experts to render the applicability of the concept of PHC rather complicated:

> "I think the more pleiotropic and more environmental effects you have in a disease, cardiovascular disease or obesity, for example, the more difficult it is. In oncology, it is about the tumour itself. In virology it is about the virus

66 D. Sidransky et al.: Identification of ras oncogene mutations in the stool of patients with curable colorectal tumors, in: Science 256.5053 (1992), p. 102; D.P. Cahill et al.: Genetic instability and darwinian selection in tumours, in: Trends in cell biology 9.12 (1999), pp. M57–M60; C.S.O. Attolini/F. Michor: Evolutionary theory of cancer, in: Annals of the New York Academy of Sciences 1168.1 (2009), pp. 23–51.

> itself. Here, in cardiovascular [disease], there are so many factors, it is not only the genetics, it is what you eat, what your mother eat... There are so many factors, that it might take some more time."

All experts unambiguously agreed that the strategy of most big pharmaceutical companies consists in selling PHC bundles combining a drug with suitable biomarkers. "The right drug for the right patient" is said to be the contemporary "mantra" of drug development.[67] It was stated that "we try to separate responders from non-responders, find the reason for the difference and come up with an assay. The same the whole industry does." It was alluded too, that basically two general strategies are conceivable for the drug market: Either selling molecules of high value, at best targeting the receptive population; or selling cheap generics. The former was considered to be an achievable goal through the deployment of a PHC strategy.

For example Roche was said to envisage selling three-quarter of their portfolio in the form of PHC packages. According to some of the experts, for Roche, this strategy makes particularly sense, as the company consists of a pharmaceutical and a diagnostic division, whose synergies could – and should – be used for the development of PHC products. The feasibility of a three-quarter share of bundle products was controversially discussed. Some designated it as "not unachievable, but still a very high expectation" and as "very ambitious goal". Others emphasised that even if possible, not much has been done. The latter was commented by one expert with the following words:

> "Make a package, selecting for the patients reacting and applying the drug just to them. It is still a dream, and I am not sure what will happen."

One interviewee pointed to the fact that from the experience with clinical trails the PHC strategy makes sense, as about two-fifths of the tested population do usually not show any reaction to the drug. Consequently the goal of PHC should be the exclusion of the non-responding fraction:

> "In clinical studies you have usually 20%, which respond strongly, then 40% medium and low responsers, and then another 40% that does not respond at all. So, the goal is to exclude the last 40%."

67 This "mantra" was discussed in detail in section on biomarker. See page 85ff.

From an economical point of view, for another expert it was not obvious that the PHC strategy will work out, as selecting for the receptive population reduces the potential market size:

> "Difficult to say from a business perspective, whether to give the drug to all of the patients, when only 30% or 40% are responding, or if it is better to focus on the patient target population, which are really responding. It is still debated. Our CRO [chief research officer] is clearly behind the PHC strategy."

Another expert mentioned that many things have to change in the drug development process itself to enable the production of PHC products:

> "To develop drugs with diagnostic tests, you have to change a lot of things in the drug development process itself. And those changes require a lot of time, thinking, implementation. So, it is not so easy, it does not come from one day to the other. It take several years till the process is in place."

A critical factor touched upon by several experts is the still not well examined problem of translating new procedures from the laboratory bench into the daily clinical routine. While science is said to produce inventions at a fast pace, their implementation and adaption in the clinical world is a slow, long and painstaking process. This was also mentioned as a reason why PHC has still not witnessed greater market penetration. Especially, physicians were made accountable for the slow implementation in the clinics.

A further, worth mentioning opinion was the expectation from the general public towards capabilities of the pharmaceutical industry to deal with almost all woes of mankind:

> "Many people believe today that things work automatically. People get always very fast adapted to what is possible, that we guarantee for every thing and that there is for every one a perfect cure. Likewise, politics should do the best for their citizens, that we do not believe anymore. Many people don't see the complexity of things. There was progress in science and technology but the expectations also rose."

Hence, some experts believe that the public opinion considers the pharmaceutical industry as being omnipotent in delivering simple applicable drugs for all kinds of diseases.

Summarizing, concerning the concept of PHC it became evident that the term in question – as it was the case for other questions from above – was not unequivocally defined. Some experts understood PHC as a treatment according to the degree of illness, whereas others saw this concept rather as the selection of receptive sub-populations in order to reach higher treatment successes. Still others considered it a kind of personalised, tailor-made *magic bullet*. More broadly supported was the notion that the more will be known about the particular diseases idiosyncrasies in individual patients the better the concept of PHC will be implemented. The field of application of PHC was generally restricted to "mono causal" diseases such as genetic aberrations, as in cancer, or to contagious diseases caused by viruses and bacteria. Diseases originating from an inoperable amount of potential causes – e.g., chronic diseases as obesity – were considered by far less suitable for the implementation of PHC. Furthermore, for the pharmaceutical industry, there are mainly two strategies: Selling efficient and costly drugs for the susceptible patient population, as generally about 40% of patients tend not to react to drugs on the market. The other strategy is to sell cheap generics to wide markets. This claim was also criticised. For some experts it is not evident whether the PHC strategy will work out financially, as high costs are generated in selecting suitable patients, which in turn logically decrease the market size. A last remark emphasised the difficulty of implementing PHC products in clinical settings, as physicians are said to be rather slow adaptors and reluctant to change.

