



Master Thesis

## Patents for biotechnological inventions current legal situation and case law in Europe, the US and Japan

**Author(s):**

Schütt, Corina

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POSTGRADUATE STUDIES IN INTELLECTUAL PROPERTY  
SWISS FEDERAL INSTITUTE OF TECHNOLOGY ZURICH

**Patents for Biotechnological Inventions:  
Current Legal Situation and Case Law  
in Europe, the US and Japan**

DIPLOMA PAPER

**Corina Schütt**

**Dr. sc. nat.**

Referee: Dr. U. Kinkeldey

Co-referee: Dr. V. Meyer

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## Summary

The object of this paper is to give a broad overview on patents in the field of biotechnology and to illuminate the topic from several angles. The legal status of biotech patents in Europe, the US and Japan is discussed as well as economic aspects of biotechnological research. Furthermore, biotechnology is compared to other technical fields concerning patentability.

Two cases were chosen to illustrate some important problems and questions on patenting living matter and to cover biotechnology in a broad way. The patents on Erythropoietin belong to the most important class of biotech patents, namely patents on DNA sequences and proteins. The economic value of these patents lead to world-wide litigation. The Oncomouse has been the first genetically engineered mammal to be patented. For the first time, decisions were made on moral issues linked to biotech patents. In this connection, ethical and political questions are discussed comprehensively.

Finally, some challenges for future developments of biotech patents are indicated by two new fields of biotechnological research - embryonic stem cells and gene therapy. The complexity and the rapid development of biotechnology renders simple solution impossible. Some questions go far beyond patent law and should only be discussed within the whole context of legal statutes, scientific and economic aspects and morality.

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## **I. Introduction**

### **I.1. General points on patents in the field of biotechnology**

In hardly any other technical field, patents are such a controversial issue and in the public interest than in modern biotechnology. Ethical, political, religious and legal questions are mixed up with fear of the power of the pharmaceutical and agricultural industry. Patents for plants and animals, but also for cell lines, monoclonal antibodies, human genes and most recently for embryonic stem cells run against opposition in the public. In the light of ethical, political and scientific consideration, the most challenging questions arise whether it should be possible to patent a substance that exists already in nature or even whole living organisms. Questions on the consequences of patents for scientific and technical progress, advantages and disadvantages of a monopoly are heavily debated. Since the complete human genome has been sequenced, discussions have grown even more. The idea that the whole genetic information should be monopolized by a few multinational companies makes many people anxious.

Legislators, courts and patent offices throughout the world deal with these questions. For some of the questions, there are legal answers, for others political and public discussion is still ongoing. Ethics and moral should neither be neglected nor should it lead to a bar for appropriate legal protection of biotechnological inventions. Some new developments to regulate these controversial issues is the “Directive 98/44/EC for Biotechnological Inventions” in Europe (1998) and the “Implementing Guidelines for Examination of Biological Inventions” in Japan (1997).

### **I.2. Historical review**

Intellectual property rights were fixed in the US constitution [1]; the first patent law was enacted in 1790. The Japanese patent law (JPL) has developed in the middle of the 19<sup>th</sup> century based on the US and French codes. In contrast to the European understanding that a patent primarily should remunerate the inventor for his intellectual effort, the goal of the Japanese patent law is the promotion of economic development and innovation [2]. The European Patent Convention (EPC) is a comparatively new law enacted in 1973, but it is based on much older national laws as well. Biotechnology, on the other hand, is a new and developing field that is certainly younger than all of the patent laws. Debates are to be

expected when an old, well-settled body of law must be applied to unforeseen technologies. This is even truer for technologies that raise public concern that goes far beyond patent law.

The US has always been one step ahead and until today is more active in patenting “living matter” (see Chapter III). The first patent issued was that by **Louis Pasteur** in 1873 claiming “*yeast, free from organic germs of disease, as an article of manufacture*” (US 141’072). Other early patents were granted on bacterial and viral vaccines. However, patenting of micro-organisms remained controversial until the famous **Chakrabarty v. Diamond** decision in 1980 before the US Supreme Court [3]. In a 5:4 decision, it was ruled that a “*man-made*” bacterium that was able to break down crude oil is patentable subject-matter. Prior to this decision, the United States Patent and Trademark Office (USPTO) had considered micro-organisms being products of nature and thus not patentable. In **Ex parte Allen** in 1987, the Board of Patent Appeals and Interferences ruled that polyploid oysters containing three sets of chromosomes instead of two were patentable subject-matter [4]. The decision led to the announcement of the USPTO that it would henceforth consider “*non-naturally occurring non-human multicellular living organisms, including animals, to be patentable subject-matter within the scope of the Statute*” [5]. This opened the way for the **Harvard mouse**, the first patent on higher animals that was granted only one year later in 1988 (US 4’736’866). Since then, hundreds of patent applications for genetically altered animals have been filed in the US. The fate of the Harvard mouse in Europe, as we will see later, was extremely complex and was decided only in July 2004. The counterpart of the Chakrabarty case in Europe was the “**Rote Taube**” decision [6]. Although the patent was revoked due to insufficient reproducibility of the invention, it was decided that a process of animal breeding based on classical crosses and selection is patentable subject-matter. The first patent for a micro-organism in Japan was on **rice yeast** in 1918 [7]. This patent was followed by a long tradition of food industry in Japan.

### **I.3. Importance of patents in the field of biotechnology**

The main difference to most other technical fields is the extremely tedious and costly development and the longevity of biotechnical products especially in the pharmaceutical field. The average time to generate a new drug is 12 years and costs approximately USD 800 million [8]. Furthermore, many biotechnology firms have no other activities than R&D and therefore do not directly exploit their inventions. They sell or license them to other companies. Without any legal protection of such high investments, it is questionable whether

research would or could continue with the same intensity. Other ways of protection like trademarks or trade secrets are less suitable for inventions in biotechnology. Since there is the immediate danger of copying a drug by chemical reverse engineering, trade secret is hardly any alternative to patents in this field. It is even easier to propagate self-reproducing micro-organisms, plants or animals. Such inventions would have no protection at all once they are out of the original lab. Moreover, trademarks, a very powerful means for protecting many consumer goods, cannot replace patent protection for biomedical products. The average “consumer” is normally not the broad public, but a medically trained person at least for prescription drugs. The value of a trademark may show up after expiration of patent protection, but not from the beginning. One example of a well-known trademark is Aspirin with acetylsalicylic acid as active substance that has attained a leading position world-wide in the prescription-free therapy of painful, inflammatory and feverish states. Aspirin was patented in 1889 and since its market introduction in the year 1899, it has been sold under the trademark Aspirin [9]. This, however, is not the rule and certainly does not protect new products coming up to the market. In summary, the financial aspects of biomedical research and the lack of alternative protection for the investment forces a reliable patent law and case law for this type of inventions.

## II. Patentable subject-matter and relevant provisions for biotechnological inventions

### II.1. Most relevant provisions regarding biotechnological inventions

(See Appendix for full text of the provisions)

- **Europe:**  
EPC Art. 52-57, 83, 84; Rules 23b-e, 28  
Directive 98/44/EC
- **US:**  
35 U.S.C. §101- 103, 112, 287(c)
- **Japan:**  
JPL Art. 29, 32, 36(4), 69(3)

### II.2. Basic requirements and exclusions from patentability

Any invention which is new, involves an inventive step and is industrially applicable/useful is patentable. Like any other technical field, biotechnology is accessible to patent protection, and there is a broad variety of granted patents for biotechnological inventions. **Proteins and DNA sequences lead on the ranking list.** However, basically all kinds of processes of genetic engineering, monoclonal antibodies, even plants and animals are patentable in Europe as well as in the US and Japan as long as they comply with the conditions of the patent laws. There is however some points that are somewhat special as far as patentability of biotechnological inventions is concerned. Although not stipulated explicitly in the patent law, an invention must be technical to be patentable. This basic requirement is stipulated in the TRIPS agreement Art. 27(1) stating that “*patents shall be available for any inventions, whether products or processes, in all fields of **technology**, provided that they are new, involve an inventive step and are capable of industrial application*“. The landmark decision for technicality in the field of biology was given by the German Supreme Court (BGH) in the case “Rote Taube” [6]. The red dove is a new race of doves as a result of selective breeding and crosses of already existing races. Although genetic crosses are biological processes, human selection has a technical aspect. The BGH concluded that a selective and systematic exploitation of natural forces including biological forces should not be excluded from patent protection. However, the pre-condition is its reproducibility which was not given in this case. This decision opened the way for patenting living matter in Europe.

Under 35 U.S.C. §101, patentable subject-matter includes inventions related to “*any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof*”. The very broad meaning of this statute was clarified for biotechnological inventions in the decision *Diamond v. Chakrabarty* which ruled that “*anything under the sun that is made by man*” is patentable subject-matter. It is now well settled, that applications under 35 U.S.C. §101 may be directed to living matter, as long as it is the product of human ingenuity. The living matter may be viruses, single cells or multicellular organisms, i.e. plants or non-human animals.

A common issue arising with respect to biotechnological inventions is the problem of novelty and the distinction between discovery and invention. Pure products of nature are not patentable. In order for subject-matter of natural origin to be patentable under 35 U.S.C. §102, a human being must impart a new form, a new quality, at least one new property, or combinations thereof, to the original product existing in nature. The main issue regarding patentability of biotechnological inventions concerns the extent to which they were made publicly available and the claimed inventions are different from what is found in nature. Products which have a higher purity or activity, distinguishing physical properties or a different physical form may be patentable.

A leading decision on patentability of naturally occurring substances and the distinction between **discovery and invention** was made by the German BPatG (Bundespatentgericht) in the *Antamanid* case [10]. The decision made clear that naturally occurring substances are patentable if they are new and have been isolated by technical means. In other words, the precondition is that the substance has been made publicly available in that form and could not have been found without technical intervention. For DNA sequences, this means that an isolated gene, which is identical to the gene found in nature, may be patentable if the gene sequence has never been isolated before (for more details, see Chapter IV.1).

