Science as Culture
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713444970

From Bedside to Bench? Communities of Promise, Translational Research and the Making of Blood Stem Cells

Paul Martin [a]; Nik Brown [b]; Alison Kraft [b]
[a] Institute for Science and Society, University of Nottingham, UK [b] Department of Sociology, University of York, UK

To cite this Article Martin, Paul, Brown, Nik and Kraft, Alison(2008) 'From Bedside to Bench? Communities of Promise, Translational Research and the Making of Blood Stem Cells', Science as Culture, 17: 1, 29 — 41
To link to this Article: DOI: 10.1080/09505430701872921
URL: http://dx.doi.org/10.1080/09505430701872921

Science as Culture
Vol. 17, No. 1, 29–41, March 2008

Routledge
Taylor & Francis Group

From Bedside to Bench? Communities of Promise, Translational Research and the Making of Blood Stem Cells

PAUL MARTIN*, NIK BROWN** & ALISON KRAFT**

*Institute for Science and Society, University of Nottingham, UK, **Department of Sociology, University of York, UK

ABSTRACT *Contemporary science and technology policy is concerned with improving the diffusion of knowledge from basic science into the clinic. Nowhere is this more apparent than in the emerging field of Regenerative Medicine. In this paper we critically explore the changing relationships between the bench and the bedside through the development of haematopoietic stem cells (HSCs). In the history of HSCs over a 50-year period, the relationship between basic science and clinical research communities has been based on a two-way flow of knowledge; clinical innovation has played a key role in the translation process. Concepts from the sociology of expectations illuminate the 'communities of promise' which are formed around such emerging technologies. From this case study, we challenge assumptions underpinning many contemporary policy initiatives.*

Introduction

Much contemporary science and technology policy is concerned with enabling and improving the diffusion of knowledge from basic science into the clinic, and nowhere is this more apparent than in the emerging field of Regenerative Medicine. The metaphor of 'translation' is now widely used to frame this problem, which has become the subject of intense government activity in many countries. Great emphasis is now placed on the exploitation of basic research and creating new policies and institutions to ensure that scientific findings can be applied in the clinic. However, we will argue that this model of knowledge production and application is flawed and rests on a number of key assumptions that do not accurately reflect the dynamic process of innovation in biomedicine.

In this paper we develop the concept of 'communities of promise' as a means of better understanding the process of 'translation' and the engagement of clinical and research science with a particular socio-technical object; in this case the haematopoietic stem cell (HSC). HSCs, both in the present and in the past, have proven themselves to be highly unstable foci for a wide range of communities crossing the worlds of clinical,

Correspondence Address: Paul Martin, Institute for Science and Society, West Wing, Law and Social Sciences Building, University of Nottingham, Nottingham NG7 2RD, UK. Email: Paul.Martin@nottingham.ac.uk

0950-5431 Print/1470-1189 Online/08/010029–13 © 2008 Process Press
DOI: 10.1080/09505430701872921

commercial and bench science. Here, we explore the way in which these groupings form and operate in reference to imagined futures for blood stem cells in therapeutic and experimental terms, and over a considerable time period stretching some decades into the past.

One central geography in the worlds of stem cell innovation, and taken up in this paper, is the spatial division between bench and bedside, and the processes of translation that are seen to occur between them. In what follows, we contextualize contemporary stem cell innovation historically and socially in the communities of expertise, research and therapy related to a particular stem cell, the HSC. Whilst many of these imagined futures have functioned to stabilize relations within and between these communities, we can also observe noteworthy reversals of position, particularly with respect to establishing the identity of blood stem cells, but also the identities of the communities arranged around them. In charting this story we question the imagined trajectories of 'bench to bedside' (noting rather the inverse, 'bedside to bench') which parallels the similarly troubled corporeal trajectories of stem cell characterization, identification, lineage and development. We offer an account of two interrelated stories of the development of clinical and research work on HSCs. The first account charts some of the early history of the clinical application of HSCs in therapy, with particular reference to the central role played by clinicians in guiding expectations of the therapeutic potential of HSCs. That picture has changed more recently (since the late 1990s), explored in the second half of the paper, where a discourse and vision of bench-to-bedside has become much more prevalent.

Our analysis is based on a detailed historical and empirical study of the development of HSCs from the 1950s to the present[1] and will be organized around a number of themes: the application of emerging HSC therapies and the socio-technical networks that have supported innovation, including private firms; the formation of stem cell identities; and the dynamic relationship within the HSC community of promise between basic research and clinical experimentation. In particular, we wish to address two main questions in this paper: how have expectations, socio-technical communities of promise and stem cell identities been co-constructed in the development of HSCs over the last 50 years? How has the relationship between the bench and the clinic changed during this period and what implications are there for understanding the process of knowledge production and application? In answering these questions we will start to rethink the problem of translation.

