

South-East Melbourne Alliance for Regenerative Therapies:

Draft SMART Six Year Plan

Author: Heather St John
Date: December 2008
For: SMART Working group



Executive Summary

The South-East Melbourne Alliance for Regenerative Therapies (SMART) was formed in February 2008. It aims to accelerate world-leading outcomes in regenerative medicine by pooling and coordinating complementary strengths in research, training, development and clinical services in the South-Eastern region of Melbourne. The alliance takes advantage of the close proximity of some of Australia's leading research and clinical teams in the fields of stem cell science, tissue engineering and regenerative medicine clustered around the Monash University site at Clayton. These include the Australian Regenerative Medicine Institute, Australian Stem Cell Centre, Australian Synchrotron, CSIRO Molecular and Health Technologies, Monash Institute of Medical Research, Monash Immunology and Stem Cell Laboratories, Monash Medical Centre and a broad cross-section of Monash University research groups, including those within the School of Biomedical Sciences and Faculty of Engineering.

SMART brings together a depth of expertise in complementary domains that underpin the emergent field of regenerative medicine. These expertise include:

- A prestigious history in fundamental stem cell science and developmental biology
- Experience in development of novel biomaterials and tissue-engineering scaffolds
- Biomedical engineering, including medical imaging technology and new synchrotron-based techniques
- Cell signalling and matrix biology, and characterisation of the stem cell niche
- Characterisation and control of differentiation pathways
- Expertise in immune tolerance issues for cell therapies
- A broad range of multidisciplinary groups developing enabling tools, including biomarkers, imaging techniques, cell culture methods and bioreactors
- Access to world class infrastructure and equipment, such as the Australian Synchrotron, Monash Antibody Technologies Facility, flow cytometry, and high content screening
- Clinically-focussed research programs in a broad range of therapeutic areas
- Access to a broad range of cell types and animal models.
- Disease specific cell lines, drug screening, in silico drug design and synthetic chemistry
- Training of the next generation of scientists and research leaders
- World-class hospital-based research and clinical services
- Successful delivery of large scale applied research programs with industry partners
- Track record in progression of novel technologies through to clinical outcomes and formation of new high-tech companies.

Australia is recognised internationally as a leading country in stem cell science, with Clayton the primary hub. However, there has been a dramatic increase in international competition in recent years, with foreign governments making large investments to establish centres of excellence in stem cell science and regenerative medicine. This reflects the belief that the fields have the potential to radically improve health care, providing options to address previously intractable or chronic conditions, and restore patients to full health. The field is at an early stage of development and is subject to disruptive changes, as it brings together the latest breakthroughs in diverse multidisciplinary fields such as systems biology, nanobiotechnology, genomics, materials science, bioengineering and advanced imaging.

In early 2008, SMART groups convened at a strategic planning workshop and identified a common goal for 2015: *to build from existing strengths and ensure that the cluster is recognised as one of the world's leading precincts for regenerative medicine*. A key element was that the group would need to engage more strategically over longer time frames, and focus resources in areas where they are truly internationally competitive. A working group formed to progress the initiative and develop this draft strategic plan for consideration by broader stakeholders.

This plan includes a preliminary overview of the key capabilities and infrastructure relevant to regenerative medicine within the Clayton precinct and a summary of key external factors driving the development of regenerative medicine. The capabilities of the alliance position them well to deliver into several areas at the forefront of the field, including:

- Delivery systems, tissue engineering and immunological strategies
- Comparison of the relative advantage of different types of stem cells (eg mesenchymal vs ESC or amnion-derived) for various clinical applications
- Cellular reprogramming and control of cell fate
- Systems biology approach to identifying and controlling regenerative pathways
- Development of bioactives targeting stem cells and in-vivo regenerative pathways
- New tools and techniques for cell handling, expansion and storage, advanced characterisation and in vivo imaging.

Maximum competitive advantage and impact will be achieved by integrating strengths in basic research, applied research and clinical translation that exist within participating organisations. Thus, five aspects have been identified as critical in the engagement model for SMART participants:

1. Early clinical input to ensure well-targeted research and translation programs
2. Focus on excellence and multidisciplinary collaborations in discovery research, and development of larger research themes in areas where internationally competitive
3. Establishment of larger, cross-organisational, therapy-focussed translation programs
4. Progression through to clinical trials with hospital partners
5. Early industry engagement and creation of an entrepreneurial environment to foster commercial development of leading technologies.

Operational objectives for 2009 are:

- Workshop with stakeholders in February 2009 to review and refine strategic direction
- Encourage multidisciplinary research; increase communication in precinct (eg: seminar series and website) and support joint PhDs/postdocs
- Identify areas of research strength, build database and develop research themes
- Host clinician-led workshops to identify opportunities to deliver major therapeutic benefit
- Analyse primary opportunity areas, eg: IP, market and competitor analysis. Development of business cases to support grant applications in priority areas
- Identify areas of clinical strength within local hospital partners and explore opportunities for greater engagement.

Eventually, it is expected that SMART will build sufficient momentum to attract and support itself via external funds. In the interim, stakeholders need to determine how they will fund the initiative. Three options are presented:

- **Model 1:** Base level funding. Priority is on building increasing communication between participants via seminar series and website. Clinician-led workshops and market and IP scoping to identify opportunity areas and refine strategic plan. In-kind contributions required for 2009: \$175,000.
- **Model 2:** As per Model 1, but with support funding for multidisciplinary research projects between participants (5 PhDs). More detailed analysis and business case development to attract grant funding for 2-3 major programs. In-kind contributions required for 2009: \$255,000. New funding required for 2009: \$240,000.
- **Model 3.** As per model 2, but with early commitment to identify and commence 2-3 major therapy-focussed joint programs by 2010. In-kind contributions required for 2009: \$470,000. New funding required for 2009: \$425,000.

Contents

Executive Summary	2
1. Introduction.....	6
1.1 History and Overview.....	6
1.2 Current Context and Drivers	9
1.3 The Clayton precinct gets SMART: the formation of the South-east Melbourne Alliance for Regenerative Therapies	12
1.4 Vision, Mission and Pathways.....	12
1.5 SMART Operational Objectives for 2008.....	13
2. External Analysis	14
2.1 Development of the Field of Regenerative Medicine.....	14
2.2 Unmet Clinical Needs	15
2.3 International Funding and Investment	16
2.4 Market Size	17
2.5 Regulatory, Ethical and Political Issues	19
2.6 Patent Issues.....	20
2.7 Major challenges to progress the field; the frontline of knowledge.	21
2.8 Contributing Disciplines	23
3. Internal Analysis	24
3.1 SMART Capabilities related to/enabling Regenerative Medicine.....	24
3.2 Key Infrastructure.....	30
3.3 Major Therapeutic Focus areas of SMART Participants.....	31
4. Strategic Analysis.....	34
4.1 SWOT (from workshop group)	34
4.2 Strategic Issues and Critical Success Factors.....	35
5. Model for Engagement	36
5.1 General Pathways for Implementation	40
5.1.1. Leverage strengths and infrastructure.....	40
5.1.2. Build collaborative networks.....	41
5.1.3. Partner participation and Decision Making.....	42
5.1.4 People: Attracting, building and rewarding excellence	42
5.1.5. Promoting Innovation – both discovery and translation	44
5.1.6 Funding and Resources	45
5.1.7 Influence Decision Makers and Community.....	46
6. Specific Initiatives	48
6.1.1 Areas of strength for establishing Research themes	49
7. Strategic Implementation	58
7.1 General Phases	58
7.2 Priority areas for 2009	58
7.3 Proposed Budget	59
8. Appendices	61
8.1 Appendix 1. SMART Stakeholders and Steering Committee.....	61

1 Introduction

1.1 History and Overview

Victoria has established international credibility in the relatively young field of regenerative medicine by remaining at the forefront of stem cell research as it has developed over the last few decades¹. Monash led the field of reproductive biology, with the first live births by IVF achieved by Alan Trounson and co-workers in the early 1980s. Monash also led the earliest research on differentiation of embryonic stem cells, initiating research on human embryonic stem cells in Australia through collaborations with University of Singapore. Further strength in early stem cell research in Victoria was exemplified by the pioneering work undertaken by Metcalfe and colleagues at the Walter and Eliza Hall Institute, notably their pivotal work on haematopoietic stem cells, growth factors and signalling pathways that regulate the immune system². World-class research at the intersection of immunology and stem cell biology has continued in the research activities undertaken by the Monash Immunology and Stem Cell Laboratories (MISCL). This group is now headed by leading immunologist Prof Richard Boyd, after the former director, Prof Alan Trounson was lured overseas to lead the recently formed California Institute for Regenerative Medicine (CIRM), with its staggering \$US3 billion bond-based fund for investment in stem cell research.

The commitment to retaining an international leadership position in stem cell research was demonstrated in 2002 by Federal and state governments' funding of \$110 million over 10 years to form the Australian Stem Cell Centre (ASCC)³. Operating largely as a virtual organisation to support stem cell research across Australia, its central administrative hub is at the Monash University Clayton campus. The hub includes the Major National Research facility, which houses the central bank of human embryonic stem cell lines and laboratories for a core group of researchers. Whilst continuing to support basic research in both embryonic and adult stem cell science, the ASCC has also pursued a focus on translational research, such as its lead program in haematology, in line with its initial mandate to pursue early clinical and commercial outcomes. The ASCC also plays an active role in fostering the development of stem cell research within Australia. For example, it provides specialist training programs in stem cell propagation and manipulation to build the skill base of new researchers. The ASCC also serves as a source of expert advice to raise community awareness, facilitate informed public debate, and promote new policy developments⁴.

The largest and most well recognised cluster of stem cell researchers in Australia are based at Monash University's Clayton campus. The ASCC hub, Monash Immunology and Stem Cell Laboratories (MISCL) and the start-up company Stem Cell Sciences are co-located in the purpose-built Scientific, Technology, Research and Innovation Precinct (STRIP) 1 building. In addition, the newly-opened Australian Regenerative Medicine Institute (ARMI), was established with an investment of \$153M by Monash University and the Victorian and Federal governments. ARMI complements existing expertise in stem cell biology with its focus on elucidating the fundamentals of the molecular and cellular processes that underpin regenerative pathways; and utilising this knowledge to develop clinical strategies, based on mobilising the body's own inherent capacity for tissue repair. The Monash precinct is expanding further with the construction of two adjacent, connected, state-of-the-art buildings (STRIP 2 and 3). This is a \$103M investment in laboratories to accommodate researchers from the Medical Faculty's School of Biomedical Sciences.

Near the Monash STRIP are a number of closely-related applied research and clinical facilities. CSIRO biomaterials researchers are predominantly based in the Division of Molecular and Health Technologies adjacent to the Monash Clayton campus. In line with CSIRO's applied research focus, this group has a

1. DTI Global Watch Mission Report, An Assessment of Regenerative Medicine and Stem Cell Technology – A mission to Australia, November 2006

2. A. Trounson and R. Harvey, A Critical Time for Stem Cell Research in Australia, Cell Stem Cell, 2008, 2, 118-122

3. ASCC web site, Centre Funding http://www.stemcellcentre.edu.au/centre_funding.aspx

4. R. Skinner, Stem Cell Research in Australia: Collaboration, Legislation, Scientists and Public Accountability. World Stem Cell Report 2008, Genetics Policy Institute 53-56



strong track record in translating research in novel biomaterials to successful clinical and commercial outcomes, generating multimillion-dollar royalty streams and equity stakes in spin-out companies. The group's capabilities in tissue engineering and the design of systems with specific cell-material interactions had led to an increasing level of collaboration with the stem cell community based at the Monash STRIP. For example, the Biomanufacturing consortium is a multimillion dollar collaborative initiative established in 2005. It comprises a multidisciplinary team of CSIRO, ASCC and Monash researchers, that are developing smart polymer surfaces for use in stem cell bioreactors for blood production.

Also nearby is the Monash health precinct that encompasses Monash Medical Centre, Prince Henry's Hospital and Monash Institute for Medical Research (MIMR). This precinct facilitates the progression from discovery to clinical trials via close collaboration and partnership between leading stem cell and clinical researchers with expert clinicians. MIMR has established a strong base in stem cell research within a number of its clinical research programs. Notable advances include the discovery of endometrial stem cells, and more recently the announcement of a major joint program with NSW researchers Sydney comparing iPSvs SCNT patient specific stem cell lines⁵.

A recent addition to major infrastructure in the Clayton precinct is the Australian Synchrotron, which offers characterisation and imaging capabilities equivalent to the best in the world. The facility opened in mid-2007. It has eight beamlines in operation, with the local medical research community eagerly awaiting the opening of the imaging and medical therapy beamline in early 2009. The synchrotron provides advanced techniques in spectroscopy, crystallography, x-ray imaging and diffraction.

Monash University has sought to ensure full utilisation of the synchrotron and nanotechnology as enablers for the research community, with the Monash Centre for Synchrotron Science and the Monash Institute for Nanosciences, Materials and Manufacture promoting broader awareness and interdepartmental research programs. The new Melbourne Centre for Nanofabrication, adjacent to the synchrotron facilitating further development of new technologies in this area. An example of interdisciplinary research using the synchrotron is the development of novel markers for synchrotron imaging of stem cells, led by Prof Claude Bernard of MISCL. This project was recently awarded a \$625,000 ARC grant. Considerable interdisciplinary activity is also underway within the Monash Faculty of Engineering, such as the development of novel bioactive scaffolds for guided neural repair, and new approaches to stem cell bioreactor technologies.

Melbourne is recognised internationally for the quality of its medical and biotechnology research. Victoria is home to 15 major medical research institutes, seven teaching hospitals and nine universities. Melbourne is one of only three cities in the world (along with Boston and London) with two universities in the global top 20 biomedical rankings. More than 43 per cent of Australia's medical research activity is undertaken in Victoria. Victoria attracts the lion's share of Australian medical research funding, receiving more than 40% of national medical research grants in 2007.

The Victorian Government has maintained a strong commitment to investment in biotech research and infrastructure as part of its focus on promoting innovation as a driver of economic growth. It has invested more than \$2 billion in science technology and innovation initiatives since 2001⁷.

5. Monash Memo 24 Sept 2008

6. Victorian Government media release, June 19 2008, Victoria-California Alliance to help turn stem cell research into treatment and cures.

7. G. Jennings, *Biotechnology the Victorian way*, Pharmaceutical Technology Asia Pacific, March 1 2008.

More than 140 biotech companies are based in Victoria, generating sales in the order of \$5.7 billion in 2005-06. In 2008, Victoria's biotech sector was valued at more than \$21 billion, with deals worth more than \$4 billion secured in the last three years.

The Victorian government has supported the establishment of technology clusters. Two high profile medical research clusters are the Bio 21 precinct in Parkville, and the AMREP precinct in Prahran. The Clayton cluster and these precincts have strong linkages. For example, the CSIRO Division of Molecular and Health Technologies has biological research laboratories in the Parkville precinct, and Monash University Faculty of Pharmacy is located in Parkville. Monash University's Australian Centre for Blood Diseases is based at AMREP. A number of initiatives are underway which seek to further strengthen the connections of the medical research community and health providers in Melbourne, such as the Monash Health Sciences cluster. Victoria is home to Australia's most well-established regenerative medicine company, Mesoblast, which listed on the ASX in 2005, and continues to progress its platform mesenchymal stem cell technology in multiple areas of clinical application, including recent clinical trials in heart repair with its US sister company Angioblast.

Australia is highly regarded internationally as a preferred location for clinical trials. It was recently ranked the number one location for pharmaceutical clinical trials in a benchmarking study by the Economist Intelligence Unit, against US, UK, Germany, Japan, Singapore and India. This rank stemmed from our combined advantages in superior quality of medical research and infrastructure, low costs (around 50-60% of similar US costs) and speed of registration and trial completion. Over the past decade, the Queensland and Victorian state governments have focussed on building a vibrant biotechnology sector, with significant investments in research, infrastructure, networks and technology parks.

In Queensland, the University of Queensland hosts the second major node of the ASCC, and the \$70M Australian Institute of Bioengineering and Nanotechnology (AIBN) is renowned for interdisciplinary research in nanobiotechnology, systems biotechnology, cell and tissue engineering and nanomaterials. In 2006, the Commonwealth government committed a further \$22M to establish the National Centre for Adult Stem Cell Research at Griffith University in Brisbane.

Australia also holds its competitive international position through its access to a range of animal models for biomedical research. This enables more effective in vivo studies of developmental biology. These include Monash University's NHMRC National Primate Facility, excellent facilities for rodent models, and the recently-opened \$5.4M zebra fish aquarium at ARMI. The zebra fish facility provides a powerful model system to study how genes control embryonic development⁸. It is the largest facility of its kind in the southern hemisphere. Future near-term investment is envisaged in increasing rodent facilities to an international, best-in-class, core facility.

Local researchers and technology companies recognise the need to be highly proactive in establishing and maintaining linkages and profile internationally due to Australia's small population and remoteness from major research and investment communities of the USA and Europe. The ASCC has taken a leading role in establishing Australia as an active member of the international stem cell community. This is exemplified by its active involvement in the International Society for Stem Cell Research (ISSCR), including hosting the annual meeting in 2007. The ASCC also played a pivotal role in the establishment of the International Consortium of Stem Cell Networks and the formation of the network for the Asia-Pacific region in 2007 – the Stem Cell Network Asia Pacific (SNAP).

8. \$5.4M Regenerative medicine facility opened, <http://www.monash.edu.au/news/monashmemo/stories/20081126/zebra.html>



These networks have the common aim of enhancing communication between participants to accelerate the realisation of stem cell therapies. Within Australia, The newly formed Australian Society for Stem Cell Research promotes collaboration, coordination and engagement of stem cell scientists across the country⁹.

An important recent boost to collaborations with the US has been the June 2008 alliance agreement between Victoria and California, to support collaborative stem cell research projects that will facilitate disease treatments. Known as the "stem cell air-bridge", the agreement allows Victorian researchers to access the California Institute for Regenerative Medicine (CIRM) funding allocated for Disease Teams, via joint grant applications with Californian researchers¹⁰. Established working relationships between the new head of CIRM, Professor Alan Trounson, and the Australian stem cell research community enhance these collaborative connections.