In the EPC, patentable inventions are defined by the general clause Art. 52(1): “*European patents shall be granted for any inventions which are susceptible of industrial application, which are new and which involve an inventive step*”. Art. 52(2) EPC contains a non-exclusive list of subjects which shall not be regarded as invention. In this article, discoveries are expressly excluded from patentability. As a consequence, pure products of nature are not patentable even if they have never before been found, but as soon as they are isolated or purified, the technical aspect of an invention is recognized, and it is no mere discovery anymore. This is in line with the practice in the US. The following catchword

comprehensively demonstrates the goal of patent protection: “*Discoveries increase the knowledge; inventions increase the technical skills*”. Patents shall promote technical innovation rather than pure knowledge.

Another bar for biotechnological patents in Europe, as we will see later, is Art. 53(a) which excludes **inventions contrary to “ordre public” or morality** and Art. 53(b) excluding “*plant or animal varieties or essentially biological processes for the production of plants or animals*”. Directive 98/44/EC and its 1:1 implementation into Rules 23b-e EPC further specifies exceptions to patentability that are in conflict with “ordre public” or morality. Excluded is cloning of human beings, modification of the human germ line, using human embryos for industrial or commercial purposes and genetic modification of animals that causes them suffering without substantial medical benefit [11].

The JPL does not mention biotechnology, animals or plants at all. In particular, there are no statements about possible exclusions of biological inventions. This means that, theoretically, all kinds of biotechnological inventions could be protected by patent law according to the general clause of Art. 29(1) stipulating that “*any person who has made an invention which is industrially applicable may obtain a patent therefor*” [12]. Traditionally, Japan is strong in fermentation techniques and food industry, but meanwhile is engaged in all modern biotechnological fields. However, foreign companies still own the most important biotechnological patents, and Japan is primarily engaged in further development of such key inventions [2]. The scope of protection in Japan used to be narrower than in the US and Europe. However, there has been an adjustment over the last years [7]. As in Europe, biotechnological inventions may fall under Art. 32 JPL excluding inventions from patentability which “*contravene public order, morality or public health*”.

The US code on the other hand does not contain specific prohibitions for patents that are contrary to public morality. There is a line of cases, however, which deny granting patents to inventions against public policy. Under this aspect, the USPTO has not been granting patents on human or partly human inventions. Although test cases have been filed, no case refusing to grant a patent on a human being or chimera has yet received judicial review. The USPTO has stated its policy as follows: “*Inventions directed to a human/non-human chimera could, under certain circumstances, not be patentable because, among other things, they would fail to meet the public policy and morality requirements of the utility requirement*” [13]. The current policy is that any claim directed to a non-plant multicellular organism has to include the limitation “non-human”.

### **II.3. Patentability of therapeutic and diagnostic methods**

Art. 52(4) EPC provides that “*methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application*”. A similar provision is found in the JPL Art. 69(3) stipulating that the effects of the patent right for products used for diagnosis, cure, medical treatment or prevention of human diseases is limited.

On the other hand, therapeutic and diagnostic methods carried out on humans are patentable in the US. However, enforcement of “medical activities” which means the performance of a medical or surgical procedure on a body, may be limited by 35 U.S.C. §287(c). Remedies cannot be sought against a medical practitioner or a health care entity with respect to such medical activity. Although the level of regulation is different - Europe and Japan exclude methods for treatment and diagnosis from patentability by law and the US limits the enforcement of such patents - the final outcome and the idea behind is the same. Medical treatment should not be monopolized and practitioners should be free to use such methods for the benefit of their patients.

### **II.4. Industrial application/utility requirements and disclosure**

Besides being novel and involving an inventive step, an invention shall be “*susceptible of industrial application*” (Art. 57 EPC), “*industrially applicable*” (Art. 29(1) JPL) or “*useful*” (35 U.S.C. §101). This third criterion for patentability which points to the economic aspect of a patent is no hurdle for most technical fields, but may be a special problem for biotech inventions. The most important category is the claims for DNA sequences. Although a sequence may be extremely valuable for industrial application, this is often not recognized at the time the sequence is isolated. The problem came up with the new research methods allowing the analysis of the human genome and modern sequencing techniques that produce huge amounts of data. Inappropriate monopolization of the genome, in particular patents on ESTs [14] shall be avoided. The current practise is that mere sequences without known function are not patentable. As soon as a function is known, e.g. a gene in a known cancer pathway, industrial applicability/usefulness is given. In this case, the gene may serve as drug target or for diagnosis.

A patent confers the owner an exclusive right to use his invention in exchange to disclose it to the public. Sufficient disclosure is another critical requirement for biotechnology patents according to Art. 83 EPC, §112 35 U.S.C. and Art. 36(4) JPL, respectively. The possibility of

supplementing a written disclosure by depositing a microorganism or DNA with a recognized depositary institution has been one of the main factors distinguishing biotechnological inventions from classical chemical products in the beginning of the era of biotech patents [15]. An invention must be described in the patent application in such a manner as to enable the invention to be carried out by a person skilled in the art. This is sometimes not possible for biotechnological inventions. For example, a transgenic cell line containing an exogenous DNA sequence is in most cases a product by chance. If the same DNA integrates to another site, the characteristics of such a cell line may be different. Therefore, even if the skilled person follows the protocol of the invention, he may not get the same result. For such cases, it is possible to deposit a sample of the biological material to comply with the disclosure requirement as set for example in Rule 28 EPC. Today however, the significance of deposition is decreasing.

The rapid development of biotechnological techniques leads to changing requirements for disclosure. What has been a tedious work with uncertain outcome a few years ago may be within the repertoire of every researcher in that particular field and also of the “person skilled in the art” today. The US is stricter with the written disclosure requirement than Europe. In the US, the inventor has to show that he was in possession of the invention at the time the patent application was filed. As an example, detailed information on rat cDNA encoding rat insulin, including the sequence and tissue source, does not provide an adequate written description for the homologous human gene [16]. In Europe, the same detailed information on rat cDNA is likely to be considered by courts as sufficient to provide a person skilled in the art with the information necessary to isolate the human insulin gene.

### **III. Focus of biotechnological research and patenting activities in Europe, the US and Japan**

Source: OECD statistics [17-19]

Besides the legal, political and ethical questions mentioned in the previous chapters, the following data should illustrate the economic side of patents in the field of biotechnology. Patent documents are a rich source of information. Besides the technical features, they also disclose information on the intensity of research in specific fields and countries. In the last decade, there has been a sharp increase in the level of patent activities across the world. This reflects the growing importance of patents in the knowledge-based economy. More than 850'000 patent applications were filed in Europe, Japan and the US in 2002, compared to 600'000 in 1992. Although nearly all technology fields experienced growth in patenting over the 1990's, two fields contributed substantially to the overall increase: Biotechnology and Information and Communication technologies. Between 1991 and 2000, biotechnology patent applications to the European Patent Office (EPO) increased by 10.2% compared to 6.6% for total EPO patent applications. At the USPTO, the numbers are 15% for biotechnology patents and 5% overall, respectively between 1990 and 2000. The US has a leading position on the international biotechnology market, and the ratio of biotechnology patents to total patents is far higher in the US than in the European Union and Japan. However, Denmark has the highest such ratio, followed by the Slovak Republic and Canada: in these countries, around one in ten patents is related to biotechnology (see Appendix, Figure 1).

There is a strong correlation between investment, research strength and number of patents. Between 1991 and 1999, a total of USD 6'332 billion was invested in biotechnology in the US and slightly under USD 2'200 billion in the European Union. Canada and the US are the countries in which the largest shares of venture capital go to biotechnology (see Appendix, Figure 1). In the US, firms in California captured nearly half of US funding in the period 1980-98. In terms of the intensity of biotechnology venture capital, however, the leaders were Canada, Belgium and Switzerland, allocating 0.23, 0.21 and 0.14% of GDP (gross domestic product), respectively, to the sector. US biotechnology disbursements were only 0.13% of GDP.

Scientific specialisation profiles can be obtained from the distribution of published articles by field (see Appendix, Figure 2). The United Kingdom was the strongest across all the health/bio-medical fields, although Italy and to a lesser extent the US were strong as well.

Japan was well below average. As for biomedical engineering, which is the field with some of the strongest links to biotechnology, the US and Germany were above average while Japan, France, and Australia were below.

Information is also gained from the profile of companies in a specific field, the number of employees or the revenue. Germany, France and the UK were taken as representatives for Europe and were compared to the US and Japan.

Germany: The leading biotech sectors are therapeutics, followed by platform technologies.

France: French biotechnology SMEs target the diagnostics and genomics market (42%) followed by health and cosmetics (33%) and agriculture, agro-food and environment (20%).

UK: Almost half of all biotechnology employment is in biopharmaceuticals (46%); it is the largest revenue generating sector (36%) and has the greatest number of firms (35%). It is also the sector that is the most R&D intensive (74%). It is followed by the biotechnology suppliers sector and diagnostics.

US: The US has the largest number of genomics firms in the world and the largest absolute number of DNA patents. In 2001, 72% out of 1'031 firms indicated that human health applications were their primary area of biotechnology-related activity.

Japan: The predominantly used technology is conventional fermentation with 87%. 24% of Japanese biotech firms are active in food and drink manufacturing which belongs to the traditional biotechnology, followed by chemicals and pharmaceuticals.

Taken these data together, we can conclude that Europe is especially strong in biopharmaceuticals, whereas the US has power on genomics and Japan on classical fermentation. The reasons for these geographic distributions are at least to some extent based on historic developments. The patent system and the slightly different views on patentability in Europe, the US and Japan however may have influenced and promoted such trends. The world-wide increase of biotech patents illustrates the importance of this technical field of research and its protection. The legal and political questions which dominate this paper have also to be considered in the light of the economic value of biotech patents and research.

## IV. Patents for DNA sequences, proteins and higher organisms

The following two cases were chosen to illustrate and discuss some aspects and problems of patenting biotechnological inventions. Patents on DNA, proteins and higher organisms, in particular on plants, belong to the most important patents in the field of biotechnology. However, there are many others that would deserve attention like patents on biotechnological processes, microorganisms, embryonic stem cells or gene therapy to name just a few of them. The rapid progress in biotechnological research allows only glancing at some selected points in this review.

