Regenerative medicine in Europe: emerging needs and challenges in a global context

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REMEDIE

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Final Report Summary - REMEDIE (Regenerative medicine in Europe: emerging needs and challenges in a global context)

Executive summary:

1) The REMEDIE project has examined in considerable detail the development of the field of regenerative medicine (RM), defined as the application of novel biomaterials - specifically cells (including stem cells), genes (via gene therapy) and biodegradable scaffolding materials, to achieve a regenerative effect. Three main aspects of the field are explored - the economic (innovation-related), the political (especially governance related) and the bioethical (including its legal aspects) - to compare Europe with other parts of the globe.
2) There is a significant European-based commercial sector, with c120 companies - the vast majority (112) small biotech firms less than 10 years old - working in the domain of regenerative medicine, including 51 cell therapy companies, of which the majority strongly favour therapies using cells from a patient's own body (autologous cell therapy) over products using cells derived from an unrelated donor or donors (allogeneic cell therapy) with very little interest in hESC approaches. The industry is concentrated in major hubs in France, Germany, and the UK, dependent on strong regional (publicly-funded) platforms.
3) There are major scientific and regulatory hurdles ahead as clinical trials increase, especially the ability to standardise cell batches for phase III trials, when the biological variation in cell behaviour must be shown to be within tolerable limits across multiple clinical sites to gain regulatory approval. While the US is extremely strong its lead on some fronts is declining as more and more clinical trials in autologous therapies gather pace elsewhere. Most trials are still in Phase 1, and focused on three areas, the cardiovascular, the gastrointestinal and the central nervous system. It is very likely that the next decade will be dominated by products and processes deploying autologous customised batch therapies rather than extensively available techniques.
4) Regulatory and political practices vary across Europe and globally. The report discusses the ways in which the sourcing of tissue - notably oocytes for research - is subject to regulatory oversight and the degree to which this is effective. It also identifies some key differences in the political cultures shaping the field as one move, from the USA, Europe to China.
5) Findings in relation to key ethical and legal issues (which overlap) are summarised. Consensus on

controversial topics such as those relating to regenerative medicine is fragile and often challenged on moral and political grounds. Moreover, consensuses tend to collapse rapidly as innovation disturbs agreed moral boundaries.
6) The full report concludes with a range of detailed policy recommendations relating to the governance, enabling and strengthening of the field and its regulatory, corporate and clinical promise.
7) The Report is accompanied by a separate series of detailed Annexes relating to the discrete results the substantive workpackages (1-7). These reports inform the range of papers both published and in preparation during the period of dissemination activity following the end of the formal contract period of the project. They are provided as a set of (Non-public) Deliverables for the Commission.

project Context and Objectives:

determining the field of inquiry

there is at present no single, universally agreed definition of RM, although recent years have seen a number of attempts to delineate the field published in the scientific literature (for example; Atala, 2007; Kemp 2006; Daar & Greenwood, 2007; Mason 2007a; Mason & Dunnill, 2008a). In order to evaluate the development of regenerative medicine in Europe, it was therefore necessary to produce a project-specific definition of RM that could be operationally applied to determine the boundaries of our inquiry - for example, in respect to which firms should (or should not) be included in the 'company universe'. Our definition therefore is as follows:

regenerative Medicine is the use of cells including stem cells, genes (via gene therapy), and bio-scaffolds to stimulate or augment the body's capacity for self-repair.

objectives of the project:

the main objectives of the project were to provide:
- A detailed analysis of the competitive position of Europe within the globalisation of regenerative medicine, the requirements of successful innovation in this field and the EU policies that need to be developed to support Europe's global advantage in the field.
- An integrated series of workpackages organised around three interrelated streams of research that constitute the platform for this analysis (the socio-economic, political and bioethical).
- An integrated quantitative relational database on the geo-economic pattern of activity within the field of regenerative medicine derived from a) ongoing review of secondary data sources and b) primary data derived from partner projects.
- The use of novel methodological techniques to interrogate results using geometric mapping of data items secured by different projects in the three streams of work.
- A continuing engagement with national and international policy makers and others to test and refine the implications of emergent findings for future European policy and regulation in particular.

project Results:

major findings

in order to integrate our results, we have organised the principal findings of the REMEDIE project according to a number of core themes which draw from various workpackages. Full reports for each WP are carried in the accompanying Annexes.

innovation and firm activity at European and Global levels

regenerative Medicine in Europe:

one of the primary objectives of the project was to investigate the contemporary position of the European regenerative medicine (RM) industry within a global context and to track and evaluate patterns of investment in RM technologies. Four discrete approaches were developed to address these objectives: a comprehensive study of the extant 'universe' of commercial companies developing regenerative medicine products; case studies of commercialisation strategies in six Member States (the Czech Republic, France, Germany, Spain, Sweden and the UK); an extensive financial analysis of the economic robustness of the global RM industry and discussion of the position of European firms in this regard; and the construction of an international SQL database of corporate, clinical trial and patenting activity in the major global regions.

companies developing small molecule or macromolecule (e.g. recombinant protein) therapies intended to have 'regenerative' effects in vivo by stimulating cell division, activation etc are out with the field as they largely share the established regulatory pathways, reimbursement strategies and manufacturing processes of bio-pharmaceutical drug development. They do not involve any significant investment in the specialised biomaterials of regenerative medicine, nor are they likely to encounter any of the same regulatory, financial or technological barriers to development. Xenotransplantation, cell-based vaccines, traditional prosthetics or implantable medical devices (such as pacemakers), antisense or interference RNA technologies, and organ transplants are also considered to lie outside the purview of the project definition of RM as they are either insufficiently novel or are not considered to act in an appropriately regenerative fashion. Data collection on European RM firms was ongoing throughout the duration of the project.