Collaborative linkages with the European community have been strengthened by Australia's recent membership of the European Molecular Biology Laboratories (EMBL). The newly formed EMBL Australia acts as the EMBL member and is administered from ARMI. Stronger ties with the international regenerative medicine community are facilitated by the established working relationships of new ARMI director, Prof Nadia Rosenthal, who currently manages the EMBL outstation in Monterotondo, Italy. Prof Rosenthal also retains a chair at Imperial College in London and has a long-standing involvement with Harvard Medical School.

A recent development in collaborative partnerships with Asia is the Australia-China Centre for Excellence in Stem Cell Research, a \$2M initiative between Monash and Peking Universities. This partnership aims to facilitate more rapid progression of clinical trials on emerging stem cell therapies. It brings together Monash's expertise in immunology and basic stem cell research with Peking's vast reagent facilities and China's advantage of a large population¹¹.

1.2 Current Context and Drivers

The field of regenerative medicine has become a 'hot' area in the past decade. Governments, clinicians, scientists and the general public have recognised the potential to radically transform the nature of health care and open a window of hope that it may ultimately provide treatment options for a range of conditions previous regarded as chronic or incurable. This has led to a dramatic increase in the level of research activity internationally, and large funding investments by some national and regional governments that have identified regenerative medicine as a key component of their biotech strategy. The most dramatic example of this is the establishment of the \$US3 billion fund in California for stem cell research, including embryonic stem cell research. This fund was achieved via a publically-driven counter-assault to the former US government's aversion to the use of Federal funds for research on human embryonic stem cells. Whilst the magnitude of this Californian fund dwarfs other international investments, there are a number of other research centres that have made substantial investments in stem cell research and regenerative medicine.

These investments are outlined in Table 1.

9. S. Hawes, Not another stem cell society, ASSCR Newsletter, 2008, 1, 1"

10. Victorian Government media release, June 19 2008, Victoria-California Alliance to help turn stem cell research into treatment and cures.

11. <http://www.med.monash.edu.au/med/news/2008/australia-china-centre-for-excellence.html>

Table 1 International investment in stem cell science and regenerative medicine (reproduced from 2008 report by R. Iannello and S. Ilancheran¹²)

State	Research Centres	Funding
California	CIRM	\$3 billion over 10 years
Connecticut	Funding will be used to provide grants	\$100 million over 10 years
Illinois	Institute of Regenerative Medicine	\$1 billion planned
Massachusetts	Harvard Stem cell Institute and others	up to \$100 million proposed
New Jersey	Stem Cell Institute of New Jersey	\$11.5 million allocated, \$380 million proposed
New York	New York Institute for Stem Cell Research	\$300 million proposed
Wisconsin	University of Wisconsin, Madison	\$375 million proposed

Although Australia's investment in regenerative medicine is large on a national scale, it is mid-range in the international context. Our competitive edge in embryonic stem cell research was assisted through its head start in the field and retained by the brakes applied by the US government in their self-restrictive funding policies. To maintain our international leadership position it will be necessary to execute strategic leadership and focus resources on those areas that Australia has, or feasibly can, secure a competitive advantage. It is also essential to improve our ability to 'work smart' and gain effective scale through collaborative use of complementary research teams. Research excellence, outcome focus and international profile in selected areas is likely to produce greater impact than mediocre performance across a broad range of small-scale, disconnected activities.

As in other scientific fields, the quality of research outcomes is measured on a global basis (e.g.: publications in peer-reviewed journals, patents), as is recruitment of key talent. However, research projects and infrastructure are mostly funded domestically. In recent years, this has led to Australia losing a number of top stem cell researchers to overseas research establishments that could provide more generous, secure, long-term funding. Whilst 'brain circulation' through the movement of researchers internationally provides enhanced opportunities for international collaboration, it is vital that future strategies also address those factors which lead to attraction and/or retention of top researchers, so that the net 'brain balance' is at least maintained and preferably enhanced. One driver for the SMART initiative is to identify strategies to enable funding levels to be more stable and secure over longer time periods.

¹². Monash University Stem Cell and Regenerative Medicine Research, S. Ilancheran and R. Iannello, 2008.



The Clayton precinct has taken advantage of the geographic density of related research activities to gain more efficient use of resources in combined, multiparty access to infrastructure and equipment. This has enabled not only optimal utilisation and cost-sharing, but also the acquisition of higher-end instrumentation that would otherwise be beyond the financial reach (or plausible justification) of a single party.

Commenting on the co-investments of more than 30 universities and government research organisations for the Australian Synchrotron, David Cookson, Head of Science, Australian Synchrotron noted to a group of new users from the biomedical community “...it just goes to show that when you're prepared to share your toys, you can have really good toys”. Further examples are the recently established MATF (Monash Antibody Technology Facility), and Flowcore, (flow cytometry facility for specific characterisation of stem cell sub-populations). Flowcare is managed jointly by ASCC and ARMI, providing fee-based services open to all stem cell researchers.

The SMART collective recognises that this can be enhanced even further. Rather than pursuing an ad hoc basis to new equipment and infrastructure, it is developing a strategic, long-term view, based on prioritisation of key research strengths and gap analysis. Through this process, SMART will identify the infrastructure most critical to securing a leadership position in the selected domains, and coordinate joint bids to secure funds. It is also improving existing infrastructure and core facilities, via activities such as streamlining access arrangements, and co-investments in upgrades that benefit a wider cross-section of researchers.

Co-ordinated marketing of the precinct is also a key driver. This is important to maximise the precinct's international profile and to attract world-class talent and potential investors. Coordinated marketing will provide cost and time effectiveness and increased impact through greater scale.

It will highlight the breadth of complementary research and clinical expertise that can be brought together to tackle particular challenges. It will also avoid the negative effects of brand confusion when parties embark on separate (and semi-competitive) marketing campaigns.

The primary driver, however, is to increase multidisciplinary collaborations in order to advance the field¹³. By their very nature, regenerative medicine and tissue engineering require the integration of research expertise from multiple scientific domains—such as biology, chemistry and engineering—to solve technical challenges. Progression of the fields will also require the involvement of fields outside the traditional scientific domains, including ethicists, health economists, regulatory advisors and production and business managers.

13. G.C. Gurtner, M.J. Callaghan and M.T. Longaker, Progress and Potential for Regenerative Medicine, *Annu. Rev. Med.* 2007, 58, 299-312

1.3 The Clayton precinct gets SMART: the formation of the South-east Melbourne Alliance for Regenerative Therapies

The South-east Melbourne Alliance for Regenerative Therapies (SMART) is a group of research and clinical organisations centred in the Melbourne suburb of Clayton. The group shares a common desire to translate research discoveries through to clinical outcomes in the field of regenerative medicine. The launching point for this initiative was a workshop held in February 2008, which brought together research and clinical leaders from Monash University, CSIRO and ASCC with interests in stem cell research, tissue engineering and regenerative medicine. (Refer to Appendix 1 for list of workshop participants).

A key theme of the discussion was the opportunity to achieve more significant outcomes in research excellence and clinical translation by combining existing complementary (but fragmented) strengths, activities and investments in a more strategic manner. The initiative coincided with the establishment of new scientific programs in regenerative medicine by ARMI. The group saw the potential for this \$153m investment to have even greater impact by serving as a catalyst to integrate and leverage off existing research strengths and the complementary capabilities of existing research teams.

1.4 Vision, Mission and Pathways

The workshop group identified a common vision:

SMART will deliver better health outcomes through scientific excellence and leadership, and will be recognised as one of the top five international locations in regenerative medicine by 2015.

The group identified outcomes that they would like to achieve by 2015 and measures to assess

performance. These are included in detail in Appendix 2, but can be summarised by the following mission statement:

To engage as partners in a collaborative, entrepreneurial and ethical manner, in order to maximise scientific excellence, clinical outcomes, commercial success and people development, and be recognised and respected by broader community

Workshop participants agreed to:

- seek to create an innovative and entrepreneurial environment that supports its people to strive for excellence in clinically-focused research, in order to establish the underpinning knowledge and radical breakthroughs that will transform the field of regenerative medicine
- work collaboratively, diligently and ethically to ensure that our complementary strengths are harnessed in order to translate these discoveries to patient benefits as quickly as possible. In this way, we hope to be recognised and respected by the community, companies, investors and our peers, as one of the top locations in the world for high-impact outcomes at the forefront of regenerative medicine.

The alliance identified the following pathways as key areas of focus:

- Leverage strengths and infrastructure
- Build collaborative networks
- Make decisions and participate as partners
- Recruit strategically
- Develop people to full potential
- Value innovation – both creativity and translation
- Optimise sourcing and use of funding and resources
- Positively and proactively influence decision makers and community



These pathways will be discussed in greater detail later in the report.

1.5 SMART Operational Objectives for 2008

The leadership team and alliance members will use the aforementioned pathways to guide their activities as the alliance develops. In the near term, a number of specific actions were identified by the workshop group. These activities aim to establish a framework for the alliance and how it will approach the next stage of development.

The actions are:

- Define structure and governance—incorporate stakeholder views
- Appoint steering group and executive officer
- Develop 2008 operational plan
- Develop a document influencing strategy
- Audit infrastructure and assess capabilities
- Understand goals and scientific focus of outcome areas through workshops and project outlines
- Scope international and national landscape
- Conduct gap analysis of partner's capabilities
- Develop a business plan for 2009-2015
- Develop a communications plan
- Engage patient advocacy groups
- Lobby and secure Commonwealth, state and other funding bodies

Given the close proximity and existing relationships between the participating groups, it was decided that a small group of committed representatives could form to build initial momentum. These parties could 'lead by example' by commitment of their own time and funds. A representative working group was nominated, and in July 2008, a project officer

was appointed to coordinate the development of the strategic plan. In the near term, the alliance intends to engage with other interested parties in the South-east Melbourne region.

This includes technology companies, other medical research precincts (eg: AMREP), hospitals and health providers. Whilst the initial focus is to make maximum advantage of a local cluster, the group intends to retain and build broader State, national and international collaborative linkages, i.e. to establish SMART as a network within networks.

The working group's operational activities for 2008 have three major themes:

Strategy development

- Preliminary analysis of key capabilities and assets
- Identification of opportunity areas
- Consideration of potential models for engagement and courses of action

Communication

- Build engagement for SMART and increasing awareness of the strategic planning process underway
- Meet with key local researchers
- Develop new website
- Additional inputs and perspectives sought in order to shape more detailed recommendations

Kick-start activities

- Scope potential for new collaborative linkages through multidisciplinary information-sharing workshops.
- Build greater interaction across departmental and organisational boundaries via new joint PhD projects and joint appointments.
- Build relationships, enhance information flow and demonstrate tangible benefits.

2 External Analysis

2.1 Development of the Field of Regenerative Medicine

Regenerative medicine is focusses on therapies that replace or restore function to tissues and organs that have been damaged, lost or aged¹⁴. This includes a range or therapeutic approaches¹⁵, including:

- **Chemoinductive approaches.** These prompt the body to self-regenerate damaged tissue, or 'turn off' the blocking mechanisms that interfere with healing in adults. This regains the inherent healing capacity that the body has at the fetal stage¹⁶.
- **Cell therapy strategies.** These provide a fresh source of cells with regenerative capacity and can also deliver the cocktail of factors and cues that guide the damaged tissue to repair.
- **Tissue engineering strategies.** These involve implantation of a combination of scaffolds, cells and signals to provide a ready-made framework for new tissue regrowth in vivo.
- **Direct transplantation of healthy tissue.** To replace lost or damaged tissue, either from donors or artificial organs grown ex-vivo in bioreactors.

The field of regenerative medicine is in its early stages of development. However, research activity and public interest in the field has accelerated in recent years¹⁷. The convergence of advances in disciplines that underpin the field have driven this acceleration, notably:

- Rapid advances in fundamental stem cell biology, and the drive to progress stem cell therapies to clinical applications.
- Successful first clinical applications of tissue-engineered products in the areas of skin, bone and cartilage, after a somewhat arduous phase of commercial development.
- Advances in bioinformatics technologies that allow a more integrated systems biology approach to regenerative biology—particularly the vast datasets from 'omics' revolution.
- Improved imaging technologies—providing a clearer window on the earliest stages of development in vivo and real-time visualisation of repair processes.
- Developments in nanotech, materials and engineering technologies, providing the next generation of biomimetic scaffolds, improved cell manipulation processes and the ability to characterise specific sub-populations of cells.

Regenerative medicine is generating more public interest than any other scientific domain, through its perception as a 'field of hope'¹⁸. The strong interest and expectations from patients for the field to deliver improved therapies for medical problems with few other solutions has led to a pull for early clinical trials before a full understanding of the actual biological mechanisms of action are understood. As a result, the early clinical results also become a vital part of the learning framework in the evolution of the field, and will drive the development of more effective clinical strategies as much as fundamental lab-based research. There is thus a need for both basic knowledge of the biological mechanisms and processes involved in regeneration, as well as focussed development of improved therapeutic strategies that build from this knowledge and other enabling multidisciplinary technologies, with guidance from clinical best practice.

14. Principles of Regenerative Medicine, edited by A. Atala et al, Elsevier/Academic Press, Amsterdam, 1st ed, 2008

15. D. Stocum, Regenerative Biology and Medicine, Academic Press, 1st ed, 2006.

16. I.V. Yannas, Facts and Theories of Induced Organ Regeneration, Adv Biochem Engin/Biotechnol, 2005, 93, 1-38

17. R. Rejzo Pera and J. Gleeson, Editorial, Stem Cells and Regeneration: Special review Issue, Human Molecular Genetics, 2008, 17, 1-2

18. Helping the body repair itself, www.ConsumerReportsonHealth.org July 2007



As the field is at an early stage, it is periodically subject to major tectonic jolts, as discoveries provide startling new insights¹⁹, which confront the early paradigms built more on aggregate tentative assumptions than bodies of scientific fact. A recent example of this has been the development of induced pluripotent stem cells, and the change in impressions of the irreversible 'solidity' of somatic cells. This discovery has had an even greater impact because it provided a fresh incendiary to the arsenal of opponents of embryonic stem cell research, many of whom argued that it obviated the need for further work in this controversial area. There is no doubt that further tectonic shifts will occur before regenerative medicine is established as a routine mode of therapy, which is probably more than 20 years away. This rapidly changing landscape means that for a long-term research strategy to be sufficiently robust, it should involve a platform/area that is relevant to multiple domains of development, as well as having the flexibility to adapt and tailor programs in response to major developments.

2.2 Unmet Clinical Needs

The degree of attention currently directed towards regenerative medicine by researchers, clinicians, patient advocates and governments is due to the potential for the field to ultimately deliver new solutions to major health issues, many of which were deemed intractable within the limited framework of existing clinical options²⁰. An example of this is hope for guided neural regeneration to provide a means to alleviate paralysis in cases of spinal damage. A particular focus is the area of progressive degenerative disorders, such as Parkinson's disease for which no effective strategy exists. Furthermore, regenerative medicine offers the prospect to not only halt the progression of degenerative disorders, but to restore function back to the original state. This potential for a cure, rather than an ongoing treatment, has major ramifications for chronic disorders such as diabetes.

An additional major clinical need that regenerative medicine addresses is the shortage of organs needed for organ replacement. The current world market for organ replacement is in excess of \$US 350B. Early analyses on the potential value of regenerative medicine have focussed on the potential to grow replacement organs *ex vivo* via tissue engineering in bioreactors, for subsequent transplantation. Indeed this has been the commercial strategy of Tengion, exemplified by their successful development of an artificial bladder, and their capability to extend this to a wide range of other tissue-engineered organs. However the greater long-term benefit is more likely to be realised by improved options for early intervention and *in vivo* repair, rather than enduring a reduced quality of life through progressive stages of organ degeneration, and a final major surgical intervention.

More recently, the attention to 'whole-of-life cost of care' approach to health economics²¹ has fuelled a greater attention by governments of the long-term investment benefits in regenerative medicine, and its potential to reshape the face of health care. Thus it offers the prospect not only of better health care, but the potential to reduce the burgeoning health budgets of aging populations. This type of analysis of the potential economic benefits of regenerative medicine was undertaken by the US Department of Human Services²², noting that:

- Healthcare costs in the U.S. are in excess of \$1.5 trillion annually
- 35 million Americans aged 65 or older, and the boom in this population segment due to the ageing population would lead to a doubling to 70M by 2040, resulting in up to 25% of GDP being required for healthcare

The majority of costs arise from tissue failure in the elderly. The baby boomer population also has high expectations for standards of health care, given the medical advances achieved in their lifetime.

19. N. Rosenthal, Youthful prospects for human stem cell therapy, *EMBO reports*, 2005, 6, 30-34

20. *Principles of Regenerative Medicine*, edited by A. Atala et al, Elsevier/Academic Press, Amsterdam, 1st ed, 2008

21. E. Cosh, A. Irling, R. Lilford, H. McAteer and T. Young, Investing in New Medical Technologies: A Decision Framework, *Journal of Commercial Biotechnology*, 2007, 13, 263-271

22. U.S. Department of Health and Human Services, 2020: A New Vision – A Future for Regenerative Medicine, <http://www.hhs.gov/reference/newfuture.shtml>

Regenerative medicine is seen as a major part of the solution, having the potential to address some of the major diseases associated with ageing such as diabetes, cardiovascular disorders and osteoporosis.