In spite of what was said above in the context of PHC or *personalised medicine* and all the praise that has been sung about this concept, looking into the literature reveals other facets worth mentioning, which extend the presented situation. First of all, the terms emphasising the personalised aspects are misleading. Most certainly medicine has been personalised ever since and is concretely mentioned already in the writing of Hippocrates from the 5^{th} century BC, where he describes who to reestablishing the patient's *eucrecia* (wellness) by addressing the cause of the disease individually based on the given phenotype, e.g. changing diet. Even though based on the concept of

the four humours, the treatment was personalised and efficacious.[68] Along the timeline of medicine one may refer also to Phillip von Hohenheim, a.k.a. Paracelsus, who ascribed the idiosyncratic sufferings of miners to their life and working conditions, or to Antoni van Leeuwenhoek, who's invention of stronger microscopes revealed the flourishing fauna in humans' very proximity, which led to the precise description of infectious diseases.[69] All three of them contributed in their way to an ever more comprehensive descriptions of patient's disease states. This trend obviously finds its continuation to the present day, a medical age being designated already as *postgenomic*. But actually present day medicine is not yet profiting from the huge bulk of newly provided information. Genomic knowledge is still based on a few complete genomes and the thereof generated genome-wide association studies, which have not provided substantial benefit in the clinical practice yet. Also genetic, eventually genomic risk profiles offered by companies as 23andMe masquerade a kind of "genetic determinism metaphysics" as rational knowledge, similar as the humour paradigm of the past, and are therefore unsuitable instruments.[70] Hence the quest is not only to get a detailed individual molecular phenotype, but also to address a particular thereof described problem in a suitable manner. One vision might be that the physician's specialisation focuses rather then on organs and their pathology on the mechanistic description based on cellular pathways: e.g. TGF-α.[71] For the time being the designations as PHC, even if sensational, remain inadequate if implying an all over new paradigm. More truly, genetic and genomic knowledge is incorporated into clinical practice allowing to draw an evermore refined picture of disease states. But it does and also should do it at slow pace, in order to be more adequately understood and preventing the risk to unnecessarilyely harming patients. An insightful example showing that in defiance of the above mentioned reservation progress in science has brought refinement is the description of what was known as blood disease. In the 19^{th} century it was described as a single disease and evolved over the description of 38 leukaemias to the present day definition of 51 lym-

68 G.P. Sykiotis/G.D. Kalliolias/A.G. Papavassiliou: Pharmacogenetic principles in the Hippocratic writings, in: The Journal of Clinical Pharmacology 45.11 (2005), pp. 1218–1220.

69 Encyclopedia Britannica; J. Zuylen: The microscopes of Antoni van Leeuwenhoek, in: Journal of Microscopy 121.3 (2011), pp. 309–328.

70 F.R. Steele: Personalized medicine: something old, something new, in: Personalized Medicine 6.1 (2009), pp. 1–5.

71 M.C. Fishman/J.A. Porter: Pharmaceuticals: a new grammar for drug discovery, in: Nature 437.7058 (2005), pp. 491–493.

phoma subtypes. Thus, more appropriate then the designation revolution describing personalised approaches would be evolution when speaking of changes pharmaceutical research and development, and clinical practice.

4.4 CONCLUSION

The expert interviews convey an insight into the complexity of many interdependent agents involved in the endeavour of developing medical drugs and its insertion into a susceptible market. A list of agents present in the process may encompass the biology, technological possibilities, researches, pharmaceutical companies, universities, state regulation authorities, finally the consumer and many others omitted here. Of course, each of the enlisted human agents are themselves a wide and heterogeneous amalgam of individuals with their own world views, desires, educational backgrounds and political agendas. And even biology, as inferred from what was said, is not a clear cut and easy to grasp entity. Rather, biology has to be conceived a continuously evolving and adapting system that is not detachable from its surrounding.

Hence, bearing in mind the given opinions concerning a wide variety of domains and concepts implicated in drug development it can be clearly concluded that within a single pharmaceutical company, there are divergent understandings and interpretations of drug development. Most importantly, among experts, terms conceived as central to the pharmaceutical industry seem perceived controversially. Likewise, the capabilities of pharmaceutical research, the direction of future efforts and the feasibility of more efficient medical treatments seem to be perceived differently by the experts. In addition, many times inconsistent views among experts were observed. This is worth of mention, as one would expect they act in concert to produce a marketable medical product.

Nevertheless, among the experts, there is seemingly a consensus about the viability of a specific and gainful exertion of influence on the human biology through the deployment of chemical entities and biological products.