the European Company Universe: Principal Characteristics

A total of 112 currently active European firms meeting the project definition of regenerative medicine were catalogued. The following section will present an initial characterisation of the European RM industry in terms of its geographical distribution, composition firm, age, size and other features.

geographical distribution of European RM firms

the European RM industry is heavily concentrated in countries in the north and west of Europe, with very little commercial activity in southern and eastern areas. There are three main hubs of European RM activity; Germany, the UK and France. The next most active states for commercial development of RM are Spain and Switzerland, while the remainder of European companies are spread across a range of territories including Belgium, The Netherlands, Sweden, Denmark, Italy and Greece where each of these countries has at most two or three genuine RM firms within its borders. Many European countries have no

commercial regenerative medicine presence at all, including the majority of states that joined the European Union in 2004.

perhaps unsurprisingly, the major national players in commercial RM are generally those countries that have strong existing life-sciences and biotechnology industries and the attendant infrastructures. Spain, as an exception, is an important example of a country which has developed a strategic approach to the support of RM as part of a broader programme to build a national biotechnology sector. It is not co-incidental that the three major European hubs all have national strategies for the development of RM. The UK stem cell initiative and the subsequent Patterson Report in 2005 was perhaps the first attempt in Europe to construct a coordinated national strategy for regenerative medicine (albeit one which was highly focused on stem cell research). Other countries have since followed suit to varying degrees. In Germany, strategic support has taken a range of forms, notably the development of five major RM research centres backed by the Federal Ministry for Education and Research (BMBF) and the German Research Association (DFG), as well as a number of scientific networks and commercialisation schemes administered by different regional authorities (such as the pioneering North Rhine Westphalia Stem Cell Network established in 2002, and Saxony's funding of RM as one of its main strategic priorities in biotechnology). France, unlike the UK and Germany, did not have a significant pre-existing tissue engineering industry as illustrated by the lack of bio-scaffold firms.

A 2007 French report by the biotechnology committee of the LEEM on 'cell therapies' made a range of policy recommendations intended to spur the development of a national regenerative medicine industry, including regulatory reform and support for the development of regional RM clusters. The outcome of this highly targeted approach is visible in that the French RM industry now has cell therapy and service sectors comparable to Germany and the UK. Moreover, like Germany, its legal constraints on hESC research are somewhat mitigated by its strong pharma/biotech sector and historic strengths in key areas such as developmental biology. As the country with the third greatest number of RM companies, it clearly has potential to be a major player, though it is unclear whether the current restructuring of the life sciences research system facilitates such a development, or proves an unwelcome distraction.

it is important to note that a country's density in terms of firm numbers does not necessarily reflect the strength of the firms based there. A number of significant European RM firms are located in countries outside the three hubs as illustrated by the cases of TiGenix (Belgium), Cellartis AB (Sweden) and Cellerix (Spain).

firm age, size and sector

the majority of European RM firms across all sectors are small (<50 employees) with only a few (N= 10) medium (<250 employees) or large (>250 employees) companies involved in the field. This is unsurprising given that there are no high-earning 'blockbuster ' RM products and the sector is regarded as highly risky by investors, even in comparison to other biotechnology fields such as genomics. Europe has historically suffered from significantly lower availability of venture capital (VC) investment compared to the US and until very recently large pharmaceutical companies have been reluctant to invest in stem cell technologies meaning there has been limited capital available to European RM firms to grow and develop. The long timescale of RM product development, the financial crisis of 2008-9 and the subsequent risk-averse

investment environment have all served to exacerbate this situation. Those few large firms recorded tend to be older companies, which have added RM products, especially products with lower technical requirements and less complex regulatory pathways such as cellular bio-scaffolds or reagents, to existing product pipelines and are often not dependent on RM products alone to make a profit.

the largest single sector of the European RM 'company universe' is cell therapy firms, but there are also significant bio-scaffold and service sectors.

the cell therapy sector

A key aspect in assessing human cell based therapies is the source and application route of the cells. Somatic 'adult' differentiated cells and stem cells from a range of sources - embryonic, foetal, cord blood, and mature tissues can all be used to develop cell therapies. Mature somatic cells can also be reprogrammed using certain biological factors to induce pluripotency - so called induced pluripotent stem (IPS) cell technology. Cell therapies can be applied autologously - reimplanted into the patient the cells were extracted from, or allogeneically - where cells from a donor are implanted in unrelated patients. Each of the possible permutations of sources and application routes has implications for the type of business model for firms developing the cell therapy products.

A total of 65 cell therapies available or in development were recorded from the 51 identified cell therapy biotechs as several firms have more than one cell-based product or product candidate.

european cell therapy firms are split almost equally between therapies based on stem cells and therapies based on somatic cells. However, there is a strong emphasis on autologous rather than allogeneic therapies. Interestingly, this is less the case with stem cell-based approaches than with somatic cell-based products. A further important dimension to this pattern is revealed by comparing those cell therapy products which are available (including through hospital exemption, named-patient licences, and the limited number of nationally or EMA approved products).

the available cell therapies are overwhelmingly based on autologous somatic cell therapies while the cell therapy pipeline shows much greater investment in stem cell technologies and in the development of allogeneic approaches to cell delivery.

cell therapy pipeline and therapeutic focus

it is largely stem cell therapies that are being developed for the more ambitious clinical indications; those that reflect the promise of RM such as cardiac repair, neuro-regenerative treatments, and autoimmune diseases. Much of this activity is currently in the early stages of clinical development and so is not likely to yield a flood of new therapies in the short term. Additionally, no stem cell therapy for this type of chronic disease application has yet made it through the ATMP regulatory system and despite efforts to harmonise European regulation and create a viable governance pathway for regenerative medicines there remain areas of uncertainty -and thus potential challenges - with regards to permissible amounts of variability in cell populations in multi site (i.e. late stage) clinical trials.

beyond corporate activity at a European level, we decided it would be useful to undertake a detailed analysis of firms operating within and beyond Europe that present themselves as falling within the regenerative medicine field and that are stock market listed.

