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Original Article

Changing cells: An analysis of the concept of plasticity in the context of cellular differentiation

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Abstract This paper analyses the changing conceptualisation of cellular differentiation during the twentieth century. This involved a move away from a view of this process as irreversible to an understanding of it as contingent. We examine the import of this shift for the transformation of stem cell biology, including the therapeutic promise attributed to this field, and how it came to challenge historical conceptions of both the cell and stem cell. We take as our starting point the 2012 Nobel Prize for Physiology and Medicine awarded jointly to John Gurdon and Shinya Yamanaka. In the view of the Nobel Committee, their work delineates a paradigm shift in the understanding of cellular differentiation, one that incorporates the concept of 'plasticity'. We explore the emergence, uses and meanings of this concept within this specific biological context, examining and emphasising its role as an epistemological tool. In this setting, 'plasticity' was introduced by cell biologist Helen Blau in the course of research undertaken in the 1980s into the genetics of cell differentiation. We argue that Blau's experimental and theoretical contributions were seminal to a reconceptualisation of this process and provide a crucial link between the work of Gurdon and Yamanaka. Overall, the paper highlights the contested process of conceptual change within the biomedical sciences. It also draws attention to the dynamic and reciprocal relationship between conceptual and technical change, exemplified here in the changing conceptions of cell differentiation following from the analysis of gene expression using new cell fusion and cloning techniques. More broadly, the paper also affords a window onto the shifting priorities, goals and values within late twentieth-century biomedical research.
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Introduction

In October 2012, the Nobel Prize for Physiology or Medicine was awarded to John B. Gurdon and Shinya Yamanaka for research carried out, respectively, in the 1960s and in the opening years of the twenty-first century for, as the Nobel Committee put it, "their discovery that mature cells can be reprogrammed to become pluripotent. This represents a paradigm shift in our understanding of cellular differentiation and of the plasticity of the differentiated state".[1] This Nobel is notable in that the research that it recognises was not only separated by several decades but was also animated by very different questions, took place in very different laboratory and disciplinary contexts, and was oriented to different goals. Gurdon, a PhD student in zoology at Cambridge, was undertaking research into developmental biology whilst Yamanaka, a senior clinician-scientist at the University of Kyoto, was working within an international collaboration specifically geared to the development of stem cell therapies (Gurdon, 1962, 1967; Takahashi and Yamanaka, 2006; Takahashi *et al*, 2007). We consider the claim of a paradigm shift by the Nobel Committee, which they see as delineated by the work of Gurdon and Yamanaka, as an important recognition of changing conceptualisations of cellular differentiation. As we will show, this conceptual transformation involved a profound and often contested shift from an understanding of cell differentiation as irreversible, to a view of this process as more versatile and contingent than historically conceived. Gurdon's work in the 1960s, involving novel nuclear transplantation techniques (in hindsight, an early foray into vertebrate cloning) provided novel evidence that represented a fundamental challenge to the understanding of cellular differentiation as irreversible. More than four decades later, Yamanaka was able to manipulate the regulatory mechanisms controlling cell differentiation to 'reprogram' fully differentiated somatic cells (fibroblasts) to a stem cell state. Likening this genetically altered cell to the embryonic stem cell, Yamanaka and Takahashi called it the induced pluripotent stem (iPS) cell. The iPS cell affords further and compelling evidence against the irreversibility model. Venerated within science, the Nobel Prizes typically attract wide public attention: we see the 2012 Prize in Physiology or Medicine as a particularly salient moment in the development of cell biology. It provides the entry point for our investigation into changing understanding of cellular differentiation.

In tackling the long history of cell differentiation, our account is necessarily compressed. Our analytical approach reflects our principal concern with conceptual change, specifically the move away from an understanding of cell differentiation as a one-way, irreversible process. We also emphasise how this became closely bound up with a reconceptualisation of the cell, abolishing the long-held view of it as a fixed entity and towards an understanding of the cell as an actively maintained state. This model allows for the possibility that cell identity can change. In accounting for this profound transformation in the conception of both process and cell, we highlight in particular the work of British-born, California-based cell biologist Helen Blau whose technical, empirical and conceptual contributions we see as providing a decisive link between the work of Gurdon and Yamanaka. For example, we argue that her development of an innovative cell fusion technique during the 1980s geared to

1 http://www.nobelprize.org/nobel_prizes/medicine/laureates/2012/advanced-medicineprize2012.pdfAccessed, August 2015.

the analysis of patterns of gene expression within the specialised somatic (muscle) cell rendered cellular differentiation newly explorable and 'do-able' in the laboratory. Blau's analysis of the genetic mechanisms underlying cellular differentiation in the muscle cell using this technique laid the foundations for a new and bold challenge to the irreversibility model, following up on Gurdon's early cloning work. But Blau is also important for our story because, in reporting these findings in 1985, she introduced the term 'plasticity' into cell biological research to conceptualise the novel understanding of cell differentiation and the possibility of changing cell identity that she was proposing (Blau *et al*, 1985). Blau went on in 1991 to argue that the fully differentiated cell represented an actively maintained state. That is to say, cell identity was continuously maintained or held in place by regulatory factors (Blau and Baltimore, 1991). This was a central plank in a novel conception of the cell, premised on the idea that cell identity was not fixed but, rather, was something that could change in response to specific signals. Here, the specialised cell did not represent a biological endpoint, but rather represented one of many possible cell identities – possibilities realised through the process of cell differentiation.

As one barometer of what, in science, is held to be important, the 2012 Nobel also acknowledges the significance of stem cell biology – a field not yet circumscribed in the 1960s, but which by the opening years of the twenty-first century occupied the vanguard of biomedical research. As we show, this shift was tightly bound up with the idea of 'stem cell plasticity'. Used in 1985 by Blau and colleagues to describe a particular set of genetic events and effects in the muscle cell, we explore how the meaning of the concept of plasticity broadened as scientists used it to think and talk about an expanding array of newly observed cellular differentiation phenomena in stem cells. We argue that for scientists, the appeal of the concept of plasticity lay in its usefulness as a means to articulate important changes in the understanding of cell differentiation, but also permitted them to convey the clinical potential of both process and cell.

Although the emerging scientific understanding of cell differentiation was uncertain and contested, the 'promissory' potential of stem cells was very important within a research culture that emphasised application and utility (Brown and Kraft, 2006). The changing context of late twentieth-century biomedical research, where ever-greater emphasis was placed on translational research, one feature of which was increasing links with commercial actors, forms another analytical strand within the paper (Kraft, 2013). We see what might be called the 'translational imperative' as one manifestation of a policy-driven culture that privileges and prioritises biomedical research which delivers, or promises to deliver, outcomes – drugs, devices, techniques, practices – that are useful in the clinic and/or have commercial potential. We argue that this became an important driver for growing interest in the science of cell differentiation. We emphasise too that changing conceptualisations of this process have been decisive in the emergence of a new kind of stem cell science, one that in the last 15 years or so has formed the basis for the new therapeutic paradigm of Regenerative Medicine (e.g. Pattison, 2005; Prescott and Polak, 2011; Harvey, 2012).

Following a brief discussion of methods, including an outline of our analytical framework, the paper is organised into four parts. It begins with a discussion of cellular differentiation as a central and multifaceted problem within biological research during the twentieth century, paying attention to how the process first came to be understood as 'irreversible' and to the ambiguities surrounding its meaning. This provides a context for

the early cloning experiments by John B. Gurdon, which provided critical evidence against irreversibility. We then consider how cellular differentiation came to be understood in molecular and genetics-based terms. Here, we emphasise the technical, empirical and conceptual contributions of Blau and colleagues, whose work in the muscle cell led them to a bold reconceptualisation of both cell differentiation and the somatic cell. In the third section, we consider developments in the 1990s, most prominently the cloning of the sheep Dolly in 1997, and reports of transdifferentiation in somatic stem cells, a phenomenon encapsulated in the arresting phrase "turning blood into brain", that rendered the irreversibility hypothesis increasingly untenable (Bjornson *et al*, 1999). We then discuss how the concept of 'plasticity' gained currency in the context of cell differentiation, and examine its use and meanings, and the work that it does. The paper concludes with a brief consideration of the iPS cell engineered by Yamanaka and colleagues in 2006. More broadly, we situate these developments within the changing context of late twentieth-century biomedicine, especially the growing emphasis on research geared to clinical utility and commercial goals, manifest in the emergence and prioritisation of 'translational' research.