Conceptualizing Communities of Promise

A key feature of the HSC story centres on expectations of how clinical developments normally emerge. This is a changing history populated by normative assumptions about the respective roles played by basic scientific research, the clinic, the commercial sector and idealizations of the dynamics between them. They are built both on memories and recollections of the past (Bartlett, 1932), together with present and future constructions of the bench and bedside relationship.

In terms of the recent past, the discourse of 'translation' has gained currency, especially in policy circles, in imagining the application of scientific findings in the clinic and improving the efficiency and speed with which research moves into routine medical practice. This has thrown into sharp relief the extremely complex and dynamic relationship between the spaces and communities of science and application in the clinic.

Earlier imaginings of the dynamics by which basic science is translated into clinical utility, and practice, as a linear and one-directional flow—from 'bench to bedside'—has been challenged by historical and social science scholarship. In her nuanced account of cancer therapies using interleukin II, Lowy draws attention to the vital contributions from the clinic, and the patients within (Lowy, 1996). In their work on cytogenetics, Keating and Cambrosio are critical of 'the tendency to view the events of the last twenty-five years as insights and technologies emanating from biology and subsequently spreading to clinical research and medicine'. Instead, they argue for an analytical frame premised on a two-way *interaction* between biology and medicine (Keating & Cambrosio, 2001). Drawing on approaches from within the sociology of expectations, Wainwright *et al.* have alerted us to the difficulties inherent in these relations, and their implications for translation; indeed, the dominant narrative has become one of the *problems of translation* (Wainwright *et al.*, 2006).

From the contemporary viewpoint, the realms of the basic scientist and of the clinician articulate contrasting understandings and expectations of one another—arising from differences in outlook, training, and what might broadly be termed the 'distinctive culture' prevailing in each setting. Typically, these differences manifest themselves in ready acknowledgement—by 'basic' scientists and clinicians alike—of tensions between those who either identify as, or work within, one or the other tradition, and of the difficulties in practice of 'working together'. The extent to which any of these imagined characterizations holds true across place and time is a pressing question, but one which lies beyond the remit of this paper. Rather, our focus here is in exploring how the worlds of 'bench' and 'bedside' articulate with each other; this lies at the heart of understanding the processes of translation and the dynamics of innovation in any setting. What, then, can we say about the interaction between bench and clinic in the context of HSC innovation?

In addressing this question, we wish to develop the notion of 'communities of promise'. Here we draw on Anderson's 'imagined communities' (Anderson, 1983), Said's 'imagined geographies' (Said, 1979), and consider some recent contributions to utopian theory by Ben Anderson (2006). Crucially, we want to rework these notions of imagination as 'material promissory communities', inescapably artefactual and corporeal. Ben Anderson (not to be confused with Benedict) draws on Bloch's utopianism to define hope as thoroughly material, shedding light on the relationship between the imagination and the materialities of contemporary techno-science. Hope is 'a distinctive type of process that is "not yet" and thus has disruptive, excessive qualities even as it is immanent to lived and material culture . . .' (Anderson, 2006, p. 698). Such materialities have a role in ordering the imagination: 'Materialities . . . anticipate new possibilities or potentialities on the "front" or "horizon"'(Anderson, 2006, p. 698). Said's 'imagined geographies' points to the problematic question of spatiality across which such communities are distributed. There is no 'real' geography against which to compare the imagination, only geographies that, in part, come into being through the work of the imagination. Importantly, imagined geographies are as temporal as they are spatial. As we will see in the discussion below, these geographies depend on a certain characterization of the present, the future and the past.

The imagination remains resolutely central to these kinds of networks. Anderson's point is that the imagination facilitates the development of a shared sense of community within otherwise highly distantiated heterogeneous groups. This can be as true for epistemic

research networks as it is for other kinds of community identity. To be sure, the networks described below depend upon a certain amount of interaction within and between communities; nevertheless, they are also often spatially and temporally situated with often limited opportunity for actual engagement. The imagination is also crucial in respect to the foci of research too, especially given the vagaries of stem cell innovation and the extent to which stem cells, as either objects or things, remain ambiguous, elusive and ephemeral. Understanding the differences, Pickering makes similar points about the constant articulation that is seen to occur between materialities and the imagination in writing of experimental practice, or the mangling of expectations (Pickering, 1995).