It has been estimated that there are approximately 300 million people in the US, Europe and Japan who could potentially benefit from stem cell therapeutics already in development, and that these people currently incur around \$US 400B in annual direct health care costs²³. The data below highlight the economic costs associated with some of the major conditions that are being targeted by regenerative medicine research²⁴

Table 2 Economic costs of major illnesses in the USA and the number of patients.
(Sourced from Table 1, C. Mason and P. Dunnill, *Regen. Med.* (2008), 3(3), 351-36)

Condition	Reference year of cost data	Direct costs (US\$ B)	Indirect cost (US\$ B)	Total costs (US\$ B)	Indirect as % of total costs	Current patient numbers (millions)	Average cost per patient p.a. (US\$)
Heart failure	2007	30.2	20.5	50.7	40.4	5.2	9750
Alzheimer's disease	2007	69.4	74.1	143.5	51.5	3.41	42,082
Diabetes, Insulindependent	2005	57.4	67.7	125.1	55	5.8	21,570
Stroke, update	2007	41.6	21.1	62.7	33.7	5.7 (2004)	11,000
End-stagerenal failure update	2004	32.5	23.8	56.3	42.3	0.47	119,790
Parkinson's, disease update	2002	6.7	16.30	23	71	0.65	35,390
Spinal-cord injury	2006	22.2	15	37.2	40.3	0.25	148,800

2.3 International Funding and Investment

It has been important that governments recognised in the longer term economic benefits of regenerative medicine, and provide supporting funding, rather than relying on shorter term market mechanisms to drive early development of the industry. Due to the high levels of uncertainty associated with rapid changes in technology, long regulatory approval timelines with as yet unclear hurdles, and uncertainties over reimbursement and business models, many of the larger biotech companies are remaining on sidelines. Much of the innovation and commercial translation is being led by small start-up companies, many of whom lack the deep pockets to progress new therapies through expensive Phase III clinical trials. Venture capital investment is also currently low in this sector, with investors slow to return after being burnt in the crash and burn of overhyped early tissue engineering companies in 2002, in which the market capitalisation plummeted from \$US2.6B in 2001 to \$300M in December 2002²⁵. The carnage in this period included both industry leaders, Advanced Tissue Sciences and Organogenesis filing for bankruptcy, and in the following three to four years early tissue-engineered products and companies struggled to achieve adequate profitability, and the majority of developmental pipelines emptied through regulatory failures or inadequate economic attractiveness. In this phase, investment was dominated by public funding, with the breakdown of the \$1B spent on stem cell research in 2004 being derived 75% from government sources, 20% from industry and 5% from venture capital.

23. U.S. Department of Health and Human Services, 2020: A New Vision – A Future for Regenerative Medicine, <http://www.hhs.gov/reference/newfuture.shtml>

24. BioPhoenix market report, Business Insights, Opportunities in Stem Cell Research and Commercialisation. Technology advances, regulatory impact and key players, 2006.

25. C. Mason and P. Dunnill, The Strong Financial Case for Regenerative Medicine and the Regen Industry, *Regen. Med.* 2008, 3(3), 351-363



A considerable amount was learnt in from this phase of industry building, which prudent entrepreneurs have factored into more street-wise development of current technologies and companies²⁶. This includes earlier consideration of distribution and reimbursement strategies, economies of scale in manufacturing (with a preference for use of contract manufacturing organisations during early company development to reduce cash burn), and a care not to let product design be optimised only for scientific and clinical elegance, with insufficient attention to whether the final product is manufacturable or affordable. In the last few years the industry has entered a renewed phase, dubbed "Regen 2.0", driven by the upswing in stem cell research internationally, and the success of California Proposition 71. A further notable highlight for 2008 was the acquisition of one of the early pioneering regen companies, LifeCell, for \$US1.7B, with sales revenue in the first quarter increasing by 27% to \$US54.3M, of which 87% was accounted for by their lead product – Alloderm, a decellularised human tissue matrix from donor skin tissue, used for shoulder, hernia and soft tissue repair. A few companies specialising in this sector, notably Kleiner Perkins Caulfield and Byers and the more recent Proteus Ventures, dominate venture capital investment²⁷. In the near term, companies with earlier commercialisation options, such as research tools, drug screening and improved manufacturing techniques, are seen as most attractive investment propositions.

The largest source of funding for stem cell research has arisen through the Proposition 71 initiative in California, with \$US3B of funds to be distributed over a 10 year period. Importantly, this funding is not limited solely to Californian researchers, with CIRM announcing partnerships with Victoria, Canada and the UK to enable the funds to be accessed for collaborative international teams working in partnership with Californian researchers.

The Victoria-California stem cell alliance, announced in June 2008, has been further supported by a \$5M investment from the Victorian government for the Biotechnology Bridges program. This augments specific investments from the state and Federal governments such as the \$50M contribution to the establishment of the Australian Regenerative Medicine Institute.

In addition to California, other regions within the US are established sizable allocations of funding to promote establishment of regen research centres, with examples previously noted in Table 1. Significant investment at a Federal level is occurring in Japan, UK, Germany, China and Australia.

2.4 Market Size

Estimates of market size for regenerative medicine vary widely due to the early stage of the field, high rates of growth, uncertainty over the progression of particular technologies, and variances in views on what is included in a regen classification (eg mobilisation agents, non stem-cell derived tissue engineered products, and organ transplantation are variably included). In 2007, the estimated market value of all public stem cell companies was \$US1.655B²⁸. Revenues from stem cell companies have been growing rapidly from a low base of less than \$US1M in 2005 to an estimated \$US36.8M in 2007, and predicted to grow to \$US8.5B by 2016. There are over 200 companies developing stem cell products worldwide, with the largest revenues from stem cell-related products currently generated by Blackstone Medical, Osiris Therapeutics, Nu Tech Medical, Viacell, Aastrom Biosciences, Cytori, Geron, Stem Cell Inc and BioE.

26. G. Bonfiglio, Funding and Exit Strategies for Regenerative Medicine Companies, Marcus Evans Conference – Commercialization of Tissue Engineering and Cell Therapy, December 2006. <http://www.proteusvp.com/Marcus%20Evans%20Conference%20Presentation.pdf>

27. L. Saad, Financing for Cell Therapy Companies, http://www.celltherapygroup.com/uploads/4_-_L._Saad_-_ISCT_2008_Workshop_1.pdf

28. Stem cell market analysis fact sheet <http://www.stemcellsummit.com/2007/stem-cell-summit-fact-sheet.pdf>

The largest established clinical application of stem cell therapies is in HSC transplantation for treatment of patients with cancer and other blood and immune disorders. Most of this work takes place outside the commercial sector, offered as a surgical procedure rather than a commercial product²⁹. However, current market revenues are overwhelmingly dominated by the associated activation and mobilisation agents, such as the cytokines EPO and GM-CSF, which are used to stimulate hematopoietic stem cells in cancer patients to increase the yield harvested for re-transplantation after chemotherapy. Revenues from mobilisation and activation agents were estimated at around \$US23M in 2005, ie around 96% of market. Amgen has the dominant products: Neupogen, for mobilisation of donor bone marrow, and Epogen (recombinant erythropoietin) used to stimulate endogenous HSCs in the bone marrow to differentiate into erythrocytes.

A rapidly growing sector of the market is the cord blood banking industry, which was worth over \$US300M worldwide in 2005, with the largest commercial operator being Cryo-Cell International. There is a strong internationally connected public cord blood banking system, as well as commercial operations for private cord blood banking. Activities undertaken include collection, storage and expansion.

Associated with this are companies with expansion technologies, such as the industry leader Gamida Cell Ltd, which is focussed on expansion of HSC, and has an estimated market potential for its cell expansion products of \$US40B worldwide. Effective expansion technologies are also needed for the range of other cell types, and more than 150 research institutions and companies are active in research in this area.

Several companies have proprietary stem cell technologies, as shown in Appendix 2. Osiris is the most established company, with Osteocel already in the market, and two more products expected to be approved by the FDA within the next two years: Prochymal, as treatment for GvHD, and Chondrogen for repair of knee cartilage.

Current applications for stem cell products include spine fusion surgery, and bone growth and void fillers for fresh and non-union fractures. Commercial applications under development include regeneration of bone and cartilage, myocardium and vascular, pancreatic beta cells, neuronal – particularly Parkinson's Disease, skin replacement and wound healing. Several treatments for heart disease are also expected to be approved within the next two years. A list of companies developing regenerative therapies is included in Appendix 2. As of 2005, the majority of specialist stem cell companies were located in the US, privately held and working on adult stem cells. Other countries with a substantial level of stem cell commercialisation activity include the UK, Germany, Sweden and Israel.

Timelines for therapeutic products from embryonic stem cells are much further out. The primary companies active in commercialisation of ESC include Geron, Advanced Cell Technology, Novocell and Neuralstem.

An additional market sector that has been growing rapidly is the use of stem cells for drug screening. Development of high-throughput assays from specific populations of human derived cells is expected to offer vastly improved prospects for drug screening, target identification and validation and toxicity testing than conventional animal testing. This is likely to be the earliest area of significant commercial and clinical value for embryonic stem cell research. It is the area of most interest to large multinational pharmaceutical companies such as Eli Lilly, Merck, Novartis, Pfizer and GE Healthcare, as a potential enabling technology for faster and more efficient drug development.

29. Biophoenix market report, Business Insights, Opportunities in Stem Cell Research and Commercialisation. Technology advances, regulatory impact and key players, 2006.



There are over 100 companies with active R&D programs in tissue-engineered products, with a market capitalisation of over \$US 5B³⁰. The main therapeutic categories being pursued by companies are cardiology, dermal, dental, neurology, orthopaedic and urology; with 60% of activity at the research or preclinical phase, and 40% clinical. The worldwide market for tissue engineered products was \$US 145M in 2005, based on skin-engineering, cartilage-repair and bone regeneration products (50%, 35% and 15% of revenues respectively)³¹. The worldwide market for tissue-engineered products is expected to grow at a compound annual growth rate of 28%, delivering revenues of over \$US 2B by 2015 (and may far exceed this as other applications such as organ replacement, spinal repair and vascular replacement are not included in this estimate). Fastest growth in this segment is anticipated for cardiovascular tissue engineered products, with a CAGR from 2005-2015 of 72%, resulting in an estimated revenue of around \$US 380M by 2015, surpassing revenues from cartilage and bone products.

Several companies are also active in the utilisation of stem cells for veterinary applications such as VetStem in the USA, VetCell Bioscience Limited in the UK, and Vet Biotechnology in Australia. The initial commercial focus for these companies has been treatment of tendon and ligament injuries in racehorses, but with a view to further expanding treatment options for other domestic animals such as treatment of osteoarthritis in dogs. Vet-Stem's technology is based on the use of adipose-derived stem cells, while VetCell and Vet Biotechnology utilise equine mesenchymal stem cells from umbilical cord blood or bone marrow. Early adoption of these cell therapy approaches in routine veterinary applications provides an important staging platform for development of the field of regenerative medicine - by providing a broader set of proof-of-concept and longer-term safety data for various regenerative cell therapy approaches, that can be drawn on as a knowledge base in the subsequent progression to human clinical use.

2.5 Regulatory, Ethical and Political Issues

One challenging aspect to the development of the field of regenerative medicine is the need to build the frameworks for new regulatory pathways for new types of clinical products and approaches, and establish the sound data sets and criteria for long term safety and efficacy, (such as agreed markers, stability criteria and recognised uniform handling protocols), that will smooth the path for subsequent regenerative therapies that follow. Also challenging is the variation in regulatory requirements in different regions, such as the US and Europe³².

The US has well established regulations for minimally manipulated cells and tissues. For manipulated products, much higher levels of regulatory oversight are applied, focussing on

- Preventing disease transmission
- Preventing contamination or damage through improper handling, and
- Ensuring safety and efficacy.

As regenerative medicine products are often combination products, the progress of these products through FDA was initially complicated by the fact that they were classified under multiple categories – device, biologic and drug, necessitating a complex, time-consuming and expensive approval process. To accommodate the changes in the field, and in response to criticism from industry, the FDA created the Office for Combination Products in 2002 to streamline the approval of combination products. The FDA also created the Office of Cellular, Tissue and Gene therapies to consolidate a number of regulatory programs in human tissues, cellular therapies, xenotransplantation and gene therapies.

30. Tengion presentation

31. MedMarket Dilligence LLC, (from Tengion presentation)

32. A. Sanderson, Stem Cells: Taking a closer look at the advancements and hurdles of stem cell research in Australia, Teaching Science, 2008, 54, 12-16

The agency has also adopted an increasingly proactive, early-engagement mode of operation to assist in providing early input of regulatory issues, requirements and pathways to facilitate more rapid progress of new technologies to clinical use. It is also playing an active role in the MATES initiative forged by multiple US government departments to facilitate the progress of regenerative medicine (Multiagency Tissue Engineering Science Interagency Working Group)³³.

Australia is regarded as having a favourable regulatory framework due to its clarity and transparency. The streamlined procedures in place for registration of clinical trials also make it attractive on an international basis for conducting clinical trials. An important aspect of this is the Clinical Trial Notification Scheme which allows trials to begin within a week of being registered³⁴, and 99% of clinical trials taking advantage of this process.

The development of the stem cell field has been highly affected by public response to certain aspects of research, such as embryonic stem cells and somatic cell nuclear transfer, and the subsequent impact that this has on government policies and preferred funding areas. In many cases this has slowed or stymied research activity in controversial areas such as ESC and SCNT, either by lack of funding or legal prohibition. The US in particular lagged the field internationally in ESC research, due to restrictions on use of Federal funding for this purpose. This led ultimately to a public revolt in California, with the establishment of Proposition 71 providing a means for the general public to provide greater direct financial support for stem cell research, including embryonic stem cell research.

In Europe, Britain, Belgium and Sweden are regarded as having the most liberal policies. Israel, Japan, Singapore, South Korea, China, Canada and Australia also have progressive policies toward stem cell research.

Australia is regarded as having found a good balance between a progressive attitude supporting stem cell research, including ESC and SCNT, but also a strong and clear regulatory framework to ensure public confidence is retained in research activities at the forefront of the field. Researchers benefit from strong Federal and State government support, as well as public support³⁵ built on hope for the field to deliver new therapies. The ASCC has played an active role in supporting the progression of new stem cell bills through parliament, providing expert advice to enable informed debate. Recent developments include the successful progression of two Victorian bills in October 2008 – the Prohibition of Human Cloning for Reproduction Bill 2008, and Research Involving Human Embryos Bill 2008. These bills are consistent with Commonwealth legislation in this area, allowing continuing permissive legislation in relation to embryo research and the creation of embryonic stem cells³⁶.

2.6 Patent Issues

Also adding complexity to the development of the stem cell related therapies is the variation in patentability of particular stem cell aspects in different regions internationally, as well as the recent development of patent thickets.

In terms of patentability, it is far easier to secure patent claims relating to embryonic stem cells in the US than in Europe. The US has permitted some very broad claims in landmark early stem cell patents, which has caused controversy as they have prevented further development of the field. Most notable in this regard is the 2001 Thomson (WARF) patent on hESC, and the Geron patent on culture of ES cells, as it is envisaged that many therapeutic applications based on hESC will require licenses to these patents. The WARF patent application was denied in Europe, as the European Patent Office excludes inventions involving the use of human

33. Multi-Agency Tissue Engineering Science (MATES) Interagency Working Group, Advancing Tissue Science and Engineering, A Multi-Agency Strategic Plan

34. http://www.business.vic.gov.au/busvicwr/_assets/main/lib60041/biotech_vic_industry_profile_2007.pdf

35. Public support for stem cell research remains strong, Biotechnology Australia, May 2006 <http://www.biotechnology.gov.au>

36. http://www.stemcellcentre.edu.au/news-events_latest-news_detail.aspx?view=33 Prohibition of Human Cloning for Reproduction Bill 2008 and Research Involving Human Embryos Bill 2008, 08 October 2008



embryos for industrial or commercial purposes³⁷. In recent years, WiCell has been more active in trying to resolve licensing issues to research organisations, in response to the widespread backlash that their unreasonable licensing terms on the Thomson patent were perceived to be stymieing progression of the field^{38,39}.

The other patent concern that has arisen relates to the exponential increase in stem cell related patent filings in the early 2000s which has created a 'patent thicket'. This has important ramifications not only for ability to file (breadth of claims allowed in US an issue), but also in terms of freedom to operate issues, as in a multidisciplinary domain such as this any particular therapeutic area is likely to require multiple cross-licenses. One suggested strategy to allow a path to market through the patent thickets is the development of regional IP clearing houses⁴⁰.

Analysis of patent filings over the 1980-2005 period has shown⁴¹:

- Adult stem cell technologies dominated filings (62%)
- Most filings were in relation to stem cell isolation and culture (53%) followed by directed differentiation (26%).
- Gene delivery was a hot area initially, then dropped off
- The majority did not claim a therapy area
- Of therapies claimed, most initially related to haematology, and then this declined as applications in neurology, IDDM, cardiology and drug screening increased.

The early strength of Monash University in the stem cell field is reflected in its ranking in international patent assignments in the 1980-2005 period, being ranked 12th internationally.

The only public research institutes exceeding Monash in this period were the Universities of California and Michigan, the California Institute of Technology and Johns Hopkins University. More recently this pre-eminence in patent activity has been harder for Monash to sustain due to the problem of patent thickets in previously established areas of strength. Increasingly research organisations have looked to patent mapping to define the 'white space' before commencement of major research investments, in order to identify the research areas which have the highest probability the new IP can be secured, and have a commercially attractive FTO position.

2.7 Major challenges to progress the field; the frontline of knowledge.

As the field of regenerative medicine is at an early stage of development, there remain considerable research challenges to be addressed across the broad range of disciplines that contribute to the field, in order for it to progress to affordable, well-established clinical therapies. These challenges include^{43,44,45}.

Reliable and diverse cell sources:

- Cell banks which encompass genetic diversity
- Resolution of stability, characterisation and contamination issues.

Developmental and stem cell biology:

- Characterisation of different SC populations and their comparative behaviours
- Assessment of relative suitability of different cell types for different applications.
- Better understanding of developmental pathways.
- Cell banks with multiple lines/types available to researchers and clinicians for benchmarking.

37. Regen 2006, NIH report <http://stemcells.nih.gov/info/scireport/2006report.htm>

38. A. Plomer, K. Taymor and C. Scott, Challenges to Human Embryonic Stem Cell Patents, *Cell Stem Cell*, 2008, 2, 13-17

39. M. Rao, Mired in the Quagmire of Uncertainty: The Catch-22 of Embryonic Stem Cell research, *Stem Cells and Development*, 2006, 15, 492-496

40. T.G.H. Diekwisch, When Genomes and Stem Cells Meet: New Perspectives for Medical Applications of Stem Cell Research through the Australian/U.S. Collaborative, *Stem Cells and Development*, 2006 15, 475-477

41. P. Batten, N.A. Rosenthal and M. Yacoub, Immune Response to Stem Cells and Strategies to Induce Tolerance, *Phil. Trans. R. Soc. B* (2007) 362, 1343-1356

43. P.C. Johnson, A.G. Mikos, J.P. Fisher, J.A. Jansen, Strategic Directions in Tissue Engineering, *Tissue Engineering*, 2007, 13(12), 2827 – 2837

44. D. Stocum, Regenerative Biology and Medicine: Research Opportunities for Physicists, Engineers, Mathematicians.

45. State of the art, Challenges ahead (courtesy G. Vunjak-Novakovic) http://www.wtec.org/stem_cell_workshop/presentations/02-shoichet.pdf

Molecular biology:

- Greater understanding of signalling cues from matrix
- Identification of chemical cues to differentiation, trans-differentiation, de-differentiation, quiescence, apoptosis, and expansion. Combination of library screening approach with fundamental characterisation.
- Improved analytical tools.
- Improved understanding of in vivo regenerative processes.