Methods and Analytical Framework

This paper can be considered as a contribution to the history of biology. It begins with an outline sketch of the historical development of cell differentiation as a scientific field of enquiry. A key element of our methodology includes close analysis of the relevant scientific literature, past and present. Placing Gurdon and Yamanaka in historical context raises an important point about the way in which the award of a Nobel Prize frames disciplinary histories in a particular way that can overlook crucial contributions to a field – to which numerous past controversies testify. Our historical approach enables us to see more clearly the importance of Helen Blau's technical and conceptual contributions. Our interest in Blau's work predates the 2012 Nobel: we came across her experiments and ideas in 2008 in the course of research into the development of stem cell biology. In the wake of the Nobel, however, it seems apposite and timely to highlight her place in the disciplinary history of cell differentiation. That said, our analysis also touches upon work by others that has likewise been important in building scientific understanding of cell differentiation.

Our approach combines this historical perspective with theoretical insights from within philosophically oriented scholarship that has examined the formation, role and influence of concepts within the biological sciences. Here, we draw on the work of Canguilhem, Fleck, Rheinberger, Müller-Wille and others to develop a framework for analysing the changing conception of cell differentiation, focussing on the relationship between empirical advance and conceptual change. Following George Canguilhem, we consider the analysis of concepts as having primacy in the history of science (Canguilhem, 1983; 2008). In a reconsideration of Canguilhem's work in 1998, Nicholas Rose proposed that "It is not so much a question what a word or even a concept 'means', – life, organism, gene, cell, reflex, reaction (…) – but of the way it functions in connection with other things, what it makes possible, the surfaces, networks and circuits around which it flows, the affects and passions that it mobilizes and

through which it mobilizes" (Rose, 1998, p. 167). This emphasis on the capacity of biological concepts to guide and organise research in very different theoretical and empirical contexts has informed our thinking about a theoretical framework within which to analyse the emergence, role and uses of the concept of plasticity within the context of cell differentiation. We have found Staffan Müller-Wille and Hans-Jörg Rheinberger's analysis of the meaning and changing conceptualisation of the gene during the twentieth century especially useful. They have argued that the concept of the gene has been empirically productive exactly because it has not been unambiguously defined (Mueller-Wille and Rheinberger, 2009, p. 11). Adopting their epistemological perspective, we consider that like the gene, plasticity is working to animate and foster research in different biological settings precisely because it remains a "concept in flux" and because every effort to conceptualise plasticity has prompted further questions about it (Mueller-Wille and Rheinberger, 2009, p. 135). As Rheinberger and colleagues later put it: "any empirically proceeding science is basically advancing through the construction of successful, but always partial models" (Rheinberger *et al*, 2015). Accordingly, we also see plasticity as exemplifying their point that the persistence of a biological concept is foremost a reflection of its utility as an epistemological tool rather than a reflection of its ontological value: "Whether and how long these models will continue to be gene-based, remains an open question. Any answers to that question will be contingent on future research results, not on an ontology of life" (Rheinberger *et al*, 2015).

In some respects, we also see 'plasticity' as resonating with Ilana Löwy's category of the "imprecise" term, especially in the sense of how within biomedical research, these can fulfil an important "heuristic role in the construction of new scientific knowledge" and facilitate conversations across disciplinary boundaries (Löwy, 1992, p. 373). Plasticity travelled readily within and between research labs and research contexts because of its ambiguity and multiplicity. Functioning too as an 'epistemological tool', it also created a framework within which empirical findings and ideas about cell differentiation could be shared and discussed, and, not infrequently, contested.

Our third analytical strand concerns the links between the conceptual shifts gathered together under the rubric of 'plasticity' and the emergence of Regenerative Medicine and a commercial stem cell sector. Specifically, we see these developments as bound up with a research context in which funding was increasingly channelled towards projects which promised clinical or patient benefits, and/or commercial potential, manifest in an emphasis on translational research. Here Jean-Paul Gaudillière's idea of a "work style", proposed as a contemporary counterpart of Ludwig Fleck's *Denkstil,* and which serves as a "reminder that science involves material action which has strong links with industrial production", is useful in thinking about the way in which commercial links were encouraged and strengthened by the translational turn within biomedical research (Gaudillière, 2004, p. 542). In considering these dynamics, we draw upon the social sciences literature, for example, the work of Paul Rabinow, Nik Brown, Catherine Waldby, which has examined the emergence and implications of the changing culture, values and priorities of life science research in the genomic and post-genomic settings.

In combining history and philosophy of biology with sociologically oriented insights, we hope to account for and offer a new explanation of the rapid expansion of stem cell biology in the late twentieth century. It also enables us to identify some of the contingencies and

contestations surrounding the novel and still emerging conceptualisations of cell differentiation which have fuelled this expansion, and which underpin the therapeutic and commercial promise of stem cell therapies.

Cellular Differentiation: Irreversibility and Early Challenges to This Model

Received biological understanding proposes that in higher organisms all cells come into existence unspecialised, and that in order to fulfil a particular physiological role, each cell undergoes a process during which it acquires a particular set of morphological and functional characteristics (Bloom, 1937). That is to say, it becomes differentiated, taking on a discernible cellular identity that reflects its specialised role in the organism. Variations in differentiation pathways are thought to account for the great range of specialised cell types. Differentiation is considered central to embryological development, but is also understood as an essential part of life-long physiological processes that involve cell renewal, for example, the routine replenishment of the different types of cell found within the blood system. It is also considered to form a central element of the organism's response to injury, in the course of various healing and regenerative processes. Seen as a fundamental biological process of relevance across a wide range of biological fields, cellular differentiation was the subject of a great deal of research throughout the twentieth century. The dominant hypothesis, formulated principally within embryological research, proposed differentiation to proceed in one direction and to be irreversible (See, for example, Wilson, 1906; 1925; Weiss, 1973). Highly influential subsequently was Conrad Waddington's concept of the epigenetic landscape which likened differentiation to the course a ball takes, as it rolls downhill, caught in a groove and following a path shaped by valleys: as the process proceeds, so the possibilities for changing direction become increasingly restricted (Waddington, 1940; Yamanaka and Blau, 2010).

The irreversibility hypothesis travelled beyond its founding context within embryology and in models of organismic development to shape understanding of cellular differentiation in the somatic setting. This influence was felt first and foremost in models of blood cell formation as, in the early decades of the twentieth century, the blood system – now recognised to be a cell renewal system – became a key site for studying cell formation (Sabin, 1928; Doan, 1939). Conceptualised as a process that moved in one direction and involved an orderly sequence of steps that result in increasing biological complexity, cellular differentiation here was understood – or rather assumed – to entail changes in the cell that restricted or excluded future possibilities. This model posits that at some point in the course of becoming specialised, the cell becomes 'committed' to becoming a particular kind of cell and specialised for a particular function, for example, a red blood cell or a muscle cell, at which point its 'fate' and therefore its identity are sealed. The conception of the fully differentiated cell as a stable entity with a fixed identity arose as one corollary of the 'directionality' embedded within the dominant model of cell differentiation. The 'branching tree' model of blood cell formation, embodied and powerfully reproduced the understanding of cell differentiation as a one-way, irreversible process which results in cells with specialised functions and fixed identities (Wintrobe, 1942).

Over time, wide use of terms such as cell 'commitment' and 'fate' had the powerful effect of obscuring the tentative nature of the model they described. Although it is tempting to say that 'irreversibility' assumed the status of what historians of science, following Fleck and Kuhn, call a dominant thought-style or paradigm, we step back from doing so because this hypothesis was acknowledged to be unproven and did not go unquestioned (Fleck, 1935, 1979; Kuhn, 1962). In 1937, for example, leading American haematologist William Bloom reflected that "practically all of the definitions of 'differentiation' convey the idea of a progressive specialization in form and function of the cells of a developing organism, but disregard their potentialities for further development" (Bloom, 1937, p. 591). Bloom perceived that the irreversibility model might not explain fully a cell's "potentiality" and also the possibility that cell identity was not fixed. As he put it, "Before we can say that a cell is differentiated in a given direction or at a particular level on the basis of its structure and function, we must ascertain through experiment whether it has lost the ability to follow other lines of development" (Bloom, 1937, p. 591).

The conceptualisation of cellular differentiation as irreversible remained dominant even as the empirical evidence remained inconclusive and was often contradictory. Advances in technique that followed the Second World War, notably radioisotope 'tracer' analysis, autoradiography and enhanced methods of tissue culture, provided new and powerful ways to investigate the dynamics of cell proliferation (Creager, 2002; Landecker, 2007; Wilson, 2011). By contrast, cellular differentiation continued to prove much less amenable to laboratory study. In the 1960s, this process remained as compelling as it was beguiling. For embryologists Michail Fischberg and Antonie Blackler, writing in *Scientific American* in 1961, it remained a "complex riddle", one that "yields its secrets most unwillingly" (Fischberg and Blackler, 1961, p. 124). Six years later, leading British leukaemia specialist Alexander Haddow, whose interest in differentiation reflected growing recognition of cancer as a disease of aberrant cell proliferation and differentiation, lamented that it was "still a great mystery" (Haddow, 1967, p. 1).