1950s to the 1990s: Haematopoietic Stem Cells in Cancer Therapy

The Origins of HSCs in Radiobiology and Cancer Therapy

Until the late 1990s, clinical interest in blood stem cells centred almost exclusively on their use in the treatment of cancer, specifically blood cancers, firstly as bone marrow transplantation (BMT) and later as haematopoietic stem cell transplantation (HSCT). However, from its origins within post-Second World War radiobiology and the search to better understand—and guard against—radiation damage, the clinical career of the HSC was driven as much by the political needs of governments committed to peacetime nuclear programmes as by the new priority being accorded to cancer, and in particular the need for improved therapies for leukaemias. This career subsequently co-evolved with new approaches to cancer therapy based on high intensity radiotherapy techniques and emerging strategies employing a range of newly available chemotherapeutic agents. At the same time, a great deal of scientific research went into isolating and characterizing the HSC, and understanding its function within 'normal' haematopoiesis (i.e. the formation of the blood and immune system) (Wintrobe, 1980).

However, it is important to note that the first clinical trial using bone marrow transplantation in the treatment of cancer, carried out in 1957, predated knowledge of the identity of the HSC, of the means for its enumeration and of the mechanism by which the bone marrow exerted its therapeutic effects (Thomas *et al.*, 1957). The orientation of the clinical communities to the future can, as Moreira and Palladino have put it, often be characterized by a 'regime of hope', proceeding on the basis of speculative potential therapeutic efficacy, even in the absence of a clear demonstration of underlying principles (Moreira & Palladino, 2005; Brown, 2007; Delvecchio-Good *et al.*, 1990). Basic science communities on the other hand, are often much more oriented to a 'regime of truth' emphasizing proof of principle over hope. Whilst 'basic' research into radiation damage paved the way for the move into the clinic, this preceded knowledge of key physiological and functional aspects of the HSC.

Crucially, in understanding this picture of early stem cell innovation, it is important to remember that these were relatively niche areas of clinical and research activity. Early trials of BMT were authorized only for small numbers of patients in whom all other treatments had failed. One consequence of this was that they were often desperately sick and almost at the end of their lives. BMT was, by any standards, physiologically challenging, and it is perhaps unsurprising that initial results were very discouraging: by 1970, of the 203 reports of BMT, just three patients survived (Bortin, 1970). Whilst the patients that underwent early BMT were desperately ill, their deaths were, in most cases, not caused

directly by their cancer, but rather by an immune reaction of the 'donor' bone marrow. The devastating effects of 'graft versus host disease', which had not been predicted in animal models, contributed to the abandonment of BMT by the early 1960s (van Bekkum & de Vries, 1967). The clinical career of BMT—and in effect, the HSC—was only resurrected in the 1970s drawing on a number of advances and following a sustained re-imagining of the approach. These long-term variations in the expectations of fields such as stem cells are highly characteristic of the biosciences, resulting in successive waves or cycles of disappointment and then re-investment (Brown, 2003; Martin, 2001).

The period is characterized by a clinically driven shift from the imagined possibilities of the clinic back into exploratory fundamental research. This helped stimulate new immunological understanding, especially the determination of the human major histocompatibility complex—human leukocyte antigens (HLA) (Brent, 1997), which enabled the resurrection of BMT in the 1970s. At the same time, BMT was also transformed, as it now became embedded within a broader 'conditioning' regime—involving tissue-matching between donor and recipient, and the development of immunosuppressive drugs, such as cyclosporine and busulphan—which together contributed to improved patient outcomes (Little & Storb, 2002).

Whilst BMT began as a radical innovation in the late 1950s, from the late 1960s onwards its use—and, by extrapolation, that of the HSC—proceeded by steady and incremental change. This proceeded through slow 'therapeutic refinement' leading gradually to improved clinical efficacy for some of the haematological cancers. Throughout these developments and into the 1980s, the clinical identity of the HSC remained synonymous with BMT and cancer. Advances in the 1980s, most notably the identification of CD34, a surface antigen marker seemingly specific for the HSC, by a group at Johns Hopkins led by Curt Civin, enabled further refinements to the BMT protocol (Civin *et al.*, 1984). These changes engendered a shift in nomenclature in the mid-1990s from BMT to HSCT. Since then, the clinical uses of the HSC have both grown and diversified. By 2005 over 1,000 clinical trials of HSC-based cancer therapy had been established in the USA alone, representing a major systematic programme of incremental clinical research (see www.clinicaltrials.gov).

The identity of the HSC is as variable as the communities arranged around it. Emerging from within post-war radiobiology, the characteristics of the HSC have been assembled slowly, and its identity remains fiercely contested. In the 1960s, the HSC was framed in terms of the Colony-Forming Unit–Spleen (CFU-S), based on the first assay used for its enumeration (Till & McCulloch, 1961); later, from the mid-1980s onwards, the HSC was defined in terms of the CD34 surface marker, a classification that is still contested. However, for clinical purposes, CD34 remains the routinely used 'yardstick' by which to assess the number of HSCs present in a given sample, and counts of CD34 positive cells are an important criteria in transplantation protocols. In the clinical setting therefore, the HSC has become stabilized in a set of routine clinical practices associated with the treatment of a range of haematological cancers. However, if the clinical identity has stabilized 'in practice' around CD34, it is important to note that there remains little agreement across clinical and bench communities about the identity of the 'true' HSC.