Systems biology:

- Interplay of physical, chemical signals; time dependence and co-dependence of factors. Particularly as it relates to regeneration, engraftment, and longevity of benefit.
- Integration of genomics and stem cell science⁴⁶

Anatomy:

- Characterisation of niche, and physical properties of tissue that affect cell behaviour, including lineage, engraftment or cancer initiation.

Enabling tools:

- Bioinformatics - particularly to integrate molecular and systems biology in 4 dimensions
- Imaging techniques for in-vivo characterisation,
- Biomarkers for better characterisation of populations, antibodies
- Automated assays and sorting technologies, high throughput and high content screening, tissue based arrays, new functional activity-based markers.
- Miniaturisation and automation of culture, and standardisation of xeno-free culture techniques for different cell lines;
- Disease specific cell lines and genetic engineering.

Immunology:

- Consideration of immune response issues in selection of optimum cell source for application.
- Approaches to enhance immune tolerance⁴⁷ and clinical effectiveness eg co-transplantation
- Increased understanding of immune-privileged behaviour of some SC sources (eg MSC and amion-derived).

Scaffolds and delivery systems:

- More advanced scaffolds that incorporate the advantages of the physical properties of polymer systems, and cell-compatibility of biological systems (eg hybrids). Incorporation of multiple biochemical signals, with time-dependent or responsive release.
- Utilisation of decellularised natural matrices.
- Design with downstream hurdles in mind: sterilisability, regulatory approval process for combination products, low-cost manufacturability, shelf-life.
- Design of structures that facilitate vascularisation and full-thickness nutrient supply⁴⁸
- Delivery – efficient localisation of cell therapy delivery with associated cues and/or recruitment or homing promoters to increase engraftment/induction/efficacy rates.

Angiogenesis and 3D cellular organisation:

- All aspects - biology, chemical cues, design of structures, bioreactors, etc

Animal models:

- Integration and correlation of information from different models – drosophila, zebra fish, mouse, small animals, primate, and human.
- Increase utility of models – eg humanised mice.

46. T.G.H. Diekwisch, When Genomes and Stem Cells Meet: New Perspectives for Medical Applications of Stem Cell Research through the Australian/U.S. Collaborative, Stem Cells and Development, 2006 15, 475-477

47. P. Batten, N.A. Rosenthal and M. Yacoub, Immune Response to Stem Cells and Strategies to Induce Tolerance, Phil. Trans. R. Soc. B (2007) 362, 1343-1356

48. M. Kikuchi and D. Kanama, Current status of biomaterial research focussed on regenerative medicine, Science and Technology Trends, 2007, 24, 51-67



Scale up/Large scale culture:

- Bioreactor technologies – automation, efficiency, tailored conditions suitable for expansion and differentiation of different cell lines.
- Enhanced production efficiency - cost, reproducibility, resilience, control. Sterility and GMP issues.
- Ability to characterise a defined and stable product.

Shelf-life:

- Cell and tissue preservation and storage.
- Markers for stability.

Clinical techniques:

- Optimisation of delivery.
- Training, standardisation, and respected opinion leaders.
- Drive design process through understanding of greatest clinical needs and impact areas.

Safety:

- Better understanding of potential tetragenicity risks of ESC-derived cell lines.

Regulatory engagement – regulatory understanding:

- Proactive 2-way engagement to accelerate establishment of new regulatory criteria as field and new therapies evolve
- Upfront consideration of regulatory thresholds/ requirements in design of new cellular therapies and combination TE products⁴⁹.

Commercialisation:

- Realistic assessment of viable business models.
- Upfront FTO analysis in major areas of investment.

- Adaptive commercial strategies, eg recognising the different business models for allogeneic and autologous cell therapies⁵⁰
- New IP management strategies to address SC patent thicket– eg IP clearing house partnerships with Asia/Europe.
- Internationalisation of VC funding arrangements and syndicates.

2.8 Contributing Disciplines

Given the nature of these challenges, a wide range of expertise is required to progress the field.

This will include:

- Anatomists
- Biochemists
- Cell and Systems and developmental biologists
- Chemists
- Materials scientists
- Engineers
- Informaticians
- Geneticists
- Nanotech fabrication experts
- Physicians
- Economists
- Advanced imaging experts
- Structural biologists
- Educators
- Social scientists
- Ethicists
- Vascular biologists
- Regulatory advisers

49. G.Daley, I. Hyun and O. Lindvall, Mapping the Road to Clinical Translation of Stem Cells, Cell Stem Cell, 2008, 2, 139-140
 50. D. Smith, Successful Business Models for Cell-Based Therapies, World Stem Cell Report 2008.

3 Internal Analysis

The following analysis represents an initial overview of the key capabilities, assets and project focus areas of the founding members of SMART. It is envisaged that this will be augmented with further detail as particular thematic areas are identified. A more detailed audit of the areas of research strength within Monash University in the area of regenerative medicine is currently being undertaken by Dr Rocco Iannello.

3.1 SMART Capabilities related to/enabling Regenerative Medicine

Fundamental Stem Cell Biology		
Embryonic	Human - Creation, isolation, cell biology, characterisation, maintenance and storage Mouse	MISCL: Prof Ed Stanley, Prof Andrew Elefanty ASCC: Dr Andrew Laslett MIMR: Dr Paul Verma SOBS (Anat): Dr Adam Hart, Dr Helen Abud
Mesenchymal	Various sources – umbilical cord, adipose tissue, bone marrow, induced from ES	MISCL: Prof Richard Boyd, Prof Claude Bernard, A/Prof Sharon Ricardo MIMR: Prof. Ban-Hock Toh ASCC: Dr David Haylock, Dr Susie Nilsson
Placental (amnion)	Immunosuppressive/ anti-inflammatory properties	MISCL: Prof Graham Jenkin MIMR: Dr Ursula Manuelpillai Med: Dr Euan Wallace
Haematopoietic		ASCC: Dr Susie Nilsson, Dr David Haylock
Cardiac	Mouse ASC	Dr Paul Verma
Endometrial	Human and mouse	MIMR: Dr Caroline Gargett
Spermatagonial	Testicular cancer and human infertility Veterinary breeding	MIMR: A/Prof Kate Loveland & Dr Julia Young CSIRO: Dr Jerome Werkmeister
Lung		ASCC: A/Prof Ivan Bertoncello
Kidney		MISCL: A/Prof Sharon Ricardo, SOBS: Prof John Bertram ASCC: Dr Andrew Laslett
Thymus		MISCL: Prof Richard Boyd
Pancreas & Liver		MISCL: Prof Ed Stanley & Prof Andrew Elefanty
Neural		Pharmacy: Dr Theo Mantamadiotis
iPS	Characterisation	MIMR: Dr Paul Verma ASCC: Dr Andrew Laslett



Cancer stem cells	Prostate (human and mouse)	MIMR: Prof Gail Risbridger & Dr Renea Taylor, Prof Neil Watkins;
	Colon cancer stem cells	Pharmacy: Fred Holland SOBS (Anat) Dr Helen Abud
	Mouse germ cell tumours – ES-like	SOBS (Anat): Dr Adam Hart
Germ cells		MISCL: Dr David Cram, Prof Graham Jenkin
SCNT	Cattle, equine, mouse, monkey and human	MIMR: Dr Paul Verma
Disease-specific cell lines	Preimplantation genetic diagnosis	MISCL: Dr David Cram
Directed differentiation	hESC	MISCL: Prof Ed Stanley and Prof Andrew Elefanty
	Mechano-directed differentiation	Eng: Dr QiZhi Chen
	Synthetic 3D niche – spatial delivery of correct cues	CSIRO: Dr Keith McLean, Dr Laurence Meagher, Dr Helmut Thissen Eng: Dr John Forsythe
Systems, Developmental, & Regen Biology		
Developmental Biology	Molecular mechanisms controlling cell differentiation in vertebrate embryo development (Esp re genetics, zebrafish models, muscle, cardiac)	ARMI: Prof Peter Currie
	Fetal development	MISCL: Prof Graham Jenkin Prof Euan Wallace
	Kidney	SOBS: (Anatomy) Prof John Bertram,
	Cardiovascular & renal cell biology	SOBS (Anatomy) Dr Jane Black
	Pulmonary development & programming	SOBS (Anatomy) Prof Richard Harding A/Prof Stuart Hooper
	Embryo and oocyte	Eng: Dr George Thouas
Regenerative and systems biology	Mouse, circulating progenitor cells, role of cell signalling in mammalian regenerative mechanisms	ARMI: Prof Nadia Rosenthal

Molecular embryology	Molecular recognition of pluripotency and specification during development and tumorigenesis. Cellular and molecular mechanism underlying SC self-renewal and differentiation. Use of transgenic and gene-targeted SC lines. Homeobox transcription factors.	SOBS (Anatomy): Dr Adam Hart
Anatomy / Structural Biology / Niche / Matrix / Genomics / Proteomics		
Bone marrow niche	Haemopoetic stem cell niche	ASCC: Dr David Haylock, Dr Susie Nilsson
Tissue Niche	Characterisation of niche in normal versus diseased tissue	MIMR: Prof Gail Risbridger
Structural and molecular biology, Proteomics		SOBS: Prof Ian Smith, Dr Jamie Rossjohn, Dr Steve Bottomly, Dr James Whisstock
Extracellular matrix and cell-matrix interactions		CSIRO: Dr John Ramshaw, Dr Jerome Werkmeister
Functional Genomics	Genetics, models of disease; gene expression; gene targeting	MIMR: A/Prof Paul Hertzog
Bioinformatics	Bioinformatics, genomics, databases; functional genomics; sequence analysis	SOBS (Microbiology) Prof Ross Coppel, (Biochem) Dr James Whisstock
Cell Signalling, Biochemistry, Molecular Biology, Peptides and Proteins		
Cell Signalling in Regen Processes	Role of cell signalling in mammalian regenerative mechanisms; growth factors; signalling pathways that induce recruitment of circulating progenitor cells to damaged tissue	ARMI: Prof Nadia Rosenthal,
Cell Signalling in Developmental Pathways	Molecular mechanisms controlling cell differentiation in vertebrate embryo development	ARMI: Prof Peter Currie
Cell Signalling – General & Human Disease	Subcellular transport, targeting signals, protein-protein interactions, signal transduction; cell development; enzyme activity; cell growth, differentiation, role in cancer, muscle development and cardiac failure	SOBS: Prof Christina Mitchell, Prof David Jans, A/Prof Tony Tiganis
Peptides and proteins	Molecular basis of protein and peptide function	A/Prof Mibel Aguilar
Molecular biology of Tumour suppression	Role of tumour suppression genes in regulating cell growth, differentiation and apoptosis; cell signalling in cancer	MIMR: Prof Bryan Williams



Function of stem cells in normal and disease states	Receptor signalling and stem cell function; Gene regulation in development and disease: and Adhesion molecule signalling during development and in disease	Pharmacy: Colin Pouton, Frederic Hollande
Molecular biology re cardiac damage	<p>Molecular Pharmacology lab.: including the cellular mechanisms responsible for cardiac hypertrophy; heart complications related to diabetes, and addressing reperfusion injury, the damage caused to the heart after a heart attack</p> <p>Experimental Cardiology and Heart Failure - Cellular, molecular and genetic underpinnings of the progression from initial heart muscle damage to heart failure, to large animal studies; mechanics of the heart and heart muscle</p> <p>Cellular Biochemistry - Mechanisms involved in atrial and ventricular fibrillation; treatments for sudden cardiac death; novel mechanisms to increase the strength of the heart beat; and identification of factors that may reduce damage to the heart during a heart attack.</p>	<p>Baker: Rebecca Ritchie</p> <p>Baker: Prof David Kaye</p> <p>Baker: A/Prof Elizabeth Woodcock</p>

Immunology

Immune Tolerance	Immune tolerance, thymic rejuvenation; immune response issues in stem cell therapies; immune privilege of cell lines, recovery from cancer	<p>MISCL: Prof Richard Boyd, Prof Graham Jenkin</p> <p>MIMR: Prof Ban-Hock Toh</p>
Immune and inflammatory Processes	<p>Immunosuppressive and anti-inflammatory properties of stem cells</p> <p>Autoimmune – MS</p> <p>Clinical immunology – respiratory</p> <p>Chronic disease progression mechanisms; fibrosis, gf, cytokines</p> <p>Clinical immunology, autoimmunity, cell division</p> <p>T cell response, allergens, asthma</p> <p>Autoimmune Glomerular Inflammation</p> <p>Human endothelial cell biology; recruitment of leukocytes to inflamed microvasculature</p> <p>PTK therapeutics against immune disorders</p>	<p>MISCL: Prof Richard Boyd, Prof Graham Jenkin,</p> <p>MISCL: Prof Claude Bernard</p> <p>Alfred Hospital: Prof Robyn O'Hehir</p> <p>Medicine: Prof Napier Thomson</p> <p>MIMR: Prof Ban-Hock Toh</p> <p>A/Prof Jennifer Rolland</p> <p>Med/MMC: Prof Stephen Holdsworth</p> <p>MMC: Dr Michael Hickey</p> <p>SOBS (Biochemistry) Prof Jamie Rossjohn,</p>

Materials Technologies; Tissue engineering Scaffolds; Cell culture substrates; Microarrays; Bioengineered systems and methodologies

<p>Novel polymers for scaffolds & cell culture</p>	<p>Design & synthesis of fit-for-function polymers; biostable and biodegradable; tissue engineering scaffolds; bioactive drug-delivery polymers;</p> <p>Smart polymer bioconjugates; UV curable injectable hydrogels</p> <p>Novel polymer, ceramic and composite scaffolds for TE</p> <p>Soft tissue engineering, biomaterials and biomechanical entrainment</p>	<p>CSIRO: Dr Tim Hughes, Dr Mike O'Shea</p> <p>Eng: Dr John Forsythe,</p> <p>Eng: Dr QiZhi Chen</p> <p>Eng: Dr George Thouas</p>
<p>Biological scaffolds</p>	<p>Recombinant collagen, other ECM, recombinant silks and resilin; Peptide chemistry</p> <p>Decellularised tissue scaffolds</p>	<p>CSIRO: Dr John Ramshaw, Dr Jerome Werkmeister</p> <p>ASCC: Dr Kathy Traianedes</p>
<p>Polymer production & fabrication</p>	<p>Scale-up, moulding, fibre production (extrusion & electrospinning) Fabrication of yarns and filaments into 2D and 3D structures (knit, weave, non-woven) eg neural conduits</p>	<p>CSIRO: Dr Mike O'Shea</p> <p>Eng: Dr John Forsythe</p>
<p>Polymer surface modification</p>	<p>Design & fabrication of specific surface chemistries for controlled biomolecule & cell-material interactions (eg maintenance/directed differentiation/expansion of stem cells); spatial and chemical cues</p> <p>Printing proteins at picolitre level: microarrays and diagnostics</p>	<p>CSIRO: Dr Keith McLean; Dr Laurence Meagher; Dr Helmut Thissen</p> <p>Eng: Dr John Forsythe</p> <p>ASCC: Dr David Haylock</p> <p>APPI: Prof Gil Garnier and Dr Wei Shen</p>
<p>Nanotechnology</p>	<p>Nanostructured materials - Self assembled scaffolds. Membrane-like scaffolds & surface treatments</p> <p>Nanomarkers – labels for assessing in vivo localisation of stem cells (synchrotron)</p> <p>Biomembrane nanotechnology</p> <p>Nanostructured surfaces; and printing of growth factors and cells</p> <p>Micronanoengineering, sonics, microbots</p>	<p>Dr Keith McLean, Dr Pat Hartley</p> <p>Prof Claude Bernard & collaborators in Chemistry</p> <p>A/Prof Mibel Aguilar</p> <p>Eng: Dr John Forsythe, Dr George Thouas, APPI: Prof Gil Garnier</p> <p>Eng: A/Prof James Friend, Dr Leslie Yeo</p>



Bioreactors	New bioreactor systems, eg Smart surfaces for stem cell expansion and controlled differentiation	CSIRO: Dr Keith McLean Eng: Dr John Forsythe, Dr George Thouas
Bioengineering	Manipulating microparticles Vascular flows, fluid eng Biomembranes, fluid mechanics near cell membranes, computer based modelling Medical imaging technology and high-resolution image analysis, model synchrotron facility	Dr Adrian Neild, Tuk-Wa Ng Prof Kerry Hourigan ProbakkharRagananthzn Dr Andreas Fouras
Chemistry, Drug Design, Screening, Pharmacology		
Drug screening and development	Use of differentiated ESCs in drug discovery Computer-aided drug design	VCP: Prof Colin Pouton, Dr John Haynes CSIRO: David Winkler SOBS: A/Prof Mibel Aguilar, James Whisstock
Animal trials, Biocompatibility, Clinical Translation		
Biocompatibility of implants		CSIRO: Dr John Ramshaw, Dr Jerome Werkmeister, Dr Meg Evans
Clinical translation	Cancer – autologous transplantation of HSC Cancer clinical trials	Dr David Haylock Prof Bryan Williams, Prof Neil Watkins