taken together, the results of the descriptive interrogation of data and a subsequent phase of regression analysis, statistically verified wider impressions that the sector was not sufficiently underwritten by venture capital to withstand the impact of the recession triggered in 2007-2008 (Pangarkar et al. 2010). Fiscal indebtedness amongst the firms appeared to be particularly problematic (see: Kewell et al 2009). Indeed, it seems to be the case that a culture of over-investment had not only caused the market to overheat but may have also, simultaneously, established adverse conditions in terms of risk position, profitability and research intensity among the initial sample population. Companies with a greater asset base, and with higher market value were, paradoxically, shown to be more risky, because of past stock market over-valuation and a lack of successful product efficacy.

the third stage of the research distilled the research sample down to 50 firms for more detailed analysis, which were separated from more peripheral firms through a painstaking process of cross-checking between Thompson DatastreamTM and accounting information published on company websites.

some notable firms are apparent within this subset. Among the highest cash accumulators (i.e. those with increasing sales revenues and a healthy net cash flow position), most were located in the US, followed by Europe, Australia and Korea. The international spread of the industry, from its antecedents in the United States (US), is confirmed by the presence, within this group, of some significant European firms.

in a sector characterised by vast performance disparities, the growth percentages were extraordinary for some firms with increased sales revenues: from 325.81 at the bottom of the top ten, to 32942.86% at its apex (c.2005-2009). The overall picture is of strong income escalation for a small number of well placed competitors in the regenerative products markets and of small group moving ahead of the field. All firms within the sector are nevertheless 'cash poor' by stock market standards, remaining ostensibly dependent upon external sources of leverage, particularly with respect to the financing of programmes of expansion and Research and Development (R&D) initiatives.

yet despite these positive signals, there is strong evidence to suggest that even the most successful or sustainable of regenerative companies are not sufficiently ready to offer a broad spectrum of marketable product lines (e.g. Geron-which attracted significant venture capital but has only been able to conduct phase 1 and 2 clinical trials thus far).

in summary, it can be said that even among the more prosperous and successful firms within the industry most are in a holding pattern where the development and testing of potential promising product lines allows them to continue to attract funding and expand the size of their operations. A smaller group of companies which has developed marketable product lines operates in niche markets (Orthovita, Tigenix, Biomimetic are all working on bone grafts for example).

in regard to another of our tasks - the construction of a global SQL database - our results enable us to identify some much wider, international trends, especially in regard to emergent activity over time, 'hot spots' of activity, and links between firms, trials, and intellectual property (patenting). REMEDIE has produced a quantitative database tracking geo-economic trends over time, starting in 2003, the year when the field of regenerative medicine/stem cells began to develop more rapidly worldwide. The original 'cut-off' date for collection was 2008 (as described in the initial proposal) but this was extended to the end of 2010 in the case of corporate and clinical trial data.

in terms of composition, n=473 entries are recorded in the 'Organisations' table, of which n=392 are companies. As expected, California has by far the most firms with other major concentrations in Maryland, Massachusetts, Florida, New Jersey, New York and Texas. Wisconsin has fewer firms than one might expect given the state's importance with regard to stem cell science. Such data illustrates the regional infrastructure (and so networks) that have been built in each State. The significance of the corporate data on RM is closely related to clinical trials activity because a prospective product must proceed through clinical development and obtain regulatory approval - in the case of the EU via the Advanced Therapy Medicinal Products (ATMP) Regulation.

A 'spike' around 2000 was observed, which continued into 2001 and 2002, which is perhaps counter-intuitive. This data call into question ideas around 'lack of investment' in subsequent years because as noted above considerable investment had already been undertaken at the start of the decade (though again, that might have had a negative effect for some firms).

mapping clinical trials activity provides a measure of the extent to which translation to the clinic is occurring in an emerging field like regenerative medicine - who is sponsoring trials, where they are located (which is not necessarily in the same country as the sponsor), what type of cell therapy (autologous or allogeneic), and at what stage (phases I, II, III) in the clinical development process. Tracing developments in clinical trials activity can also inform analysis of emerging regulatory frameworks.

WP7 has collected trials data by region and key countries for illustrative purposes (USA, UK, China, Japan and S Korea, and India). These countries were selected because they are amongst the most active in terms of RM clinical trials and provide a global 'spread' across regions. In the context of REMEDIE, comparisons between countries and regions can provide useful information about the positioning of European companies relative to global competitors (e.g. type of product, translational processes etc.) as well as trends and overall prospects in what is a fast moving field.

the US conducts more clinical trials than any other country in autologous cell therapy. However, US dominance has decreased in recent years as a proportion of all trials conducted with this cell-type. Interestingly, clinical trials data collected via industry-orientated sources shows no automatic correlation between the number of companies in EU Member States and current clinical trials (CTs) activity.

developments of note with regard to clinical trials during the course of the project, because they utilise embryonic stem cells and mark the first of such trials, are the Geron trial for treatment of spinal cord injury, which received FDA approval in 2010; and the ACT trial for Stargardt's macular dystrophy, also with FDA approval. Both platforms use in vitro fertilized blastocysts (derived from embryos) as cell source.

of the 15 main stem cell companies (worldwide) currently developing therapies, more than half have competing programmes in three major disease areas: cardiovascular, gastrointestinal and the central nervous system (CNS).

it should be noted that regulatory approvals may vary affecting product markets. For example, Belgium's TiGenix ATMP approval for ChondroCelect, has not been secured in the US: the FDA has demanded another trial before it can submit for US approval, with a 5 year delay before market approval if likely. Within a regulatory universe, difficulties can also arise over the trial period for technical or financial reasons. These programmes have however received technical set-backs and their future is unclear at this time. The UK-based Intercytex, once a leading European SME in the RM field, developed a series of non-stem cell autologous and allogeneic cell therapies for wound care, facial rejuvenation, and hairloss, which had been under clinical development for a number of years. Typical of the company's product portfolio were ICX-SKN and Cyzact (formerly ICX-PRO), topical wound care products designed to stimulate active repair and closure in persistent chronic wounds, with Cyzact completing a Phase III trial. However this and much of the company's other IP has recently been sold to other parties to meet needs for financial restructuring, the company retaining rights to one product, Valveta which is continuing in clinical development.