The First Wave of Commercial Interest in HSCs

The vision for HSCs during this period was highly influential in enrolling a third community beyond the bench and bedside, commercial bioscience. A number of almost

exclusively US based firms in the 1980s were established by leading research clinicians to work on the purification and genetic modification of HSCs. The period 1982 to 1993 saw the formation of six such companies (Martin *et al.*, 2006). At around the same time, the larger and long-established firm Baxter, with a track record in blood-based innovation and products, also became involved in HSC-based R&D.

These companies channelled their efforts into developing techniques for the isolation and purification of HSCs using a variety of methods. The main application continued to lie within cancer therapy as a commercial extension of existing clinical practice. Nevertheless, a new vision or schema centred on using CD34-based HSC-separation as a platform for *ex vivo* gene therapy for the treatment of other cancers, HIV and a number of genetic disorders. Expectations of gene therapy were very high at the time, making HSCs commercially attractive, promising a potentially far broader range of clinical applications (Martin & Thomas, 1996). However, CD34 became the subject of a number of intellectual property claims, and the focus of long-running and bitter litigation between Baxter Healthcare Corporation and CellPro (Bar-Shalom & Cook-Deegan, 2002).

During this period the commercial potential of HSC-based cell and gene therapies started to attract considerable interest from the mainstream pharmaceutical industry, which began to place very high valuations on the technology. In 1995 Applied Immune Sciences was acquired by Rhone-Poulenc Rorer (RPR, now Aventis-Sanofi) for $220M and in 1997 SyStemix was acquired by Sandoz (now Novartis) for over $600M. However, in retrospect this represented the high water mark of expectations for the nascent stem cell industry, peaking just before becoming embroiled in a series of high profile patent disputes about the ownership of the CD34 antibody and suffering a number of scientific set-backs and disappointing clinical trials of HSC-based gene therapy. As van Lente (1993) notes in *Promising Technology*, claims of future potential are often seen to reach new levels of exuberance shortly before a dramatic downturn in expectations. This happens as key stakeholders invest extra effort into shoring up a threatened vision.

By the end of the 1990s there was large scale disinvestment. Despite their very considerable stake in the field, both RPR (Aventis) and Sandoz (Novartis) had effectively closed their research programme in this area by the early years of the new millennium.

Innovation Model: The Changing Relationship between the Laboratory and the Clinic

Over the last half century, the interaction between bench and bedside in the course of HSC innovation has changed markedly. As we discuss elsewhere, what began as a scientific problem within radiobiology—that of radiation damage—evolved into what gradually became a search for the HSC. The radiobiological researchers concerned with understanding radiation damage were drawn to, and their research was funded, because of the clinical uses that might flow from it and were driven by that prospect.

The settings in which many scientists worked at the time were research institutions that existed in close association with a cancer hospital: physical proximity between these clinical and bench communities fostered close collaboration between both sets of practitioners. In these situations this kind of collaboration held out the possibility of ‘friendship’ between clinicians and scientists working within these settings. This, of course, then maps to broader but no less important questions of professional politics, institutional culture, and managerial policy.

The clinicians who first brought bone marrow transplantation into the clinic readily acknowledge that their work drew heavily on the findings of 'basic' radiobiological research. In reflecting on the history of the relationship between clinical and basic research science, many working in the field of blood stem cells refer back to both the origins of a division between these communities and also the development of an intellectual divide, dating back to the 1970s and 1980s.

The explanation for changes in the relationships between these communities was mainly the result of increased institutional specialization. Research funding policy and priorities have also served at various points in time to deepen the separation between basic and clinical research. The existence of this fault-line became embedded in professional politics (concerning, for example, jurisdiction over and responsibility for technologies and techniques), and within institutional structures and practices. This created the conditions in which innovation is spatially understood, having a 'direction' and being conceptualized as a largely linear and one-directional progression 'from bench to bedside'.

Since the 1990s: Blood Stem Cells in Regenerative Medicine

Creation of a New Promissory Field

Towards the end of the 1990s a major shift in the framing and vision of the whole field of cell therapy and tissue engineering occurred with the cloning of Dolly in 1997 and the creation of the first human embryonic stem cell (hESC) lines in 1998. These two events supported the idea that there are many different types of tissue-specific stem cells, and opened up the possibility of creating a wide range of different tissues or even complete humans (clones) from fully differentiated adult cells. By 2000 a new term, 'Regenerative Medicine', had gained wider currency to describe the broad field of cell therapy and tissue engineering, which marked an important shift to a discourse that combined concepts from developmental biology, genomics, anti-aging medicine and tissue engineering. Specifically, it framed therapy in terms of self-repair or rejuvenation rather than the idea of replacement or substitution that had marked the early development of the first cell therapies, including HSCs.