3.2 Key Infrastructure

FACILITY	TECHNIQUES	KEY PERSON
Flow Core	FACS – cell sorting	Mr Andrew Fryga
Synchrotron	Materials analysis, medical imaging and model synchrotron facility	Dr David Cookson, Dr Daniel Hausermann, Prof Rob Lewis Dr Andreas Fouras
MATF (Monash Antibody Technology Facility)	Antibody production, microarrays	Mr Alan Sawyer, Mr Mike Spiegel
Micro Imaging	Optical, fluorescence & Confocal microscopy; SEM; TEM; Live cell imaging; cryo tissue prep; Digital imaging and image analysis	Dr Ian Harper
Meso-scale tissue and whole animal imaging	Electron Paramagnetic Resonance structural and functional imaging	Prof Harald Schmidt, Prof Kerry Hourigan
ProteinCoreProduction:	Mammalian protein production & high throughput protein purification.	Prof Ross Coppel, Prof Ian Smith, Prof Jamie Rossjohn
Structural biology & Bioinformatics:	Protein crystal isolation & sequence analysis	
Proteomics:	Protein identification & analysis	
Mouseworks	GM-mice generation, housing and screening - Transgenics, knockouts, rederivation, cryopreservation, phenotyping	Dr Tim Cole
FishCore	Zebra fish facility - Mutant screens, phenotyping	Prof Peter Currie
GeneCore	Micromon (DNA sequencing, oligonucleotide synthesis, PCR); expression profiling, HTP sequencing; recombineering	Ms Jeanette Rientjes
Stem Cell Bank	hESC bank, as well as access to broad range of cell lines	Dr Andrew Laslett
Polymer synthesis & fabrication	Scale-up synthesis of monomers and polymers; fibre production (twin screw extruder; carbon nanotube fibres); facilities for weaving, knitting, non-wovens; electrospinning of scaffolds for tissue engineering	Dr Mike OShea
Polymer Characterisation	NMR, FT-IR, GC/MS, DSC, DMTA, DMA, XRD, Instron, rheometer	Dr Thomas Gengenbach
Polymer surface modification and Analysis	Plasma reactors, liquid handling robot, microarray robots, sputter/spin coating, AFM, QCM-D, SPR	Dr Laurence Meagher, Dr Keith McLean
Biocompatibility & Cell culture	Cell and tissue culture Cell and tissue biomechanics Small animal facilities	Dr Jerome Werkmeister Dr George Thouas
High throughput screening	h content screening Microarrays	Dr Trevor Wilson Dr Helmut Thissen



3.3 Major Therapeutic Focus areas of SMART Participants

Monash University has a broad range of health-related teaching, research and clinical activities covered within its overall organisational umbrella and partnerships. The Faculty of Medicine, Nursing and Health Sciences undertakes research programs including clinical medicine, medical imaging and radiation sciences, biomedical science, nutrition and dietetics, social work, psychology, ambulance and paramedic studies, nursing and midwifery, physiotherapy, epidemiology, health management and occupational therapy. The faculty's biomedical research activities are concentrated in the MBio biomedical precinct on the Clayton campus, involving around 650 researchers, managed by the School of Biomedical Sciences. The precinct was ranked 22nd in the world for life sciences by the Times Higher Education Supplement, and has particular research strengths in the areas of cancer, neurosciences, foetal and baby development, obesity and metabolism, infectious diseases, regenerative medicine, stem cell science, structural biology and drug design and vascular health. In 2007, MBio staff published 403 papers, (35 in high impact journals) and secured research income of \$46 million. The Faculty also has strong links with the other entities which are partners in the Monash Institutes for Health, which includes several major teaching hospitals of Monash University – principally Monash Medical Centre, the Alfred and Box Hill (within the Bayside, Southern and Eastern health services) and affiliated medical research institutes, including Monash Institute of Medical Research, Prince Henry's Institute of Medical Research, Baker IDI Heart and Diabetes Institute, the Burnet Institute and the Monash Institute of Health Services research.

Monash Immunology and Stem Cell Laboratories

Within the MBio precinct, the Monash Immunology and Stem Cell Laboratories has research activities which address a range of therapeutic areas including: foetal development, human reproduction and embryology; immune disorders (such as multiple sclerosis) and immune tolerance; and stem-cell based repair and regeneration approaches for renal, pancreatic, respiratory, blood, liver, thymic and neural applications⁵¹. MISCL also has interests in areas which may provide more near term commercial benefits, such as cell banking, pre-implantation genetic diagnosis and veterinary applications for tissue repair.

Australian Regenerative Medicine Institute

Through a joint venture between Monash University and the Government of Victoria, a state-of-the-art regenerative medicine research capacity building on Monash's existing strengths in biomedical research has been established. This capacity takes the form of a new institute, the Australian Regenerative Medicine Institute, which has capital funding to support the critical infrastructure including:

- Fully fitted out laboratory space and core research facilities
- accommodation for the EMBL Australia Partner Laboratory research groups.

The committed investment of \$153 million in the ARMI project by Monash University and the Victorian State Government demonstrates a significant commitment to the foundations of the EMBL Partner Laboratory.

51. <http://www.med.monash.edu.au/miscl/about.html>

The recently formed Australian Regenerative Medicine Institute is scheduled to open its laboratories in late 2008. Whilst the exact program areas are still being defined, a major initial strength is in the area of muscle regeneration, relevant not only to 'healthy ageing' by reducing muscle wasting, but also addressing conditions such as muscular dystrophy and cardiovascular disease. With an underpinning research strength in developmental and systems biology, future research programs will also deliver outcomes into a broader range of therapeutic areas, such as kidney disease, immune disorders, diabetes and cancer. The Institute has a particular focus on providing world-class training and an environment for young scientists to excel, which will be delivered through hosting EMBL Australia Partner Laboratory research groups. This is modelled on the program conducted at the European Molecular Biology Laboratory, and ARMI will retain strong links to EMBL, as it will serve as a central laboratory and administrative hub to the newly established EMBL Australia, the entity established to oversee EMBL related activities in Australia.

Monash Institute of Medical Research

The other Monash institute with a high level of activity in stem cell science is the Monash Institute of Medical Research, which is regarded as one of Victoria's premier medical research institutes due to its strong track record in medical research discoveries, such as advances in the areas of assisted human reproduction, reduction of AIDS, and treatment of arthritis. It is home to over 400 researchers, clinicians and staff, and its medical research encompasses a range of therapeutic areas including cancer, innate immunity and infectious disease, male infertility, women's health, pain medicine and palliative care, women's health and neonatal and fetal physiology.

Australian Stem Cell Centre

The Australian Stem Cell Centre is Australia's Biotechnology Centre of Excellence, undertaking not only fundamental and applied stem cell research, but also serving as a national base for specialised training, expert advice, and services (such as provision of cell lines, antibodies and cell sorting). A major therapeutic focus in recent years has been in the haematology area, with a longer term goal of developing transfusable blood products. In supporting programs, research activities have also been relevant to therapeutic areas such as cardiology, respiratory, and immune modulation. The ASCC is currently reviewing the prioritisation of its therapeutic focus areas, which will be supported by its fundamental research platforms that are in the areas of pluripotent stem cells, adult stem cells and bioreactor technologies.

CSIRO

The CSIRO has research activities which cover nearly all fields of endeavour. In the health area, its strategic focus is to deliver high impact clinical outcomes by being a provider of innovative enabling technologies, usually developed in partnership with an expert clinical and/or commercial partner. In the Biomaterials theme, the focus has been on the development of novel polymers and surface coatings for medical devices and tissue engineering constructs. A major area of clinical focus in the past decade is the ophthalmic area, such as in its long-term collaborative project with Ciba Vision to develop the world's first extended wear contact lens. Over the past decade it has developed a number of enabling platform technologies, such as novel polymers for tissue engineering scaffolds for cartilage and bone repair, artificial cornea, and bioadhesives. It has utilised its expertise in design of polymer surface chemistries for specific cell-material interactions to develop systems for control of stem cell expansion and differentiation, as undertaken in the collaborative CRC for Polymers research program for the ASCC on stem cell bioreactors for blood production.



4 Strategic Analysis

4.1 SWOT (from workshop group)

At the meeting of stakeholders in February, the following factors were identified as strengths, weaknesses, opportunities and threats.

Strengths	Weaknesses
<ul style="list-style-type: none"> • Good core technology • Multi-disciplinary • Diversity of cultures • Multiple Organisations and strengths • Strong and visionary leadership • Collaborative can do culture • Clinical access • Amazing infrastructure • Breadth of interested participants • Monash University existing reputation • Interdisciplinary access • Animal models of disease classic and molecular • Willingness to work together • Good science record • Co-leveraged infrastructure 	<ul style="list-style-type: none"> • Three different cultures i.e. academic, translational and commercial • Multiple Organisations • Lack of awareness of each others capabilities • Non secured long-term funding • Protracted establishment timeline • No collaborative interactive space • Difficulty in creating momentum in the past • Geographical separation • Lack of defined champion of each node • Lack of focus • Unclear governance structure • Multiple overlapping brands • Low involvement of clinicians • Lack of lobbying strength
Opportunities	Threats
<ul style="list-style-type: none"> • Define regenerative and biomedicine community in Victoria • Increase positive community attitude • Be a complimenter • Funding uncertainty • Significant unmet clinical needs • Australia's roles in Pacific rim • Embrace alternative technologies • Impact of clinical trials • High cost of chronic disease • Disruptive technologies • Increased recognition of returning expats • Increased recognition multi component interaction • Early and significant funding for stem cells • Rapidly advancing technology delivering results • Australia research strength • Capture synergies through collaboration • Pharma pipelines drying up • Ageing population 	<ul style="list-style-type: none"> • Human capital Recruitment Retention u/grad and p/grad return to Monash • University Retain most productive years Education appropriate • Alternative technologies not embraced • Funding failure Political changes, community attitude e.g bad medical outcomes, decreased benefit • Non competitive Not gain industrial support • Non competitive regulatory environment • Inadequate infrastructure • Failure to deliver



4.2 Strategic Issues and Critical Success Factors

Developing a common sense of purpose and shared ownership of future initiatives. Active engagement and support for SMART must be established at both an individual and organisational leadership level for it to achieve momentum. SMART must be representative of the needs and goals of its stakeholders.

Recognition that the process is opt-in. SMART initiatives must add significant value over and above what participating organisations could achieve individually, otherwise it will be just a bureaucratic overhead and distraction. Strategy development and implementation will therefore be inherently different from funding-driven 'carrot' strategies such as CIRM⁵². There must also be upfront acknowledgement that participating organisations are free to pursue separate initiatives outside the SMART consortium in line with whichever path best serves their individual organisational mission.

Building collaboration across organisational and discipline boundaries. Early integration of clinical expertise, establishment of greater multidisciplinary research activity, and efficient transfer of basic research knowledge and discoveries into translation programs, will be essential to leveraging existing strengths into internationally competitive hub. Imbuing a culture of collaboration across areas which have traditionally been discipline-focussed silos which view each other as competitors for a limited funding pool is non-trivial and requires active strategies and leadership.

Obtaining the correct balance of investigator-driven discovery research and translation-driven research teams. This will require an acknowledgement of the importance of both in achieving overall goals, and securing early wins which reinforce this (eg larger scale, longer-term funding).

A respect for the different organisational cultures (and possibly use of different types of reward/funding systems) will be necessary to maximise both research excellence and clinical/commercial translation.

Positioning for impact. It is not realistic to expect leadership will be achievable in each of a broad scattergun of activities. Optimum use of limited funding will require more detailed impartial analysis of the areas in which SMART activities will be an Australian leader and internationally competitive, and a preparedness to prioritise resource allocations to support these. Determination of the right measures of success will be important, and should reflect the overall goals for research excellence, translation and clinical outcomes. Realistic gap and hurdle analysis along with regular external review will be highly desirable, as technology 'push' strategies can be highly susceptible to rose coloured glasses on the value of a home-developed technology or capability.

Adaptability and responsiveness. As the field of regenerative medicine is rapidly changing, the strategy and initiatives must be sufficiently flexible to respond to major disruptive changes in the field, occurring both internally and externally. It is thus envisaged that research themes and translation programs should and will evolve over time to reflect the areas which are delivering, or expected to deliver, highest impact.

Learning from other technology precincts and collaborative innovation models. A considerable amount can be learnt from other international and national efforts to establish innovation-driven clusters. Attention needs to be given to specific differences for the SMART cluster, notably that its initiation is driven by research organisations rather than an industry collective, and that the relative geographic isolation of Australia means groups need to be more proactive than most countries in maintaining links with the international scientific & investment community.

52. CIRM California Institute for Regenerative Medicine Scientific Strategic Plan 2006

5 Model for Engagement

The participants in SMART have already demonstrated their ability to individually achieve positions of excellence in their given domains. However, as each group, institute and organisation operates on a largely independent basis, there has not been visibility to the broader external community of the depth and breadth of interrelated expertise located in this region. This collection of research groups is one of the few in the world to have established research teams which cover the spread of scientific domains regarded as pivotal to progression of the field over the next decade, notably:

- Developmental and regenerative biology
- Characterisation of niche, extracellular matrix, signalling and transcription factors
- Novel scaffold and biomaterials development for tissue engineering
- Immunology, particularly in relation to immune strategies for cell therapies
- Bioinformatics, structural biology and computer-aided drug design
- Advanced characterisation and imaging, eg FACS and synchrotron
- Transgenics and cellular reprogramming

However, this cumulative strength has not been represented in the past, as has been achieved in other international regenerative medicine clusters such as Harvard Stem Cell Institute⁵³, and the Pittsburgh Tissue Engineering Initiative⁵⁴. This is particularly important with the increasing level of competitive activity in the international environment, where national and regional governments have allocated large blocks of investment to their regenerative medicine initiatives. Attraction of leading researchers, measured impact of research outcomes and attraction of major investment partners are done on an international basis, and it is therefore imperative that the cluster is able to demonstrate benchmarking performance on this international scale.

For the SMART groups to secure a position at the forefront in an increasingly competitive international environment, they will need to fully leverage their combined strengths, and make strategic choices to position in those areas where they can have maximum impact, that is, to focus on those areas where there is a realistic assessment that the work undertaken is truly internationally competitive.

The greatest potential opportunity for the SMART cluster is to more effectively harness the diversity of the complementary research, translational and clinical activities. Whilst there are some collaborative connections between the groups, past interactions have occurred largely on an ad hoc basis through the initiative of a particular champion, rather than being strategically planned or fostered, and there is considerable scope to increase the degree of interaction. Regenerative medicine is a highly multidisciplinary field, and hence many of the areas identified as key challenges to progression of the field require depth of expertise from disciplines that have traditionally been separated into functional domains.

Given the different mandates of the different organisations, each has a different degree of emphasis on their proportion of activities in basic research, applied research, commercialisation and clinical delivery. Optimum overall outcomes are more likely to be achieved by a framework which allows each to excel in its point on this spectrum, rather than attempting to homogenise the outputs in each component against a common set of performance metrics.

The proposed model for engagement for the participants in SMART is represented diagrammatically in Figure 1.

53. <http://www.hsci.harvard.edu/node/40>, Harvard Stem Cell Institute – Community Overview
54. <http://www.ptei.org/index.php> PTEI web page



The key elements are:

- early clinical input to define key challenges and current best practice
- a focus on world-class research in the disciplines critical to progression of the field, with an emphasis on multidisciplinary collaboration.
- a series of translation programs focussed on therapy areas in which SMART can build off its collective research strengths in order to deliver patient benefits at the forefront of the field.
- better integration of therapy-focussed research teams through to Phase I/II clinical trials with local hospital partners
- early consideration of market, regulatory and IP drivers in order to develop the optimum path-to-market and partnering strategies.
- creation of an entrepreneurial environment and skilled labour force to support the growth of a local biotech industry.

The comments from participant interviewees that led to this model for engagement are discussed in more detail below. In particular, the participants have noted an opportunity to improve quality of research program definition by greater incorporation of clinical expertise at the earliest stages of design of research projects, in order to ensure the key clinical challenges and constraints are well understood (i.e. to get the best answers, you must first ask the right questions). It is also regarded as critical that clinical and regulatory insights are incorporated in the development of appropriate animal models and trials, in order to build meaningful data sets that facilitate rapid progression into later clinical trials. Maintaining strong clinical review and/or oversight by a committed clinical champion also ensures that translation programs rapidly adapt to whichever technologies will deliver the best therapeutic outcomes to patients and in doing so stimulate the team to remain at the forefront of the field, rather than suffering from inertia by participants remaining overly committed to their particular 'heritage' technologies.

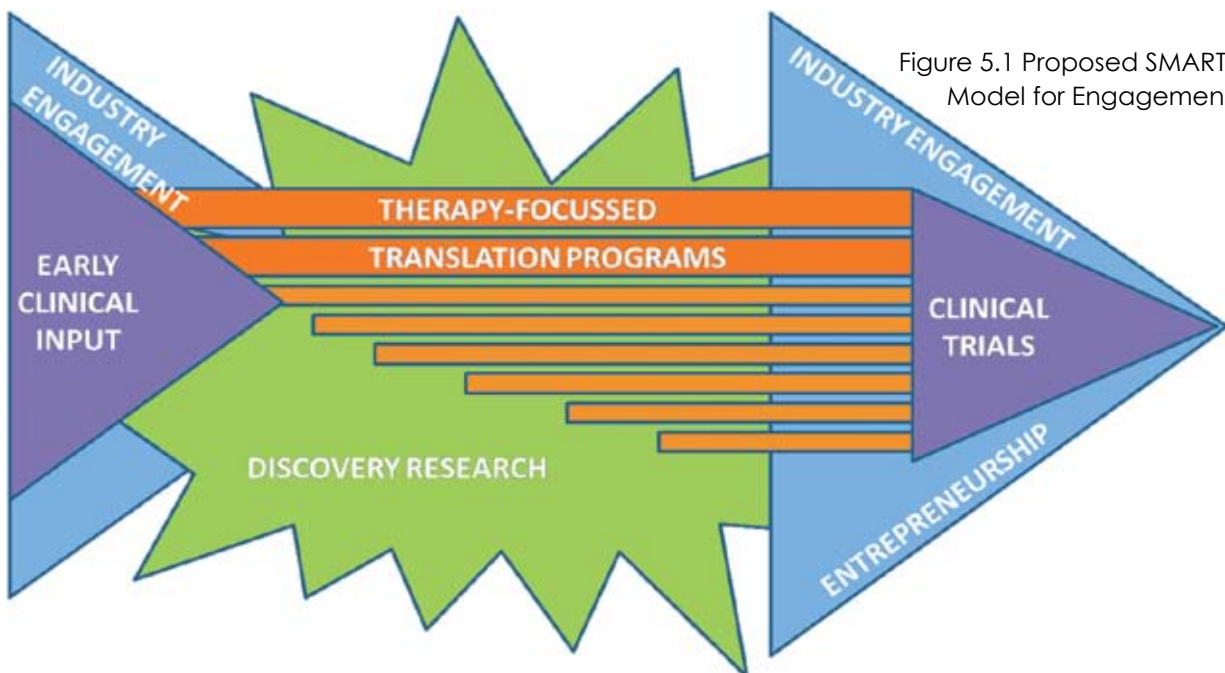


Figure 5.1 Proposed SMART Model for Engagement

In establishing a framework for collaborative innovation, there is always a healthy debate as to the most effective way to balance the flexibility desired by researchers to pursue creative individual insights that lead to radical breakthroughs, versus a more structured context in which translation-focussed programs can provide clarity, coherence and critical mass for multiple groups to focus their efforts toward a particular goal. In order to progress regenerative medicine, it will be necessary to provide a structure that ensures excellence in both basic research and translation. As a relatively new field, there is still an enormous amount of basic research required to understand the underlying biological processes involved in tissue development, disease and repair.

