CIRM and UKRMP: different ways to invest in regenerative medicine

Irving L. Weissman1* and Fiona M. Watt2*

1Institute for Stem Cell Biology and Regenerative Medicine and Stanford Ludwig Center for Cancer Stem Cell Research and Medicine, 265 Campus Drive West, Room G3167, Stanford, CA 94305-5461, USA

2King’s College London Centre for Stem Cells and Regenerative Medicine, Floor 28, Tower Wing, Guy’s Hospital Campus, Great Maze Pond, London SE1 9RT, UK

*Corresponding authors: irv@stanford.edu fiona.watt@kcl.ac.uk

The California Institute for Regenerative Medicine (CIRM) and the UK Regenerative Medicine Platform (UKRMP) have similar objectives, but their histories, funding mechanisms and governance could hardly be more different. Here, we compare the two programmes and explore their impact in translating stem cell research into clinical applications.

Scientists cherish their autonomy, mobility and international perspective. We are just as likely to know what is happening in a colleague’s lab in a different country as to know the latest data from a lab just across the hallway. One thing that is heavily influenced by location, however, is our source of funding. This in turn depends on the political climate of the country in which we work, as exemplified by research on stem cells.

CIRM was launched in 2004 amid considerable publicity, with $3 billion to spend on regenerative medicine within 10 years. In contrast, the UKRMP began with little fanfare in 2013 and is investing £25 million (roughly $38 million) over 4 years. To put these figures into perspective, the annual extramural research budget of the US National Institutes of Health (NIH) is approximately $25 billion. In the UK the government-funded Medical Research Council (MRC), the counterpart of the NIH, spent £771.8m on research last year while the UK’s other major biomedical research funder, the Wellcome Trust spends more than £700 million a year. In this piece we examine the impact of these two initiatives on stem cell research and translation.
History and geography

California’s Stem Cell Agency, CIRM (https://www.cirm.ca.gov/), has its origins in the US government’s opposition to funding research on human embryonic stem cells (ES cells) under the presidency of George W. Bush. Frustration that this was holding back fundamental research and clinical applications resulted in a remarkable coming together of scientists, patient advocates and lawyers in California to exercise the right of individual states to pass and fund propositions not funded by the federal government. Led by lawyer Bob Klein, they wrote a ballot proposition, Proposition 71, which was submitted to the electorate of California and approved into law by 59% of voters. This law raised funds directly from the public rather than indirectly via a national funding body by authorizing the sale of State bonds to fund $3 billion of stem cell research in California (https://www.cirm.ca.gov/sites/default/files/files/about_cirm/prop71). Proposition 71 not only emphasises the health benefits of research but explicitly states that it will benefit the California economy by creating jobs, creating California centers of stem cell research, and by advancing the biotech industry.

Meanwhile, in the UK regulations governing research on human ES cells were framed in the context of existing legislation known as the Human Fertilisation and Embryology Act 1990, which had led to the creation of the Human Fertilisation and Embryology Authority (HFEA) (http://www.hfea.gov.uk). The legislation was updated in 2001 to accommodate advances in human embryonic stem cell research and further revised in 2008, in part to address hybrid or admixed embryos. In 2002 the UK Stem Cell Bank was created to store, characterise and distribute human ES cell lines; new lines created in the UK under license from the HFEA must be deposited in the Bank. The HFEA thus has a dual role in overseeing UK fertility clinics and in licensing and regulating human embryo research.

In contrast to CIRM, restrictions on human ES cell research were not driving the creation of UKRMP (http://www.ukrmp.org.uk/) Instead, it was designed to target translational barriers, since the UK government’s research councils (equivalent to institutes of the National Institutes of Health in the USA) perceived that the UK was strong in the basic science underpinning regenerative medicine but weaker in the translation. This in turn reflected a fundamental shift in UK government thinking since 1997, now considering research as a vehicle for wealth creation rather than solely a part of the higher education portfolio.

In 2012, the UK government announced that regenerative medicine was one of its strategic priorities in science (https://www.gov.uk/government/publications/eight-great-technologies-regenerative-medicine). By this time the UK research councils were establishing the UKRMP.
and Innovate UK (a public body that reports to the Government’s Department for Business, Innovation and Skills) was setting up the Cell Therapy Catapult (https://ct.catapult.org.uk/), one of a network of UK technology and innovation centres, to grow the UK cell therapy industry. The nature of the UKRMP was determined by a strategic review led by the MRC in partnership with three other research councils and Innovate UK, in consultation with the research community. ‘A Strategy for UK Regenerative Medicine’ was published in 2012 (http://www.mrc.ac.uk/news-events/publications/regenerative-medicine-strategypdf/).

**Governance**

In addition to creating CIRM, Proposition 71 created a governing Board called the Independent Citizens’ Oversight Committee (ICOC), composed of academic leaders (mainly Deans and Presidents of Universities and Medical Schools), business leaders and patient advocates. The Board has responsibility for adopting scientific, medical, ethical, and intellectual property policies; making final decisions on all grant and loan awards; and overseeing the operations of CIRM. Not only is the governing Board distinctive in its membership (contrasting, for example, with NIH study sections that draw their membership largely from the academic community), but also in conducting its meetings in public. Anyone can attend CIRM governing board meetings and comment on agenda items, and meeting agendas and outcomes are available on the CIRM website.