The rise of Regenerative Medicine was instrumental in providing many of the key concepts that have shaped the whole field of stem cell therapy since 2000. Its rise was marked by a number of important changes from the socio-technical regime established around HSCs in the 1980s and 1990s. These have included the creation of a new set of expectations about the use of a wide range of stem cell types to treat a large number of chronic degenerative conditions, heavy public investment in basic research and renewed commercial interest in cell therapy.

Central to this has been a discursive separation of embryonic and adult stem cells, with hESCs now being seen as having greater therapeutic potential than cells taken from particular adult tissues. This reconstruction of the HSC as an adult stem cell has been important in facilitating a collective forgetting of the history and significance of what might justifiably be called the first stem cell. This temporal reversal has occurred to such an extent that many scientists and social scientists now believe that the very phrase 'stem cell' is shorthand for hESCs. This can be seen to symbolize a political struggle for dominance over research funding, legitimacy and public support in which the promise of adult stem cells is believed to undermine the case for work on embryonic stem cells.

At the same time, the possibilities opened up by the idea that adult cells had much greater plasticity and developmental potential than previously thought was also reflected in work on HSCs. A new set of expectations started to coalesce around the possible use of HSCs in Regenerative Medicine following a number of papers published in the late 1990s suggesting that HSCs might be able to contribute to the creation of a number of tissues outside the blood and immune system, including the heart and nervous system (Lagasse *et al.*, 2000; Orlic *et al.*, 2001).

Evidence that the HSC might possess broader developmental potential was largely unanticipated by many in the field. However, the extent to which transdifferentiation occurs is highly contested, especially by researchers working on hESCs. This is an important point to which we return shortly.

Commercialization of HSCs in Regenerative Medicine

Despite a lack of conclusive evidence that HSCs can contribute to the regeneration of tissue outside the blood and immune system, and the commercial disappointment that surrounded the field in the 1990s, the possibilities opened up by Regenerative Medicine have formed the basis for a significant amount of industrial interest, with a number of established and new firms moving into this area. For example, Aldagen, founded in 1999, argues that 'The use of adult stem cells for the purpose of tissue regeneration offers the opportunity to revolutionize treatment of a broad range of serious diseases affecting millions of patients' (www.aldagen.com). Other companies established in the 1980s and 1990s, such as Aastrom Biosciences, are using bone marrow-derived adult stem cells for the treatment of bone, cardiac and neural regeneration (www.aastrom.com).

Amongst the most significant growth areas for private investment has been the establishment of commercial umbilical cord blood (UCB) banks, which store the blood harvested from the umbilical cord of the new born child (Brown & Kraft, 2006). This is a rich source of HSCs, and UCB cells have been successfully used as an alternative to traditional bone marrow transplantation for a very specific subset of patients. UCB banking is very much premised on the promise and vision of Regenerative Medicine, but also represents an ancillary extension to long-standing networks of blood services, cryopreservation, etc. Over 30 private cord blood banks have been established internationally by a number of companies, such as CyGennics, Cytomatrix, Pluristem and ViaCell (Martin *et al.*, 2006).

Companies typically emphasize the growing repertoire of potential therapeutic applications of UCB-derived HSCs, for example, ViaCell claims that these can be used to '... regenerate damaged heart tissue and be an effective, standardized product for heart repair' (www.viacell.com, accessed 10 March 2007). However, attempts to further widen the sources, applications, and the community of promise surrounding HSCs have met with limited success and many of the expectations surrounding cord blood have yet to be realized due to lack of technical progress.

Reconstructing the Identity of the HSC

The expectations surrounding the use of traditional bone marrow derived HSCs in Regenerative Medicine have been embodied in the establishment of clinical trials, which are experimentally testing a range of novel HSC therapies. For example, in the

USA at the end of 2006 there were some 10 completed trials and another 30 clinical trials being initiated to explore the use of bone marrow stem cells for the treatment of coronary heart disease, heart failure and myocardial infarction (following heart attack) (see www.clinicaltrials.gov). At the same time there were also a small number of trials being set-up to look at the use of HSCs to treat several other conditions, such as Parkinson's disease (see www.clinicaltrials.gov). Nevertheless, many of these early expectations have yet to be realized, with trials typically demonstrating only relatively modest results.

The recent controversy about the developmental plasticity of the HSC—its existence, incidence and underlying mechanism—has destabilized some of the longstanding tenets of HSC biology (Lemischka, 2002). The HSC has, historically, been understood to be 'tissue specific', that is, capable of giving rise only to the constituent cell lineages of the blood/immune system. The emerging literature on HSC plasticity challenges this paradigm, and argues that, under some circumstances, the HSC can give rise to cells and tissues other than those of the blood/immune system. It also suggests that transdifferentiation—the possibility that cells 'committed' to a particular lineage can 'switch' to a different lineage—previously not thought possible, can take place. Much of this emerging research goes 'against dogma' and has ignited fierce debate within the HSC community and within the wider stem cell biology community.