Based on the interview, no discernible clear-cut trend, concerning the point of view in the investigated fields and the expert's educational backgrounds can be made. Of the nine experts, two had a degree as medical doctors and another one had a background in chemi-

cal engineering. All others had an education in biology with various specialisation as, for example, in biochemistry (4), biotechnology (1) and neurobiology (2). Rather, their daily occupation as well as their experience seems to shape their opinion. It is worth mentioning that the older the interviewees were and the higher their position in the hierarchy of the company, the more hard-boiled, sceptical and cautiously was their judgement concerning the pharmaceutical potential of the drug development aiding technologies and the drug development it-self. The following sentence by one of those older experts illustrates the difficulty of developing drugs in a straight forward way, employing available technologies as omics and the others discussed above: "we still think on a very small scale". Another expert added that "we are still not there", pointing into the same direction and referring to RDD. One of the most radical statements put forward by the experts was expressed in the view that the prize for having discovered most drugs through serendipity is that one does not know how to develop a new drug. Careful observation and hope appear to be a *de facto* agent in drug development.

Conversely, younger employees together with those in lower hierarchical positions seemed more in the line of company's official view of the state of affairs, and, as such, held a more euphoric vision of the contemporary possibilities in drug development. They also showed much stronger confidence in the explanatory power of rational drug development methods, omics technologies and biomarkers. They also expressed confidence on the existence of a potential cure for every physical disease. As one young expert stated: "per definition being ill means to have a dysfunction, which should be traceable". According to this view all origins of diseases are potentially discoverable. Furthermore, the younger experts show trust on the efficacy and on the informative value of available and applied technologies in drug development, which when employed properly lead to a usable drug straight forward.

Obviously, the number of experts interviewed here is too small to gain a conclusive impression on the diversity of opinions currently present within a multinational pharmaceutical company. Therefore, every conclusion throughout this work will necessarily need further confirmation. Nevertheless, the work itself still allows for a rough estimate of the scope of conceptions in the field of pharmaceutical research.

For these reasons, to draw a final conclusion or even to distill a well meant advice from the views expressed here concerning present and future capabilities in drug development is a challenging issue clearly out of the scope of the present work. One might be tempted to argue in favour of streamlining the disparity of opinions, which, at least in theory, would allow for a more straightforward collaboration between the various staff members lined up along the development process of a drug. A rationalist's dream could be made up in the following terms: The more alike the conceptions, the less friction, the speedier the development process and the better the final product. But, bearing in mind the portrayed opinions, it is questionable whether this would indeed lead to a higher productivity besides from being an apparently almost unachievable goal. As stated in the interviews, most of the drug development history was at least partly influenced by serendipity. Hence, unintended findings in drug development contributed significantly to this process. Most certainly, serendipitous findings would occur less frequently under conditions of unified opinions.

Along the interviews, it became clear that the general focus in drug development still lays upon the specific modulation of molecular "master switches". In theory, drugs, *magic bullets* alike, are supposed to modulate single molecular targets to re-equilibrate the nuisance and hereby cure the treated disease. It is indeed an interesting question how this paradigm centred in a master switch has established and held itself until the present days. This is particularly interesting, as also the interviewed experts alluded at various instances to the fact that at the very end, only in rare cases the single target strategy works out to its last consequences. This is not to say that this strategy has not lead to beneficial medical products, but it is out of question that in most cases the strategy was not applied to its last consequence. On the one hand, drug development seems to be opportunistic having reached an acceptable balance of beneficial drug action and moderate side-effect profile. On the other hand, feasible alternatives seem to have a difficult stand in the current legal framework they are embedded. Even more, there are the ever stricter ethical standards, which have to be considered in developing a drug. As one expert pointed out rightly, it would be probably unethical to endow physicians with potentially drug-like substances so that their action will be tested directly in the clinical setting, even though this would be an effective way to proof the efficacy of new drugs. Like

the supposedly most efficient way of testing drugs – direct tests in humans – drug testing in animals has become scrutinised more and more. Animal rights groups successfully attract both public and media attention leading to legal consequences, which renders drug testing, particularly in so-called *higher* animals ever more difficult. On the other side, scientific evidence has piled up, which withdraws the assumed predictive power of the actions in humans of toxicological examinations and drugs tests carried out in animals.

Last but not least, the notion that "a human is not a human is not a human..."[72] – even though not heard literally by the expert – appears to have gained ground as a general notion in pharmaceutical sciences. Several times, the interviewed experts referred to the fact that drugs tend to work, as a rule of thumb, on just every fifth patient. Keeping this in mind, the efforts should concentrate to the endeavour of selecting the susceptible fraction of patients through the deployment of screening for arrays of antibodies. This is a strategy many global pharmaceutical companies try to implement in selling most of their drugs in combination with a biomarker test. But many experts expressed their concern about the successfulness of such an approach. Mainly two reasons were here central: Shrinking the patient population means shrinking the potential market size and hence diminishing profits. Further on, besides the problematic of diagnosing a particular disease state through a biomarker, the notion was brought up that the more is measured the more is/will be found. This was evaluated as inevitably leading to an accumulation of false positive results that are followed by unnecessary treatments. Furthermore, it was emphasised that the focus of medical treatment should reside on the individual subject, which can be best assessed by a trusted physician with a long relationship to the patient. To draw back on the patient's personal and family history, social circumstances and afflictions combined to medical and biochemical examination was said to lead to far better results than blind and straight forward testing. To conclude, this position clearly favours the rehabilitation of the general practitioner as a central player of the medical consultation. The latter can be clearly seen as a counterpoint to a rampant *expertitis*.