Not surprisingly, UKRMP governance is quite different. The director and programme manager are MRC employees who work with an executive group comprising representatives from each of the three sponsor research councils. UKRMP activity is overseen by a programme board with strong international representation and a mixture of academics and representatives of biotech and Pharma. Funding decisions are made by the executive group on the advice of the programme board, following conventional and confidential peer review.

**Spending the money**

Figure 1 shows the major categories of CIRM expenditure. Initially, education and training were a high priority, to grow a new generation of stem cell researchers. A further priority was to build new research facilities, which would not only support existing researchers but also encourage an influx of young scientists to California. Examples of new buildings funded by CIRM are the Stanford SIM1 building (Figure 2),
funded with an award of over $43 million, and the UCSF CIRM building, awarded almost $35 million.

While CIRM has invested heavily in basic biology, in 2008, the agency awarded grants to encourage scientists to form ‘disease teams’ to develop pathways for translating fundamental research into therapies, and assigned project managers to focus on specific deliverables. This led to more substantial investment, from 2009, in translational projects, with a similar objective to that of the UKRMP to move stem cell research closer to application. Some potential therapies involve cell transplantation; others involve biologics such as antibodies and viral vectors. Drug discovery and in vitro disease modelling are also funded.

Notably, CIRM has awarded substantial funds in the form of loans to the commercial sector. In some cases this has been a roller coaster ride. For example in May 2011 CIRM provided $25 million to Geron Inc to support clinical development of cell therapy for spinal cord injury, but in November 2011 Geron discontinued its stem cell programs and returned the money. Asterias Biotherapeutics/BioTime subsequently acquired Geron cell stocks in 2014 was awarded $14.3 million by CIRM to restart the spinal cord injury trial. In an interesting recent development, CIRM and BioTime have reached an agreement that will enable California researchers to obtain ampules of the cells at a modest cost. This neatly circumvents a problem facing the UK stem cell bank, which is that the commercial sector is uncomfortable with others being able to access the same cell stocks because of the possibility of ‘contamination’ of their product through academic results that may concern regulators.

Compared to activity at CIRM, the UKRMP has distributed its funds in two major tranches. The first phase of funding established five interdisciplinary research Hubs with partners in different parts of the UK. The Hub themes reflect similar research priorities to those within the CIRM portfolio: cell behaviour, differentiation and manufacturing; engineering and exploiting the stem cell niche; safety and efficacy, including imaging; acellular approaches for therapeutic delivery, and immunomodulation. In the second tranche of funding, in 2014, the UKRMP initiated five clinically focused research programmes, some in partnership with non-profit disease-focused charities. UKRMP funds do not go directly to the commercial sector, which can access government support via the Catapult and Innovate UK. The Hubs have a particular focus on creating tools, protocols and shared resources. Money is ring-fenced to be spent on partnership awards, bringing new research into the Hubs and fostering cross-hub projects.
Are CIRM and UKRMP a success?

From a broad perspective, new sources of research funding are always welcome. However, it is human nature that scientists in different disciplines become annoyed (and vocal) when they feel that money for new initiatives comes at the expense of their own research. CIRM funding is arguably new money that would not otherwise have gone into research and it seems unlikely that any other state would be able to raise an equivalent amount in the same way. In contrast, the UKRMP is seen as a potential model for government-backed initiatives in other areas, and indeed the MRC is providing £12m to support the creation of the Dementias Platform UK (DPUK) (https://www.mrc.ac.uk/research/facilities/dementias-platform-uk/).

There is no doubt that stem cell research in California has been boosted at many different levels by CIRM. The Agency has not been without its problems, however, including sudden changes in leadership, accusations of conflict of interest and slow decision-making. To address these CIRM invited the Institute of Medicine of the US National Academies (IOM) to review its operations, resulting in a report, published in December 2012, that suggested improvements in CIRM governance structure, scientific program, and policies (http://www.iom.edu/cirm). Importantly, although many of their suggestions were taken into consideration, some of their proposals were inconsistent with standard policies followed by other oversight committees including at NIH institutions. For example, the IOM report considered an oversight board that included university representatives and disease advocates to be a conflict of interest, even through they recused themselves from voting on grants from their own institution, yet all NIH councils also have university and diseases advocacy group individuals as members. Nonetheless, Alan Trounson, then President of CIRM, developed an international Scientific Advisory Board as a result of the IOM report, which has not been used by his successor.

As a government funded initiative that does not directly award grants or loans to industry, UKRMP has been largely immune from the problems that have affected CIRM. However, it is probably fair to say that initially Hub researchers were unused to the milestone-driven approach of the programme board, and that the system for distributing funds between universities within a Hub makes it hard to respond to shifting priorities.