However, this move to render the HSC future more plastic can be seen as part of the general trend across the whole field that stresses the plasticity of cellular identities. At the heart of the controversies lies the question of the identity of the 'true' HSC. In all likelihood any future use of the HSC in the regenerative paradigm for diseases other than cancer will be premised on the use of the 'true' HSC in pure form. It thus becomes imperative for advocates of Regenerative Medicine to be able to identify, isolate and understand this cell.

Innovation Model Associated with Regenerative Medicine

Following the cloning of Dolly and the creation of hESCs there have been high hopes that these 'breakthroughs' in basic science can be readily translated into clinical applications. The shift to Regenerative Medicine has been marked by the ascendancy of a particular discourse in policy making and commentary around stem cell innovation, which is summed up in the phrase from 'bench to bedside'. This stresses the progressive move from experimental applications in basic science to applied clinical medicine, and has become embedded in the structure of UK research policy and funding. For example, the Pattison Report on the UK Stem Cell Initiative (Pattison, 2005), whilst acknowledging the central role of incremental clinical research, still adopts a largely linear model of innovation that is commonly used to describe the discovery and development of pharmaceutical products. In its depiction of the Stem Cell Development Process (Pattison, 2005, p. 61) it shows the move from basic research, to banking and production, and then to clinical research, with fundamental science playing a key role in all stages. Similarly, the UK Stem Cell Foundation was established in 2005 following the recommendations of the Pattison report 'to support the speedy transfer of promising stem cell techniques from the laboratory bench to patient bedsides' (http://domain883347.sites.fasthosts.com/foundation/index.htm). Here also the emphasis is placed on the importance of basic laboratory research as the main driver of clinical innovation.

However, as the story of the HSC has demonstrated, the bench is far from being ahead of the bedside and is not the only source for understanding the basic mechanisms behind stem cell therapy. Despite this, clinical research is often seen as problematic and lacking in rigorous scientific validity; a contrast that is founded in a range of both tacit and formalized comparisons. As a consequence, there have been widespread calls from basic research communities for a return to the bench in those instances where the shift to the clinic has been seen as a premature move, for example in the use of HSCs in treating damaged heart tissue (Chien, 2004).

Conclusions

In the course of this paper, we have sought to make sense of the dynamic relationships between commercial, clinical and laboratory networks in their engagement with the memory, expectations, and prospects for haematopoietic stem cells. This has been used to reflect on two questions relating firstly to how expectations, socio-technical communities of promise and stem cell identities have been co-constructed in the development of HSCs, and secondly to how the relationship between the bench and the clinic has changed during this period and what implications this has for understanding the process of knowledge production and application. In particular, we have used the idea of communities of promise as a way of exploring the enrolment and alignment of different groups of actors within the innovation process, the development of clinical applications, the construction of expectations and futures, and the formation of particular stem cell identities. Each of these has emerged through a process of mutual shaping, with the membership of the community of promise playing a central role in the formation of stem cell networks, identities and futures. Throughout the clinical career of the HSC new groups have been recruited to these promissory communities as new expectations have been created and these have, in turn, helped the reconstitution of HSC futures amid changing ideas about the very nature of this stem cell.

Within this context, expectations extend from and contribute to the stabilization of networks, specific socio-technical identities and the creation of particular relationships between actors and within communities based on mutual imagined understandings. The construction of expectations cannot therefore be separated from the creation of knowledge and the building of networks. It is notable that whereas HSCs in the 1980s and early 1990s were stabilized within a narrowly defined clinical niche, the shift to Regenerative Medicine and the expansion of the community of promise coincided with the destabilization of ideas about the nature of the HSC itself. In this sense, the HSC has become more diffuse and has greater plasticity, in terms of the object itself, the networks revolving around it and its future application.

One of the more important points we want to highlight about the HSC story is how it speaks to wider normative expectations and assumptions about the way in which basic science and clinical research communities relate to one another. In particular, we problematize assumptions about the pathways or routes by which objects make their way from the laboratory into the clinic. These underpin much contemporary commentary and policy around emerging stem cell economies. Specifically, we have identified three broad periods during which particular alignments have been constituted between these two groups, both real and imagined. This relationship lies at the heart of the community of promise that has surrounded the HSC and has powerfully influenced applications and expectations.