72 In reference to Gertrude Stein's tautological sentence "rose is a rose is a rose is a rose" in her 1913 poem *Sacred Emily*.

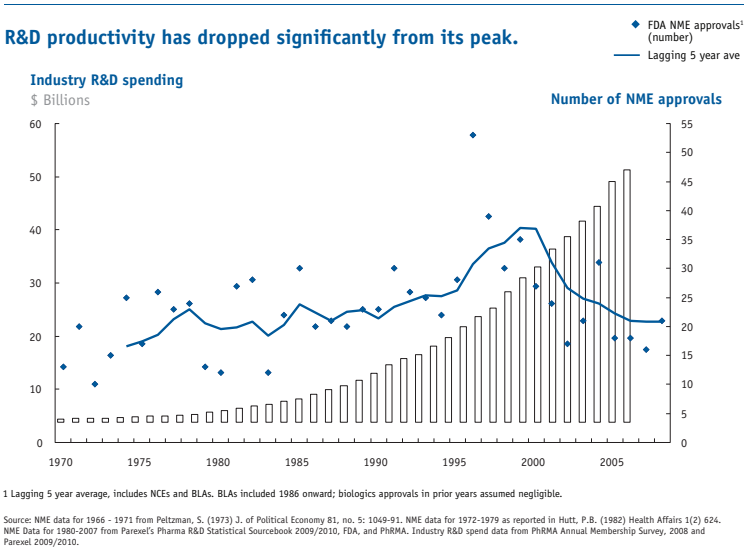

Figure 8: The graph illustrated the steady and significant increase in spending on research and development in the pharmaceutical industry, even as the number of NME approvals has decreased dramatically in the last decade. The graph was taken from the following FDA publication: FDA: Pathway to Global Product Safety and Quality (2011).

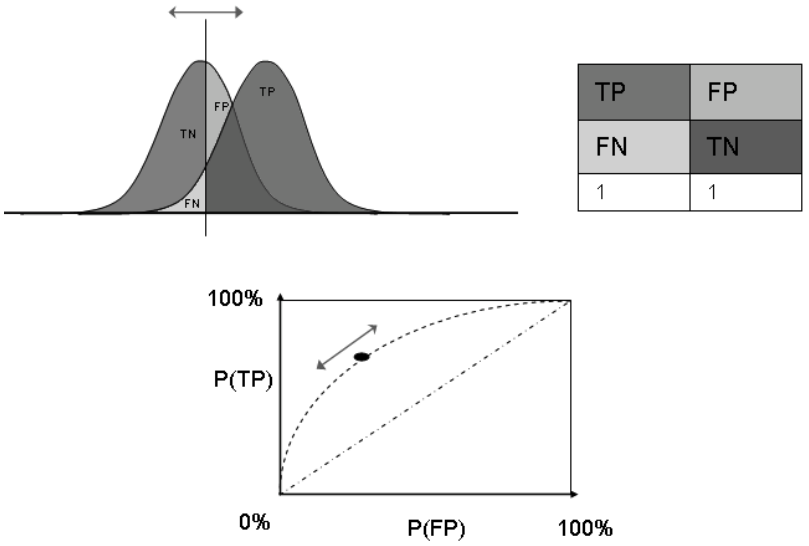

Figure 9: The receiver operating characteristics (ROC) compares the fraction of true positives out of the positives (true positive (TP) rate) with the fraction of the false positives from the negatives (false positive (FP)) in order to select potentially optimal applications of biomarkers. The goal is to bundle a set of biomarkers in such a way to maximise predictiveness, hence to drive the TP and minimise the FP. Therefore, as it might seem obvious, applying a set of biomarkers of mixed qualities to evaluate a disease state entails the risk of getting false positive results. This scenario get even worse with increasing numbers of biomarkers. The example given above depicts the comparison of two populations of flue infected persons. The separation criterion of diseased and non-diseased is set according to a threshold of body temperature (e.g. 36.6°C). Subpopulations are classified wrong, either FP or false negative (FN). Generally both population are not equally distributed, which implies that the increase of TP is followed by relatively smaller increase of FP. Figure adapted from: *http://de.wikipedia.org/w/index.php?title=Datei:Receiver_Operating_Characteristic.png*

5

SYNTHESIS AND OUTLOOK

5.1 SYNTHESIS

An account on fictions and realities in drug development was given and most certainly more questions were raised then answers given upon the problem on how useful medical products have been, currently are, could be and how they will be developed. Nevertheless, the surface has been scratched and new insights have appeared upon which it will be concluded here.