one factor which may be exacerbating the investor caution in Europe we noted above is lack of certainty concerning intellectual property rights, such as patents. The issue of whether cell therapies will be patentable in the EU appears an obstacle to investment and again this is an area where stakeholders believe that US competitors enjoy a comparative advantage. However, divergent views about IP were expressed during our fieldwork: for instance, patenting in the RM field is regarded as difficult not because of EU blocks on stem cell-based patents, but because of the amount of prior art. One pharma executive described IP as 'a minefield' because of the lack of certainty about who owns what and about which IP is going to be most important, and suggested that the twenty-year life of a patent was too short for cell therapies because the much lengthier R&D process left companies insufficient time on the market to recoup their investment before the entry of competitors. The relative importance of alternative forms of IP such as trade secrets and know-how were emphasised by a number of interviewees, again suggesting a marked difference between the RM sector and the wider biopharmaceutical industry.

interim conclusion: the current state of play

regenerative medicine firms were, and remain, commercial undertakings burdened by profound anticipation, as enterprises in which substitutive medicine has long since staked its future (Johnson et al. 2010; Pangarkar et al. 2010). Thus, regenerative sciences are increasingly considered as valuable for the treatment of cancer, heart disease, and diabetes, as well as a plethora of orphan diseases for which there are few alternative conventional treatments. The possibility that the regenerative sciences might one day achieve this type of broad spectrum appeal, that is to say, diversify 'beyond substitution' is perhaps the key driver behind continued investment in the sector, despite its history of financial underperformance and negligible profitability (Lysaght, Jaklenec and Deweerd 2008; Mason and Dunhill 20008b; Pangarkar et al. 2010). However, whilst the licensing system has been centralised, the EU remains a fragmented healthcare market with diverse reimbursement systems and varied uptake of new medical technologies.

demonstrating cost-effectiveness and gaining positive decisions from Health Technology Assessment (HTA) bodies is a significant challenge for industry and there is concern that HTA bodies have not begun to address the question of how to evaluate RM products and services. In relation to cost-effectiveness industrialists expressed concern that many of the cost-savings that RM products might offer would be outside the healthcare budget and that current methods of assessment would not take these into account. This is a key issue that needs to be addressed. Linked to the question of cost-effectiveness was the issue of business models. Many interviewees expressed the view that the RM sector had yet to demonstrate the sustainability of business models for producing cell therapies.

regulation and the Governance of Regenerative Medicine

the REMEDIE project explored the regulatory aspects of the field in a number of ways. We examined (in WP2) the ways in which the sourcing of tissue - notably oocytes for research - was subject to regulatory oversight and the degree to which this was effective. We also gathered international data on the diverse and divergent political cultures shaping the field (WP4), and the specific forms and levels of governance that characterise it, as one moves, for example, from the USA, Europe to China (WP3).

in regard to the first of these, despite being such a contentious issue, comparatively little is known on an empirical level about oocyte procurement for research. Most literature focuses on normative and/or theoretical questions related to the question of commercializing the (female) body, questions of ethical permissibility of oocyte procurement for research, or questions of optimizing regulation. Existing empirical knowledge about oocyte procurement largely refers to oocyte procurement for IVF purposes (Waldby 2008; Ikemoto 2009). Some studies have critically analysed particular models of oocyte procurement and individual policy debates (Throsby and Roberts 2008; O'Riordan and Haran 2009), but no empirical overview of oocyte procurement practices for research purposes in Europe has been available so far. The objective of WP 2 was to close this gap and to map out and analyse the practices and institutions of human oocyte procurement for research purposes in Europe.

oocyte donation for research purposes is among the most contested issues related to stem cell research. Although it has not become as politicized as embryo protection, oocyte donation has caused considerable concern among academics, NGOs, feminists and researchers. In the past few years, it has attracted increased attention and became subject of a series of policy recommendations, guidelines, reports and debates. The main concerns are that the practice is onerous and bears a number of health risks to donors and that it may bring about a new form of exploitation of women.

human oocytes are required for somatic cell nuclear transfer and for the generation of parthenogenic stem cells. When somatic cell nuclear transfer (SCNT), also known as research cloning or therapeutic cloning, began in the late 1990s, it reinforced concerns among feminists about the emergence of a new biotech industry that would rely on access to women's bodies and bodily materials and might bring about new forms of exploitation of women.

we found that in Europe research in SCNT requiring human oocytes is rare. Yet this situation might change again if the factors that influence demand and supply for oocytes in the field of stem cell research change.

For instance, many stem cell researchers have switched from SCNT research to induced pluripotent stem cells (iPS), viewing them as an alternative source of patient-specific stem cells without the logistical and ethical problems of using human oocytes or embryos. However, if iPS turns out to be too difficult and/or unsafe to deal with in the long run, this situation may change.

one of the most significant reasons why this type of research is relatively rare in Europe, is the enormous logistical difficulty of acquiring sufficient numbers of human eggs, in particular of 'good quality' eggs. Good quality eggs, from the point of view of research are mature, 'fresh', recently extracted eggs - in contrast to immature eggs or so-called failed-to-fertilize eggs left over from IVF. Further, oocytes derived from younger women are of better quality. Logistical difficulties, however, do not exist in isolation from institutional and cultural contexts. The institutional and cultural embeddedness of procurement logistics becomes most obvious with regard to non-payment provisions and mechanisms of health care coverage. In Belgium, for instance, egg sharing has become rare since Belgian IVF couples were granted up to six free cycles of IVF in 2003 (Pennings 2006). Many interviewees told us that IVF patients and clinics are rather reluctant to give away oocytes which the woman could use for her own IVF treatment. So-called non-patient donors, on the other hand, are reluctant to undergo the onerous procedure of oocyte donation without financial gain. On the whole, several researchers we talked to emphasized that very few women were willing to go through the process of egg retrieval without being offered a material incentive.