Initial trials of stem cell therapies (such as cell therapy treatments for myocardial infarction) have had mixed results, which has highlighted the current lack of understanding of the actual mode of therapeutic action in new stem cell treatments, and whether the actual mode of therapeutic benefit is achieved more through a paracrine “drug delivery” effect, rather than the actual engraftment of the stem cells as initially envisaged. Better therapeutic outcomes are therefore heavily dependent on establishing a more complete understanding of the basic mechanisms involved, which may result in completely different paradigms for treatment. There is also an expectation that the field is most likely to be progressed by serendipitous discoveries at the interface of the disciplines e.g. stem cell biology, materials science and engineering, with venture capitalists commenting that this is the area they watch for the innovations most likely to disrupt the field. Excellence in basic research is also an important driver of the participating research organisations. This is both at an individual level (for researchers given that publication levels in high impact journals are a key measure of performance and factor in ability to secure future grant income) and at an organisational level (such as in demonstrating cumulative performance levels in research quality frameworks for universities).

A central premise to investments and efforts in medical research is the desire to identify ways to create better health outcomes for patients, and significant attention therefore needs to be given to how insights achieved through basic research will be translated through to clinical outcomes. Specific programs targeted at particular areas of disease or therapy provide a means to concentrate and coordinate all the different capabilities and tasks that need to be brought together in order solve the multi-factorial challenges of a given clinical area, from initial research phase through development, scale-up, production and clinical trials. As highlighted earlier, regenerative medicine requires inputs from a range of disciplines, not only in understanding the underlying disease state and developing the most effective pharmacological or cellular therapy, but also in mediating or enhancing the immune response, providing the most effective delivery format, and developing efficient production, storage and characterisation processes. The formation of well-integrated cross-functional teams is therefore essential to solving key challenges in regenerative medicine and progressing these through to meaningful patient benefits. Despite protestations from a segment of researchers that focussed translation programs limited their scope for creative serendipitous discovery, many other researchers interviewed commented that they had done their most rewarding, innovative and highest impact research within the context of translational programs. Some noted that they found the discussions of key challenges with end users or clinicians as a great stimulant to new lines of work, and that the problem-focussed discussions with scientists in complementary research areas gave a breadth of insights and unique combinations of expertise that they could not have achieved in isolation. That is, they highlighted that active involvement in a translation focussed program increased their research performance, rather than detracting from it, and noted that they gained a great sense of personal satisfaction in seeing their research lead to real products or



therapies that benefited the wider community. It is important however to acknowledge the tensions which can be created for researchers where involvement in translation or commercialisation activities results in limitations on ability to publish, their key performance measure, and no alternate recognition, reward or compensatory structures are in place. Effective translation and commercialisation frequently requires publications and presentations to be deferred until after IP has progressed through critical milestones, and hence funding structures need to be long enough to sustain researchers through this period, so that it does not negatively impact on career progression, and hence become a deterrent to involvement in translational activities.

A further important point raised by researchers is that frequently their discoveries are highly valued/valuable platforms which can be utilised across a broad range of therapeutic areas or applications. For example, novel biodegradable polymer scaffolds developed by CSIRO initially for bone and cartilage repair, were subsequently used in applications ranging from burn treatments to biodegradable stents. New technologies such as improved in vivo imaging on the synchrotron medical beam line, or nano tagging systems to monitor cell distributions and engraftment also provide advances which cut across multiple therapeutic areas. Greatest overall benefit will therefore be achieved with a structure that has sufficient flexibility and interconnectedness that discoveries either in basic research or a particular therapy program can be transferred across to other therapy programs, or indeed drive the growth of new therapeutic programs where they provide a new distinct advantage.

The SMART cluster has a distinct advantage in encompassing a number of hospital and clinical research facilities within the umbrella of Monash University and its allied partners in the Monash Health Sciences cluster.

Whilst there is some interaction between researchers and hospital-based clinicians, there is considerable scope to expand this further. In order to be competitive with international clusters for regenerative medicine such as at Harvard and London it will be imperative to achieve this more comprehensive integration of leading edge hospital based clinicians with the therapy focused programs. This would have the double advantage of streamlining and more rapidly progressing new therapies through to clinical trials, but also ensure that local clinicians and hospitals were recognised as being at the forefront of medical care.

Whilst initially driven by a grouping of research providers, the development of SMART programs will seek to take an active role in engagement with industry leaders and capital providers in determining which research and program areas which will be most attractive to subsequent investment and/or partnering. This factor is important not only in maximising likely potential commercial benefits for the participants, but indeed in increasing the probability that developments actually progress through to patient benefits, by selecting those areas which will secure sufficient external support to make it through the long, expensive and risky process of production development, phase III clinical trials, regulatory approval and market development. Prioritisation will therefore be given to the areas in which have large market potential and in which a strong IP position could feasibly be secured, mindful of the patent thickets and key blocking patents already evident in some areas of the field. A proactive approach will be taken in the timing and selection of industry partners, with an aim to progressing the technology to critical value inflection points prior to partnering, but remaining open to earlier industry partnering with those partners that could address any identified gaps in capabilities, hold strong complementary/enabling IP positions, or provide substantial resourcing which would increase the international competitiveness of the research effort.

SMART also seeks to foster an environment which will support the establishment and growth of innovative local biotech companies – that is, “a Silicon Valley of regenerative medicine”. Existing building blocks in this regard are the training programs in technology commercialisation through the Asia Pacific Centre for Science and Wealth Creation, and the \$30M Trans Tasman Commercialisation fund established in mid 2008 to commercialise promising early stage technologies emerging from local Universities⁵⁵. Both are based within the STRIP building at Monash, and provide a basis to foster an entrepreneurial, innovative culture, as well as provide associated training and expertise to support the establishment of new spin-out ventures.

5.1 General Pathways for Implementation

At the initial strategic planning meeting of stakeholders in February 2008, several pathways were identified by the group as a means to achieve their goal of maintaining the precinct as a world leader in the field of regenerative medicine. These were:

- Leverage strengths and infrastructure
- Build collaborative networks
- Make decisions and participate as partners
- Recruit strategically
- Develop people to full potential
- Value innovation – both creativity and translation
- Optimise sourcing and use of funding and resources
- Positively and proactively influence decision makers and community

The intent for operational implementation in each of these areas is discussed in more detail below.

5.1.1. Leverage strengths and infrastructure

As noted previously, progress in the field of regenerative medicine requires the integration of knowledge from a broad array of different disciplines. Other initiatives around the world have recognised that greater innovation activity and more rapid progress can be achieved by bringing together complementary expertise, and have made it a priority to develop specific initiatives that promote multidisciplinary collaboration.

This however is not a trivial task, as has been found by Harvard in its attempts over the past decade to integrate activities across campus toward an overarching goal of establishing a world-recognised regenerative medicine precinct.

The Clayton precinct is in an envious position of having outstanding researchers in all the key capability areas that underpin regenerative medicine. At present however, a high proportion exhibit expertise in their individual given domain, but cross-disciplinary projects and interactions are limited. Whilst some collaborative linkages have formed, there is considerable scope to enhance this further, to take advantage in a more comprehensive way.

Strong feedback was received from researchers that meaningful collaborative interactions were most effectively achieved when initiated by researchers themselves, driven by an identification of a complementary capability, such as tools or techniques that could advance their research interests beyond what they could achieve within the bounds of their existing group (i.e. bottom up rather than top down drivers). In this line, one of the primary services that a SMART initiative could provide would be to assist as a central point for communication to a local community of practice, to increase the level of awareness of activities, tools and techniques used by others in the precinct.

55. <http://www.monash.edu.au/news/newsline/story/1276> , New A\$30 million trans-Tasman research fund to drive life-saving research, 17 June 2008



A relatively easy first step would be the establishment of a regular 'tools and tricks' seminar series, in conjunction with providing an easy way for the local regen med community to be informed of related seminars taking place within the different institutes, departments and organisations. In addition, where demand was evident, periodic workshops could be hosted focussed on particular topics, which would bring together local experts and potential new users, and serve as a focal point for building communities of practice. A central website could serve as a convenient portal with updates on seminars and workshops.

One of the best advantages of having multiple related research groups in a tight geographic location is that it permits the most effective utilisation of specialised infrastructure and instrumentation. This is attractive to funding bodies, in ensuring optimum deployment of funds, and attractive to researchers, in providing access to a broader range of state-of-the-art equipment that would otherwise be beyond the budget of an individual institute.

An objective of SMART is to therefore adopt a coordinated strategic approach to investment, management and access arrangements for infrastructure and equipment of benefit to the wider group. This will include:

- Identification of new infrastructure / equipment critical to advancing the joint goals
- Coordinated approaches to applications for funding for new infrastructure
- Efforts to increase awareness of facilities available to researchers in the precinct
- Coordinated management of operational costs, management and access arrangements.
- Identification and attention where facilities are inefficiently utilised, suffer access difficulties or require upgrades to be competitive or have broader utility.

5.1.2. Build collaborative networks

As outlined above, fundamental to capturing the potential of the precinct will be to establish greater active collaboration between groups. There is an opportunity to take advantage not only of the different discipline skills, but also the different cultures and mandates of the organisations, such as the strength in basic research within the University departments and institutes, the focus on applied research and longer term outcome-oriented translation projects within CSIRO, and expertise in clinical context and delivery from hospital-based clinicians and researchers. Thus cross-organisational engagement will facilitate the progression of technologies through from bench to bedside, build the value of the technology, and present a more coherent and attractive proposition to funding bodies or industry partners. A commonly expressed desire by participants was to establish an earlier integration of clinicians into the R&D process, such as in initial brainstorming workshops with cross-functional teams, to focus on key clinical challenges, and innovative ways these may be addressed.

Interviewees have noted the importance of establishing working relationships to facilitate the flow of information between groups. Geographical co-location is not sufficient for the success of a cluster – it is a useful pre-requisite, but active engagement between the parties is the determinant on whether productive output jumps to the next level. Many interviewees noted that the most productive starting point was through joint PhD or postdoctoral appointments, where the appointee had the freedom to move between the laboratories/sites and hence built a shared awareness of people and techniques in the different sites, and joint supervision necessitated regular engagement of research leaders in an area of common interest. This is also consistent with the success of the EIPOD program within EMBL (EMBL Interdisciplinary Postdoc).

It is therefore recommended that a funding structure is established to support the establishment of joint PhDs and/or postdocs; with a particular emphasis on those which cross discipline and organisation boundaries where there has previously been limited engagement; and are consistent with the goals or overarching goals of research excellence, therapy-focussed translation and clinical integration.

As well as promoting new cross-group engagement it will be essential to also examine any current blockages which exist, or are perceived to exist, between members of different research teams, and openly address these. These may include tangible issues such as physical or IT access constraints, or intangibles, such as concerns regarding confidentiality or competitive intent. Unless attention is given to the underlying framework, and whether it is truly conducive to collaboration at the coal-face, then any new specific activities to promote collaborative engagement will ring hollow and engender scepticism rather than active support.

5.1.3. Partner participation and Decision Making

The formation of SMART allows the participating organisations to engage in more strategic joint planning, to identify and focus on areas of common interest where a joint approach would achieve greater impact. An important element will be the development of a set of agreed principles that guide cross-organisational engagement, and then support a culture that promotes leadership and initiative at all levels. The proposed governance structure is via a small executive team that includes a representative from each of the main participating organisations, plus an executive officer. This group will have the task of developing and implementing initiatives in line with the overall goals and strategic plan of the consortium, and providing regular engagement with the broader group of stakeholders for input and review of progress.

The formation of a senior leadership team with visibility across the range of capabilities and programs provides a means to identify which areas may have greatest overall impact, and then ensure focus, prioritisation and co-ordination of resourcing so that these areas will have the critical mass necessary to be internationally competitive. This may be either through allocation of existing internal resources, or development of coordinated grant bids to secure new funds to support growth of these areas.

Important to the next stage of development will therefore be:

- Completion of an audit of capabilities and assets and benchmarking analysis to determine areas of excellence
- Analysis of external environment, including emerging technology areas, IP white space and hurdles, areas of major clinical need, and market and partnering opportunities.
- Development of major research themes and focussed translation programs

5.1.4 People: Attracting, building and rewarding excellence

Success in innovation is strongly driven by the people factors – the creativity, goal orientation and work ethic of those involved, the support they are given in skills development, whether a fertile environment is provided in which they can flourish to full potential, and whether they are recognised and rewarded for their contributions and achievements. SMART has an objective on supporting the development of successful people, and becoming a location that attracts the world's best scientists and clinicians. This will be pursued through strategic recruitment, staff development and training and attention to culture, rewards and the supporting environment.



Strategic Recruitment

A priority for the precinct is to establish a reputation for research excellence, and to build on the strengths of existing key personnel by attracting the best and brightest researchers from around Australia and overseas. Attraction of high profile 'stars' has the knock-on benefit of attracting additional top up and coming researchers, drawn to work with recognised leaders in the field. This has the effect of being self-propagating, building high performing teams with international profile. An additional aspect of strategic recruitment within SMART will be an increase in joint appointments.

This will not only have the benefit of facilitating greater collaborative engagement, but may also provide greater incentives to attract top talent, such as greater role flexibility and funding. Development of a strategic recruitment policy will also enable the partners to address broader goals, such as building critical mass in priority areas and progressing translation teams by recruiting complementary expertise that addresses identified gaps.

As SMART increases its international profile of the precinct and its partners, it will provide greater benefits in joint marketing and recruitment strategies through international events and promotional material. Greater impact can be achieved by clearly presenting the overall research assets and performance of the precinct, rather than separate individual marketing of each component group.

Education and Training and People Development

As well as attracting in high performers, SMART will provide integrated education and training programs tailored specifically to careers in regenerative medicine that will include:

- Development of an integrated undergraduate program which incorporates the leading edge of research knowledge and practical

experience, in order to attract the best students to the field. An example of a recent initiative in this regard is the new program in Developmental Biology offered by the Department of Anatomy and Developmental Biology, which is the first undergraduate program in Australia that brings together the cross section of subjects relevant to the field, and includes practical experience in local leading research laboratories.

- Open access training programs in specialist techniques for staff and technicians to build the local base of experienced personnel, (building on existing programs such as ASCC's programs in stem cell expansion and handling).
- Training programs designed specifically to enhance career development, such as the EMBL training program for new lab managers, or courses through Asia Pacific Centre for Wealth creation to increase the understanding of IP protection and technology commercialisation.

Retaining the Best, as an Employer of Choice.

As the precinct also seeks to build a reputation as the preferred location for a career in regenerative medicine, with the objective of having happy, successful motivated people. Success in this regard not only increases the productive output, but also helps to retain top talent, and hence obtains maximum benefit from the investments made in people development. Pivotal to achieving this will be obtaining regular direct feedback and appraisal from staff, such as the measures used in the Employer of Choice survey.

5.1.5. Promoting Innovation – both discovery and translation

Promoting Creativity and Discovery

A priority for SMART is to establish recognition for the precinct as a leader in regenerative medicine research. Underpinning this will be initiatives to identify, support and reward research excellence.

The focus will be on providing support to:

- Areas/people with established international leadership
- Innovative project proposals that address key challenges at the forefront of the field
- High performing mid career researchers (eg EMBL future scientific leaders program)
- Multidisciplinary projects which bring together complementary research areas in novel ways
- Strong collaborative linkages with other leaders in the field, both nationally and internationally
- Research activities that are expected to provide platform technologies/capabilities that can be leveraged across multiple programs; or strong IP in a commercially attractive area
- Clear benchmarking relative to international standards to highlight the areas of current research excellence
- Identification of critical infrastructure and equipment requirements needed to retain or secure an internationally competitive research position
- Development of overarching research themes which bring together complementary capabilities in high impact areas, in order support future development of these areas and guide external promotion.

Promoting translation of discoveries through to clinical outcomes

A key driver in the formation of SMART is the recognition that integration of the capabilities in basic research, applied research and clinical delivery will not only ensure the most rapid transfer of discoveries through to patient benefits, but also be the basis for competitive advantage for the precinct relative to other international regenerative medicine clusters.

The intention is to build from existing research and clinical strengths and focus on those areas in which major therapeutic advances could be achieved. An important factor in selection of therapeutic focus areas is identification of the areas of acknowledged clinical leadership, either within the allied hospitals of the southeast Melbourne zone and Monash Health Sciences cluster, or through established national and international collaborations. A priority nominated by participants is the early integration of clinical expertise in the design and development of new research programs, and closer partnerships to progress emerging technologies through to clinical trials.

In line with the 'disease team' approach adopted by CIRM, is the intention to form cross-functional teams that are focussed on specific clinical problems, and ensure that these have sufficient critical mass in terms of resourcing and capabilities to be internationally competitive. As also identified in development of CIRM's models for funding disease teams, sound project management is so inherently critical to the success of translational programs that this should be an essential criteria for funding.



A particular strength that CSIRO brings to the alliance is its experience with product-focussed research programs in long term translational projects, an established culture and systems for coordinated IP management, regular review processes for monitoring outcomes versus milestones, and a proactive approach to industry partnering and technology transfer to progress technologies through to commercial product launch.

This provides a complementary framework to the discovery research within university departments and institutes, and an opportunity to add significantly greater value to new technologies prior to licensing or partnering by taking new them through to value inflection points such as demonstrated proof of concept.

Development of at least one major therapy-focussed translation team will be a priority for 2009.

This will be pursued via:

- Therapy-focussed workshops in which the key clinical challenges will be presented by expert clinicians, followed by a brainstorming session involving a cross-section of researchers from different research areas to assess how existing capabilities may be utilised to develop a targeted research program. This approach has previously proven productive, as in the establishment of the renal regeneration program by Prof John Bertram and Dr Melissa Little.
- Identification of local champion and interested collaborators, and further development of proposed research program, including assessment of areas of anticipated technological/capability advantage relative to international research efforts.