The tripartite approach taken here set forth on how rational procedures were established in pharmaceutical drug development along the history on the first-ever successful and *rational* development of a chemotherapeutic drug by the German scientist Paul Ehrlich. The following chapter illustrates through the case study on the development history of the cancer drug Sunitinib how drugs are developed under present day circumstances. Special focus laid on the alleged rationality applied in the development process. The final chapter deals, among others, with the questions on how straightforward or rational procedures can currently be applied in industry-scale drug development. Through expert interviews with leading scientists for a major pharmaceutical company insight was gained about the state-of-the-art of contemporary drug development.

In the following, I am going to recapitulate what was shown above.

5.1.1 *Paul Ehrlich's chemotherapy*

The second part of the present work explored the origins of this approach designated from its very beginning as *rational*. As was set forth above, this procedure roots in the tradition of *tannery*. The advent of synthetic chemical dyes and their industry scale production heralded a deeper understanding of biology by enabling a more diverse and alike more specific histology. Organs, tissues, individual cells, microorganisms, eventually even viruses could hereby be discriminated, specified and isolated. Through the varying of the molecular structure of those specific dyes molecules were produced, which featured

besides the specific binding also a specific physiological effects damaging, or at least altering, the functioning of their target. This procedure established a new and target centred approach in developing drugs.

The first successful account of specificity targeting a disease was the drug Salvarsan developed by Paul Ehrlich, which was directed at the syphilis causing micro-organism *Treponema pallidum pallidum*. Salvarsan was not, – as Ehrlich desired – a side-effect-free *magic bullet* in its true sense. The arsenic contained in the drug accumulated in the treated organisms to toxic amounts. But still, Ehrlich's achievement triggered the establishment of a new paradigm in pharmacological research. What has proven to be a feasible approach in the domain of infectious diseases, was in the following, as Ehrlich had anticipated and inspirited, applied to other diseases, including systemic diseases and cancer. In the course of the 20th century this process was abetted by the inter-depending advances of both tools – microscopes, DNA technologies, centrifuges, etc. – and the knowledge about the functioning of biological systems. Of particular relevance was the introduction of computer-aided technologies allowing molecular design, quantitative structure-activity relationship calculations and virtual screening to be performed. These technologies filled the missing link across the various levels of organisation to molecular dimensions. It enabled the construction of models explaining holistically drug actions from the binding of drug molecules at specific sites of regulatory receptors to its macroscopic effects.

5.1.2 *Sunitinib*

The case study on the cancer drug Sunitinib, retraced at hand, scrutinises the official, partially over euphorically reception and description of Sunitinib and its development history as presented in the literature. The drug was attributed to be the straightforward result of ingenious and *rational* application of the understanding of a biologic system, in this case angiogenisis. Once the underlying biology was allegedly understood, target structures were selected, *drugable* compounds were found in biological assays, the efficacy of one compound was proven and selected, its safety was proven and then the rest of the development to its approval and marketing was so to speak "pure routine". So far the official account. This apparent success story was further emphasised by the rewarding of several innovation prizes.

As could be shown, the putative *rationality* employed in the development was clearly a sophism in its true sense. Not only were two compounds produced, which showed indeed high affinity for their pre-defined targets in preclinical trails, but which were useless for the application in humans due to their deficient solubility in water, which hindered them in reaching their supposed target. But in addition, it was rather this very mistake, which enabled the finally much more efficient compound to be developed in the following. In producing a molecule, whose side-groups have been extended – hence, similar in structure –, which rendered it orders of magnitude more water-soluble, the target specificity of the preceding molecules was by far not accomplished any more. The new structure showed a high affinity beyond the structures targeted by the proceeding molecules. This is a clear-cut deviation from the antecedent *magic bullet* premise aiming at a single structure for precise interaction and control, and also aiming to obviate inadvertent side effects, as well. Nevertheless, exactly these structural changes gave the drug its overall beneficial activity profile. These facts let the last section of the clinical trails to be cancelled in order for the fraction of test subjects receiving placebo to benefit from the curing effects of the new drug. Thereafter, the drug was developed to marketability and approved for clinical application.

The retraced story of development stands in sharp contrast to the reception of the drug in the aftermath of its development. Such a drug development history raises a set of questions concerning fictional and real application of employed methods and technologies in drug development.

The evident fixation to cure by means of specific and controlled targeting and modulation of single structures, employing the *magic bullet* and *key-and-lock* metaphors, seemingly implies that some sort of *rationality* is involved – as much in the development, as in the application of drugs. The paradigm of rational drug development - or, design - frames a strictly defined connection of macroscopic disease symptoms, specific defined "master switches" involved in the establishment of a disease and a specific molecular modulator pointing at the latter. The emergence of this paradigm is linked to the constitution of Paul Ehrlich's chemotherapy.

But, the fact that the understanding of biology and the capacity to interact with it through the available technology has reached remarkable levels of development stands in sharp contrasts with the attested decline in productivity, the invested amounts of money and

the output of new and substantially beneficial medical substances. Thus, knowing more does not inevitably lead to an increased output, at least for the domain thematised here. This clearly raises the question on how *rational* rational drug development really is. Or to put in other words the methods may well bear a rationale for their goal, but their application might well be improper.