thus, one of the findings is that the feasibility and comparative attractiveness of stem cell research strategies which rely on human oocytes should not be overrated. In Europe, they are on the contrary, rather limited. Limiting factors are ethical concerns, both researchers' own concerns and perceived or anticipated public concerns, legal restrictions, availability of alternative research strategies such as iPS cells, logistical difficulties related to the delicate nature of human oocytes (e.g. spatial distance between clinic and lab) and a great reluctance of women to donate without being paid.

on this last point the Council of Europe's Convention on Human Rights and Biomedicine of 1997 (Oviedo Convention) applies, but its provisions are rather vague. It prescribes in Art.21 that 'The human body and its parts shall not, as such, give rise to financial gain.'

A factor which is hugely important for this type of research is the infrastructural connection between stem cell research and IVF facilities, the IVF-stem cell interface (Franklin 2006), especially in the form of personal overlaps and close spatial proximity. Good quality oocytes are an object of fierce competition between research on the one hand and IVF patients and clinics on the other. Offering financial incentives is a way for research to become more independent of these connections.

in regard to the broad, second theme relating to political cultures WP3 compared three major geo-political regulatory spaces of biomedicine and regenerative medicine: the US, Europe, and China. All three political systems have explicitly dealt with these pressing issues at a political and policy level, facing similar challenges. Most visibly, all three systems have undergone more or less significant institutional innovation. Pointing to convergence, all three systems have created and (partially) implemented some kind of risk-based approach to regulating regenerative therapies. However, debate over what a 'regenerative' therapy is, how to define it, and whether to subsume it under existing legislation or to create some sort of lex specialis, has been a contentious issue.

we found important structural differences between the three countries regarding the regulation of the bio-economy and so regenerative medicine more specifically. Although outcomes are similar in the US and Europe, the ways in which cell products are managed are strikingly different. What was true for the GMO regulatory process, seems to hold true also for regenerative medicines regulatory policy making. As Vogel observes: 'The United States initially chose to regulate both GM food and seeds under existing laws, while EU legislation established a distinctive and complex set of new regulatory requirements that apply only to this new agricultural technology.' (Vogel 2003, p 564).

ethical and Legal Developments and Tensions in the Field

national regulations and practices on RM differ, therefore, in the major regions of the global bioeconomy. This variation is extremely important and much more intense than in other fields of health technology. For instance, each legal system establishes specific regulatory frameworks regarding the derivation and use of stem cells. This fragmented regulatory landscape leads to forum shopping, stem cell tourism and exploitation of vulnerable population rights. This variation has also proved to be extremely inefficient from the point of view of resource allocation. An optimal level of international ethical and legal harmonization has proved to be very difficult.

REMEDIE aimed at understanding the origin, nature and consequences of the regulatory variation in which stem cell research is conducted throughout Europe. Laws in each jurisdiction are supposed to reflect a social consensus on the boundaries of what is considered acceptable for each society; however, legal frameworks for RM in each country cannot be fully explained by or attributed to the prevalence of a particular moral or political standpoint. The process of debate which leads to policy making is subject to degrees of contingency.

consensus on controversial topics such as those relating to regenerative medicine is fragile and often challenged on moral and political grounds, with national states' sovereignty playing a key role in this matter, deflecting moves towards harmonisation. Moreover, consensuses tend to collapse rapidly as innovation disturbs agreed moral boundaries in this fast-moving field of science and technology. Finally, ethical consensus on RM is also dependent on other contingencies, including historical constraints, the existence of pressure groups, the prevalent political ideology, individual leadership of policy makers and their ability to create pragmatic regulations which 'do the job' while avoiding controversy.

does ideological similarity play a relevant role in mapping the communities of bioethics? Throughout the development of this research and the interviews with experts in the field, we have concluded that this hypothesis was only true in the case of major religions, especially Catholicism. Researchers who support the Church's official position on matters related to regenerative medicine create very cohesive and well-organised communities of bioethics, with their own media, impenetrable to those who are not members of these communities. Aside from this specific context, we have identified discrete communities of bioethics differentiated by cultures - especially shared language - and different academic traditions. The Anglophone area is the more internationalized or globalized one, in terms of participation of multinational bioethicists and international networks. It is also the strongest area in terms of number of participants, publications, active organisms, and funding.

one of the key domains within which bioethics affects the RM field is in regard to its role in the legal provisions surrounding patenting. Intellectual property rights, patents in particular, can be especially important for bringing hESC inventions in regenerative medicine to the market.

stakeholders in regenerative medicine need to exploit the benefits generated by the utilitarian trade-off between private and public interest in patent systems. Patents generate returns for publicly or privately funded research and attract investment from the market for expensive downstream activity when productivity is low or non-existent. Patents signal success in research and business, and when placed in the public they attract the attention of investors, competitors, patients and health care providers. Patents bring inventions into the public domain and enable access for others to the invention and further benefit generating activity based on the invention.

there are two challenges related to the possibility of establishing bioethical limitations on patenting human biological material:
- The diversity of local approaches to the applicable bioethical limitations in law; and
0 The boundaries of the applicable bioethical limitations remain unclear and contested in law.