### IV.1. Erythropoietin and the world-wide patent war

#### IV.1.1. Background

The patents on **Erythropoietin (Epo)** are probably the commercially most valuable patents in the field of biotechnology and, as a consequence, also belong to the most disputed ones. They were and still are litigated in around 30 countries throughout the world with extraordinary investment. It is not the aim of this paper to comprehensively list all disputes. I will rather go into some interesting aspects and landmark decisions in order to illustrate patentability of DNA sequences and proteins in general [20-21].

Epo, a glycoprotein, acts as a hormone that stimulates the production of red blood cells and is mainly produced in the kidney. It is well known to make the headlines as doping in sports. Its main use and also value, however, is the treatment of anaemia associated with kidney insufficiency and other chronic anaemias, e.g. resulting from chemotherapies, bone marrow transplantations or HIV infections. The volume of the global market for Epo has been estimated to nearly USD 10 billion per year, and patent protection plays a key role for access to this market [22].

Epo is a weakly expressed, single-copy gene. The protein has been isolated in the 1970's from patients with aplastic anaemia who excrete higher amounts of Epo with their urine (**uEpo**) [23]. However, the world-wide request for this hormone could not be satisfied. The situation has only changed in the early 1980's when **Amgen**, today the largest biotech company in the world, and **Genetics Institute (GI)** independently cloned the Epo gene and could produce **recombinant Epo (rEpo)** in mammalian cells in unlimited amount. Amgen filed the first patent in November 1984 in the US (US 4'703'008; European equivalent EP 0'148'605) and obtained market approval for rEpo in 1989. GI filed its first patent in January 1985 (US

4'677'195; European equivalent EP 0'209'539). Both patents were granted in 1987 in the US, and world-wide litigation started. The third player is **Transkaryotic Therapies (TKT)** who filed a patent in November 1992 (WO 9'309'222). All of them had following-up patents (for details of all mentioned patents and claims, see Appendix).

Amgen's basic patent claims the purified and isolated Epo sequence in claim 1 and all DNA sequences encoding a protein with the biological activity of Epo in claim 7 [24]. Its European equivalent (EP 0'148'605) additionally claims a process for the production of the Epo protein. GI filed patents on a homogenous Epo protein (US 4'677'195 and EP 0'209'539). In the early 1990's, TKT developed a completely new technology to activate the endogenous Epo gene within human cells. They introduced a strong promoter by homologous recombination. By this process, TKT could activate the normally silent human Epo gene and could produce Epo protein in human cells.

On October 27, 1987, the day the '008 patent issued, Amgen filed suit charging GI with infringement of their patent '008 and charging the Japanese company Chugai to have induced or contributed to direct infringement. They further sought a declaration of invalidity of GI's patent '195. GI answered by claiming invalidity of patent '008 under 35 U.S.C. §§101, 102, 102 and 112, counterclaiming for infringement of patent '195, asserting unfair competition by Amgen and facing with an interference process [25-29].

The situation in Europe is even more complex. This is not only due to the fact that apart from the decisions by the EPO, national courts decide on infringement and validity, but also because in contrast to the US where Amgen basically has a monopoly on Epo, in Europe also GI holds valid patents.

#### ***IV.1.2. Attacks on novelty***

US 4'703'008 claims purified and isolated DNA sequences, but not the protein. The very broad claims of this patent cover a big number of DNA sequences and reflect the common US practice. Based on the Chakrabarty decision "*a new mineral discovered in the earth or a new plant found in the wild is not patentable subject-matter*" [3]. Yet the USPTO allows claims for purified, isolated natural products even if the very same product exists in nature. The newest guidelines of the USPTO explicitly allow patents for purified and isolated DNA sequences. However, a credible and substantial function of the DNA sequence is required [30]. Therefore, patents for ESTs are probably hard to obtain today [31]. It is important to mention that the invention of Amgen and GI is not the Epo gene in its natural context, but the purified and isolated sequence which codes for Epo protein.

In Europe, or more precisely in Germany, it has been set even before the era of gene technology that natural products are patentable if they are isolated by technical means [10]. This is consequently applied to DNA sequences and proteins. Therefore, the European equivalent of US 4'703'008, EP 0'148'605 was granted. Although broad claims basically are allowed, they have to be disclosed and enabled. Amgen as well as GI run into problem with this requirement (see Chapter IV.1.4).

Epo protein has already been isolated before the priority date of Amgen's and GI's patents from human urine [23]. Nevertheless, GI got the patent '195 with claims for purified Epo. The District court of Massachusetts considered them to be novel since the biological activity of rEpo was higher than of uEpo [25].

One of the main arguments challenging the validity of patent '008 was priority under 35 U.S.C. §102g. GI claimed to be first to conceive a strategy to clone Epo. The court of first instance and also the CAFC (United States Court of Appeals for the Federal Circuit) both held that for conception, "*the idea must be sufficiently complete as to enable anyone of ordinary skill in the art to reduce the concept to practice*". The chance of success to isolate the Epo gene by this strategy was held to be very uncertain. It was concluded that isolation of DNA falls under the doctrine of simultaneous conception and reduction to practice. A mere idea how to isolate a gene is not sufficient until the sequence is isolated. In the Epo case, it was no dispute that Amgen was the first to clone the gene and therefore patent '008 was found to be valid [29].

#### ***IV.1.3. Attacks on inventive step/obviousness***

The Epo protein has been isolated before the priority date of Amgens's patent, but it was neither sufficiently characterized nor was the DNA sequence known. Based on the connection between a particular amino acid sequence and the corresponding DNA, the DNA sequence theoretically is determinable. Due to the degeneration of the genetic code, however, there exist a definite but big number of combinations. Therefore, disclosure of a particular DNA sequence of which the protein was already known may be new at least according to EPO decisions. However, without any surprising effect of such a sequence, inventive step is likely to be denied. In the Epo case, however, the situation was easier. Not even the protein sequence was known completely. Therefore, the claimed DNA sequence of the Epo gene has not been implied by the earlier isolation of uEpo.

The validity of patent '008 was further challenged for being obvious under 35 U.S.C. §103, because Epo was cloned using degenerated probes which is widely used in biotechnological industry. However, since a genomic library - and not a cDNA library - was used as starting point, the District Court and CAFC found no reasonable expectation of success. It was considered that none of the prior art references suggested this strategy and that others who tried failed [25-26].

Using the problem-solution approach, the EPO came basically to the same conclusion and confirmed inventive step of patent '008 [32].

#### ***IV.1.4. Attacks on disclosure and enablement***

Amgen was confronted with insufficient disclosure and enablement. This attack is quite common for biotechnological inventions. The question was whether the procedure to isolate the Epo gene and to produce rEpo was sufficiently enabled for the skilled person to repeat the invention without undue experimentation. Amgen did not deposit the cells they used for their invention. In the US, the opponent also argued that Amgen failed to disclose the best cell line under 35 U.S.C. §112.

Both, the EPO and the British High Court stated that the patent specification was sufficiently enabling to isolate the Epo gene [32-33]. If it takes a long time to reproduce an invention, but the way how to do it and the outcome is predictable, this is no reason for revocation of the patent due to undue experimentation. In connection with deposition of the cells, the Epo stated "*there is no suggestion that deposit should be for the purpose of making something already possible easier. [...] If the route is certain but long and laborious, the patentee is under no obligation to assist the disclosure by making actual physical samples, i.e. the "factory" available*" [32]. The question on enablement has been interpreted by the US courts and most other national courts in the same way. Deposition may lower the danger of litigation, but on the other hand it may also facilitate putting into practice the invention by competitors. Therefore, the risks of deposition have to be evaluated when filing a patent application.

Concerning the best mode requirement, the CAFC confirmed that the patentee does not have to point out his preferred embodiments as long as they are disclosed in the specification. Since the used cell line was disclosed in one of the examples, the skilled person would have found this best cell line without undue experimentation. Furthermore, since these cells were freely available, deposition was stated not to be necessary [25-26].

Claim 7 of patent '008 is a generic claim covering all possible sequences with functional analogy to Epo. By replacing just one amino acid out of the 166, 3'600 analogs could be made. Due to the unpredictability of the physiological activity of such variants and the fact that Amgen has told how to make and use only a few of them, the US courts came to the conclusion that claim 7 was insufficiently enabled and required undue experimentation for the skilled person [25-26]. Therefore, claim 7 was invalidated.

EP 0'148'605 claims genomic DNA sequences and the resulting rEpo. In dependent claim 3, the corresponding cDNA is also claimed. The Board of Appeal of the EPO regarded this claim as not sufficiently disclosed since no way was described to get the cDNA from genomic DNA and at that time, the skilled person would not have had the knowledge to do it without undue experimentation [32]. Claim 1 however was maintained unchanged. The Board of Appeal stated that it was not certain whether cDNA falls within the scope of claim 1. Interestingly, during later infringement processes, Epo cDNA has always been regarded to fall within the scope of claim 1.

Claim 19 of EP 0'148'605 claims a higher molecular weight than uEpo. The British High Court found that the molecular weight of uEpo varies tremendously. As a consequence, a particular rEpo would once fall outside the scope of the patent and another time is within which would lead to legal uncertainty. Claim 19 was therefore regarded as insufficiently disclosed [33].

Not only Amgen, but also GI was confronted with the problems of disclosure and enablement. However, the outcome was much more severe; US 4'677'195 and EP 0'209'539 both were revoked by the US courts and the EPO, respectively. Patent '195 was invalidated by the CAFC since the court had severe doubts that GI ever had at hand a protein with an activity of 160'000 IU. The experiments disclosed only 83'000 IU in connection with 50% contamination. From this value, the patentee extrapolated to 160'000 IU. As a result, claim 1 was decided not to be enabled [26]. The EPO revoked the equivalent European patent '539 because of lack of clarity based on Art. 84 EPC [34]. The value of activity depends very much on measuring methods which were not defined in the specification.

#### ***IV.1.5. Scope of protection***

The last interesting question concerns the new technology of TKT. TKT for the first time was able to activate the normally silent human Epo gene through introduction of a strong promoter

by homologous recombination. This leads to **“gene activated” Epo** in human cells (**gaEpo**). In contrast to Amgen and GI who transfected rodent cells with exogenous rEpo DNA, TKT did not isolate the Epo DNA at any step, but ectopically expressed it within human cells. This case was followed with much attention by the biotech industry because it has been the first serious threat to Amgen’s monopoly on Epo. The key issue was whether Amgen’s patents would be interpreted broadly enough to cover gaEpo. Furthermore, it touches one of the fundamental questions of how far a substance found in nature can be covered by patents.