5.1.3 *Expert interviews*

How the available tools facilitate *rational* procedures in present day drug development and how they are reciprocally involved in the wider framework of the pharmaceutical industry, the economy and the society in general is being questioned in the third part of the present work: the expert interviews. The interviews reflect this facet from within the daily business of drug development taking place in a single research division of a major pharmaceutical company from a variety of perspectives. The latter appears to depend as much on the narrower field of expertise as on the hierarchical level and the length of career of the individual interviewee within the company. An impressive spectrum of opinions was given about how and whereby drugs are, should be, and will be developed, and how this task is embedded in a wider frame-work of legal, regulatory and economical practical constraints. To find such a diversity of convictions within a single research division of a major pharmaceutical player is stunning, since all of the experts are in one form or another involved in the *parkour* of drug development, even though not necessarily in same disease areas and, hence, not at the very same projects.

However, the seemingly dissonant choir of diverging opinions should not necessarily represent a disadvantage for any pharmaceutical industry. Endeavours in transdisciplinarity, as for example carried out in the laboratories of the Collegium Helveticum[1], have proven to successfully deliver advantageous insights beyond the conventional borders of segmented scientific sub-disciplines. Crucial hereby is to peel off the layers of sub-disciplinary idiosyncratic language in order to render the key concepts understandable for and manageable by others. Hence, putting disciplinary key concepts on common grounds – evidently, without trivialising their essence – enables their fusing, po-

1 To find out more on the implementation of transdisciplinarity in state-of-the-art science please consult the homepage of the Collegium Helveticum: *http://www.collegium.ethz.ch/*

tentially leading to the emergence of unprecedented scientific instruments. With this in mind, the goal for industry based drug development should ideally be to integrate the available voices in a consonant canon adequately encompassing the concourse of multiple layers of bio-systemic, economical, political, and legal complexity. Likewise, it would be advisable to bowdlerise the individual voices from exaggerated components solemnly directed at distinguishing themselves in the political intrigues for resources and eligibility, which may hinder the adequate application of their actual intrinsic core competences. Obviously, this last advice cannot be easily achieved for many of the named obstacles.

Most of the issues tackled in the assessment questionnaire had in common that they focused on the gap between the premises of methods, models and technology, and their real-world implementation and their successful applicability. Searching for the threshold between controllability of the treated systems and coincidental – or, serendipitous – findings, the beliefs of the experts concerning a wide range of mental and physical tools was scrutinised and discussed individually at length. From the compiled answers it crystallises that the evaluation of the applicability of particular tools is hardly separable from their putting into operation in individual projects. As a matter of fact, the idiosyncrasy of drug development projects does not appear to allow for generalised assessments of applied technologies.

Notwithstanding the circumstantial dependencies of the value of applied technologies it became clear that, irrespective of their degree of sophistication, their explanatory power seldom meets up with the complexity of the biological system they are analysing: hence, they intrinsically lack the desired predictive power. Still, besides giving hints about systemic relations these tools restrict the focus of attention upon the field where they are able to through light upon.[2] This is not to say that they are futile in general; but rather one should be better prepared to find in stead of what was anticipated something completely different.

The reference to *rationality* of, or, the *rationale* for any research endeavour is given in relation to models developed from previous research, and the extrapolation thereof. Nevertheless the validity of these models tend only to be proven by *in vivo* examination, i.e., finally in clinical trails in humans. There was allegedly a strong agree-

2 There is an old joke making sarcastically reference to the discussed issue: A drunkard is looking for his keys under a street light instead of in the dark backstreet where he dropped them. “Why?”, he is asked. He replies: “Because the light is better here.”

ment among experts that drug development still focused strongly on specifically targeting single molecular targets, or "master switches" as mentioned above. The focus on single target structures is also framed as *rationale* for guaranteeing safe and controllable interactions. But besides that, it renders circumstances of the case simple and explicable: the disease symptoms, their origins, hence, the drug targets, and the drugs can be lined in an understandable and plausible manner. Nevertheless, most experts agreed upon the notion that pure *rational drug design* – or even, *in silico design* –, as imagined with the introduction of powerful computers in pharmaceutical research, still has to be considered an unfulfilled dream. Even so *rationale* procedures are in place in current pharmaceutical research, a straight forward approach involving crystallographically derived three-dimensional computer models of molecular target structures for the computer aided design of a suitable ligands – is not operable. Following this line of argumentation it was mentioned that drug research programs tend not to be as linear as retrospectively narrated. Rather, the courses of development are and also should be both circular and linear. Whereby circularity as employed here designates the moving back and forth between consecutive milestones in drug development. Too, it was mentioned that at least small scale testing in humans should be enabled much earlier in the course of drug development. This would make the assessments of disease models and of drug efficacity possible much earlier; and it is thought to shorten development times and cut down costs. Furthermore, as it was lamented that the informative value of toxicological assessments carried out *in silico*, *in vitro* and *in vivo* in model organisms is rather low, direct testing in humans early in development would lead to clearer results and, too, it would omit many idle processes. Therefore, early "real-world" testing should definitely be taken in to consideration.