In the period from the 1950s to the 1970s, during the early development of HSCs within cancer medicine, there was a dynamic two-way relationship between laboratory science and clinical research, with close physical and disciplinary linkages and a strong sense of interdependence. This shifted during the 1970s–1990s, with the growth of disciplinary barriers and greater institutional separation between the bench and the clinic. This also coincided with the growing ascendancy of clinical research on HSCs following the therapeutic proof of principle of CD34 positive cells in the early 1980s and attempts to broaden its application to include gene therapy. Finally, in the contemporary period marked by the promise of Regenerative Medicine, there has been a reversal of this picture and the hegemony of a linear model of translation which sees a largely unidirectional flow of knowledge from bench to bedside. This has been driven by high expectations following key breakthroughs in basic science relating to hESCs and evidence, albeit contested, that the HSC may have greater developmental potential than previously thought. In a discourse dominated by laboratory science, experimental clinical research is now criticized as premature and unscientific.

The geographies of stem cell innovation have thus become dominated by a particular spatial imagination in which laboratory-based research is seen to take the lead in developing new techniques and applications for subsequent clinical deployment. This helps account for a mushrooming of basic research activity taking place globally since the late 1990s, but as yet little clinical application. However, the historical narrative of the HSC instead tells of a strong intertwining between these two communities and a key role for clinical experimentation. In many instances, basic laboratory science has been concerned with validating already existing clinical knowledge and practice of therapeutic applications. The recent move towards clinical trials in a variety of HSC-related regenerative techniques—even in the absence of a firm experimental understanding of basic mechanisms—is actually highly consistent with this history of clinically driven innovation. Such reversals of the bench to bedside framework are far from uncommon (Keating, 2002; Keating & Cambrosio, 2001), but are certainly at odds with prevailing discourse in the context of hECS and Regenerative Medicine.

At the heart of contemporary discourse about stem cell innovation is the notion of 'translation'. A dictionary definition of this term might stress the interpretation of the meaning of a text in one language and the production of an equivalent text in another language that had the same meaning. Implicit in this metaphor is the idea that new scientific knowledge can form the basis for equivalent clinical knowledge. However, clinical practice cannot be simply reduced to the appliance of laboratory science, and draws on a range of other forms of knowledge and expertise. Furthermore, insights from the sociology of science would challenge this assumption by stressing the way in which knowledge is socially organized and embedded in particular local networks and epistemic communities. From this perspective the problems of translation within contemporary biomedicine can be thought to revolve around the construction of overlapping and intertwined communities, as described in this paper, and the creation of the conditions for interaction between practitioners who by training, outlook and institutional context are very different. In order to do this it means overcoming differences in perception, working practices and norms, and establishing the means for dialogue and collaboration across structural boundaries.

The analysis of expectations and the communities of promise in which they are embedded has a performative function in reshaping stem cell futures. Specifically, our account of the evolving expectations surrounding HSCs has implications for contemporary

policy in the context of embryonic and other adult stem cells where the imagined trajectory of technical change foresees the near-term clinical potential of objects conceived in the laboratory. In recent years there has to some extent been a collective forgetting of the fact that clinical experimentation is a crucial driver in many of these fields and its absence from accounts of stem cell innovation may prove to be a serious omission. In particular, this has produced a central element in the narrative around hESCs in which a clean and scientifically produced stem cell future emerges without the messiness of the clinic.

In contrast, we believe the HSC story powerfully demonstrates that the development of novel stem cell therapies, both adult and embryonic, is not simply the appliance of science and that clinical experimentation is a crucial driver in producing new knowledge and translating this into routine practice. This involves a slow and long-term process of incremental trial and error in which a series of bottlenecks are identified and overcome through interaction and feedback between the laboratory and the clinic. To dismiss clinical trials as unscientific when the underlying biology is still poorly understood is to miss the point and reflects the danger of buying into particular futures promoted by laboratory scientists enthralled by the promise of Regenerative Medicine. Furthermore, it fundamentally misconceives the relationship between the bench, the bedside and the complex dynamics of 'translation'. If progress is going to be made in realizing a future based on the power of embryonic stem cells, this lesson will have to be collectively rediscovered.

Acknowledgements

The research was supported by ESRC Project Grant 'Haematopoietic Stem Cells: The Dynamics of Expectations in Innovation'. Principal investigator was Paul Martin.

Note

[1]The data contained in this paper are based on extensive historical documentary analysis, a survey of the stem cell industry and over 30 interviews with key informants involved in the development of the field over the last 50 years.

References

Anderson, Ben (2006) Transcending without transcendence: utopianism and the ethos of hope, *Antipode*, 38, pp. 691–710.

Anderson, Benedict (1983) *Imagined Communities* (London: Velso).

Bar-Shalom, A. and Cook-Deegan, R. (2002) Patents and innovation in cancer therapeutics: lessons from CellPro, *The Milbank Quarterly*, 80(4), pp. 637–676.

Bartlett, F. C. (1932) *Remembering: A Study in Experimental and Social Psychology* (Cambridge: Cambridge University Press).