There is no doubt that the TKT technology was not foreseen at the date of priority of Amgen’s patents. On the other side, TKT was dependent on the sequence information given by Amgen to develop its technology. Until now, there are two court decisions on this subject, one in Europe and one in the US.

The British High Court had to deal with the question whether claim 26 of EP 0’148’605 was infringed by the TKT technology. The court came to the conclusion that in both cases, recombinant Epo was produced. Since at the time of Amgen’s patent application, gaEpo did not yet exist, it could neither have been included nor excluded from the scope of protection. In this light, the skilled person would not have limited the scope of protection to rEpo and therefore, infringement of claim 26 by TKT was confirmed [33]. This decision was reversed by the Court of Appeal [35]. The court stated that Amgen’s patent did not cover the Epo DNA per se, but only the exogenous DNA sequence. Therefore, it would be unfair to broaden the scope of this patent to cover the new and innovative technology of TKT. The final decision of the House of Lords has not yet been handed down.

In the US, Amgen sued TKT and Hoechst for infringement of US 5’621’080 [36]. Since TKT’s gaEpo has 165 amino acids and Amgen’s rEpo has 166, literal infringement of US 5’621’080 was denied. Amgen however could prove that the deletion of this single C-terminal amino acid has no impact on the biological activity of the protein. Under this aspect, the District Court found equivalent infringement.

#### ***IV.1.6. Concluding remarks***

It is no question today that DNA sequences are patentable as long as the basic requirements for a patentable invention are fulfilled. In this respect, DNA is considered to be a chemical molecule no different from other chemicals.

One problematic issue may concern novelty of DNA sequences in the post-genomic era. By claiming a short DNA sequence as selection invention as it is possible for chemical inventions, it should be possible to circumvent this obstacle. However, there is no case law

yet in Europe. Inventions of selection are known in the US as well, i.e. a species may be novel and inventive over a genus but not vice versa. The hurdles for novelty and non-obviousness seem to be somewhat harder to overcome in an invention of selection. Without any unexpected results or benefits, it may be difficult to get a patent.

The uniqueness of the genetic information and its connection to life makes DNA patents a sensitive field and a favoured target for opponents of biotechnology in general. It is important to mention here, that not life as such is patented with a DNA sequence. It is the isolated DNA molecule taken out from the context. In that respect, DNA patents do not seem to be problematic. Life is much more than a few DNA sequences.

However, regarding the opposition for DNA patents, it may be worth spending a few words on the scope of protection [37]. DNA is not patentable without disclosing a function. This is in line with the general requirement of industrial application or usefulness [31]. But also the requirement of the inventive step has to be considered under this aspect. Unlike the time of the isolation of the Epo gene, DNA isolation today is a basic technology commonly used and known by molecular biologists. Therefore, the hurdle for inventive step today is higher than it has been a few years ago. But even today, it may be difficult to find a particular gene within the huge genome. If an invention overcomes such difficulties, the inventive step is accepted. Two decisions by the Board of Appeal of the EPO illustrate that it is the chance or expectation of success which is relevant to decide on inventive step. Whereas it has been extremely difficult to isolate Epo since this gene is only weakly expressed and commonly used techniques to clone it could not be applied [32], isolation of Chymosine which is produced in huge amounts in the stomach of cows did not cause any technical difficulties and as a consequence, the patent was revoked [38].

One immediate follow-up question is how broad the protection for DNA sequences should be. Does a patent on a DNA sequence give an absolute protection in case a second function is found later? This is not a hypothetical question, since many genes have several unrelated functions at different developmental stages or in different parts of the body. A second question is whether variants of a sequence due to degeneration of the genetic code which still encode the same or a very similar protein should be protected as equivalents. The reverse situation would be two different proteins that arise e.g. through alternative splicing by one and the same gene sequence.

All these questions are not easy to answer. This is also reflected by the different outcome of the Amgen v. TKT case in the UK and US. In my eyes, courts should strongly focus on inventive step when dealing with the scope of protection. It is questionable whether it is

inventive to find a sequence variant or a splice variant that was not covered by the original patent without giving further information on it. However, if a sequence has a second function, that was neither foreseen by the first inventor nor disclosed in the patent application, this may be a second dependent invention that deserves individual protection. We can find here strong parallels to patents for second medical use which are allowed in some jurisdictions. This is in line with the basic idea of patent protection. The inventor should be remunerated for his effort in exchange of disclosing the invention to the public. An unforeseen effect that involves an inventive step by its own should not be covered by the former patent. If it were, this would rather hinder innovation than promote it. On the other hand, a weak protection which can be circumvented very easily and does not protect the real idea of the invention is also no motivation for scientific research.

It follows from the above that the practices of the three patent offices EPO, USPTO and JPO when dealing with DNA and protein patents are very similar. For a detailed analysis, I refer to the Trilateral project [39]. There are no substantial differences in the big lines as they are pointed out in this chapter. This is in sharp contrast to the following chapter on patenting higher organisms.

## **IV.2. The “Oncomouse”**

### ***IV.2.1. Background***

The debate surrounding whether or not higher life forms should be patentable has largely been centred on one particular patent application which relates to what has been colloquially termed the “**Oncomouse**” or the “**Harvard mouse**”. The problematic of this case is completely different from the Epo case. It is not the commercial value that has led to opposition, but rather ethical and political aspects. It is understandable that the public is sensitive to this delicate issue and that many people have an objection to patenting animals (or other forms of higher life) irrespective of the use to be made of the animals. Prior to the Oncomouse application, it was uncertain whether a patent would be granted where the claims cover a higher life form. In the US, it had already been determined that genetically engineered living organisms could be patentable. This was established in the Chakrabarty case for micro-organisms and in *Ex Parte Allen* for multicellular organisms. However, the Harvard mouse has a new dimension: It was the first genetically engineered mammal to be patented, and it was one of the most controversially discussed patents especially in Europe. The discussions went far beyond patent law and challenged biotechnology and genetics in general.

The Oncomouse has been genetically engineered to carry an activated oncogene, the so called *myc* gene. The activated oncogene significantly increases the susceptibility of the mouse to cancer rendering it a useful model for researchers trying to develop treatments and cures for cancer or for testing the carcinogenicity of different compounds. A patent application covering the Oncomouse was filed in 1985 based on a US priority application in 1984.

#### ***IV.2.2. The US Patent (US 4'736'866)***

The very broad first claim of the US Oncomouse application reads:

*“A transgenic non-human mammal all of whose germ cells and somatic cells contain a recombinant activated oncogene sequence introduced into said animal, or an ancestor of said mammal, at an embryonic stage.”*

Though the broadest patent claims pertain to a “mammal”, the preferred embodiment, and one claim, reads to a “mouse”, which has been the basis for the decision by the EPO nearly two decades later.

The USPTO was the first to grant a patent to the Oncomouse in 1988. This ruling by the USPTO was challenged by a consortium of animal rights groups [40]. One such group brought suit against the PTO on July 29, 1988. The group included “The Animal Legal Defence Fund”, “The American Society for the Prevention of Cruelty to Animals”, “The Humane Farming Association”, “People for the Ethical Treatment of Animals”, “The Wisconsin Farm Family Defence Fund” and individual farmers. The complaint challenged the PTO Commissioner's post-Allen notice of April 1987, which was supposed to have resulted in the so-called “mouse patent”. Thus, the status of animal patentability in the US seemed to be in the midst of controversy at that time. However, few of the arguments have anything to do with patenting, none recognizes that a patent lasts only 20 years, none mentions the disclosure role of patents, and none deals with the alternative courses of secret development or total prohibition of genetic engineering. Ethical, ecological, economic, and social reasons were raised. On the other side of the fence, some farmers and agricultural groups voiced support for animal patents, stating that they are necessary for the American farmer to maintain a competitive advantage in the world agricultural community. Genetic engineering, they argued, cannot be viewed as inhumane because most domestic animals have their ecosystems distorted by generations of selective breeding long before.

In May 1987, the Senate reacted to the debate by introducing a “Supplemental Appropriations Provision” to bar the PTO from spending funds during 1987 to grant patents on genetically altered or modified animals [40]. Though the provision was later dropped, activity in the

Congress continued. No legislation has been enacted, but a number of bills have been introduced finally. Since only an applicant can seek review of an examiner's decision in the US, the government has no right to review in the courts if an applicant prevails before the examiner or the Board of the USPTO. The patent will issue and its validity can only be attacked in later litigation between the patent owner and an accused infringer. The Oncomouse patent has never been judicially reviewed for validity as patentable subject-matter in court. Although in the mid-eighties there has been public concern on patenting animals in the US as well, this is no issue anymore today; it is basically accepted [41]. This is in sharp contrast to Europe.

#### ***IV.2.3. The Japanese Patent (JP 61'081'743)***

It is generally assumed that the Japanese would be more open to biotechnological products than Americans or Europeans. However, there are fewer consensuses on the use and regulation of biotechnology than it appears at first sight [42]. The concerns most frequently raised, are the danger of human misuse, interference with nature, and ethical concerns with respect to genetic engineering. The acceptance for genetically engineered food, for example, is low. Local groups have protested against the application tests of both plants and pharmaceuticals. The broad public however is not aware of the kind of tests that take place. In addition, the traditional cultural background of the Japanese contravenes public debates.

In the Japanese patent law, there are no statements about possible exclusions of biological inventions other than the morality provision in Art. 32 JPL. This means that all kinds of biotechnological inventions could be protected by patents if they are in conformity with general patent law. The Oncomouse is therefore patented in Japan. The first claim of the Japanese patent refers to a "non-human animal". It resembles more the US patent than the European patent. Like the US patent, it is very broad in its wording and does not only cover mice as in Europe. However, in the US, only the animals themselves are claimed, whereas it is the animal and a method to produce it both in Europe and Japan.