The key means for tackling cell differentiation was an experimental approach developed in the early 1950s by Robert Briggs and Thomas King working with the American frog, *Rana pipiens*. This involved the transplantation of nuclei from different types of cell, including differentiated and undifferentiated, into enucleated oocytes (Briggs and King, 1952). The characteristics of any ensuing development and the extent of differentiation were understood to "reveal the character of the transplanted nucleus" and hence its capacity to direct early development (Briggs and King, 1952, p. 456). Briggs and King, by this time respected and influential figures, interpreted the results of their experiments, which included impaired, partial or the total absence of development post-nuclear transfer, as supportive of the irreversibility of differentiation (King and Briggs, 1955). However, their findings and the irreversibility hypothesis were challenged in the 1960s by British zoologist John B. Gurdon based on his results in a similar experiment carried out in the South African clawed frog (*Xenopus laevis)* (Gurdon, 1962, 1967). Gurdon reported that in this animal model, nuclear transplantation – the term cloning was not yet current – resulted in the development of normal frogs. This observation led him to propose that genes were neither lost nor permanently inactivated in the course of cellular differentiation. For Gurdon, this indicated that the developmental capacity of the nucleus in the differentiated cell seemed, under the conditions of his experiment, to be greater than that permitted by the prevailing model of

irreversibility. His challenge came in a bold, carefully worded conclusion that "(…) the differentiation of a cell cannot be dependent upon the incapacity of its nucleus to give rise to other types of differentiated cells" (Gurdon, 1962, p. 638). Gurdon was questioning the assumption of genetic loss or permanent inactivation underlying the irreversibility model and asking whether even the differentiated cell might retain the capacity to acquire a different functional state, i.e. change its identity. His work and ideas met with scepticism: "After all, I was only a graduate student at the time and, as a graduate student, you shouldn't contest the results of famous people [Briggs and King] in the field. There were understandable reservations" (Gurdon, 2009). In spite of this challenge, irreversibility was consistently and successfully defended by the argument that if cell differentiation was reversible, this was restricted to lower vertebrates and not found in mammalian development. The irreversibility model remained in place even as it remained unproven and although, from time to time, was contested (Hay, 1968; Illmensee and Hoppe, 1981).

Differentiation: Parallel Research Worlds, Multiple Meanings

The manifold relevance of differentiation across biology made for a complex pattern of development within the evolving institutional and disciplinary framework of twentieth-century biological research. In an organic and pragmatic way, different strands of research took shape around particular aspects or instances of differentiation in various biological contexts. It became the subject of study within diverse research worlds, each animated by its own questions, priorities and aims, and with its own experimental approaches, animal models and literature. Within these parallel research worlds, cellular differentiation acquired multiple meanings: as early as 1937, William Bloom noted the "haziness" of the "concept 'differentiation'" (Bloom, 1937, p. 593). Thirty-five years later, leading developmental biologist Paul A. Weiss of the Rockefeller University in New York, lamented that 'differentiation' referred to a "broad and highly diversified complex of phenomena which arbitrarily bear that label" (Weiss, 1973, p. 3). From an analytical point of view, differentiation was functioning as an umbrella term encompassing processes taking place during cell formation in diverse tissues in a range of physiological contexts.

Weiss also voiced concerns about the lack of a coherent, coordinated approach to the science of cellular differentiation (Weiss, 1973; Brauckmann, 2004). Initiatives to foster cross-disciplinary exchange included symposia, edited books and, in 1973, the creation of a new journal, *Differentiation,* which sought to provide a forum for disseminating research, sharing technical know-how, and for discussing concepts, results and problems (Viza, 1973). To this end, leukaemia specialist Alexander Haddow and embryologist Conrad H. Waddington had organised an international symposium held in 1967 at the Ciba Foundation in London. This brought together leading geneticists, cell biologists and embryologists, including Weiss, and John Gurdon, to try to foster 'more effective collaboration' between those for whom cellular differentiation had relevance (Haddow, 1967, p. 2; de Reuck and Knight, 1967). Weiss was frustrated by the continuing ambiguities and the "dearth of factual information" about cell differentiation, and often reminded colleagues that the irreversibility model remained unproven (Weiss, 1973, p. 7). He was hopeful, however, that newly emerging techniques would lead to a "sharper dissection" of the process (Weiss, 1973, p. 9).

By this time, the potential clinical import of exercising control over these processes was recognised. Writing in 1975, the Manchester-based radiobiologist Laszlo Lajtha spoke of having "the capability to manipulate the system: proliferation and differentiation control in the patient's interest" (Lajtha, 1975, p. 533). In different ways, Weiss and Lajtha were anticipating developments that would soon transform the biological sciences generally and research into cellular differentiation in particular.

Important here was the growing dominance of molecular biology and the 'biotech revolution' of the 1970s which brought a novel toolbox of powerful techniques for analysing the genetic aspects of cellular life (Hopkins *et al*, 2007). The rise of molecular biology with its emphasis on technique, its focus on macro-molecules generally and its privileging of the gene and DNA in particular, was accompanied by an increasingly reductionist view of the cell (Kay, 1996; Brenner, 1979). Evelyn Fox Keller has defined molecular biology in terms of three conceptual shifts: the relocation of life into the gene, the redefinition of life into the genetic code and the recasting of the goals of biological science towards the "effective mastery over the processes of making and remaking life" (Fox Keller, 1990). The new techniques for manipulating DNA and genetic mechanisms provided the practical means for the "mastery" envisaged by Fox Keller.[2] The growing repertoire of techniques for the analysis of gene expression and intervening in the genetic make-up of the cell began also to be applied to cellular differentiation, providing for what Weiss had called the "sharper dissection" of this process. In the forefront of such approaches stood Helen Blau.

The Blau Lab: The Genetics of Cell Differentiation – New Evidence Against Irreversibility

On graduating from the University of York in Britain, Helen Blau moved to the U.S., completing doctoral work at Harvard before moving to a postdoctoral position in San Francisco, staying on the west coast to study molecular pharmacology at Stanford. In the mid-1980s, and taking advantage of the relative freedom she enjoyed as an outsider – being junior, female and British – Blau set about tackling the problem of cell differentiation. For Blau, the timing was propitious in that she perceived an intellectual and technical environment that offered novel opportunities to characterise the genetic mechanisms underlying this process. As she later recalled, "I wanted to test whether cells are really terminally differentiated (…) At the time, the prevailing dogma was that once cells became differentiated, that the pattern of gene expression was essentially irreversible. I wanted to challenge that" (Blau, 2002). Blau's interest in cellular differentiation was sparked by the work of both Paul Weiss and John B. Gurdon. As she recalled, Gurdon's "bold interpretation" of his nuclear transfer experiments in the 1960s provided a "powerful spur" to thinking about the irreversibility question, whilst Weiss's "tinkering around with gene expression" in the context of cell differentiation in the early 1980s inspired her own

2 These changes were not universally welcomed. For a perhaps jaundiced but interesting criticism of the rise and growing power of molecular biology within research and within universities, see Wilson (1994, chapter 7). The seemingly inexorable rise of molecularisation and geneticisation as *the* approach to the biological sciences was also linked to the commercialisation of the life sciences. For one interpretation of this dynamic, see Wright (1986).

genetics-based approach to analysing this process (Blau, 2002). In setting about this work, Blau chose to focus on the fully differentiated somatic cell, specifically the (mammalian) muscle cell.

In 1983, Blau and her colleagues reported their development of a novel in vitro experimental system, using a cell fusion method to generate heterokaryons, which offered a means to track gene activation, gene silencing and gene reactivation in the muscle cell during cell differentiation (Blau *et al*, 1983).[3] This paper also reported new evidence for the reactivation of previously silent genes in mammalian cells (Yamanaka and Blau, 2010). The cell fusion/heterokaryon technique afforded a window onto the very early stages of differentiation, from 'commitment' through the 'maturation' process. At the same time, it rendered the relationship between genotype and phenotype newly open to investigation and intervention, providing the means for analysing the genetic mechanisms involved in the generation and the maintenance of cellular phenotypes. Their findings using this innovative system suggested that the differentiated state of specialised somatic cells (here, the muscle cell) was not fixed. That is to say, the muscle cell, whilst stable, could not be considered as a fixed entity, but rather represented a differentiated state – one which, crucially, could be changed. This stood in direct opposition to the model of cell differentiation and to the historically embedded idea of the specialised cell. Accordingly, as she later recalled, this report met with scepticism: "This demonstration of nuclear reprogramming was at first met with incredulity, because the prevailing dogma held that the differentiated state of mammalian cells was fixed and irreversible" (Yamanaka and Blau, 2010, p. 707). Their work and ideas posed a new set of questions about how differentiation was regulated and how cell identity was controlled.