- Supporting analysis of proposed research programs to assist with the development of a business case for funding - including identification of areas of highest commercial and IP potential, and options for future industry partnering. Key hurdles will also be considered (such as regulatory issues and major blockages in freedom to operate), and an accompanying gap analysis to identify complementary assets, capabilities and IP required. This will assist in identification of those programs likely to deliver significant impact, and provide a basis for prioritisation of internal resource allocations.
- Support in securing funding for an integrated program, whether from government grants, philanthropy or industry partners.

5.1.6 Funding and Resources

More strategic engagement via SMART will ensure the most effective deployment of the existing sizable investments already made within the precinct, such as the recent investment of \$153M to establish ARMI. Thus a starting premise for SMART is optimum usage of existing budgets, such as through coherent joint promotional activities and management of shared core facilities.

In the future, it is envisaged that the proactive approach by participants to develop larger scale integrated programs in high impact areas will be beneficial in their common goal to attract a more stable flow of longer-term funding, through diversified sources.

In addition, establishment of a set of regularly updated performance measures will aid promotion of areas of excellence, and attraction of further funding to support these. The development of integrated grant requests in common areas of interest will not only establish a stronger case to funding bodies, particularly for expensive items of infrastructure or equipment where evidence of demand from a broad user base is desirable, but also minimise the amount of time taken up drafting multiple smaller grant applications by different groups.

Funding support will be sought for SMART in two phases. In the initial phase, funding will be sought to promote greater communication and collaboration, along with workshops and analysis to identify the potential research and translation themes likely to be most internationally competitive. In the second phase integrated proposals will be developed and funding sought for the areas prioritised to have highest probability for significant impact. Development of clearly articulated therapy-focussed programs and evidence of research and clinical achievements will also be an important factor in broadening the funding base beyond traditional grant sources, such as support from philanthropic and patient advocacy groups, or via earlier industry partnering

5.1.7 Influence Decision Makers and Community

SMART can serve to enhance the overall profile and awareness of the depth and breadth of capabilities, activities and achievements within the precinct, and present a clear unified identity of to the key external decision makers it seeks to influence. Attention will need to be given to the specific information needs of each external group:

Researchers: In order to attract leading researchers from around the world, SMART can convey the range of state-of-the-art facilities accessible within the precinct, profiles of the resident leading researchers, and details of funding and recruitment opportunities. Consideration should be given to joint promotional material at international events and conferences, but undoubtedly the most successful 'advertising' will be through high quality publications and presentations by leading researchers and clinicians from the precinct.

Public: Increased awareness of specific therapy-focussed initiatives and a more proactive engagement with patient advocacy groups is likely to engender not only a greater groundswell of public and hence political support, but may also engender more direct philanthropic support. Public outreach events such as Stem Cell Awareness Day are vital contributions in this regard. The success of Proposition 71 in California is evidence of the extent to which public support can drive major new investments in regenerative medicine. It will also be essential to maintain a reputation for the highest ethical standards to ensure ongoing public and political support, as loss of confidence in this sensitive area can be difficult to rebuild.



Companies: SMART intends to promote and facilitate early engagement with industry leaders, capital providers and local biotech companies. In the initial stages this will provide inputs in selection of which areas may be most attractive for later industry uptake, as well as identification of specific path-to-market issues. Efforts to build dialogue and relationships will also facilitate selection and establishment of optimum industry partners for co-development programs, and a proactive approach to showcasing local capabilities and technological developments will be pursued, via international trade events and bodies such as Austrade, as well as targeted company engagement and marketing materials. Input will also be sought from local biotech companies and Victorian government innovation leaders to gain identify how SMART may contribute to growth of the local biotech industry.

Funding Bodies: An objective is to demonstrate to funding bodies that investment in projects and infrastructure within SMART represents best-in-class use of funds. This will be aided by clear performance measures showing excellence and outcomes, proactive approaches to effective utilisation of current funds, and integrated proposals with sound supporting business cases.

Government and stakeholders: Australia's credible international position has been achieved through the foresight of State and Federal governments commitment to the field, with a progressive stance on policy development and significant block funding. SMART needs to convey how it is delivering on prior investments, as well as presenting a sound case for future investment to maintain leadership. This should be considered in light of the recent Innovation Review and Victorian Government's strategies for building a local innovation economy, and how SMART activities can contribute toward these targeted outcomes.

Regulatory: A key challenge in progressing new regenerative medicine therapies toward common clinical practice is the uncertainty associated with regulatory hurdles. SMART has the opportunity to take a proactive role with regulatory agencies in building the understanding of new developments in the field, and inviting guidance on the safety and efficacy criteria that will need to be demonstrated as new technologies are brought forward.

International research community: To be recognised as an international leader, SMART will need to take an active role in international regenerative medicine bodies in establishing networks, protocols, etc, as exemplified by ASCC's active involvement in ISSCR, SNAP etc.

6 Specific Initiatives

The aforementioned section describes the general principles that SMART will follow in the overall development of initiatives. However, many of these approaches are common to best-practice endeavours that would be pursued in many other collaborative research alliances. In an international environment where there is dramatically increasing research activity and large investments in the establishment of regional regenerative medicine initiatives, it will be necessary for SMART to identify its unique strengths and focus on those particular areas in which it has an internationally competitive stance. As a group, the participants have the opportunity to combine and build critical mass in selected areas where they could have an internationally leading position, rather than being a mid-rung player in all areas. Given the current breadth of capabilities, SMART can leverage this by identifying particular challenges that require a cross-disciplinary team, and co-ordinating efforts to tackle these. These may be, for example

- larger scale translational programs that bring together a cross-functional team of researchers, engineers and clinicians, and feed into an area of established clinical expertise within SE hospital partners, or
- an underlying capability that draws on particular local advantages and serves as a springboard for multiple other program areas – such as use of the synchrotron for advanced in vivo imaging to elucidate early developmental mechanisms, or monitoring cell distributions and engraftment using novel nanotech taggants.

A priority for SMART in 2009 will be the completion of more detailed analysis to more fully understand the areas of strength within SMART partners, and how these may be combined into larger research themes or translational programs in areas which would be internationally competitive.

In tandem, a ground up approach will be adopted to promote greater awareness, information sharing and collaboration between participants, in recognition of the fact that the identification of innovative new multidisciplinary projects will come from direct engagement of the researchers themselves.

The primary activities for the next phase will therefore be:

1. Communication activities to increase awareness of regen-related capabilities and activities in precinct
2. Database of capabilities, and benchmarking to highlight areas of excellence
3. Development of research themes
4. Clinician-led workshops to define opportunities for translation programs
5. Analysis of competitiveness, attractiveness of proposed programs
6. Development of business case to support funding/partnering for specific programs/themes.

Specific initiatives to address these areas will be developed in conjunction with the broader group of participants within SMART.



6.1.1. Areas of strength for establishing Research themes

Preliminary analysis of the capabilities of initial participants in SMART has shown that there are a range of research areas in which SMART already has a strong base in the core discipline area and the potential to deliver even greater impact through the integration of multidisciplinary expertise.

Examples of these include:

Delivery Systems, Tissue Engineering and Immunological Strategies: -

The intersection of materials technologies, biology and clinical technique provides SMART with an opportunity to have a significant impact in developing more effective systems for delivery and effective integration of cells, signals and scaffolds to the site of repair. The field of tissue engineering is relatively immature in terms of integration with stem cell biology; cell therapies are currently limited by suboptimal capacity to localise/engraft cells at the desired site, and in vivo regenerative strategies may require methods to recruit cells to the desired site and present activating cues. Contributing aspects could include:

- **Anatomy:** characterisation of niche environment and tissue properties in diseased versus healthy tissue, and how this impacts on efficacy of engraftment, cues for cell differentiation and regenerative capacity.
- **Materials science:** development of smart scaffolds or which enable presentation of signalling cues in the correct spatial and/or temporal configuration, or novel delivery/encapsulation systems to deliver cells/bioactives to desired site. Design of systems to optimise mechanotransduction, localised oxygen tension, capacity for nutrient supply and angiogenesis, etc.

- **Molecular/Cell/Systems Biology:** identification of signals and mechanisms to enhance homing, recruitment or localised delivery of cells to the desired site, techniques to improve engraftment, and cytoprotective factors.
- **Clinical:** benchmarking data of efficacy of current surgical delivery techniques, new strategies for tissue 'priming'
- **Imaging and Characterisation:** tracking of localisation of delivery of cells and measurement of tissue response
- **Immunology:** strategies to mediate/optimize immune response on delivery
- **Chemistry and Pharmacology:** development of small molecule bioactives to enhance engraftment and/or serve as localised cues in scaffolds.

Comparison of relative advantage of cell types for different clinical applications

SMART has access to a broad range of cell lines within participating groups. Whereas other centres and companies may focus around a particular cell type, eg embryonic or mesenchymal, SMART's competitive advantage lies in the diversity of its cell lines and the depth of its expertise in fundamental stem cell biology in characterising particular features of each cell type, such as telomere length, capacity for expansion, stability, tumorigenicity, etc. Also important is resident expertise in the immunological advantages of particular cell types, such as amnion-derived or mesenchymal stem cells. At present, the field is hampered by fragmented clinical data in which cell lines used for clinical trials reflects accessibility more than suitability, and limited knowledge exists as to the relative advantages of particular cell types for given applications. SMART would be able to establish a high-profile clinical leadership position by impartial comparative clinical trials, which correlate the clinical efficacy of particular cell types with specific characteristics.

An initial example of this is the recent establishment of a study to compare SCNT vs IPS cell lines. Further consideration should be given to the ease of cross-access for cell lines held by particular groups, such as a database or virtual cell bank with streamlined pre-arranged access arrangements for participants

Cellular reprogramming and control of cell fate

An understanding of the factors which control stem cell differentiation/lineage, plasticity/dedifferentiation, quiescence, expansion and apoptosis are an essential prerequisite to developing techniques for independent control, such as for cell production systems, activating endogenous stem cells for in vivo repair or effective treatments for cancer. At the forefront of the field is the development of strategies for induced pluripotency which may provide patient specific cell lines for cell therapies, and also provide fundamental knowledge on how analogous approaches may be used to initiate regenerative processes in vivo in damaged tissue.

- Contributing research expertise/activities may draw on
- directed differentiation of embryonic stem cells.
- smart surfaces and bioactives for control of cell fate
- Basic research in genetics, transcription factors, bioinformatics
- Impact of tissue and systems biology on cell fate – more detailed characterisation of stem cell niche
- Manipulation of microenvironment – eg scaffolds of varying mechanical properties to studying mechanotransduction; or recreation of hypoxic conditions
- Novel approaches for iPS not involving gene insertion
- Screening of compound databases

- Development of biomarkers and characterisation techniques
- Gene therapy approaches for correction of underlying disease state in pluripotent cells

Systems Biology approach to identifying and controlling regenerative pathways

Fundamental studies in regenerative biology are required to develop a clearer understanding of the mechanisms which enable regeneration of damaged tissue in fetal tissue and certain lower species, and why these mechanisms are lost in adult tissue. This knowledge can then be used as the foundation for development of more effective regenerative medicine strategies across a range of therapeutic areas. The formation of ARMI, and recruitment of Nadia Rosenthal and Prof Peter Currie launches the SMART precinct into an international leadership position in this domain through their established international scientific reputation and collaborative research and clinical linkages.

The systems approach biology approach draws together information from multiple levels – molecular, cell and organism, and thus draws on expertise across areas such as cell signalling, biochemistry, anatomy, developmental biology, genetics and bioinformatics. There is a strong array of supporting core facilities, including genetic engineering, MATF and access to a range of developmental models, most notably the newly established zebra fish facility.

The ability to undertake advanced in vivo imaging via the medical beamline at the synchrotron will also be of particular advantage in studies of early development biology and regenerative response.

Fundamental knowledge gained in regenerative systems biology will be relevant to the range of therapeutic strategies, including tissue engineering, cell-therapies and pharma based approaches, but is particularly important in the context of the latter.



It represents a window on the future direction of the field; with the replacement by bioinert devices, or ex vivo reconstruction of organs having declining relevance as a better understanding is gained of how to harness the body's own capacity for self repair, and more non-invasive and pre-emptive repair strategies are adopted.

Bioactive Development

Research programs studying regenerative mechanisms and stem cell fate, particularly in relation to cell signalling and response to environmental factors, can provide a sound basis for identification for key bioactive species that promote in vivo regeneration. Combined with local expertise in structural biology, in-silico drug design, combinatorial chemistry, antibody production, high content screening and microarrays and pharmacology, this provides a very strong capability framework for development of novel bioactive agents for regenerative medicine.

Increasing awareness of that in many cases one regenerative function that stem cells may fulfil is as a delivery system of therapeutic agents – such as trophic and cytoprotective molecules, and factors which exert anti-inflammatory effects, decrease scarring or promote angiogenesis⁵⁶.

This area has the potential to leapfrog many cell therapy approaches in regenerative medicine, moving more towards pharma-based approaches which initiate and support the body's own self-repair mechanisms, eg through mobilisation and recruitment, activation of endogenous stem cells or induction of dedifferentiation of neighbouring somatic cells, or reduction in mechanisms impeding regeneration, or mediation of adverse inflammatory or fibrotic processes in diseased or damaged tissue.

This would have the added advantage of not having the complexity of immune-related transplantation issues. It is also likely to offer an appealing patenting position, both in terms of clarity of composition of matter filings, and greater freedom to operate.

This area is very appealing commercially, as it has a more attractive 'fit' with the conventional pipeline structure and business models for large pharmaceutical companies, than cell therapies currently present. It therefore presents a higher probability for finding a partner willing to make the large investments necessary for later stage clinical trials in order to actually translate discoveries through to a therapeutic outcome. This has the flow-on effect of also being a more attractive proposition for early venture capital investment, as there is a clearer pathway for subsequent stages of financing and more exit options.

One example of a specific opportunity exists is the utilisation of MATF for development of antibodies for cancer therapeutics.

An opportunity also exists for drug screening platforms, through existing strengths in pre-implantation genetic diagnosis and ability to produce disease-specific cell lines. (And also potentially via SCNT, iPS and genetic modification of ESC). Combined with capabilities in directed differentiation and development of cell and tissue based assays, SMART has the ability to commercialise this either via supply of new cell lines and assays for the broader research and pharma community, an in-house screening capability, and/or a focus on development of therapeutics for particular disease areas.

56. I. Singec, R.Jandial, A.Crain, G.Nikkhah and E. Snyder, The Leading Edge of Stem Cell Therapeutics, Annu. Rev. Med. 2007, 58, 313-328

New tools and techniques; for cell handling, expansion, storage and advanced characterisation and in vivo imaging.

Another primary area of commercial interest is in new techniques for manipulation of cells, leading for example to new research tools or more efficient production methods for cell therapies. Research tools present an opportunity for earlier revenue streams (albeit lower than therapeutic targets) and do not suffer the same risk and time hurdles of regulatory approval. Both research tools and production techniques have receptive potential industry partners, and are also appealing investment candidates for stem-cell focussed venture capital funds. As an area which is strongly dependent on cross-disciplinary contributes from both biology and the physical sciences, it represents an excellent opportunity for collaborative projects within SMART. Examples of research project areas include:

- Bioreactor technologies (eg stem cell bioreactor project involving CSIRO, Monash and ASCC via CRC for Polymers, and Faculty of Engineering bioreactor project with Indian collaborators.
- Microarrays – eg CSIRO project utilising ability to develop specific surface chemistries to control cell fate.
- Research reagents – eg ASCC collaboration with Millipore
- Storage technologies, eg capability within ASCC, and also interests in cell banking within MISCL
- Opportunity to develop new high throughput screening approaches with different biological readouts
- Strong opportunity for utilisation of advanced nanotechnology approaches, eg for safer iPS, xeno-free cell culture, etc
- Novel constructs, tags and biomarkers, and characterisation methods.

- Advanced imaging, particular in relation to real-time in vivo imaging on the synchrotron medical beamline.
- Increased integration of bioinformatics and IT in combining multiple aspects of characterisation data.

Veterinary Applications

An additional area with near-term commercial prospects is veterinary applications of stem cell technologies. The primary initial veterinary application has been in the use of cell therapies for repair of tendon, ligament, cartilage and bone injuries in racehorses. This area has substantial market demand as injuries and illnesses of racehorses cost around US\$6.5B pa⁵⁷. Within alliance partners, this opportunity is being pursued by Dr Paul Verma at MIMR in his work with US company ViaGen⁵⁸, developing genetically-matched equine ESC lines, and a corresponding matched cell bank for individualised treatment of performance horses.

Monash also has an interest in veterinary applications through the long term collaboration between MISCL director, Dr Richard Boyd, and Norwood Stem Cells, a subsidiary of Norwood Immunology, which have recently formed Norwood Veterinary (NVET). In addition to the aforementioned orthopaedic racehorse applications, NVET plans to explore opportunities to use stem cell technologies to address inflammatory conditions in companion animals, such as arthritis and skin conditions in dogs. The companion animal market is also commercially attractive, with an estimated expenditure of \$US 9.4B on veterinary care and OTC medication in 2007. Australia has one of the world's highest levels of pet ownership, spending \$AUS 4.6B on pet care. There is also an increasing willingness for pet owners to spend substantial amounts on veterinary care for their companion animals, and a preparedness to adopt new technologies.

57. R. Tecirlioglu and A. Trounson, Embryonic stem cells in companion animals (horses, dogs and cats): present status and future prospects, *Reproduction, Fertility and Development*, 2007, 19, 740-747

58. <http://www.theaustralian.news.com.au/story/0,25197,24565617-27703,00.html>



For example, despite the relatively high cost of stem cell treatments (\$1500- \$4000 per cycle), Vet Stem predict that their patient pool will switch from being 90% horses, 10% dogs at the start of 2008 to 60% dogs, 10% cats and 30% horses by the end of 2008.

CSIRO's interests in veterinary applications of stem cells have been mainly in the area of livestock breeding, as part of the Food Futures Flagship program. A focus has been on the use of the technologies for production of premium breeds, such as through male germ cell transplantation in livestock, as an alternative to IVF⁵⁹. The CSIRO Clayton group have developed new technologies to support this endeavour, such as high throughput screening of smart surfaces, and development of basement membrane particles, to enable in vitro expansion of bovine spermatogonial stem cell with control of phenotype.