#### ***IV.2.4. The European Patent (EP 0'169'672)***

The case before the EPO lasted 19 years and resulted in two landmark decisions concerning Art. 53(a) excluding inventions contrary to "ordre public" or morality and Art. 53(b) excluding plant or animal varieties from patentability [43]. Although the Oncomouse might be of no commercial and not even scientific value due to high lethality of such mice, this case

has been continued to clarify the situation on patentability of genetically modified animals in Europe once and for all.

In a first step, the Examining Division of the EPO rejected Harvard's patent application, excluding it under **Art. 53(b)** as an "animal variety" and Art. 83 EPC. The Examining Division interpreted Art. 53(b) as excluding not only certain groups of animals from patentability but, in fact, animals as such.

In decision T 19/90 [44], the Board of Appeal decided that the application satisfied the provisions of Art. 83 since there were no serious doubts substantiated by verifiable facts that the invention could not be carried out over the whole claimed scope, i.e. could be extended to mammals other than mice. Furthermore, the Board was unable to accept the interpretation of Art. 53(b) as excluding the patenting of animals as such. The Board held that the text of the Convention should be construed strictly so that when reference was made to a "variety" not being patentable, the prohibition did not apply if the claim was directed to a broader taxonomic grouping, e.g. to a species or higher classification. However, it should be mentioned that the terminology in the EPC is unclear since the German "Tierart" refers to "animal species" and not "animal varieties". Although the intention of the EPC clearly is to exclude varieties and not animals as such, from the point of view of systematic nomenclature, the terminology is misleading. The Board of Appeal remitted the case to the department of first instance for further prosecution with the statement that "*the question under Art. 53(b) was not whether the claims embraced an "animal", but whether the claims embraced an "animal variety" ("race animale", "Tierart") within the meaning of Art. 53(b)*". This decision, which recognized a distinction between "animal" and "animal variety", laid the groundwork for interpreting patent exclusion under Art. 53(b). Taking the guidelines of the Board of Appeal into consideration, the Examining Division finally decided that the subject-matter of the application did not constitute an "animal variety" within the meaning of that provision.

The second issue to be dealt with was whether the Oncomouse might violate public policy under **Art. 53(a)**. Morality exceptions to patentability are found in many laws, e.g. Argentina, Brazil, China, India, Japan, New Zealand and most European countries, but not in the US, Australia and Canada [45]. The Board of Appeal of the EPO however was the first court to host a detailed debate on a morality provision in relation to animals. The issue of morality has been handled by weighting the environmental risks and potential for cruelty to animals against the potential benefits to mankind. In this case, it was found that the interest in developing

anticancer treatments was of great value, and that overall animal suffering would actually decrease, since fewer animals would be needed for such experimentation with the patented mouse available. Furthermore, there was no danger to the environment, since testing would only be done under controlled circumstances and by qualified staff, and no release into the wild was intended. However, it was clearly stated that this opinion applied solely to the Harvard mouse patent and that other cases of transgenic animals could result in a different conclusion when applying Art. 53(a). As a result, the EPO granted its first patent on a transgenic non-human animal, the Harvard mouse in 1992.

Opposition notices were filed by 17 different parties claiming revocation of the patent under Art. 52(2) and (4), 53(a) and (b), 54, 56, 57 and 83 EPC. The number of opponents demonstrates the public concern. Opposition mainly arised from animal rights and anti-vivisectionist groups from the UK, Germany and Austria. The most controversial matter was the European morality provision Art. 53(a). In 2001, the Opposition Division decided that the patent as amended during the opposition proceedings by introducing auxiliary request 4 restricting the patent to transgenic rodents meets the requirements of the EPC. It was considered that Art. 53(a) does not prohibit patenting of this invention when the claims are limited to rodents instead of transgenic non-human mammalian animals in general. The interest in developing anticancer treatments was again balanced to overall animal suffering, and rodents were found to comprise representative animal species useful for allowable animal testing.

Finally, notices of appeals were filed in 2003 by several former opponents based on wrong interpretation of Art. 53(a). Grounds for appeal besides Art. 53(a) and (b) were again Art. 52(2) and (4), 54, 56 and 83 EPC. In July 2004, after 19 years of proceedings, the ultimate decision by the Board of Appeal held that the patent meets the requirements of the EPC if it is further restricted to mice instead of rodents [46]. This final decision [47] cannot further be challenged at the level of the EPO. Validity suits would now have to be litigated at national courts. Since the patent term ends in June 2005, this is rather not expected. Even if it were litigated, it would be alarming for the European patent system if after such long-standing and painstaking considerations of the EPO and after several milestone decisions concerning biological inventions, some countries would challenge the decision.

#### ***IV.2.5. The Canadian exception***

Canada is the only country where the Oncomouse patent has been litigated in court and has finally been revoked. In a 5-4 majority decision, the Supreme Court of Canada decided that a patent could not be granted for a higher life form [48]. The majority decided that the wording of section 2 of the Canadian Patents Act should be strictly construed and that higher life forms were not implicitly incorporated within the definition of an invention. Although the Supreme Court of Canada's rejection of the application was based on the definition of the "invention" in question rather than a morality exception, the court acknowledged that it was influenced by the controversial nature of the subject-matter when opting for a narrow interpretation [45].

#### ***IV.2.6. Concluding remarks***

With the final decision of the Board of Appeal at the EPO on the Oncomouse case, the debate on patentability of laboratory mice is over. Patentability of animals is basically confirmed everywhere in the world with the exception of Canada. In my eyes, the considerations by the EPO attract attention. Morality and ethics is an unusual issue to deal with in patent law, and biotechnology is an exceptional case where morality provisions have to be applied. On the other hand, morality provisions are hard to deal with and provide an easy and attractive target for opponents. It is to be expected that disagreeable patents are attacked via morality also in future. Argumentation is often blocked on both sides of supporters and opponents of biotechnology. The balancing act of possible benefits for mankind on one hand and suffering of the affected animals or danger for the environment on the other hand is at least one way to deal with this delicate issue in a serious way.

The exclusion of plant and animal varieties from patentability is based on history: legislators wanted to inhibit double protection for plants via patents and separate plant variety acts. Such protection via plant variety act exists in Europe as well as in the US and Japan [49]. For animals, however, there exists no second way to protect them. Exclusion of varieties from patent protection seems to draw an artificial line between animals. Today, Art. 53(b) is of no importance anymore. As long as no variety is claimed literally, a claim does not fall under this provision [50].

## V. Political and ethical questions

The first point to be clarified is the rights conferred by a patent and the function of patent offices. Without that, no serious discussion on political and ethical questions is possible. A patent gives the patent holder the right to exclude others from exploiting his invention for a limited time in a defined territory. It does not give the right to use the invention if this is in conflict with other regulations. This has the consequence that no decision of any patent office can overrule democratic political decisions and other more specific laws. It is not the aim of patent offices to make politics, but to approve patents exhibiting novelty and inventiveness, i.e. to rule on the quality of human intervention and human creativity. The patent office is neither the forum nor has it sophisticated experience to judge on delicate or controversial issues concerning ethics and morality. This should be up to national legislators and finally to the public. Nevertheless, patent offices as the EPO and JPO have to deal with morality standards since they have such provisions in their law. It can be expected that inventions have to comply with general morality standards to be patentable such as defined for example in Rule 23d-e EPC.

A second issue is the 20 year term of a patent. Moral values may change, scientific progress may render questionable inventions unobjectionable, but a rejected patent can never be revitalized. Under this aspect, it seems to be more reasonable to regulate implementation of the invention rather than the issue of patents because implementation can be adapted to the current scientific and legal situation. From all this, we can conclude, that exclusions from patentability under patent law should be interpreted narrowly.

Nevertheless, I would like to deliberate on some moral and ethical questions. Ethical reflections for patents should be on a sophisticated, problem-oriented level, and not on a fundamentalist level as celebrated by some social groups. Main formal principles of modern ethics should apply. The question should be what is culturally and politically accepted in broad lines. This has neither to do with unconditional praise nor with condemnation of modern biotechnology, but with balancing different interests and considering consequences of an action in an impartial way.

Public reactions on patents vary within biotechnology depending on the subject, but there are also country- and culture-specific differences. Whereas debates are over in the US and hardly existed in Japan at any time, they are still ongoing in Europe. For animals and embryonic stem cells, it is mainly the ethical aspect, but also questions on ownership. The argument that one should not patent and own life can be counter-argued by saying that life is not equal

to a genetically engineered organism. The patent on the Oncomouse does monopolize life as less as a dog holder possesses life. It is not life as such that can be or should be patented, but only practically useful and creatively applied knowledge or material derived from living matter. The main concerns on patents for plants and microorganisms are environmental damages and effects on human health. As far as agricultural plants are concerned, it is the consumer who should and probably will decide on survival of such products and not the patent system. Gene patents have never been so controversially discussed as patents for animals and plants [51]. In terms of patentability of sequences, it has mainly been the question on whether ESTs should be patentable. There are certainly exceptions coming from groups who oppose patents, commercialization, monopolies and expropriation of genetic material in general. Indeed, these fundamentalist objections are probably not even primarily targeted to patents, but to biotechnology and genetic engineering as such. Since it is more difficult to have influence on legislation, patents are an easier target to block disagreeable developments, and patent offices are used to spread concerns regarding biotechnology.

To conclude with, one can assume with some confidence that patents for biotechnological inventions will have no other impact than patents in other fields of basic research in future. As many new technologies, biotechnology and genetic engineering in particular raises fears. Misuse cannot be excluded. The patent system however seems not to be the appropriate forum to give answers on delicate questions. There are other authorities like such for drug admission, animal experiments or approval of releasing agricultural plants into nature.

The main unsolved problematic of biotechnology in my eyes is not even the technology itself with its potential dangers and possible misuse, but the social questions of who has access to the information gained by the new technologies. To raise just one question: when somebody decides for a genetic test, who should know the genetic constitution of that particular person? Social insurances, health insurances, employers, the patient himself? Conflicts and misuse on all sides can be predicted. Such questions go far beyond patent law and biotechnology and illustrate that regulations should be initiated at the proper level.