human biological material is in fact regarded as patentable subject matter in the patent jurisdictions of the world. In Europe patent legislation, the European Patent Convention (EPC) and the EU Biotech Directive (Article 5(2)), provides for the patenting as inventions of isolated elements of the human body or elements produced by means of a technical process subject to meeting the other requirements of patentability (novelty, inventive step, industrial applicability and not being excluded on public order or morality grounds). In contrast, in Europe, the simple discovery of one of the elements of the human body is not a patentable invention (Article 5(1)). In the US the human contribution of isolation, purification or modification renders human biological material as 'products of human ingenuity' as opposed to 'products of nature' and thus patentable subject matter.

patent regimes in Asia also accept the patentability of human biological material. Indian patent law denies patentability from a 'discovery of any living thing occurring in nature', but when the discovery leads to establishing practical use patentability is no longer refused. The South Korean patent examination guidelines hold that 'the method for artificially isolating substances from things in nature, not a mere discovery, is considered to be a statutory invention. So are the isolated chemical substances and microorganisms.' The Japanese patent examination guidelines include similar provisions.

diversity and contested boundaries: human DNA patents

patent laws, within the above framework, have acknowledged isolated human DNA as patentable subject matter. The US and the European patent regimes both granted patents for the BRCA 1 and 2 genes and the associated diagnostic method. In Europe their patenting relied on the clear legal provisions of 'isolation' and 'technical process'; the ethical oppositions against the patents, a characteristic of European patent law, were rejected. The US process focused on the fuzzy distinction between products of human nature and human ingenuity in US patent law which is now under reconsideration in an ongoing lawsuit by the American Civil Liberties Union against the BRCA 1 and 2 patents. The 2010 district court judgement,

opposing previous practice, declared that isolated DNA must be regarded as products of nature, and thus unpatentable, as the process of isolation does not produce markedly different characteristics than those possessed by genes in the human body. The case is now under appeal, and its outcome may change US patenting policy regarding isolated human DNA. The potential global impact of US policy change is difficult to predict; in Europe only the amendment of the current liberal legislation would lead to alignment with the US practice.

diversity and contested boundaries: human stem cell patents

in the current state of the law isolated human stem cells in general constitute patentable subject matter. Adult stem cells, pluripotent human embryonic stem cells (hES) and induced pluripotent stem cells (iPS cells) isolated from the human body are patentable products of human activity. Isolated human totipotent stem cells may, however, attract opposing legal characterizations. Patent regimes focusing on the act of isolation may treat totipotent stem cell lines as elements isolated from the human body by way of human activity and regard them as patentable subject matter. On the other hand, patent jurisdictions may also take into account the biological characteristics of totipotent stem cells and treat them not as products but as (potential) living (human) beings.

the clearest indication that totipotent cells may not be considered as patentable subject matter can be found in the European patent law. There is no evidence that other patent jurisdictions would follow the same approach and exclude from patentability isolated human totipotent stem cells under the bioethical principle of non-instrumentalisation of the human body expressed in the above provision of European patent law. The invention/discovery or the products of nature/human ingenuity distinctions may not be able express the same restriction to patentable subject matter, though the general public morality clause, if a patent regime contains one, may prevent patentability. The diversity of local solutions may increase if the developing approach to human DNA patents finds ground in US patent law, which may be applied so as to exclude isolated human totipotent cells from patentable subject-matter on the ground that their characteristics are not sufficiently distinct from the characteristics they demonstrate in nature.

the European approach remains contestable. First, it effectively equates without further justification isolated totipotent cells, which are isolated biological material, with the human embryo and confers them the same moral status. Second, it avoids addressing the issue that totipotency is relative to the environment and isolated and modified totipotent cells are different from totitpotent cells in their natural environment. Third, it ignores an ethically relevant distinction alternative to the toti-/pluripotent concept pair; that between modified and unmodified stem cells. This was raised in EGE Opinion No. 16 (2002) on the ethics of hESC patenting, which found that 'unmodified' hES cells and cell lines are not patentable as their patenting may violate the non-commercialization principle, whereas in the light of the economic and social purpose of patent systems 'modified' hESC patenting could be allowed.

patent regimes, with the exception of the US, are equipped with clauses which exclude inventions from patentability on grounds that the exploitation of the patent violates public order or morality, as enabled in international law by Article 27(2) of the TRIPS Agreement. The WTO (and TRIPS) member China's patent law contains an exception similar to that in other states stating that 'no patent right shall be granted for any invention-creation that is contrary to the laws of the State or social morality or that is detrimental to public

interest' (Article 5 of Patent Act). The 1970 Indian Patent Act's morality clause provides that 'inventions the primary or intended use or commercial exploitation of which would be contrary to morality' are 'not inventions' (Article 3b). The morality exception in South Korean patent law reads that 'inventions liable to contravene public order or morality or to injure public health shall not be patentable' (Article 32 of Patent Act). The 1959 Japanese Patent Act's morality clause is formulated in the same way (Article 32).

these morality clauses lack the detail and the distinctions applied in the European regime. Nonetheless, they offer potential bioethical limitations to the commercial exploitation of biomedical inventions. In the Indian patent office's interpretation being contrary to morality means that the use of the invention would 'violate the well accepted and settled social, cultural, legal norms of morality'. It produced an example, a 'method of cloning', for an invention in breach of the requirements of morality. The South Korean examination guidelines interpret the morality clause in the patent act as morality meaning a 'moral sense generally accepted by a society or particular group of people'. There is no evidence that pluripotent hESC patents have been subject to opposition on public morality grounds in these states.

the explicit public morality exceptions indicate that European patent law gives more weight to the ethical limitations of biomedical inventions than other patent regimes. More importantly, the European patent regime has not refrained from applying the exceptions to morally contestable patents. The 'industrial or commercial use of human embryos' clause proved especially controversial in the European history of human stem cell patenting separating Europe from the global market of stem cell patents and causing considerable tensions between European states with different moral approaches to human stem cell research.