In 1985, Blau and colleagues restated their audacious reconceptualisation of process and cell in an article published in *Science* entitled "Plasticity of the differentiated state" (Blau *et al*, 1985). Reporting early investigations into the question of "how tissue-specific phenotypes arise and are maintained", they proposed the differentiated state to be continuously and "actively maintained" by regulatory factors operating at the genetic level. This 'state' was stable, but contingent in the sense that the cell retained within its genome the possibility of adopting other genotypic and, therefore, phenotypic options depending on its environment: as they put it, "gene expression by nuclei of highly specialized cells is remarkably plastic" (Blau *et al*, 1985, p. 759). Here, "plastic" was used to capture the way in which the nucleus of the highly differentiated (muscle) cell seemingly retained the capacity to both (re)activate and silence genes in ways that could – under certain conditions – change the identity of the cell. In this move, the concept of plasticity was introduced into the empirical framework, where it was used to convey the idea that cell fate was not irreversible and cell identity was not fixed. Thereby, plasticity gained novel and specific meaning in relation to cell differentiation.[4]

3 Technical note: This provided the means to identify which genes in the nucleus were silenced or activated, casting light on differentiation pathways, and allowing for the determination of the genetic events underlying this process. It also facilitated comparison of gene expression patterns in the muscle and non-muscle cell.

4 It is important to note that plasticity was/is used in other disciplinary and biological contexts: in the neurosciences, it was routinely used to refer to adaptive changes of different components of the nervous system in response to functional demands, and also to injury or disease. For other meanings/contexts, see Morange (2009) and Baranski and Peirson (2015).

Analytically, following Müller-Wille and Rheinberger, we propose that here plasticity can be understood as an epistemic object, its coming into being within a specific biological and research context being directly linked to a change in experimental practice where it was serving as a means to articulate an emerging model of cell differentiation (Rheinberger and Mueller-Wille, 2008, p. 3). The novel heterokaryon system devised in the Blau lab exemplifies the way in which new techniques can redefine what is 'do-able' experimentally and can change scientists' perceptions of a particular problem and, in turn, shape the kinds of questions that guide research. Her work likewise illustrates the entanglement between technical change and conceptual innovation, seen as one hallmark of the experimental life sciences during the twentieth century (e.g. Creager and Landecker, 2009, p. 705).

In 1991, in a paper written with Nobel Laureate David Baltimore, Blau elaborated on earlier work from within her lab and by others, proposing that the differentiated state was subject to "continuous regulation" and that the stability of this state – in effect, the identity of the cell – was held in place by an "active control mechanism" (Blau and Baltimore, 1991). 'Active control' involved an on-going interplay between internal and extrinsic factors bearing upon the cell, i.e. regulatory forces operating between the genome within the cell nucleus, the cell cytoplasm and the cellular environment. In effect, they were proposing a genetics-based explanation of Gurdon's (1962) argument that genes were 'neither lost nor permanently inactivated' during cell differentiation. Tackling the implication of 'genomic completeness' (as this was now called) they asked: What would be the advantage of keeping muscle genes accessible in the liver? This led them to posit the idea of "essential plasticity" (Blau and Baltimore, 1991, pp. 781–782). As used by them, the concept of plasticity articulated the idea that it was possible to mobilise or reactivate hitherto 'silent' genes resident within the genome of fully differentiated cells so as to change the identity of the cell. This posits the genome to have a functional mode and a responsive mode with change operationalised at the level of gene expression and manifest phenotypically, i.e. in the (changed) identity of the differentiated cell. "Essential plasticity" refers to the difference between what the cell *does* in the course of its physiological role and what it *can do* if called upon to do so, e.g. in response to changes in its environment. Answering their own question, Blau and Baltimore argued that this duality offers the advantage to the living cell of being able to respond to change, to adapt.

Cell differentiation was increasingly understood as a complex and dynamic choreography of genetic events, as "an orchestrated silencing of some genes and activation of others", involving a complex array of transcription factors and cascades of molecular events (Theise and Krause, 2002, p. 542). As the process that gives form to altered patterns of gene expression, differentiation articulates between the genome of the cell and cellular identity, it links genotype to phenotype, and is the mechanism for realising both actual and possible cell phenotypes (Morange, 2009, p. 495). Emerging from all of this was a fundamental challenge to the understanding of cellular differentiation as irreversible and the idea of cell identity as fixed. Returning to Waddington's epigenetic landscape, Blau now proposed that "The differentiated cell, instead of being caught in a groove, appears to require continuous control to prevent it from wandering into another valley" (Blau and Baltimore, 1991, p. 782).

The Blau group was always cognisant of how their reconceptualisation of cell differentiation opened up a new site for intervention, i.e. it became theoretically possible to reconfigure the relationship between genotype and phenotype, to change the differentiated

state – that is direct or control – cell fate and identity. As they noted in 1985, this had "practical importance in implementing genetic engineering and possibly gene therapy" (Blau *et al*, 1985, p. 758). Here, they were echoing Laszlo Lajtha's thoughts some 10 years earlier about manipulating cell formation, but with two key differences: first, the possibility of exercising control over cell specialisation and differentiation was now understood in genetic terms, i.e. the gene and gene expression. Second, the clinical vision now rested on genetic engineering and gene therapy techniques arising out of 1970s biotechnology and which, in this period, were seen as heralding a new therapeutic era.[5]

Meanwhile, the context and conditions in which biological research took place was beginning to change. Blau and Baltimore's (1991) paper came at the beginning of a decade in which the values and culture of the biomedical sciences underwent seismic change, much of which was closely bound up with the Human Genome Project (HGP) and its medical and therapeutic promise (Watson, 1990). For Daniel Kleinman, this marked a shift in which "(…) a broad commitment to sharing in the name of scientific advance has been largely displaced by a commitment to private property associated with the development of the biotechnology industry" (Kleinman, 2005). A new set of practices, techniques, values and priorities was reconfiguring the research culture of the life sciences, including the strengthening influence of commercial interests (Gaudillière, 2009; Hopkins *et al*, 2007; Smith-Hughes, 2001). The HGP at once symbolised and legitimated the power and authority of molecular biology, consolidated the dominance of genetics-based understandings of disease, and promised a new chapter in drug innovation. It exemplified the way in which therapeutic hopes and expectations had since the 1970s come to focus on DNA and the gene (Martin, 2001). Moreover, the much-vaunted therapeutic promise and commercial potential of the HGP proved persuasive within a western healthcare system confronting two unpalatable realities: an ageing demographic that brought with it a rising burden of chronic disease and a pharmaceutical industry grappling with an intensifying productivity crisis (Kraft, 2013).

One of the striking changes that became apparent as the HGP was underway was the increasing emphasis on deriving clinical utility from biomedical research. In short, the political economy of biomedical research became much more explicitly oriented to research that promised patient benefit and/or commercial success. In some quarters, this sparked concerns about how the evolving relations between biology and commerce were changing the values and goals of biomedical research – exemplified in the often-cited words of Paul Rabinow:

> More than ever before, the legitimacy of the life sciences now rests on claims to produce health … the bioscience community now runs the risk that merely producing truth will be insufficient to move the venture capitalists, patent offices, and science writers on whom the biosciences are increasingly dependent for their new found wealth (Rabinow, 1996, p. 137).

Catherine Waldby, Melinda Cooper and others have analysed such changes within the theoretical framework of the bioeconomy, tissue economies and the concept of "biovalue". Here, biological molecules, cells and tissues become endowed with value because of their clinical utility, real and/or promissory, such that in effect they form the currency within

5 In the 1980s the clinical promise of gene therapy was eliciting great excitement – but by the end of the 1990s this vision had floundered amid devastating side effects in patients.

novel networks which operate on the economic principles of capitalism (Waldby, 2002; Waldby and Mitchell, 2006; Cooper, 2008; Harvey, 2012).