If we reflect back to the initial aim of patents, namely the function to promote innovation and remunerate scientific efforts, whilst disclosing the invention to the public, it becomes clear that the disclosure should be in line with the counter-value for the public to justify a temporary monopoly and that the scope of protection should not be too broad, i.e. should protect the real technical invention not to hinder innovation rather than promoting it. Given these pre-conditions in combination with basic moral and ethical considerations, patents constitute an appropriate means of protection also for biotechnological inventions. The

question of how far we should go in future is not a question on patent law, but more on public debate and acceptance of biotechnology with all its advantages and disadvantages.

## VI. Future developments

The rapidly developing field of biotechnology necessitates permanent discussions and adaptations for patent law as it recently occurred with the Directive 98/44/EC in Europe. Embryonic stem cells (ES cells) and gene therapy are two examples of research areas which are highly promising and may revolutionize medical progress in near future. However, like hardly any other field of research, they are very delicate and complex issues and interconnected with many other technical fields. Discussion is even more complicated since there exist a variety of legal regulations besides patent law. This last chapter only touches some problems and questions without solving them or going into any detail.

Patenting of **embryonic stem cells** is one of the politically very “hot” topics in Europe as well as in the US [52-53]. There exist basically two types of ES cells. Totipotent ES cells have the capacity to develop into all of the around 200 cell types and to form a complete human body. They are derived from embryos up to the 8-cell stage. Pluripotent ES cells are able to give rise to many, but not all cell types. It depends on the status of their development what cell types they are able to differentiate. Ethical considerations for patents on embryonic stem cells are even more delicate than for animals. The basic legal framework in Europe is set by the general clause Art. 53(a) EPC and Rule 23d-e EPC or Directive 98/44/EC. In particular, the following is not regarded as patentable invention:

- *Processes for cloning human beings;*
- *Processes for modifying the germ line genetic identity of human beings;*
- *Uses of human embryos for industrial or commercial purposes;*
- *The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene.*

One of the basic ethical questions in this respect is the time point from which an ES cells can be considered as a human being with the right to human dignity. To isolate totipotent ES cells, the embryo has to be destroyed. Whether this is a legal action, is very controversially discussed. Some jurisdictions allow using superfluous ES cells for research purposes. In the US, public subsidy is limited to research with already existing cell lines [54]. Similar to the Oncomouse patent, these questions go far beyond patent law and should only be discussed within the whole legal and scientific context.

**Gene therapy** is another issue that is in the focus of scientific and legal interest [55]. There are several different methods of gene therapy having a big potential to cure many diseases.

One possible way is to use viruses or other particles as vehicle for gene transfer. Apart from interference with the human germ line, gene therapy is of no ethical objection. Germ line modification is explicitly excluded from patentability by Rule 23d.

Although, somatic gene therapy is a very powerful technique for the future, it is still confronted with many technical problems. As a result, there is no case law yet in Europe, at least not at the level of the Board of Appeal of the EPO.

Art. 52(4) EPC excluding methods for treatment of the human body may apply for gene therapy. There has to be distinguished between patents for in-vivo and ex-vivo gene therapy [55]. In-vivo gene therapy is based on genetically modified cells that permanently or transiently express a human gene within the body, e.g. IL-2, TNF, ADA+ or CF+. This is comparable to biotechnological processes for pharmaceutically active substances and is therefore not excluded from patentability. The same is true for ex-vivo gene therapy as long as the expressed protein and the process to produce it otherwise complies with patentability. Art. 52(4), however, becomes an insurmountable obstacle in case of ex-vivo gene therapy where a whole complex process including surgical removal of tissues, transfection and reintroduction of genetically modified cells is claimed.

This is in contrast to the US practise. Diagnostic methods carried out on humans are patentable in the US. However, enforcement of “medical activities” may be limited by 35 U.S.C. §287(c). There are a few exceptions to the limitation of enforcement based on 35 U.S.C. §287. The use of a patented machine, manufacture, or composition of matter in violation of a patent or processes covered by biotechnology patents are still enforceable. Thus, gene therapy is not limited in the US.

## VII. Conclusions

The intension of this review is to give a broad overview on the legal and economic situation of patents in biotechnology. The selected cases represent two currently very important fields of biotech patents, namely DNA sequences and whole living organisms. The patents on Epo and the Oncomouse have in common that they were both litigated throughout their lifetime. The reasons for challenging them, however, were very different. On one hand, it is the economic value, on the other hand the public concerns. Both cases raised new questions concerning patentability and lead to landmark decisions. Today, it is accepted that DNA sequences and proteins are patentable if a function is known. Higher organisms are patentable; however in Europe under strict conditions only. The Oncomouse may be not the ideal case to demonstrate the importance of patents for whole living organisms. Genetically engineered agricultural plants are a better example for the importance of such patents because their world-wide impact is larger. Some considerations made by the EPO in the Oncomouse case may be adapted to patents for plants. The balancing act between possible benefits for human health and suffering of the genetically engineered animals is extendable to plants. For the latter, it is the positive effect of increasing the world-wide production of food which has to be balanced to possible and irreversible damages of the environment. Although this strategy of balancing is a starting point, conflicts will not be completely solved. The next challenging question will be how to weight positive and negative effects of an invention. This is a subjective matter.

Despite all political and ethical concerns, public debates and world-wide litigation, the importance of biotechnological research in general and of patents in particular is likely to further increase rather than decrease in future. The interest of most people to increase lifetime whatever the costs are, searches for new sources of nutrition for the expanding world-wide human population, but also the curiosity and motivation of scientists to find inventions on one hand and high investments in this field on the other hand, renders this branch of technology extremely lucrative, but also makes IP protection necessary.

I tried to give an overview on the current situation of patentability of biotechnological inventions without having the pretension to be complete. There are many more interesting issues on patents in this field. As there has been entered a new field with the application for the Oncomouse and Epo 20 years ago, there will be new challenges for patent protection in future due to the rapid development of biotechnological research. Europeans seem to be more critical what patents and biotechnological research in general concerns than Americans or

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Japanese. The EPC also contains more subtle regulations than the US Code and the JPL. A permanent dialog can certainly help to find fruitful solutions. Further milestone decisions may therefore rather be expected from Europe. On the other hand, the US is likely to be more industry-friendly which has a global impact on economy. The two forces are not mutually exclusive. To find a middle way between appropriate protection for the industry and regulation of ethically or environmentally delicate inventions will be a challenge for the future.

## VIII. References

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## **IX. Appendix**

### **European, US, Japanese and Canadian Statutes**

#### **European Patent Convention**

##### **Article 52: Patentable inventions**

(1) European patents shall be granted for any inventions which are susceptible of industrial application, which are new and which involve an inventive step.

(2) The following in particular shall not be regarded as inventions within the meaning of paragraph 1:

- (a) discoveries, scientific theories and mathematical methods;
- (b) aesthetic creations;
- (c) schemes, rules and methods for performing mental acts, playing games or doing business, and programs for computers;
- (d) presentations of information.

(3) The provisions of paragraph 2 shall exclude patentability of the subject-matter or activities referred to in that provision only to the extent to which a European patent application or European patent relates to such subject-matter or activities as such.

(4) Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application within the meaning of paragraph 1. This provision shall not apply to products, in particular substances or compositions, for use in any of these methods.

##### **Article 53: Exceptions to patentability**

European patents shall not be granted in respect of:

- (a) inventions the publication or exploitation of which would be contrary to "ordre public" or morality, provided that the exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States;
- (b) plant or animal varieties or essentially biological processes for the production of plants or animals; this provision does not apply to microbiological processes or the products thereof.

##### **Article 54: Novelty**

(1) An invention shall be considered to be new if it does not form part of the state of the art.

(2) The state of the art shall be held to comprise everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application.

(3) Additionally, the content of European patent applications as filed, of which the dates of filing are prior to the date referred to in paragraph 2 and which were published under Article 93 on or after that date, shall be considered as comprised in the state of the art.

(4) Paragraph 3 shall be applied only in so far as a Contracting State designated in respect of the later application, was also designated in respect of the earlier application as published.

(5) The provisions of paragraphs 1 to 4 shall not exclude the patentability of any substance or composition, comprised in the state of the art, for use in a method referred to in Article 52, paragraph 4, provided that its use for any method referred to in that paragraph is not comprised in the state of the art.

**Article 56: Inventive step**

An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art. If the state of the art also includes documents within the meaning of Article 54, paragraph 3, these documents are not to be considered in deciding whether there has been an inventive step.

**Article 57: Industrial application**

An invention shall be considered as susceptible of industrial application if it can be made or used in any kind of industry, including agriculture.

**Article 83: Disclosure of the invention**

The European patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

**Article 84: The claims**

The claims shall define the matter for which protection is sought. They shall be clear and concise and be supported by the description.

**Biotechnological inventions****Rule 23b: General and definitions**

(1) For European patent applications and patents concerning biotechnological inventions, the relevant provisions of the Convention shall be applied and interpreted in accordance with the provisions of this chapter. Directive 98/44/EC of 6 July 1998<sup>30</sup> on the legal protection of biotechnological inventions shall be used as a supplementary means of interpretation.

(2) "Biotechnological inventions" are inventions which concern a product consisting of or containing biological material or a process by means of which biological material is produced, processed or used.

(3) "Biological material" means any material containing genetic information and capable of reproducing itself or being reproduced in a biological system.

(4) "Plant variety" means any plant grouping within a single botanical taxon of the lowest known rank, which grouping, irrespective of whether the conditions for the grant of a plant variety right are fully met, can be:

- (a) defined by the expression of the characteristics that results from a given genotype or combination of genotypes,
- (b) distinguished from any other plant grouping by the expression of at least one of the said characteristics, and
- (c) considered as a unit with regard to its suitability for being propagated unchanged.

(5) A process for the production of plants or animals is essentially biological if it consists entirely of natural phenomena such as crossing or selection.

(6) "Microbiological process" means any process involving or performed upon or resulting in microbiological material.

**Rule 23c: Patentable biotechnological inventions**

Biotechnological inventions shall also be patentable if they concern:

- (a) biological material which is isolated from its natural environment or produced by means of a technical process even if it previously occurred in nature;
- (b) plants or animals if the technical feasibility of the invention is not confined to a particular plant or animal variety;
- (c) a microbiological or other technical process, or a product obtained by means of such a process other than a plant or animal variety.