the first indication that (the prohibition on) 'embryo destruction' would become a common bioethical and legal principle in European patent law by way of the interpretation of the 'industrial or commercial use' clause was the European Patent Organisation (EPO) Enlarged Board of Appeal decision concerning the Wisconsin Alumni Research Foundation (WARF) hES cell line patents. The decision in 2008 established that the 'industrial or commercial use' clause, which was introduced to prohibit the commodification of the human embryo, excludes the patentability of hES cells or cell lines on grounds that the production of hES cells requires the destruction of the human embryos used as sources. The Board held that the creation of the claimed product is part of its industrial or commercial exploitation, and when it involves the destruction of human embryos it will violate the said prohibition. In this case the performing of the invention (the embryo destruction) was contrary to the specific morality provision of the EPC.

the question is now before the EU Court of Justice equipped with jurisdiction to interpret the EU Biotech Directive which originally introduced the 'industrial or commercial use' clause to European patent law. The case before the EU Court of Justice originated from Germany, where the Federal Patent Court held following EPO practice that the hESC patent in question, the 'Brustle patent', was in breach of the 'industrial or commercial use' clause as the destruction of human embryos was a 'real and integral part of the invention.' The German court's interpretation was strongly influenced the German Embryo Protection Act which prohibits the use of human embryos for purposes other than those from which the embryo may receive direct benefits (e.g. diagnosis or treatment of that embryo).

on the level of decision-making in the European patent system the solution accepting the plurality of local

bioethical approaches would cause considerable difficulties. Without being able to rely on an explicit morality clause imposing uniform requirements on the Contracting States the EPO will need to apply the general morality clause of the EPC (and the EU Biotech Directive) having regard to the diversity of national approaches on the use of human embryos for research purposes. Adopting the highest standard under the general clause and denying patentability from hES cells would satisfy the States with a prohibitive attitude to human embryonic research but it would be incompatible with the leeway granted under the general morality clause to all States in the European patent system. In contrast, allowing the patentability of hES cells under the general morality clause, having been unable to establish the 'embryo destruction' principle as a common European moral requirement, would satisfy the States with liberal regulation on stem cell research and it would enable States with a prohibitive regime to refuse enforcing the patent within their jurisdiction. This is a compromise solution and the only workable solution in a pluralist, multi-layered regime. However, the fragmentation of the system, which would follow from this approach is contrary to the rationale of the EPC and the EU Biotech Directive (Article 6(1)).

potential Impact:

the potential impact of the project and its wider societal implications

the REMEDIE project has, for the first time, provided a detailed and critical analysis of the current and likely future prospects of regenerative medicine within Europe and more widely. We summarise below its key lessons concluding with a series of policy recommendations for European MS, the Commission and Parliament.

within Europe the RM industry is highly heterogeneous, not only in terms of the different sectors, but also in terms of the multiple technological approaches - different cell sources, in- and ex-vivo gene therapies etc - being developed within each sector.

at the same time, it is important to note that the different sectors and technologies do not operate in isolation but can also act in combination with each other to develop novel regenerative strategies, for example genetically modified cells and combined cell and bioscaffold treatment options. In terms of the challenge of regulating this variety of novel technologies the centralised ATMP has been generally welcomed by industry stakeholders, primarily because of its focus regulating the means and not outcomes of innovation. However, it is also worth noting that the only cell therapy approved so far via the ATMP pathway has been an autologous, somatic cell TE product for cartilage repair. It is likely that a few well-placed 'trailblazer' firms, somewhat analogous to Geron in the US, will be the first to bring one or more of the stem cell therapies currently in clinical trials through the ATMP approval process. These 'first in' firms may well need additional support in order to establish an accepted approach that other firms will be able to follow, but will depend on access to public resources (e.g. facilitation through healthcare systems) and not just venture capital support, important though this is.

at present, all our data indicate the current significance of autologous-derived therapies, trials and patenting activity. In all cases, compared with Europe, the US is the leading region globally and by a significant order. This is despite having had a restrictive legal regime at the Federal level over recent years, demonstrating the importance of the local, State-based sponsorship of the field, especially in

California and Massachusetts. Although there are strong indicators pointing towards a potentially competitive position for the EU within the global RM bioeconomy - a solid research base, a high level of scientific output and a diverse group of RM firms - the global picture in the wider biotech sector suggests that the US will rapidly establish an unchallengeable dominance, based on three key advantages, namely, higher levels of R&D funding, greater access to VC finance, and the single largest market for health technologies. One leading EU firm suggested that their main US competitor was 'playing in a different league' with five to ten times the amount of VC funding. One venture capital executive emphasised the disparity in growth funding, suggesting that European VC firms can build a firm to a EUR 50M valuation but are then forced to sell because they lack the resources to continue to the next stage. This lack of capital could have a number of consequences for commercial strategy with companies being forced into premature decisions to seek a public listing or to enter clinical trials.

REMEDIE has identified diverse regimes regulating the ethical boundaries of biomedical research activity and the ethics of commercializing biomedical innovation in the world. These differences have an impact on the research environment, the model for financing research and translational activity and the use of intellectual property rights in the course of biomedical research. The taxonomies label the different national regimes on biomedical research as permissive (liberal), intermediate and restrictive.

the introduction of a human rights perspective on human embryonic/stem cell research has not affected the diversity of ethical and moral approaches. The Oviedo Convention on Human Rights and Biomedicine , created to establish a European framework concerning the human rights limitations of biomedical research and therapy, builds on the protection of human dignity and integrity. The Convention accepts the margin of appreciation of Contracting States on bioethical issues and leaves the question of hES research partially open by the provision that 'where the law allows research on embryos in vitro, it shall ensure adequate protection of the embryo' (Article 18(1)). Arguably, this could encompass the destruction of human embryos in an adequately safeguarded process for the purpose of hES derivation. The more contentious provision in Article 18(2), which has prevented the ratification of the Convention by all Council of Europe States considering it as either liberal or conservative, prohibits the creation of embryos for research purposes.