In the broader context of a regenerative medicine initiative, veterinary applications also provide a means to assess the therapeutic benefit and longer term safety of new regenerative approaches, as an interim measure to support progression towards human use. Companion animals such as dogs, cats and horses serve as excellent models for human disease, as approximately half the equine, feline and canine genetic diseases are homologous with human genetic defects.

A recent assessment of Monash's strengths in stem cell technologies has identified veterinary medicine as an area of significant opportunity, not only because of the potential to develop therapeutics from existing research platforms, but also related technologies such as biomarkers, diagnostics and germline propagation.

Development of Therapy-focussed Translation Teams

An important aspect in securing competitive advantage on an international scale and high-impact outcomes for the precinct will be the development of therapy-focussed translation teams which will take full advantage of the range of expertise in basic research, applied research and clinical translation in the different participating organisations. As noted previously, the health outcomes targeted by the participating organisations cover a very broad range of areas. To maximise impact on an international scale will require resources to be focussed on those areas in which the quality of the research is truly at the forefront of the field, and where there is sufficient 'critical mass' in terms of team size, skills, and supporting infrastructure to remain competitive with other international efforts. A priority for the next phase of SMART in 2009 will be to analyse the level of opportunity in each of the main therapeutic areas that SMART may feasibly target. This will require a consideration of the existing areas of research strength, and the potential to bring collaborative teams together to address major unmet clinical needs. This will be supported by detailed analysis of the competitive environment, patent landscape in that particular domain, and development of strong research proposals, business cases and grant applications to draw funding and grow the areas prioritised as having the highest potential for impact.

A full audit of regen-related research strengths within Monash University is currently being undertaken by Dr Rocco Iannello, and will serve as an important starting point in this process. An important next step will be the clinician-led workshops in potential therapy target areas. These will bring together a cross-section of research expertise from the different organisations, and consider how the existing capabilities could be combined to tailor a focussed research program targeted to address major clinical challenges.

59. J.R. Hill and I. Dobrinski, Male germ cell transplantation in livestock, *Reproduction, Fertility and Development*, 2006, 18, 13-18

Where there is a major opportunity identified, and a strong ground-up drive to establish a collaborative team, further support will be given to detailed analysis of the current leading edge of the field and competing research groups/technologies, and more detailed market and IP analysis to build strong cases to attract larger scale funding. A preliminary overview of factors which may be considered in evaluation of potential therapeutic focus areas is included below.

Cardiovascular

- Significant area of strength within Monash University – spread of CV-related research activities across a range of disciplines
- Established clinical network and review panel
- Strong clinical expertise within SE hospitals – Baker and Alfred
- International profile in cardiac regenerative medicine via recent recruitment of Nadia Rosenthal to ARMI
- Collaborative linkages to international and national leaders eg: Magdi Yacoub at Imperial College London (via Nadia Rosenthal) and Victor Chang (via Prof Peter Currie)
- New innovative projects at intersection of stem cell biology, cell signalling and materials science being initiated – cardiac patch project involving CSIRO, ARMI and Faculty of Engineering
- Large clinical demand and market potential
- Crowded space in terms of MSC cell therapies, but clinical results have been varied and disappointing, reflecting a lack of understanding of basic mechanisms of repair
- Opportunity for step-jump to pharma/signalling-based approaches for in-vivo repair
- Established clinical and regulatory experience in stem cell therapies for cardiac repair via Mesoblast
- Active area at Bernard O'Brien Institute of Microsurgery via adipose-derived stem cells; opportunity for collaboration.

Cancer

- Emergent area. Opportunity to build competitive position at forefront of field. Strong need for basic research to fully characterise cancer stem cells, their origin, relative importance in different types of cancer, and consequences for optimum treatment approach.
- Also significant area of research strength within Monash University, but more fragmented than CV; cancer audit and network under development
- Considerable strength within MIMR, including preclinical research in prostate cancer, cancer stem cells, and clinical trials
- Basic research to understand impact of tissue/ niche properties and cell signalling on induced pluripotency, cell fate and tumorigenicity will deliver benefits across multiple program/ research areas
- Significant strength in cancer research in Melbourne at Peter Mac, and also Cancer CRC. Would need to define innovative new areas and/or be complementary, rather than duplicating or competing.
- Opportunity to utilise MATF for development of antibody therapeutics.

Haematology

- Has been the major commercial focus and integrated translation program within ASCC, with major established collaborative research programs with CSIRO and Monash University (including MISCL and Faculty of Engineering).
- Considerable research strength in knowledge of HSC, bone marrow niche (Haylock and Nilsson, ASCC), and directed differentiation of ESC to mesoderm, and in silico drug design of bioactives for HSC expansion



- Cell culture and bioreactor systems for expansion of HSC and blood production
- Clinical expertise available through Hatem Salem at Australian Centre for Blood Disorders
- One of more appealing ESC-derived cell therapies in terms of regulatory safety hurdles due to short residence time
- Most established stem cell application (40 years+ in bone marrow transplants)
- Increasing competitive intensity; dual cord transplants may mitigate unmet need for expansion of HSC for adult transplants.
- Crowded IP space, but companies receptive to incremental improvements in manufacturing technologies.

Inflammation and Immune Disorders

- Strength in MISCL in use of stem cells for autoimmune disorders, and in thymic rejuvenation for enhanced immune system
- Strong capabilities in inflammation within School of Biomedical sciences. Opportunities for leadership position at intersection of inflammation and stem cell science⁶⁰

Established MIIN network

- Established cross-disciplinary links to nanotechnology area and synchrotron imaging – eg cell tagging
- Greater understanding of strategies for mediating immunological and inflammatory response will cut across multiple clinical programs in tissue repair and transplantation. Primary therapeutic benefits observed in initial stem cell therapies may be more to do with concomitant release of anti-inflammatory factors than actual cell integration.
- Opportunity to drive development of bioactives, through understanding of anti-inflammatory properties observed in current stem cell therapies

Musculoskeletal

- Bone and cartilage are two of the most heavily studied areas in tissue engineering. Initial cartilage tissue engineering products are already in the marketplace. Crowded IP space in terms of scaffolds, MSC approaches and delivery of BMPs. Significant cross-licensing and FTO issues.
- Despite intense activity, there remains an unmet need for a biodegradable osteo-inductive scaffold system that is conducive to cell delivery and support, with a strength that enables normal load-bearing activities during healing.
- Orthopaedic market is one of the more progressive industry segments in relation to combination devices and cellular therapies. Workable opportunities to traverse IP minefield exist via strategic partnering with industry leaders holding required complementary licenses.
- CSIRO has significant experience in development of novel materials technologies for bone and cartilage, eg collaborations with ITRI in cartilage development, and spin-out of biodegradable polymer technology.
- MISCL has recently developed stem cell approaches for spinal fusion.
- Highest market growth is in spinal area. Significant unmet need for early intervention strategies to address disc degeneration.
- Ageing population – need for better therapies for age-related degenerative conditions such as osteoporosis or muscle wasting.
- Expertise in muscle regeneration through ARMI – established international profile of Nadia Rosenthal and Prof Peter Currie in muscle regeneration.
- Strong asset in new zebra fish facility – musculoskeletal developmental models for vertebrates.

60. I. Singec and E. Snyder, Inflammation as a matchmaker: revisiting cell fusion, Nature Cell Biology, 2008, 10, 503-505

Neurological

- Victoria has an established strong research base and clinical network through Neurosciences Victoria.
- Monash clinical strengths in neuro are primarily in mental health
- Best approach may be for SMART to operate as a complements to Neurosciences Victoria, where it has a particular capability that adds value, eg materials science or fundamental stem cell biology.
- Monash Materials Engineering has research activities in development of smart scaffolds containing bioactive cues for guiding neural regrowth in collaboration with the Howard Florey.
- CSIRO has experience in development of new biodegradable polymers for neural regeneration, and utilisation of fibre and weaving capabilities for production of neural conduit prototypes, in conjunction with Bionic technologies Australia.
- MISCL's capabilities in pre-implantation genetic diagnosis have the ability to provide disease-specific cell lines. Cell lines for Huntington's disease would serve as a productive base platform for research, providing useful knowledge for other neurological disorders. This may link to the bioactives program for novel drug development.

Renal

- Strong local champion for establishment of applied program – Prof John Bertram, with previous experience in establishment of renal translation program. Currently building framework and momentum for new renal initiative.

- Expertise in renal stem cell biology through Sharon Riccardo's team at MISCL and Dr Andrew Laslett at ASCC. Established collaborative relationships.
- Ability to tap into local clinical expertise in kidney. Strong local clinical base at Prince Henrys. Emerging edge of field fits well with teams that could be developed utilising broader SMART capabilities – eg tissue engineering incorporating stem cells⁶¹ and in vivo regeneration.

Respiratory

- Primary attraction is very early stage of stage of the field – relatively low research intensity internationally.
- Complementary research capabilities needed to address key clinical challenges exist locally, though may not be initially apparent as not currently directed at respiratory therapies.
- Recognised international profile in respiratory regen med and participation in primary international conferences via Ivan Bertonecchio of ASCC. Also strengths in respiratory stem cell biology in MISCL, and respiratory-related research at MIMR.
- Potential for links with CIRM
- Need for novel materials technologies – eg scaffolds of varying elasticity to study effect of mechanical properties on cell differentiation
- Utilisation of synchrotron for advanced in vivo imaging in respiratory – Stuart Hooper's studies of early respiratory development
- Significant clinical challenges in effective delivery, engraftment and long-term stability, provides links to research theme in delivery technologies.
- Clinical strength in heart-lung transplants at the Alfred

61. E. Rosines, R. Sampogna, K. Johkura, D. Vaughan, Y. Choi, H. Sakurai, M. Shah and S. Nigam. Staged in vitro reconstitution and implantation of engineered rat kidney tissue, PNAS, 2007, 104, 20939-20943



Diabetes

- Clinical strength in SE region is resident at Baker IDI
- Also various diabetes-related research across Monash
- Fundamental research in directed differentiation of ESC to pancreatic cells at MISCL
- CSIRO has prior experience in encapsulation of islet cells
- Strong competitive intensity in this area internationally. Companies approaching clinical trials. Would need to take care in defining protectable IP.

Urogenital and intestinal

- Potential collaborative development of tissue-engineered pelvic sling – CSIRO and MIMR
- Research strengths in endometrial stem cells
- MIMR: Prostate tissue grown from hESC to study prostate cancer and benign prostate disease⁶²
- Helen Abud's intestinal SC research

Skin and Wound Repair

- One of the most active areas of development initially in the tissue engineering field. Several products in the marketplace.
Eg: Allodermdecellularised scaffolds and various cell treatments for burns.
- Basic research in developmental biology may identify mechanisms which enable wound healing without scarring in the fetus.
- Market opportunity for bioactive agents or strategies to reduce scarring, for both topical and surgical wounds. Partnering options with established industry leaders – main interest from wound repair companies is in new bioactives to augment current products. Significant opportunities also in cosmetic / plastic surgery industry.
- Need for scaffolds which provide correct mechanotransduction cues to mitigate scar formation

62. <http://sequencingfacility.med.monash.edu.au/pdf/mi-news-may-06.pdf>

7 Strategic Implementation

7.1 General Phases

Phase	Actions
2008	Plan for a plan. Engage. Scope. Outline intended direction.
2009	Stakeholder review. Increase communication and collaboration. Define key areas of strength and potential research themes and translation programs. Refine strategic plan.
2010	Establish funding support for key programs. Assist development of teams.
2011	Build ground-up innovation, increase marketing of precinct, and industry engagement
2012	Review progress and direction. Analyse emergent strengths and opportunities.
2013 - 2015	Build next phase of programs, and support growth of local biotech hub.

- Examine opportunities for special interest groups to engage – email expander list (advise on upcoming seminars of interest within each department/org), social events, workshops on specific theme
- Identify research strengths and SMART research themes
- Build database of relevant local research capabilities, including complementary capabilities that could be brought in
- Benchmark international competitiveness to identify areas of strength for showcasing and for determination of research themes
- Seek proposals for innovative new cross-disciplinary projects
- Develop funding mechanisms to support innovative multidisciplinary projects.
- Assess competitive strength of proposed research themes – including IP mapping and assessment of international research intensity. Develop plan for external communications and engagement.

7.2 Priority areas for 2009

1. Review strategic direction and draft plan

- workshop with stakeholders in Feb 2009 to review draft strategic plan
- gather inputs on proposed direction and specific initiatives
- revise strategic plan and operational plan for 2009 in line with inputs

2. Discovery Research : Enhance communication and collaboration

- Increase communication between regen researchers in precinct, and awareness of complementary capabilities
- Establish 'tricks and tools' seminar series
- Build information on local capabilities/people/projects on central website

3. Earlier clinical integration and development of therapy-focussed translation programs

Scope:

- Facilitate clinician-led workshops on potential translation themes. Brainstorming session with representatives from multiple disciplines and organisations on potential ability to combine existing research strengths to address major clinical challenges.



Analyse and Prioritise

- Assess pre-requisites – local champion, clinical connection, meaningful technical offering in line with identified clinical need
- Opportunity assessment – analysis of IP, potential for commercialisation, industry partnering or external funding, existing and competing technologies, etc
- Support growth and source funding
- Assist with development of business cases / grant proposals for strongest cases.
- Commence external engagement – potential funding sources and industry partners.

4. Clinical Engagement

- Identify areas of clinical strength in partners in SE region
- Scope potential for more active engagement eg with Alfred, Baker or clinical networks
- Consider alignment with other health initiatives, eg Monash health sciences cluster and London Melbourne Cooperative Research Agenda

5. Industry engagement and commercialisation strategy

- Seek input from external biotech industry leaders, VC and local commercialisation and IP experts
- In parallel with development of research themes and translation programs, conduct more detailed commercial analysis to areas of greatest IP and commercial opportunity.
- Commence industry engagement – showcasing of capabilities for partnering opportunities on new major programs
- Consider alignment with DIIRD initiatives for building local biotech industry and innovation hubs.

6. Define direction and objectives for phase III of SMART

- Operational plan for 2010
- Proposals for specific research themes, translation programs and other initiatives
- Next review point with stakeholders Dec 2009.

7.3 Proposed Budget

In moving into the next phase of SMART, stakeholders will need to decide the level of financial commitment they wish to allocate to the initiative before it builds sufficient momentum to be self-funding through attraction of external funds. In this regard, stakeholders may wish to consider 3 optional levels of commitment.

Model 1: Base level funding. Priority on building increasing communication between participants via seminar series and web site. Clinician-led workshops and market and IP scoping to identify opportunity areas and refine strategic plan.

Model 2: As per Model 1, but with support funding for multidisciplinary research projects between participants. (5 PhDs). Also more detailed analysis and business case development to attract grant funding for 2-3 major programs.

Model 3. As per model 2, but with early commitment to identify and commence 2-3 major therapy-focussed joint programs by 2010.

ACTIVITY	Source	Cost in \$ 000s					
		Model 1		Model 2		Model 3	
		2009	2010	2009	2010	2009	2010
	Existing capability - Possible in-kind contribution Or New funding allocation						
Communication							
Website set-up & maintenance	Monash, ASCC	10	10	10	10	10	10
External web host	<i>Allocate funds</i>			15	5	15	5
Seminar series	ARMI project officer	10	10	10	10	10	10
Promotional Activities	Monash, CSIRO, ASCC		10	10	10	10	50
Identify & Build Opportunity Areas	Monash, CSIRO, ASCC	20	20	20	20	20	20
Clinician-led workshops	ASCC	30	30	30	40	60	80
Market and IP analysis	Monash, CSIRO, ASCC			20	40	40	80
IP FTO searches	ASCC	30	30	70	70	100	100
Business case development	<i>Allocate funds</i>	20	20	50	70	50	70
Grant funding cases	Monash IEC, CSIRO Monash						
Strategy and Engagement							
Alliance Leadership	Alliance senior exec	20	20	20	20	20	20
	<i>Appoint Exec Officer</i>					60	80
Industry, Govt & stakeholder engagement	ASCC, Monash IEC	30	30	30	30	30	80
Joint Alliance Initiatives							
Joint PhDs (x5)	<i>Allocate funds</i>			200	400	200	400
Joint Postdocs / Researchers	Existing staff					150	200
	<i>New postdocs</i>					100	300
Review							
	WG	5	5	5	5	10	10
	<i>External experts</i>			5	5	10	10
Total in kind: existing staff		175	185	255	285	470	650
Total new fund allocation				240	450	425	875
Total budget consideration		175	185	495	735	895	1525



8 Appendices

8.1 Appendix 1. SMART Stakeholders and Steering Committee.

Participants in February 2008 Strategic Workshop Group

Prof Edwina Cornish
Deputy Vice Chancellor (Research), Monash University

Dr Graeme Woodrow
Chief, CSIRO Molecular and Health Technologies

Dr Stephen Livesey
CEO, Australian Stem Cell Centre

Prof Nadia Rosenthal
Director, Australian Regenerative Medicine Institute

Prof Rob Norris
Dean of Science, Monash University

Mr SilvioTiziani
Chief Operating Officer
Australian Regenerative Medicine Institute

Dr Keith McLean
Theme Leader – CSIRO Biomaterials and
Regenerative Medicine

Prof Bryan Williams
Director, Monash Institute of Medical Research

Prof Tam Sridhar
Dean, Faculty of Engineering, Monash University

Prof Ian Smith
Deputy Dean, Research and Commercialisation,
Faculty of Medicine, Nursing and Health Sciences,
Monash University

Prof Prof Richard Boyd
Director, Monash Immunology and
Stem Cell Laboratories

Prof Christina Mitchell
Head of School, School of Biomedical Sciences,
Monash University
Australian Regenerative Medicine Institute

Prof Abid Khan
Director, Monash Institute for Nanosciences,
Materials and Manufacture

Prof Hatem Salem
Head of Department,
Australian Centre for Blood Diseases

Prof Michael Berndt
Vascular Biology Laboratory, Monash University

Working group

Mr SilvioTiziani
Chief Operating Officer
Australian Regenerative Medicine Institute

Dr Keith McLean
Theme Leader - Biomaterials and Regenerative
Medicine
CSIRO Molecular and Health Technologies

Prof Bryan Williams
Director, Monash Institute of Medical Research

Prof Hugh Niall
Monash Medical Research Advisory Board

Prof Steve Wesselingh
Dean, Faculty of Medicine,
Nursing and Health Sciences
Monash University

Dr Heather St John
Strategy Development Manager, SMART

Ms Margaret Hansford
Director, Partnership Solutions