**Rule 23d: Exceptions to patentability**

Under Article 53(a), European patents shall not be granted in respect of biotechnological inventions which, in particular, concern the following:

- (a) processes for cloning human beings;
- (b) processes for modifying the germ line genetic identity of human beings;
- (c) uses of human embryos for industrial or commercial purposes;
- (d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

**Rule 23e: The human body and its elements**

(1) The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions.

(2) An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.

(3) The industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application.

**Rule 28: Deposit of biological material**

(1) If an invention involves the use of or concerns biological material which is not available to the public and which cannot be described in the European patent application in such a manner as to enable the invention to be carried out by a person skilled in the art, the invention shall only be regarded as being disclosed as prescribed in Article 83 if:

- (a) a sample of the biological material has been deposited with a recognised depositary institution not later than the date of filing of the application;
- (b) the application as filed gives such relevant information as is available to the applicant on the characteristics of the biological material;
- (c) the depositary institution and the accession number of the deposited biological material are stated in the application, and
- (d) where the biological material has been deposited by a person other than the applicant, the name and address of the depositor are stated in the application and a document is submitted satisfying the European Patent Office that the latter has authorised the applicant to refer to the deposited biological material in the application and has given his unreserved and irrevocable consent to the deposited material being made available to the public in accordance with this Rule.

[...]

## 35 US Code

### § 101. - Inventions patentable

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title

### § 102. - Conditions for patentability; novelty and loss of right to patent

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or

(c) he has abandoned the invention, or

(d) the invention was first patented or caused to be patented, or was the subject of an inventor's certificate, by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this country on an application for patent or inventor's certificate filed more than twelve months before the filing of the application in the United States, or

(e) the invention was described in –

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a);<sup>[2]</sup> or

(f) he did not himself invent the subject matter sought to be patented, or

(g)

(1) during the course of an interference conducted under section 135 or section 291, another inventor involved therein establishes, to the extent permitted in section 104, that before such person's invention thereof the invention was made by such other inventor and not abandoned, suppressed, or concealed, or

(2) before such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it. In determining priority of invention under this subsection, there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other

### § 103. - Conditions for patentability; non-obvious subject matter

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

**(b)**

- (1) Notwithstanding subsection (a), and upon timely election by the applicant for patent to proceed under this subsection, a biotechnological process using or resulting in a composition of matter that is novel under section 102 and nonobvious under subsection (a) of this section shall be considered nonobvious if –
- (A) claims to the process and the composition of matter are contained in either the same application for patent or in separate applications having the same effective filing date; and
  - (B) the composition of matter, and the process at the time it was invented, were owned by the same person or subject to an obligation of assignment to the same person.
- (2) A patent issued on process under paragraph (1) –
- (A) shall also contain the claims to the composition of matter used in or made by that process, or
  - (B) shall, if such composition of matter is claimed in another patent, be set to expire on the same date as such other patent, notwithstanding section 154.
- (3) For purposes of paragraph (1), the term "biotechnological process" means –
- (A) a process of genetically altering or otherwise inducing a single- or multi-celled organism to –
    - (i) express an exogenous nucleotide sequence,
    - (ii) inhibit, eliminate, augment, or alter expression of an endogenous nucleotide sequence, or
    - (iii) express a specific physiological characteristic not naturally associated with said organism;
  - (B) cell fusion procedures yielding a cell line that expresses a specific protein, such as a monoclonal antibody; and
  - (C) a method of using a product produced by a process defined by subparagraph (A) or (B), or a combination of subparagraphs (A) and (B).

**(c)** Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person

**§ 112. - Specification**

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A claim may be written in independent or, if the nature of the case admits, in dependent or multiple dependent form.

Subject to the following paragraph, a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

A claim in multiple dependent form shall contain a reference, in the alternative only, to more than one claim previously set forth and then specify a further limitation of the subject matter claimed. A multiple dependent claim shall not serve as a basis for any other multiple dependent claim. A multiple dependent claim shall be construed to incorporate by reference all the limitations of the particular claim in relation to which it is being considered.

An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof

**§ 287. - Limitation on damages and other remedies; marking and notice****(c)**

- (1) With respect to a medical practitioner's performance of a medical activity that constitutes an infringement under section 271(a) or (b) of this title, the provisions of sections 281, 283, 284, and 285 of this title shall not apply against the medical practitioner or against a related health care entity with respect to such medical activity.
- (2) For the purposes of this subsection:
  - (A) the term "medical activity" means the performance of a medical or surgical procedure on a body, but shall not include
    - (i) the use of a patented machine, manufacture, or composition of matter in violation of such patent,
    - (ii) the practice of a patented use of a composition of matter in violation of such patent, or
    - (iii) the practice of a process in violation of a biotechnology patent.
  - (B) the term "medical practitioner" means any natural person who is licensed by a State to provide the medical activity described in subsection (c)(1) or who is acting under the direction of such person in the performance of the medical activity.
  - (C) the term "related health care entity" shall mean an entity with which a medical practitioner has a professional affiliation under which the medical practitioner performs the medical activity, including but not limited to a nursing home, hospital, university, medical school, health maintenance organization, group medical practice, or a medical clinic.
  - (D) the term "professional affiliation" shall mean staff privileges, medical staff membership, employment or contractual relationship, partnership or ownership interest, academic appointment, or other affiliation under which a medical practitioner provides the medical activity on behalf of, or in association with, the health care entity.
  - (E) the term "body" shall mean a human body, organ or cadaver, or a nonhuman animal used in medical research or instruction directly relating to the treatment of humans.
  - (F) the term "patented use of a composition of matter" does not include a claim for a method of performing a medical or surgical procedure on a body that recites the use of a composition of matter where the use of that composition of matter does not directly contribute to achievement of the objective of the claimed method.
  - (G) the term "State" shall mean any state or territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico.
- (3) This subsection does not apply to the activities of any person, or employee or agent of such person (regardless of whether such person is a tax exempt organization under section 501(c) of the Internal Revenue Code), who is engaged in the commercial development, manufacture, sale, importation, or distribution of a machine, manufacture, or composition of matter or the provision of pharmacy or clinical laboratory services (other than clinical laboratory services provided in a physician's office), where such activities are:
  - (A) directly related to the commercial development, manufacture, sale, importation, or distribution of a machine, manufacture, or composition of matter or the provision of pharmacy or clinical laboratory services (other than clinical laboratory services provided in a physician's office), and
  - (B) regulated under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Clinical Laboratories Improvement Act.
- (4) This subsection shall not apply to any patent issued based on an application the earliest effective filing date of which is prior to September 30, 1996

## Japanese Patent Law

### 29. Patentability of inventions

(1) Any person who has made an invention which is industrially applicable may obtain a patent therefor, except in the case of the following inventions:

(i) inventions which were publicly known in Japan or elsewhere prior to the filing of the patent application;  
(ii) inventions which were publicly worked in Japan or elsewhere prior to the filing of the patent application;  
(iii) inventions which were described in a distributed publication or made available to the public through electric telecommunication lines in Japan or elsewhere prior to the filing of the patent application.

(2) Where an invention could easily have been made, prior to the filing of the patent application, by a person with ordinary skill in the art to which the invention pertains, on the basis of an invention or inventions referred to in any of the paragraphs of Subsection (1), a patent shall not be granted for such an invention notwithstanding Subsection (1).

### 32. Unpatentable inventions

The inventions liable to contravene public order, morality or public health shall not be patented, notwithstanding Section 29.

### 36. Applications for patent

(4) The detailed explanation of the invention under the preceding Subsection (iii) shall state the invention, as provided for in an ordinance of the Ministry of Economy, Trade and Industry, in a manner sufficiently clear and complete for the invention to be carried out by a person having ordinary skill in the art to which the invention pertains.

### 69. Limits of patent right

(3) The effects of the patent right for inventions of medicines (namely, products used for the diagnosis, cure, medical treatment or prevention of human diseases - hereinafter referred to as "medicines" in this subsection) to be manufactured by mixing two or more medicines or for inventions of processes for manufacturing medicines by mixing two or more medicines shall not extend to acts of preparing medicines in accordance with the prescriptions of physicians or dentists or to medicines prepared in accordance with the prescriptions of physicians or dentists.

## Canadian Patent Act

### Definitions

2. In this Act, except as otherwise provided,

[...]

#### "invention"

"invention" means any new and useful art, process, machine, manufacture or composition of matter, or any new and useful improvement in any art, process, machine, manufacture or composition of matter;

[...]

## **Erythropoietin patents**

### **US 4'703'008 (filed by Kirin-Amgen on November 30, 1984)**

#### **DNA sequences encoding erythropoietin**

1. A purified and isolated DNA sequence encoding erythropoietin, said DNA sequence selected from the group consisting of:
  - (a) the DNA sequences set out in FIGS. 5 and 6 or their complementary strands; and
  - (b) DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (a).
7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.

### **EP 0'148'605 (filed by Kirin-Amgen on December 12, 1984)**

#### **Production of erythropoietin**

1. A DNA sequence for use in securing expression in a prokaryotic or eukaryotic host cell of a polypeptide product having at least part of the primary structural conformation of that of erythropoietin, to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and to increase hemoglobin synthesis or iron uptake, said DNA sequence selected from the group consisting of:
  - (a) the DNA sequence set out in Tables 5 and 6 or their complementary strands;
  - (b) DNA sequences which hybridize under stringent conditions to the protein coding regions of the DNA sequences defined in (a) or fragments thereof; and
  - (c) DNA sequences which, but for the degeneracy of the genetic code, would hybridize to the DNA sequences defined in (a) and (b).
3. A cDNA sequence according to Claim 1 or 2
19. A recombinant polypeptide having part or all of the primary structural conformation of human or monkey erythropoietin as set forth in table 6 or table 5 or any allelic variant or derivative thereof possessing the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and to increase hemoglobin synthesis or iron uptake and characterized by being the product of eukaryotic expression of an exogenous DNA sequence and which has higher molecular weight by SDS-PAGE than erythropoietin isolated from urinary sources.
26. A polypeptide product of the expression in a eucaryotic host cell of a DNA sequence according to any of Claims 1, 2, 3, 5, 6 and 7"
50. A process for the production of a polypeptide having part or all of the primary structural conformation and one or more of the biological properties of naturally-occurring erythropoietin, said process comprising: growing, under suitable nutrient conditions, procaryotic or eucaryotic host cells transformed or transfected with a DNA vector according to claim 37, and isolating desired polypeptide products of the expression of DNA sequences in said vector.