Bortin, M. M. A. (1970) A compendium of reported human bone marrow transplants, *Transplantation*, 9, pp. 571–587.

Brent, L. (1997) *A History of Transplantation Immunology* (London: Academic Press).

Brown, N. (2003) Hope against hype: accountability in biopasts, presents and futures, *Science Studies*, 16(2), pp. 3–21.

Brown, N. (2007) Shifting Tenses: Reconnecting Regimes of Truth and Hope, *Configurations*, 13(3), pp. 331–355.

Brown, N. and Kraft, A. (2006) Blood ties: banking the stem cell promise, *Technology Analysis and Strategic Management*, 18, pp. 313–327.

Chien, K. R. (2004) Stem cells: lost in translation, *Nature*, 428, pp. 607–608.

Civin, C. *et al.* (1984) Antigenic analysis of hematopoiesis. III. A hematopoietic progenitor cell surface antigen defined by a monoclonal antibody raised against KG-1a cells, *Journal of Immunology*, 133, pp. 157–165.

Delvecchio-Good, M.-J., Good, B., Schaffer, C. and Lind, S. (1990) American oncology and the discourse on hope, *Culture, Medicine and Psychiatry*, 14, pp. 59–79.

Keating, P. (2002) From screening to clinical research: the cure of leukemia and the early development of the cooperative oncology groups, 1955–1966, *Bulletin of the History of Medicine*, 76(2), pp. 299–334.

Keating, P. and Cambrosio, A. (2001) The new genetics and cancer: the contributions of clinical medicine in the era of biomedicine, *Journal of the History of Medicine and Allied Sciences*, 56(4), pp. 321–352.

Lagasse, E., Connors, H., Al-Dhalimy, M., Reitsma, M., Dohse, M., Osborne, L., Wang, X., Finegold, M., Weissman, I. L. and Grompe, M. (2000) Purified hematopoietic stem cells can differentiate into hepatocytes *in vivo*, *Nature Medicine*, 6, pp. 1229–1234.

Lemischka, I. (2002) A few thoughts about the plasticity of stem cells, *Experimental Hematology*, 30, pp. 848–852.

Little, M. T. and Storb, R. (2002) History of HSCT, *Nature Reviews Cancer*, 2, pp. 231–238.

Lowy, I. (1996) *From Bench to Bedside. Science, Healing and Interleukin-2 in a Cancer Ward* (Cambridge: Harvard University Press).

Martin, P. A. (2001) Great expectations: the construction of markets, products and user needs during the early development of gene therapy in the USA, in: R. Coombs, K. Green, A. Richards and V. Walsh (Eds) *Technology and the Market: Demand, Users and Innovation* (Cheltenham: Edward Elgar).

Martin, P. A., Coveney, C., Kraft, A., Brown, N. and Bath, P. (2006) The commercial development of stem cell technology: lessons from the past, strategies for the future, *Regenerative Medicine*, 1(6), pp. 801–807.

Martin, P. and Thomas, S. (1996) *The Development of Gene Therapy in Europe and the United States: a Comparative Analysis*. Final project report/STEEP Special Report No 5, Science Policy Research Unit, University of Sussex, 151 pp.

Moreira, T. and Palladino, P. (2005) Between truth and hope: on Parkinson's disease, neurotransplantation and the production of the 'self', *History of the Human Sciences*, 18, pp. 55–82.

Orlic, D. *et al.* (2001) Bone marrow cells regenerate infracted myocardium, *Nature*, 410, pp. 701–705.

Pattison, J. (2005) *Report of the UK Stem Cell Initiative* (London: Department of Health).

Pickering, A. (1995) *The Mangle of Practice: Time, Agency and Science* (Chicago: Chicago University Press).

Said, E. (1979) *Orientalism* (London: Vintage Books).

Thomas, E. D., Lochte, H. L., Lu, W. C. and Ferrebee, J. W. (1957) Intravenous infusion of BM in patients receiving radiation and chemotherapy, *New England Journal of Medicine*, 257, pp. 491–496.

Till, J. E. and McCulloch, E. A. (1961) A direct measurement of the radiation sensitivity of normal mouse bone marrow cells, *Radiation Research*, 14, pp. 213–222.

Van Bekkum, D. W. and de Vries, M. J. (1967) *Radiation Chimeras* (London: Logos/Academic Press, Preface).

Van Lente, H. (1993) *Promising Technology—The Dynamics of Expectations in Technological Developments* (Delft: Eburon).

Wainwright, S. P., Williams, C., Michael, M., Farsides, B. and Cribb, A. (2006) From bench to bedside? Biomedical scientists' expectations of stem cell science as a future therapy for diabetes, *Social Science and Medicine*, 63, pp. 2052–2064.

Wintrobe, M. (1980) *Blood, Pure and Eloquent: A Story of Discovery, of People and Ideas* (New York: McGraw-Hill).