By the late 1990s, however, it was clear that realising the founding visions of the HGP would take much longer than initially hoped (Rothman and Kraft, 2008). One response to this situation within senior biomedical and healthcare policy-making circles in the US and in Britain was a growing emphasis on what was called 'translation' which arose from a concern to improve the efficiency of the innovation process, not least to help speed findings from the HGP into the clinic (Kraft, 2013). Into the vacuum created by the delay in realising on the founding promise of the HGP, and in a research culture in the grip of the 'translational imperative', came a different vision of a therapeutic panacea, one centred on the new found 'plasticity' of stem cells, and packaged into what was called Regenerative Medicine (Maienschein *et al*, 2009).[6]

Stem Cells in the 1990s: Controlling Cell Differentiation, Constructing Clinical Visions

The idea that the stem cell had potential clinical application was not new. In the 1970s, Laszlo Lajtha had perceived the enormous clinical potential of being able to control differentiation in these cells (Lajtha, 1975, 1979). Two decades later, the rise to prominence of stem cell biology was contingent on a number of scientific and technical advances in the late 1990s that cast new light on and posed new questions of cell differentiation (Graf, 2011). Here, we highlight the birth in 1997 of the cloned sheep Dolly. We then consider a flurry of controversial papers around this time reporting that some somatic stem cells, in particular those understood to be resident in the blood system and in the brain, might have hitherto unrecognised capacities for differentiation. Referred to as transdifferentiation, dramatically rendered in the phrase "turning blood into brain", these reports added to the excitement about stem cell therapies (Bjornson *et al*, 1999). Transdifferentiation was framed as a form of 'stem cell plasticity', a move that added another meaning to this concept, one that referenced hitherto unknown differentiation capacities of somatic stem cells. We then discuss plasticity, the work that it does and how it acquired wider and multiple meanings as in the mid-late 1990s, as it was used in relation to novel differentiation phenomena in the somatic stem cell. For the purposes of our analysis, these developments have particular significance because of their importance for changing conceptions of cell differentiation and because they placed Blau's work in new light and prominence.

Dolly

Born in Edinburgh in 1997, Dolly was the first mammal to be successfully cloned using somatic cell nuclear transfer. Methodologically speaking, Dolly was not so remarkable, since she arose from a variation on the cloning technique used by Gurdon in 1962 (Wilmut *et al*, 1997). Conceptually, she was, however, extremely important: Dolly engendered a profound

6 There were other important strands in the development of regenerative medicine, not least arising out of the tradition of tissue engineering. See Lysaght and Hazlehurst (2004) and Morrison (2012).

shift in thinking about the process of cellular differentiation. For our analytical purposes, that is to say within the framework of plasticity and changing models of cellular differentiation, her impact cannot be overstated: she embodied biological events not deemed possible under the dominant (irreversible) model of cell differentiation (Franklin, 2007).

Here we 'flashback' briefly to the 1980s, to highlight how Gurdon's early challenge to the irreversibility hypothesis was continued by others, for example, in work in the mammal (mouse) by Illmensee and Hoppe (Illmensee and Hoppe, 1981). Their report on the cloning of mice supported Gurdon's ideas and likewise was viewed with scepticism. The response to their work casts light on the tenacity of the irreversibility hypothesis and reveals the power relations at work in the process of conceptual change in science. Leading developmental biologists James McGrath and Davor Solter refuted Illmensee and Hoppe's findings, moving to reinforce the orthodox position of irreversibility, arguing that "(…) the results presented here suggest that the cloning of mammals by simple nuclear transfer is biologically impossible" (McGrath and Solter, 1984, p. 1319). This staunch defence of irreversibility carried weight. As embryologist Anne McLaren noted, Solter was highly respected and influential, and on "authority principle" his stance deterred many from this line of research (McLaren, 2000).

Dolly, however, changed everything. Her birth marked a major turning point in the conceptualisation of cellular differentiation. She constituted a decisive proof against irreversibility and, at the same time, was irrefutable evidence for the changeability of cell fate and cell identity – evidence all the more powerful for its in vivo mammalian context. Dolly showed that under certain conditions the nucleus of a fully differentiated mammalian cell could revert to the earliest embryonic stage, that of the fertilised egg. Put differently, the differentiated (specialised) adult cell could be 'reset': cellular differentiation was not irreversible, but rather could seemingly be stopped and started at will. She was evidence for the principle of 'genomic completeness' within the genome of the highly specialised mammalian cell, i.e. for the conservation of biological possibilities and developmental pathways that could be called upon in response to changes in the cellular environment.

In one sense, Dolly was Blau's thesis writ large. She was living proof of the difference between what cells do, and what they can do; she embodied the principle of genomic completeness and was stunning evidence for the potential for cells to change. For Sarah Franklin, with Dolly, biology had been recast as *unconditional*:

> An implication of Wilmut's definition of control is that a shift has occurred from the idea of the biological as *subject to conditions*, which can be deciphered and understood, to a view of biology as *entirely unconditional*, and thus subject only to limits imposed upon it from the outside (Franklin, 2007, p. 33).

At the heart of Franklin's 'entirely unconditional' biology lay a view of cell differentiation as other than irreversible. Dolly also put the cell in new light: for Hannah Landecker she marked a "transformation of the cell as a technical object" (Landecker, 2007, p. 14). The cell was reconceived as potentially malleable in the sense that it was theoretically possible to change cell fate and identity by manipulating the process of cellular differentiation.

Dolly can also be seen as an extension of Gurdon's work, but she was the product of research undertaken within a very different research culture, one which privileged application. Work in Wilmut's lab was not primarily animated by a concern to elucidate

the fundamental science of cell differentiation *per se*. Rather, as Sarah Franklin has noted, it was oriented to application and to commercial goals in the agricultural and medical sectors (Franklin, 2007, p. 155). Dolly brought the possibility of manipulating cell differentiation into the mammalian setting and, crucially, closer to human medicine, even if this remained a remote prospect. In the application-oriented, translational ethos of late twentieth-century biomedical research, Dolly captured the imagination of biologists, policy-makers and, by way of intense media coverage, the public alike.[7] She also generated excitement within science, becoming immediately a powerful reference point in the vibrant research nexus now coalescing around changing understanding of cellular differentiation.

Dolly posed a fundamental question: "how 'fixed' is any cell within an organism?" (Bjorklund and Svendsen, 1999). She prompted – or rather demanded – a new engagement with cell differentiation, with the model of irreversibility and with the idea of the cell as having a fixed identity. As we have seen, these were questions long of interest to Helen Blau. Indeed, in David Baltimore's view, Dolly placed Blau's work and ideas in new light, serving as he put it, as a "real vindication of the importance of the work she'd been doing" (Blau, 2002).

Transdifferentiation: "Turning blood into brain" (Bjornson *et al*, 1999)

Beginning in the mid-1990s, fresh challenges to the irreversibility hypothesis also arose from research into different kinds of somatic stem cell, specifically those associated with the blood system and the brain. The blood stem cell and the neuronal stem cell became 'hotspots' in a rapidly forming research nexus looking anew at the characteristics of and capacities for cell differentiation in the tissue-specific somatic stem cell.

The idea of the blood stem cell arose following recognition in the late nineteenth century that blood was a dynamic system characterised by the constant replenishment of its constituent cells continually being produced in the blood forming tissues, especially the bone marrow (Wintrobe, 1980). The ultimate source of blood cell renewal was conceptualised as a distinctive kind of cell referred to since 1896 as the stem cell, a term first coined in this context by German physician and blood specialist Artur Pappenheim (Ramalho-Santos and Willenbring, 2007; Maehle, 2011). The model of cellular differentiation as a one-directional, irreversible process *demanded* a cellular starting point, i.e. the existence of a cell of origin, conceptualised since the 1890s as a discrete cellular entity endowed with unique powers of proliferation and differentiation (On the search for this cell, see Fagan, 2007; 2010). By the 1930s, the differentiation or developmental potential of this stem cell was defined by the range of its progeny, that is to say, by its perceived ability to give rise to all the different kinds of blood cell.[8] In technical terms, it was said to be multipotent, as well as tissue specific. Meanwhile, the twentieth century saw established a model of the mammalian brain as an intricate network of neuronal and non-neuronal cells tightly coupled to each other. In contrast

7 The in vitro cultivation of the human embryonic stem cell by the Thomson group in 1998 was also hugely important in the new prominence of stem cell biology (Thomson *et al*, 1998). This ignited hopes that this 'totipotent' cell might herald a new era of stem cell therapy – a vision soon stymied by ethical controversies about its sourcing and use, and by on-going technical and scientific difficulties.

8 A key element in this model proposed that the stem cell existed *qua* stem cell because it was protected from the signals and cues that initiate differentiation and set cells on a pathway towards specialised function and a specific identity.

to the blood system, the adult mammalian nervous system was understood to be a largely immutable network, the complexity of which was mainly established during development. Models of the mammalian brain did not involve neuronal regeneration. In striking contrast to the hugely dynamic blood system, neuronal cells were considered a stable population, not replenished, but diminishing in number with age (Rubin, 2009; Rees, 2016).