### **US 4'677'195 (filed by Genetics Institute on January 11, 1985)**

#### **Method for the purification of erythropoietin and erythropoietin compositions**

### **EP 0'209'539 (filed by Genetics Institute on November 27, 1985)**

#### **Homogeneous erythropoietin**

1. Homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least 160,000 IU per absorbance unit at 280 nanometers.

**US 5'621'080 (filed by Kirin-Amgen on June 06, 1995)****Production of erythropoietin**

1. An isolated erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6 and has glycosylation which differs from that of human urinary erythropoietin.
2. An isolated erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6 and is not isolated from human urine.

**WO9309222 (filed by Transkaryotic Therapies, Inc. on November 05, 1992)****Transfection of vertebrate cells e.g. by homologous recombination**

1. A transfected primary or secondary cell of vertebrate (e.g. mammalian) origin having stably integrated into its genome:
  - a) exogenous DNA which encodes a therapeutic product or is itself a therapeutic product and
  - b) DNA sequences, sufficient for expression of the exogenous DNA in the transfected primary or secondary cell, which are of non-retroviral origin, the primary or secondary cell being capable of expressing the therapeutic product.

## **Oncomouse patents**

### **US 4'736'866 (filed by President and Fellows of Harvard College on June 22, 1984)**

#### **Transgenic non-human mammals**

1. A transgenic non-human mammal all of whose germ cells and somatic cells contain a recombinant activated oncogene sequence introduced into said mammal, or an ancestor of said mammal, at an embryonic stage.

### **EP 0'169'672 B1 (filed by President and Fellows of Harvard College on June 24, 1985)**

#### **Method for producing transgenic animals**

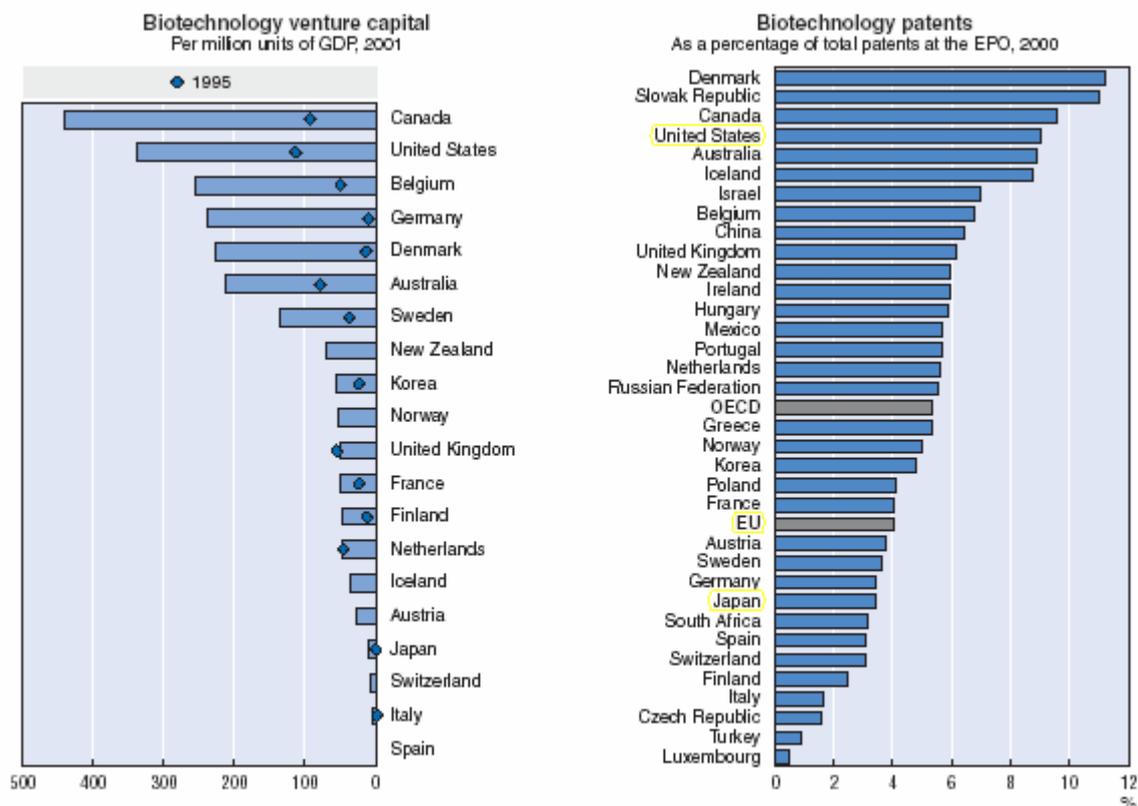
1. A method for producing a transgenic non-human mammalian animal having an increased probability of developing neoplasms, said method comprising chromosomally incorporating an activated oncogene sequence into the genome of non-human mammalian animal.  
(This claim has been restricted to rodents in opposition and to mice in appeal procedures, respectively.)
17. A transgenic non-human mammalian animal whose germ cells and somatic cells contain an activated oncogene sequence introduced into said animal, or an ancestor of said animal, at a stage no later than the 8-cell stage, said oncogene optionally being further defined according to any one of Claims 3 to 10.

### **JP 61'081743 (filed by President and Fellows of Harvard College on June 21, 1985)**

#### **Gene-transferred animal**

1. A gene-transferred non-human mature nucleus animal of which the embryonic cells and the somatic cells are characterized by having an activated tumor gene array, which was introduced into the animal or the ancestor of this animal in the embryo stage.  
(English translation by Saeko Ishihara and Daniel Citterio)

Figure 1. Investment and number of patents

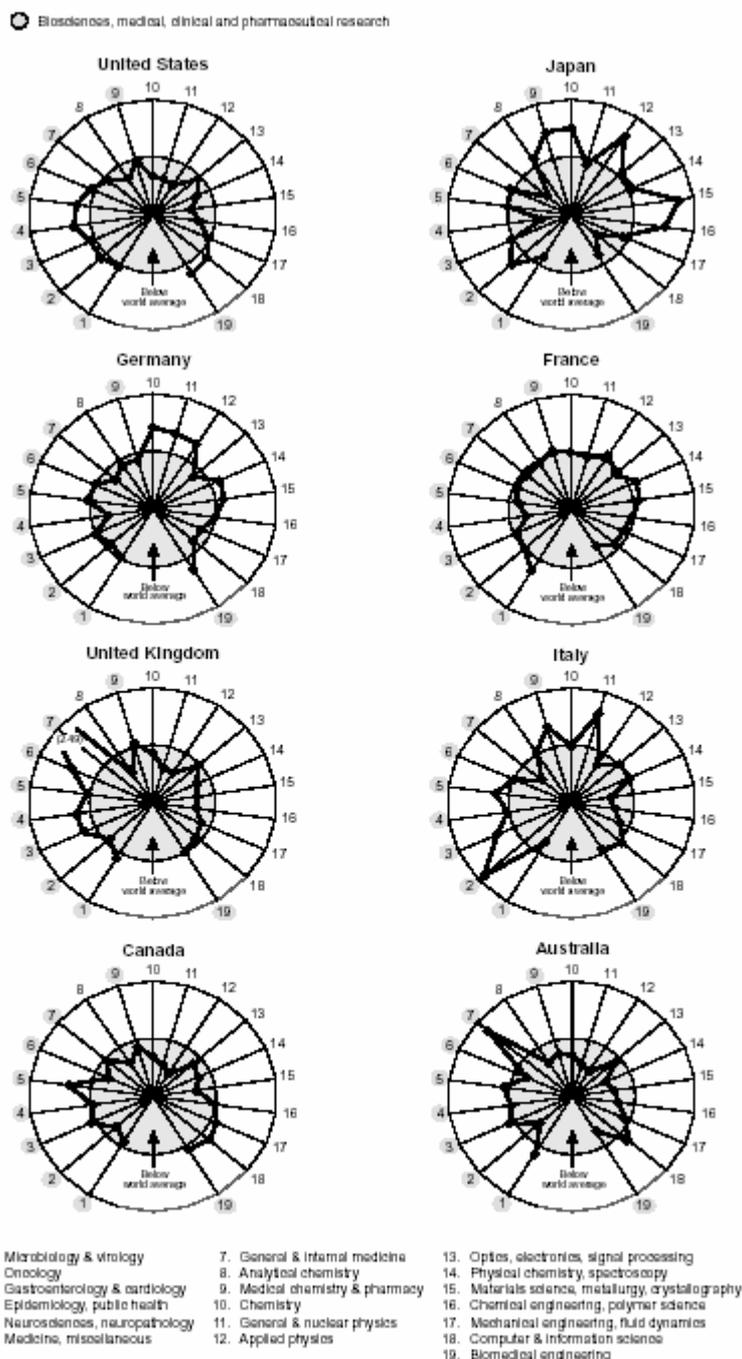


Source: OECD, Venture Capital and Patent databases, 2003.

There is a strong correlation between investment, research strength and number of patents. Canada and the US are the countries in which the largest shares of venture capital go to biotechnology.

The US has a leading position on the international biotechnology market, and the ratio of biotechnology patents to total patents is far higher in the US than in the European Union and Japan. However, Denmark has the highest such ratio, followed by the Slovak Republic and Canada.

**Figure 2. National profiles of relative scientific specialisation**



Source: OECD, Industry-Science Relationships: Interim Report, Paris 2000, Figure 7, page 19. Based on OST special tabulations of data from the Institute for Scientific Information.

Categories one through seven, nine and nineteen (shaded) are in the health, pharmaceutical and biomedical engineering fields. In those fields where the country has a better than average publication performance, the line is outside of the grey shaded circle, in those cases where it is below average, it is inside the circle. Each country analysed has an above average strength in at least one health/bio-medical area. The United Kingdom was the strongest across all the health/bio-medical fields, although Italy and to a lesser extent the United States were strong as well. Japan was well below average in a few of the fields. As for biomedical engineering, which is the field with some of the strongest links to biotechnology, the United States and Germany were above average while Japan, France, and Australia were below.