key lessons relating to corporate policy and practice:
- European RM firms are not distributed evenly among member states but are concentrated in established (France, Germany, UK) and emerging (Spain, Switzerland) hubs.
- The majority of firms in all states are small and financially vulnerable, and the concentration of companies in certain locations does not necessarily reflect the individual strength of those firms.
- Having a national strategic plan for the support and development of regenerative medicine is a key pre-requisite for the development of an RM sector. Most national strategies to date have focused on supporting basic or translational research but there is also support for commercialisation via state pump-priming - for example the UK Technology Strategy Board has recently committed £21.5M to fund commercially-oriented RM projects. This may help to relieve the pressure on firms often associated with dependency on venture capital.
- The following core components of national strategies for RM have been identified: a enabling legislative framework for hES research (though this need not be seen as determinant of a country's capacity to promote the field, as in Germany and, in part, the US); dedicated funding including the development of

major research centres and shared infrastructure such as stem cell banks; the creation of a national network to promote scientific collaboration; the promotion of public-private partnerships and international research collaborations.
- There may also be examples of best (and worst) practice to be gleaned from national strategies and practices - Sweden and Belgium, for example do not have many RM firms but they do have a few highly performing RM biotechs.
- As part of the broader reform of EU innovation strategy, it is likely that greater coordination of the multi level governance framework will be necessary to ensure more effective support for the RM sector and to avoid unnecessary duplication of regulatory activity.

key lessons relating to ethical and legal policy and practice

overall, there are two issues here which deserve attention: the sourcing of RM tissues, and the patentability of tissues derived specifically from embryonic material. We found that two different models have evolved over the past few years that allow researchers to offer economic incentives while circumventing non-payment provisions: 'egg sharing' and the reallocation of compensated oocytes.
- One conclusion that could be drawn from these data is that the trend towards material incentives is a strategy to release researchers from the infrastructural requirements that tie them to the IVF sector.
- What the empirical data show is that there is a strong tendency to undermine and circumvent existing non-payment provisions through introducing material incentives in a legal grey zone between outright payment and strict non-payment, inter alia through 'compensations' without the requirement to document expenses.
 With respect to the question of patentability, inventions in human embryonic/hES research represent a particularly difficult ethical issue for European patent law as many issues within this area remain ethically controversial.
- The destruction of the embryo in order to harvest stem cell lines regardless of the origin of the embryo (viable donated supernumerary IVF from a parental project, non viable IVF embryo from a parental project, IVF and SNCT research embryo) is the main source of the ethical controversy surrounding this technology. The implementation of an 'embryo destruction' principle in patent law within the examination of patentability remains a pressing question in different patent jurisdictions.

overall lessons for policy: recommendations from the REMEDIE project

the findings of this report clearly illustrate that RM innovation within the European Union is taking place within a complex multi-level governance framework which comprises sub-national, national and transnational networks and institutions. International alliances, whether within the EU or beyond its borders, are seen by most stakeholders as a vital part of this. Our key policy recommendations below seek to address this and to do so informed by an understanding of the scientific, corporate, clinical and ethico/legal and political challenges that have been discussed above:

governance

coordination for effective policymaking requires cooperation across departments and between member states. A forum should be established which brings together all relevant EU departments and bodies, e.g.

DG Research and Innovation, DG Sanco, DG Enterprise and the EMA. There are many substantive issues we have noted that need cross-department collaboration; for example, the tendency to undermine and circumvent existing non-payment provisions in regard to sourcing tissue; the need to review existing clinical trials requirements and further moves towards harmonisation; the need to clarify patenting law in relation to the destruction of embryonic material, and so on.

creating a strategy:
- Leading actors within RM in the EU should be brought together to explore potential for coordination and cooperation.
- JRC IPTS (Seville) has a strong track-record in policy reports on health biotechnology (including ATMPs) but has recently discontinued this activity. Additional funding should be provided to IPTS so that it can resume this activity.

research Infrastructure:

Long-term funding should be given to infrastructure which facilitates research: creation of a European RM network including funding of annual meetings, renewed funding for a hES registry and enhanced cooperation between stem cell banks within the EU. The network should play a leading role in public engagement on RM issues as well as sharing practice on national strategies (especially drawing on practice within the three European hubs we have identified).

public sector innovation and link to the wider health care system:
- Increasing policy attention is focused on the role of innovation within the public sector. This may be of particular importance if, as many believe, hospital-based service delivery may be the best way to get (autologous) cell therapies in the clinic in the near-term.
- Many of the cost-savings that RM products might offer will be outside the healthcare budget and current methods of assessment (HTA) do not take these into account: this failure needs to be factored into clinical procurement and reimbursement programmes.

exporting RM products outside the EU.

the European Union should facilitate RM companies establishing themselves in markets outside the European Union.

regulatory harmonization

the EU has been characterized as a regulatory state, an institution whose primary mode of policy making is regulation. The creation of a single EU process for the licensing of RM products through the ATMP has been a major achievement. The EU has unique strengths in the formation of regulatory networks and the processes of regulatory harmonization which may be of significant utility in supporting RM innovation within the EU.

intergovernmental alliances and international harmonisation

RM forms part of a global value chain of innovation. The EU should plan to access this value chain more efficiently.
- The EU should seek intergovernmental alliances with states where RM is a priority and which have particular strengths from which the EU would benefit through an exchange relationship.
- EMA should be given additional funding to enhance its work on international harmonization that promotes the EU model of innovation. Building on existing activity (e.g. the bilateral relationship with the FDA on pharmacogenetics, work within the ICH, and bilateral relationships with regulatory agencies in NIEs like China and India), the EMA could deepen and bolster its regulatory advisory and enabling capacity.

list of Websites:

http://www.york.ac.uk/satsu/remedie

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Documents connexes

Final Report - REMEDIE (Regenerative medicine in Europe: emerging needs and challenges in a global context)

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