Within haematology and neurobiology, these models held until the mid-late 1990s when both came under fresh scrutiny. Within neurobiology at this time, a protracted and heated debate about adult neurogenesis was resolved in favour of a reconceptualisation of the mammalian brain, now recast as a regenerative organ harbouring specific neuronal stem cell niches. This stood in contrast to an earlier understanding of the brain that held it to be a largely static organ, lacking the capacity for neuronal renewal (Rubin, 2009; Rees, 2016). At the same time, the tissue-specific model of the blood stem cell was challenged by research suggesting that, in some circumstances, it could give rise to cells other than those of the blood system, i.e. that it was not tissue specific (e.g. Pereira *et al*, 1995; Ferrari *et al*, 1998; Gussoni *et al*, 1999; Lagasse *et al*, 2000; Theise *et al*, 2000). A further dramatic twist came in a report by Bjornson and colleagues suggesting that, under certain circumstances, adult neural stem cells could give rise to blood cells, as they concluded "Now the brain is making blood" (Bjornson *et al*, 1999). Meanwhile, work by Mezey and colleagues also indicated that haematopoietic cells could give rise to glial cells and neuronal cells (Eglitis and Mezey, 1997; Mezey *et al*, 2000). This phenomenon, referred to as transdifferentiation, was fiercely contested (Morrison, 2001).

These empirical observations of transdifferentiation were unexpected and challenged the model of the tissue-specific somatic stem cell. Some envisaged a "major paradigm shift" (Hoffman, 2002, p. 847). From the point of view of the central themes of this paper, the concept of plasticity was now being used to capture, articulate and talk about the newly identified differentiation capacities of stem cells. These findings were the subject of an especially fractious debate: within the research world concerned with the blood stem cell, some spoke of a "plasticity polemic" (e.g. Lemischka, 1999, 2002; Quesenberry *et al*, 2005). This was because conceptual change was tangled up with professional, disciplinary and institutional interests. As New York-based liver pathologist Neil Thiese noted, plasticity registered an "unravelling of the status quo" (Theise, 2010, pp. 529–530).

Theise was a key protagonist in the plasticity controversy. Together with Diane Krause, he argued that disciplinary tradition and the power of prevailing paradigms had powerfully shaped the questions guiding blood stem cell research which, in turn, set the parameters of what was known about this cell (Theise and Krause, 2002, p. 547). In short, the historical framing of the blood stem cell as tissue specific had narrowed the questions asked of it, shaping the contours within which it had been perceived and understood, and experimental approaches to it. In a sense, Theise was critiquing the tenacity and powerful influence of historically embedded ideas about cellular differentiation and the somatic stem cell. Linked to this, it is perhaps notable that reports that the marrow stem cell might give rise to liver, cardiac and brain cells arose *outside* the blood stem cell field (Lagasse *et al*, 2000; Theise *et al*, 2000). That is to say, the challenge to prevailing dogma came from those who, in Ludwig Fleck's terms, were not bound by the particular way of seeing, perceiving and understanding that characterises a particular research community (Fleck, 1935, 1979).

Reports of transdifferentiation lent momentum to the accelerating pace of research into stem cells and into cellular differentiation, both now endowed with new clinical significance. The

newly found differentiation potentials ascribed to stem cells collecting under the concept of 'plasticity' and Dolly, living proof of the principle of cellular reprogramming, were contribuing to a therapeutic vision in which stem cells were recast as the basis for a novel form of cell therapy centred on tissue regeneration. A powerful 'pull' factor, that of unmet clinical need, was also operating. Stem cell therapies were seen as particularly relevant to those incurable, degenerative diseases of middle and old age which, in the west, constituted an ever-growing proportion of the health burden and, from a business perspective, potentially lucrative markets. For example, the identification of adult neurogenesis in the human brain has been closely linked with projections of the very large medical market of prevalent neurological diseases, including the neurodegenerative and psychiatric disorders, for which cell-based therapies might offer new hopes of effective therapies (Rubin, 2009; Rees, 2016; Ruan *et al*, 2014; Martin, 2015).

For a time, *Dolly*, and reports of stem cell plasticity were enveloped in the hype and promissory potential surrounding new therapies that was characteristic of late twentieth century biomedicine – even as the science was contested, and clinical utility at best a distant prospect (Brown, 2003; Brown and Michael, 2003; Martin *et al*, 2006). An indication of the perception within science that a transformation was underway came with the announcement in 1999 by the influential US journal, *Science,* of stem cells as the "breakthrough of the year" (*Science*, 17.1, 1999; Brown, 2000). Certainly, by the turn of the century, cellular differentiation in both stem cells and in specialised (fully differentiated) cells was perceived differently. The irreversibility hypothesis appeared increasingly untenable. New questions were being asked amid gathering evidence that this process was seemingly more versatile and contingent than hitherto conceived. Looming large in all these conversations was the concept of plasticity.

Plasticity

Used initially in 1985 by Blau to refer specifically to the capacity for altered gene expression in the fully differentiated (muscle) cell, by the late 1990s, plasticity gained currency as a means to group together and talk about the range of hitherto unrecognised differentiation phenomena, including that of transdifferentiation, in the somatic stem cell. Here, it now came to the fore playing a crucial part in the rhetoric that repackaged the perceived clinical utility of stem cells into the new paradigm of Regenerative Medicine (Quesenberry *et al*, 2002). Plasticity was serving as a means to articulate both new science and its perceived potential uses. On the one hand, it retained what we see as its epistemological role within science as a means to conceptualise novel findings about cell differentiation and the changeability of cell identity. On the other hand, it was deployed by those wishing to develop stem cell therapies in ways that helped attract research funding and/or investment for commercial enterprises geared to this goal. The observation of veteran blood stem cell expert Ihor Lemischka that the suggested plasticity of somatic stem cells "may revolutionize the way we think about tissue transplantation therapies and regenerative medicine" affords some sense of how, in this setting, plasticity was immediately and emphatically coupled to a vision of clinical utility (Lemischka, 2002, p. 848).

In terms of the work that plasticity does, we would highlight the following areas where it was effective and highly productive. In the mid-1990s, it came to connote 'cutting edge'

science *and* therapeutic potential, helping to attract research funding and private investment into the stem cell field. For scientists, plasticity afforded a pithy means to communicate, or portray, the therapeutic promise of stem cells, and therefore the usefulness of their work, not least to funding bodies and policy-makers. Rapidly adopted in the scientific literature, plasticity was the subject of special issues in leading science journals, editorials and commentaries.[9] As a by-word for the science and clinical potential of cellular differentiation *and* stem cells, it became an engine for the spectacular growth of stem cell research – increasingly framed as stem cell biology. Journals provide one barometer or index of this effect. For example, as plasticity rose to dominate the research agenda, subscription and submission to *Stem Cells*, first published in 1981, increased markedly and its 'impact factor rating' soared; the journal's on-line readership, launched in 2000, rose from an initial 2000/week to over 80,000/week just 2 years later and by January 2007 stood at 120,000/week (Civin and Gewirtz, 2002; Solberg, 2002). Some scientists began to talk of plasticity as a 'field' emerging in its own right or as the basis for a 'new' stem cell biology (Theise, 2010; Quesenberry *et al*, 2002).

This coincided with the growing importance of stem cell therapies in national healthcare plans and strategies, the rising use of the term 'regenerative medicine' in policy discourse and an expanding commercial sector centred on stem cells (Franklin, 2001; Lysaght and Hazlehurst, 2004; Pattison, 2005; Martin *et al*, 2006). Meanwhile, the unique biological properties of stem cells present in umbilical cord blood, including their immunological naivety, formed the basis of a new business sector based on 'banking' these cells at birth because they might prove to be of use therapeutically later in the child's life (Brown and Kraft, 2006). Stem cells were taking their place within the history of biotechnology in the twentieth century and becoming part of the bioeconomy. In a sense, these developments added a further dimension to Hannah Landecker's point that the "contemporary cell" has become "an important economic entity, patentable and productive" (Landecker, 2007, p. 3). Commercial enterprises such as cord blood banks and a raft of clinical trials involving stem cells lent a new materiality to the perceived therapeutic potential of these cells, and brought this to public attention (Hauskeller, 2005; Rubin, 2009; Rees, 2016).

Underpinning this potential was what scientists called plasticity. Paradoxically, however, the meaning of plasticity remained unclear. Attempts to define it were typically couched in broad and vague terms, for example, in 2010 senior editors at *Nature* referred to plasticity as "the capacity of organisms or cells to alter their phenotype in responses to changes in their environment" (Skipper *et al*, 2010). In 2004, Helen Blau joined the conversation, proposing with colleague Jane Pomerantz, that plasticity meant simply "the ability to change or adapt", adding the caveat that as a "a descriptive term that relies on context", like others, they called too for its precise meaning always to be specified (Pomerantz and Blau, 2004; Lemischka, 2002; Theise, 2010). Following Mueller-Wille and Rheinberger, and Löwy, we see this ambiguity as key to understanding how and why 'plasticity' became one hallmark of the fast-moving science of stem cells. For all its fundamental 'slipperiness', and even as the science was contested, plasticity signalled a deep and profound shift in understanding of the process of cellular differentiation – in the context first of the fully differentiated cell (the

9 See Special Issues of leading journals dedicated to the plasticity theme including, for example *Current Opinion in Cell Biology* 16(6) (2004); *Experimental Hematology* 30 (2002); *Journal of Pathology* 197 (2002); *Reviews in Clinical and Experimental Hematology* 1 (2004).

work of the Blau laboratory since the early 1980s) and later, the tissue-specific stem cell (reports of transdifferentiation since the mid-1990s).