The technological and scientific progress witnessed in pharmaceutical drug development since the times of Paul Ehrlich reveals to be both a blessing and a curse. Developments of new drugs have to compete with existing, well established medical products and have to prove their superiority in multiple respects: be more efficacious, be more specific, show better ration of beneficial and adverse effects, and be less toxic. Analytic tools were brought up as a central example of chimeric advances. On the one side they led to biological insight and sharpened the understanding of diseases, on the other side they enabled tightening of the regulatory frame-work permitting less and

less deviations from the targeted sub-systems. This last point was mentioned by the experts to be one of the driving forces of a diminished productivity and of the cost explosion in drug research. The weakened productivity is also, among others, nourished by an ever changing landscape of influences: the widespread, highly interdependent network of sciences, the various idiosyncratic languages of scientific disciplines seemingly unable to talk to each other, stricter guidelines of regulatory authorities, risen public expectations concerning drug efficacity and quality, the public aversion against animal testing[3] and the already well supplied and well equipped markets for common diseases and the ever growing fraction of off-label drugs, as well as the changing demographic structure – at least in the Western world – and higher pressure on drug prizes due to already stretched budgets of national health systems.

The concept of repositioning encountered much benevolence among experts and was considered a gainful strategy, whose potential has not been fully exhausted yet. Through structural similarities of many central biological control modules and the mostly unintentional lack of specificity of drugs acting on the latter, a variety of potentially useful effects in various indications can be accomplished by single chemical entities. This indicates that the specific structures targeted by the drugs are evolutionarily and, hence, structurally akin with other structures implicated in the regulation of a diversity of biochemical networks. A further advantage of repositioning is that already much is known about the drugs' safety profile and about their efficacy in individual patients, which may already show hint about their application in other disease areas.

It appears notable that pharmaceutical companies intend to explore this resource. Repositioning basically permits to make a virtue out of necessity: Drug development usually struggles with potentially adverse side-effects, which are worth-while to be explored blow-by-blow in order to get the possibility to explore alternative modes of action for the drugable molecule in question or a derivative thereof.

The realm of analytic tools discoursed above includes three further fields discussed by the experts, which are enlisted here for completeness: omics technologies, biomarkers and personalised healthcare (PHC).

3 An in-depth discussion on ethical problems in animal testing can be found here: Hans Sigg/Gerd Folkers (eds.): Güterabwägung bei der Bewilligung von Tierversuchen. Die Güterabwägung interdisziplinär kritisch beleuchtet, 2011.

Omics technologies were described as not having reached up with the expectations yet. The immaturity of the technologies and the hardly manageable bulk of data generated are considered to be the major drawbacks. Still, omics technologies find useful application in the drug development process as assessment tools. As with other technologies discussed, also omics technologies are thought to have brighter future. So, time probably will tell.

The potential of biomarkers was discussed controversially. Not so much the concept itself, but rather its practical implementation in vendible bundles of biomarkers – or, companion diagnostics – and drugs as presently aimed at by the pharmaceutical industry, is thought not having been put in place. The main obstacle hereby is the cost and time expensive validation of biomarkers set forth by the regulatory authorities. Notwithstanding, in spite of all the potential drawbacks of contemporary approaches to the development and employment of biomarkers, it was also stated that various biomarker measurements are daily practice in clinical settings, aiding in the evaluation of diseases states.

Discussing the concept of PHC it became clear that the term was not unambiguously defined. PHC is understood in various ways: the treatment according to the degree of illness, the selection of subpopulations, the personalised and tailor-made *magic bullet*, etc.. The opinions were in concert about the prerequisite of measuring the idiosyncratic disease state of individual patients for the implementation of PHC. The application of PHC was generally restricted to "mono causal" diseases such as genetic aberrations or to contagious diseases. For some experts, it is not plain whether the PHC strategy will work out financially, as picking out suitable patients lessens the market size. Here, once more, financial more then health benefits appear to dictate the disease area and the course of drug development.

Biologics, as compared to small synthetic drugs, were not thought of as having an intrinsic advantage in applicability. Rather, biologics crystallised towards being a valuable additional option to interfere with the biology of the human body. Choosing biologics or small molecules as treatment appears to depend on factors as the disease area, the temporal structure of application, the market situation and many other factors. Therefore, here once more, open questions on what kind of hierarchies among these factors one should expect remain to be clarified.

5.2 OUTLOOK

The field of pharmacological drug development keeps on being a tricky enterprise. It appears to be stuck between an already flooded market of prescription drugs, the ever increasing number of generic medical products, the cautious, self-protecting regulatory authorities, the desires of patients and consumers, the shapes of national health systems and national economical situations, the assets and drawbacks of technological advances, and, last but not least, the mere, inadequately understood, individual and general complexity of human biology. A multitude of opinions are inconsistent with one another when it comes to drug development. One may emphasise what one of the interviewed experts put forward for discussion: The prize for serendipitous discoveries in drug development has been so high, that no one does know how to develop any new drug based on previous discoveries. It might be, as stated by Louis Pasteur, that chance favours the prepared mind[4]. Hence, for the time being, drug development will keep an adventurous endeavour.