In addition to research funding there have tangible financial benefits to California in terms of job creation (for example in construction) and tax revenue; recipients of CIRM grants must ‘buy California first’ when it comes to grant expenditure. CIRM supporters point to the growth
in Californian Biotech since CIRM was created. However, there has been a similar growth in the Boston area, which has not received the same injection of cash for regenerative medicine. It seems likely that Biotech companies favour close proximity to centres of research excellence and in that sense CIRM has had a positive effect (http://www.massbio.org/economic_development/the_massachusetts_supercluster). Both CIRM and UKRMP promote a culture of collaboration and translation (Figure 2) and are keen to help researchers in their negotiations with the regulators and the commercial sector.

The bottom line, however, is that the people of California voted CIRM into being because they seek cures. Although CIRM has moved over 20 projects into clinical trials most are a long way from becoming standard therapies. This is not unexpected, as the interval between discovery and FDA approved therapeutic via clinical trials is in excess of 10 years minimum. With a change in leadership in 2015 CIRM’s principal funding was overhauled to become CIRM 2.0, with an emphasis on faster funding mechanisms, partnerships and patients. In December 2015, CIRM announced its plans to make projects attractive to nascent and established biotech and investors who could fund large clinical trials, including the creation of ATP³, ‘Accelerating Therapies through Public-Private Partnership’.

The UKRMP is not under the same pressure as CIRM, partly because of its provenance and partly because it is a younger initiative. Nevertheless, there are heartening signs that UK researchers are becoming more active in cell therapies and the Cell Therapy Catapult has documented a steady rise in cell therapy trials in the UK since 2012, with 51 trials now ongoing. Given that a major driver for the creation of CIRM was the potential of treatments based on human pluripotent stem cells it is interesting that most of the cell therapies currently in the clinic, both in the US and in the UK are based on somatic cells, and – at least in the UK – on autologous cells (https://ct.catapult.org.uk/clinical-trials-database). Thus, ironically, most current CIRM-funded trials would also have been eligible for federal funding.

What next?
Devotees of British comedy will recognise the Monty Python quote “‘Nobody expects the Spanish Inquisition...because our chief weapon is surprise!” Over the years veterans of stem cell research (including the authors) have learned to expect the unexpected. CIRM began in the pre-iPSC era at a time when no one anticipated the prospect of off-the-shelf HLA-matched lines from which therapeutically useful cell types could be derived or the fundamental change in the Japanese regulatory environment from highly conservative to highly supportive for cell transplantation. Furthermore,
when CIRM started, gene therapies were facing major obstacles, in particular serious adverse effects in some patients and the difficulty of commercialisation. Few would have predicted the huge successes in cancer immunotherapy, including combinations of gene and cell therapies, which have boosted confidence in the biotech sector generally and led investors to eye up the prospects of making money out of cell therapies. Most recently the advent of CRISPR/Cas9 technology offers the prospect of highly efficient therapies based on gene editing of tissue stem cells.

While the UKRMP is only in its second year of operation, with an expectation that – if successful - it could have a lifespan of 10 years, CIRM’s original 10 years are up in 2017 and the budget will be spent by 2020. Americans for Cures, the legacy nonprofit organization behind California’s Proposition 71 is leading a public awareness program about the progress in stem cell research in an effort to convince Californian’s to continue funding CIRM. They are also seeking to establish new sources of funding to support stem cell research internationally and are exploring how to create an international bond issue from the World Bank to support long term funding. Existing research investments may provide other sources of funding. Unlike NIH funding, any entity receiving or licensing CIRM funded research and/or translation grants must split its royalty income to CIRM, which can be used for future funding. Such entities also have an obligation to provide CIRM-funded products at a small profit margin to Californians who otherwise cannot afford the treatments. Even if no new money becomes available, the legacy of CIRM, in terms of infrastructure, spotlight on translation, and attracting research talent to California, will be appreciated for some time to come.

In conclusion, both CIRM and UKRMP have similar goals but different routes (and funding) to achieving them. Connecting people to work together to move regenerative medicine into the clinic is an over-arching objective and one that, we hope, will benefit patients regardless of where they live.

**Disclosures:** ILW is a co-author of Proposition 71, co-founder of Stem Cells, Inc, grantee of CIRM, and inventor of patents held by Stanford University in the areas of CIRM funding. He has also recently co-founded Forty Seven, Inc, a company taking CD47 related therapeutic antibodies through clinical trials. FMW receives UKRMP funding and was involved in the consultation process that influenced creation of UKRMP. She was also a member of the CIRM scientific advisory board created in response to the IOM review and is a non-executive director of the Cell Therapy Catapult.
Figure legends

**Figure 1 CIRM expenditure** This chart, downloaded from the CIRM website, shows the five major funding categories and the amounts of money (out of the first $1.9 billion) distributed to each category.

**Figure 2 Collaborative laboratory space to accelerate translational stem cell research.**
Top: The CIRM-funded SIM1 Building at Stanford has dedicated lab space to support collaborations between basic scientists and clinical researchers working on targeted disease areas. Bottom: The Centre for Stem Cells and Regenerative Medicine at King’s College London, which receives UKRMP funding, has opened a ‘Stem Cell Hotel’ for in vitro phenotypic analysis of cells from healthy individuals and disease cohorts.

Web resources:

A list of all the web links will appear here.