Blau's Plasticity Thesis Revisited: From Muscle Cell to Stem Cell

Watching the 'plasticity polemic' unfolding within stem cell biology was Helen Blau. Now a senior figure at Stanford, Blau recognised that her earlier reconceptualisation of cell differentiation within the somatic cell – her thesis about the plasticity of the differentiated state – was relevant to the arguments raging over transdifferentiation and stem cell plasticity. This literature tended not to cite her work. Partly, perhaps, this was because her work centred on the muscle cell – a realm of research far removed from stem cell biology. Also in play, perhaps, were the practices and habits of citation in scientific papers or, put differently, the way in which scientists "handle history in their publications" (Jablonka and Lamb, 2013, p. 564). Scientists tend to favour a particular set of work, which has the effect of defining what is important and establishing a pattern which, over time, builds a narrative about the development of the field. In short, this powerfully shapes disciplinary histories. The fundamental rethinking of cell differentiation occasioned by new empirical evidence about this process had the effect of forcing scientists to look beyond their own immediate intellectual milieu and to engage with cell differentiation from a different vantage point. 'Plasticity' brought diverse research worlds into new and closer connection: here, Helen Blau was quick off the mark. In 2001, together with colleagues Brazelton and Weimann, Blau imported her thesis of the "plasticity of the differentiated state" forged, as we have seen, in the context of the muscle cell, into the stem cell setting (Blau *et al*, 2001).

In this paper, entitled "The evolving concept of a stem cell: Entity or function?", Blau *et al*, noted that stem cell biology was in a "state of flux" amid challenges to some of the central tenets of stem cell biology (Blau *et al*, 2001, p. 829). As we have seen, Blau's work in the muscle cell had challenged the irreversibility model and the concept of cell identity as fixed. For her, reports of transdifferentiation, of "turning blood into brain", begged the question as to whether somatic stem cells might likewise exist in an actively maintained 'state'. Perhaps, like the muscle cell, the stem cell was not 'fixed', but instead retained within its genome the potential to detect and respond to changes in the "cellular neighborhood", with implications for its capacity for cell differentiation and for the nature/range of its progeny (Yamanaka and Blau, 2010, p. 704). Here was a novel theoretical explanation of transdifferentiation – one that required a profound reconceptualisation of the stem cell. More radically, and as the title of this paper inferred, perhaps the stem cell was not a distinct, discrete entity, but rather represented a stem cell 'state', expressing the property of "stem-ness".

Developing this line of reasoning, they proposed that "rather than referring to a discrete cellular entity, a stem cell most accurately refers to a biological function that can be induced in many distinct types of cells, even differentiated cells" (Blau *et al*, 2001, p. 829). Here, the stem cell was conceived as "more plastic and dynamic than previously thought", stem-ness was reframed as a biological property, and the cell manifesting this property was in a stem cell 'state'. Like the differentiated cell, such as the muscle cell, the adult somatic stem cell was not a discrete and fixed entity, but is "subject to change and most accurately reflects a regulatable function, rather than a discrete cellular entity" (Blau *et al*, 2001, p. 838). Here,

the stem cell state is actively maintained: at once, stable yet contingent, stem-ness, that is to say, the capacity for cell production, was now recast as a function associated with this state. Following from this, it was theoretically possible that any cell might, contingent on prevailing conditions, be able to enter into or adopt the 'state' of "stem-ness" – a term increasingly appearing in the literature (e.g. Zipori, 2004, 2005; Leychkis *et al*, 2009).

In her earlier work on the muscle cell, Blau's "plasticity of the differentiated state" thesis had engendered a reconceptualisation of the process of cell differentiation (as other than irreversible) and had called into question the idea that cell identity was fixed. This idea now posed a fundamental challenge to the 'tissue-specific' model of the stem cell. If, under certain conditions, for example, a change in environment, this cell was able to change the range of its progeny, then it possessed the capacity to reset its differentiation profile. Like Blau's muscle cell, the stem cell could perhaps best be understood as representing a 'state' rather than a fixed entity.

The concept of plasticity now encompassed differentiation phenomena in specialised (muscle) cells and somatic stem cells. This exemplifies the way in which plasticity conflates different instances of/capacities for change in different cellular and physiological contexts. These novel phenomena have been detected using newly available techniques, and/or as scientists looked "in places they never looked before" (Reyes and Verfaillie, 2004, p. 98). As discussed herein, plasticity came to connote all of the possibilities, in different cellular settings (muscle; stem), arising from an understanding of cellular differentiation as other than irreversible. The model of 'directionality' historically applied to cell differentiation – a consequence of the process having been studied first in a context of organismic development (embryology) – may not be the whole story. Thinking in terms of a change from 'irreversibility' to 'reversibility' is problematic because it connotes a linearity that fails to fully capture and articulate an understanding of cellular differentiation as contingent and versatile. The emerging model is less about directionality, and more about versatility and temporality, which combine to create a mechanism able to meet the changing and contingent needs of the organism for cell production.

But challenges to the irreversibility model also carry profound implications for the cell. A view of cell differentiation as contingent rather than irreversible destabilises historical conceptions of the cell and, potentially, collapses the distinctions that hitherto have defined cell categories. Thus, Blau's proposal of the (specialised) cell as an "actively maintained state" calls into question the historical model of the cell, a model that sets it apart from the stem cell. Meanwhile, the idea of stem cell plasticity calls into question the idea of the tissue-specific stem cell, the historical distinction drawn between it and other types of cell and, from this, its status as a special kind of cellular entity. These empirically driven conceptual developments thus call for a completely different framework for thinking about cellular differentiation and the nature of cell identity. As yet, this task remains in the making.

As we have seen, stem cell plasticity provided a further powerful spur to the idea that the process of cellular differentiation could be harnessed for clinical use, a vision in which the stem cell moved to the fore. As Blau and colleagues put it, "the ability of stem cells from multiple sources to regenerate diverse tissues greatly increases the flexibility and applicability of tissue regeneration strategies" (Blau *et al*, 2001, p. 836) This was both clinically compelling and commercially appealing. Research along such lines was by now being pursued in laboratories around the world using different kinds of cell and the diverse array of experimental techniques that now formed a routine means for analysing the genetic

mechanisms underlying cell differentiation. One such laboratory was that at the University of Kyoto in which Shinya Yamanaka was working.

Engineering Cellular Differentiation: From Specialised Cell, to Stem Cell, to iPS Cell

In Japan, Shinya Yamanaka and Kazutoshi Takahashi were part of an international research collaboration focused on developing the clinical potential of cellular differentiation and stem cell therapies. They were not alone: by the early twenty-first century, this was a richly endowed, 'cutting edge', highly competitive, global research field (Hauskeller and Weber, 2011). In 2006 and 2007, the Japanese group published two papers that registered another unexpected twist in the science of cellular differentiation. Working with both the human embryonic stem cell (hESC) and the human fibroblast, they reported the successful induction of a so-called pluripotent state in fully differentiated cells using what were now regarded as relatively simple genetic manipulation techniques (Takahashi and Yamanaka, 2006; Takahashi *et al*, 2007). This experiment showed that the introduction of a particular combination of just four transcription factors into the cellular milieu was sufficient to transform the basic 'state' of the differentiated cell (here, the adult human fibroblast), into that of the so-called induced 'pluripotent' stem (iPS) cell – with powers approximating those of the embryonic stem cell.[10] In an avowedly reductionist and methodologically very simple approach, Yamanaka and colleagues had changed the identity of the fully differentiated cell (fibroblast) to produce a cell with characteristics and powers historically attributed to embryonic stem cells.