Bearing all this in mind, not so much for the pharmaceutical industry as for the nation states more imperative preventive strategies should be considered. It should be taken into account that potentially, the major share of diseases treated nowadays are a consequence of the impact of civilisation. Systemic diseases appear to be a good example thereof. These are also fostered by demographic changes.

Many symptoms can already by treated, and here the experts interviewed agree, by changing habits of locomotion and nutrition. May be that alike the liberal organisation of the financial sector, societies in general are ill prepared to handle the abundance of aided mobility and of highly refined and energy rich nutrition. Evidently, preventive measurements are not *per se* a panacea and many grave diseases won't be cured thereby. This is where the strength of chemotherapeutic treatment come into play. Pharmaceutical research should focus on its core capabilities: the delivery of synthetic drugs. Some pieces of advice can be summarised potentially helping making medicine better: The concentration on high specificity of drugable molecules for the target does not guarantee efficacy in treating a disease. Rather, as was shown in the case of Sunitinib and other drugs as Aspirin, high efficacy was reached by comparable low specificity of the drug. Researchers and regulatory authorities would be well advised revis-

4 Pasteur: Oeuvres de Pasteur (see n. 16).

ing their opinions and weaken their strict focus. Even combinatory approaches, as recommended by Paul Ehrlich, should be considered, where several weakly dosed drugs are combined. Such an approach might also be a step into the right direction accommodating the evolutionary grown complexity. Target structures might be structurally similar to their evolutionary siblings having similar or divergent functions. Low specificities of drugable molecule, hence, fosters a more congruent interaction with the self-redundant complexity of biology. This is also where repositioning may come into play. The intrinsic low specificity of utile drugs opens up the potential of the drug to be applied in different disease areas successfully. As a last point, it should be averted that most models building the fundament of research endeavours are themselves constructs deduced from segmented systems and, therefore, they represent solemnly this abstraction in its idiosyncratic boundary conditions, which for the most part does not allow for extrapolation concerning system-wide involvements. This latter critique does also apply to the validity of the idea of rationality or giving a rational in drug development: their prediction is intrinsically tied to the followed model.

It might be, that the will to admit the shortcomings of the starting position, the openness to find things other then the one searched for and the early inclusion of the human complexity might help making pharmaceutical research more productive.

A

APPENDIX I: EXPERT-INTERVIEW QUESTIONAIRE

1. General questions:
    a) Do you see a central / common paradigm in drug development?
    b) Which are the crucial steps in the development process, how are they related to this paradigm?
    c) Is the drug development process as linear as it is presented?
    d) What is the role of serendipity in the drug development process?
    e) Ration Drug Design is a buzz word in the drug development litereature. Among scientists this term was left unheard during my internship. Could you comment on that?
2. The research and development costs for new drugs rose, according to the GOA, dramatically over the last two decades, while the mean output of newly approved prescription drugs stay constant or decreased slightly:
    a) In which ways have you experienced the shortage in innovation?
    b) What has changed since the 1980's in drug development and regulation to cause such an increase?
    c) How do you reckon the costs to develop in the proximate and further future?
    d) Did this cost increase shift the focus towards other disease areas?
    e) Are there implications of the cost pressure for the selection of disease areas?
    f) Do this cost increases diminish profitability? Can it be transferred, where is the limit?
3. Technologies: The omics fields seem central today in drug development.
    a) How do you see their value?

   b) Reviewing the literature of ‚Äòomics fields, one gets struck by the few concrete examples contrasted by visionary outlooks of what might be possible concerning the development of new drugs and biomarkers. What are the real possibilities of these technologies nowadays?

4. Biomarkers, the base of personalized health care, are intensively searched for as disease markers, as progression/treatment markers and as a way to restrict the population to whom a drug is applied.
   a) Where are they applied today?
   b) How accurate are they?
   c) Are the expectations towards biomarkers accomplished? Are there any successful examples?
   d) The aim is to find a single biomarker for a particular medical problem. Would not several biomarkers in combination give better and more reliable information? Is this technically feasible today?

5. The best way to find a new drug is to start with an old one. Repositioning is central to drug development.
   a) What are the advantages of this procedure?
   b) How does one proceed?
   c) Are there eminent examples of successful drug repositioning? (apart from Viagra)
   d) What are the implications of the potential to reposition drugs for our understanding of the biochemical fundament of their mechanism of action?

6. The share of biologicals in the pharmacopeia is steadily increasing and their potential application is far reaching:
   a) What are the main differences apart from the route of application and the production method?
   b) Can their potential concerning applicability, specificity and affinity be compared to small molecules?
   c) Bear biologicals a special condition to make them more easily applicable in the concept of personalized healthcare?
   d) Can biologicals interfere more appropriately with the systemic biochemical information transduction cascades?

7. Personal healthcare is an issue of focus in many pharmaceutical business ideas and is coupled to much hope for the future.

    a) In which field is this realized?

    b) Where are the next expected steps?

    c) Which is the ultimate goal?

    d) Are tailor-made therapeutic approaches expected to yield more effective therapies? Are there concrete examples available already?

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