Scientists have always 'tinkered' at the bench and, in a moment of serendipity, this was how Takahashi and Yamanaka created the iPS cell. That said, chance favours the prepared mind and the Japanese group could not have been other than alert to the on-going conceptual upheaval in the stem cell field and regarding the process of cell differentiation. They were also working in a resource rich setting geared to translational research and with the explicit goal of developing science and techniques that would be clinically useful and, ideally, commercially lucrative. In technical terms, the iPS cell provided a proof of principle that it was possible to engineer in somatic cells the 'state' of pluripotency, that is to say, the property of 'stem-ness'. The iPS cell rendered it theoretically possible to generate any of the many different cell types found in one organism. This was perceived to be a major step towards exercising precise control over cellular differentiation and to represent a 'seismic shift' in stem cell research (Holden and Vogel, 2008). Especially critical, in terms of potential clinical application, was the way in which iPS cells could be derived from the somatic cells of the individual organism and would share its highly specific immunological imprint. As a regenerative therapy or strategy, iPS cells provided a means to circumvent the immunological barrier and the serious clinical difficulties this would otherwise create – which had long bedevilled organ and bone marrow transplantation. As the Japanese team emphasised, "successful reprogramming of differentiated human somatic cells into a pluripotent state would allow the creation of patient and disease-specific stem cells" (Takahashi *et al*, 2007, p. 861). IPS cells therefore offered several important advantages over regenerative strategies

10 Specifically, OCT4, SOX2, KLF4 and c-MYC.

based on both the hESC and adult somatic stem cells, the development of which was, in any case, by this time stymied by a range of ethical, scientific, technical and political issues. As Gottweis and Minger put it:

> In short, iPS cell research shows promise for a broad range of stakeholders: for stem cell researchers, it is a scientific breakthrough that opens new avenues for regenerative medicine; for the principled opponents of hESC – research, iPS cells confirm what they have argued all the while, namely that adult stem cell research was the only way to go; and for policy-makers, iPS cells signify the end of an inconvenient political quarrel with religious fundamentalists and pro-life groups (Gottweis and Minger, 2008, p. 271).

IPS cells brought together the beguiling power of stem cells with the engineering ethos of genetics to harness the process of cellular differentiation in the quest to develop an economically fruitful *and* ethically appropriate means of treating disease (Rubin, 2008). Nevertheless, treatment strategies based on directing cell differentiation and controlling cell identity will likely raise another set of ethical, legal and societal implications which remain to be explored.

Within the framework of our analysis, the iPS cell represents an endpoint – one that in the wider context can only be provisional, since it represents an understanding of cell differentiation at a particular moment in time, one that is contingent on prior concepts and models and on the technical means to hand. Within biomedical research, the iPS cell constitutes a starting point for new investigations into cell differentiation, in which it will be both a research tool and a site of novel experimental practices that will likely yield further insights into this process that, in turn, will inform changing conceptualisations of it.

We have shown how, following its introduction into the field of cell biology in the mid-1980s, plasticity came to serve a powerful conceptual role in enabling a reconsideration of cell differentiation. It provided a framework within which researchers could conceive theoretical changes and interpret empirical evidence and, from this, advance a novel understanding of cellular differentiation first in somatic cells and then in stem cells. We have found it helpful to draw upon Müller-Wille and Rheinberger's work on the concept of the gene in analysing the epistemological role played by plasticity within cell biology, although there are important differences. In contrast to the gene which has a conceptual pedigree spanning the twentieth century and which took on a material reality within the realm of molecular biology, plasticity – insofar as the context explored here – has a much shorter history and references a process, rather than a material entity. That said, this process, or set of processes, called differentiation, is inextricably bound up with the nature of the cell. For us, on a conceptual level, the comparison between plasticity and gene is appropriate and legitimate because, like the gene, and as we have shown, plasticity functioned to both make possible and to frame "radical epistemological ruptures" (Rose, 1998, p. 159). Plasticity was associated with the emergence of a novel understanding of cell differentiation, now reconceived as contingent. Following Müller-Wille and Rheinberger's arguments on the epistemological work done by biological concepts, we anticipate that new empirical findings will in the future engender further refinements to both existing models of cell differentiation and the concept of plasticity. Whether, and in what ways, the concept of plasticity will continue to play a part as an epistemological tool in such developments remains to be seen.

This will also depend on how plasticity relates to other concepts, including epigenetics and regeneration, which are gaining prominence as a means to describe and convey the dynamic nature of life in a wide range of empirical and theoretical contexts (Rubin, 2015).

Concluding Remarks

In this paper, we have explored some of the central twists and turns in the four decades that separate the work of John Gurdon and Shinya Yamanaka. The analysis reveals the journey towards changing conceptions of cellular differentiation to have been faltering, contested and contingent on empirical advance. Especially important were new techniques and analyses that formed the basis for challenges to the understanding of this process as irreversible. Here, we have argued that Helen Blau's experimental work and theoretical insights have been crucial in developing a new conceptual framework for rethinking cellular differentiation. We see her thesis of the *plasticity of the differentiated state* as especially important – its significance evident in the Nobel Committee's reference to this concept in 2012. We have linked conceptual change to an experimental lineage that runs from Gurdon, via Blau, to the cloning of 'Dolly' and reports of transdifferentiation in stem cells, to Yamanaka. This experimental pedigree proposes a dynamic interplay between cloning and genetics, in a sequence: cloning–genetics–cloning–genetics. In one sense, this body of work is being retrospectively recast as forging a pathway to a new therapeutic era – one that rests on the possibility of reprogramming the cell by intervening in and controlling the process of cellular differentiation. We have emphasised the role played by the concept of plasticity in these developments.

'Plasticity' can be considered an important conceptual tool for rethinking and reconceiving cellular differentiation. We have identified and examined the factors that enabled and shaped the emergence, meaning(s) and use(s) of the concept of plasticity, initially in the somatic cell and subsequently in the tissue-specific stem cell. Our focus on plasticity is novel, it obliged us to confront its ambiguous and multiple meanings. We have been able to make sense of 'plasticity' by drawing on the work of Müller-Wille, Rheinberger, Löwy, Rose and others which has enabled us to develop new understanding of the work done by biological concepts and the process of conceptual change within the specific context of cell differentiation.

We have sought to highlight the value, meanings and uses of the concept of plasticity in functioning as an epistemological tool in the developing science of cell differentiation. Our account of plasticity opens a window onto the productivity of scientific uncertainty and the work done by concepts in what Hans-Jörg Rheinberger has called the "chaotic moves (…) at the experimental divide between the known and the unknown" (Rheinberger, 2000, p. 275). The changing conceptions of cell differentiation discussed in this paper signal a potentially far-reaching transformation in cell biology and stem cell biology. Of utmost significance is the reconceptualisation of the cell as a 'state' rather than a fixed 'entity'. Indeed, this 'state versus entity' thesis constitutes arguably *the* major conceptual shift arising from within plasticity/cell differentiation research.

Two major implications flow from this transformed conception of the cell. First, it destabilises the historical conception of the cell which now appears more contingent than fixed, has a phenotypic repertoire rather than a phenotype and retains the possibility of multiple identities whilst at any one moment expressing a single identity. These ideas remain in flux, but

have far-reaching implications, not least for the classification of cells into the distinct categories such as 'specialised', 'differentiated', 'somatic' and 'stem'. What is clear is that evolving understanding of the genetic mechanisms underlying cellular differentiation have repositioned the cell and, in turn, the relationship between genotype and phenotype, more prominently within contemporary biomedical research. Secondly, cell fate/identity is seen as something that can be 'directed' and the living cell becomes something that can be 'reprogrammed'. It is these possibilities that have ignited so much interest in cellular differentiation.

We have situated that these developments in the context of the shifting priorities, goals and values within late twentieth-century biomedical research are important for understanding the upsurge in interest in cell differentiation and the growth of stem cell science. Here, we have emphasised the importance of a research culture geared to application and/or commercial goals. That said, stem cell science has also been powerfully influenced by societal demands, not least for novel and better therapies. These aspects, together with the various ethical, legal and societal issues raised by stem cell therapies and Regenerative Medicine, remain questions for future investigation.

The history recounted here is in part about how cellular differentiation is being reframed as a site of intervention with a view to developing medically useful and potentially commercially lucrative biological technologies, i.e. the possibility of changing cells – conceived in terms of plasticity – underpins the vision of novel cell therapies in which the cell is repositioned as a therapeutic tool, albeit one currently still very much in the making. Following from this, plasticity, as it pertains to cell differentiation, can be viewed as another dimension of Hannah Landecker's "life as technology" thesis. As such, we see our account of plasticity as it pertains to cell differentiation and especially in the stem cell setting as another exemplar for her argument that "the history of biotechnology from 1900 to now may be described as the increasing realization and exploration of the plasticity of living matter" (Landecker, 2007, p. 10). As a concept open to interpretation, plasticity served to both articulate and carry ideas and hopes about the potential therapeutic uses of stem cells beyond the laboratory into the realms of policy-making, industry and society at large. In so doing, plasticity has functioned as a central site in which the interests of diverse actors within and outside science could converge around the development of a novel understanding of cell differentiation.

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Beatrix P. Rubin explores the role which the concept of plasticity has played in framing the understanding of the nervous system as changeable and adaptive during the twentieth century. Her work investigates the characteristics of related concepts which are enabling a novel understanding of living systems as dynamic and interactive.

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