



Review of Australian Cell and Cell-Based
Therapy Research and Infrastructure

Part A: Sector Situational Analysis

7 October 2009



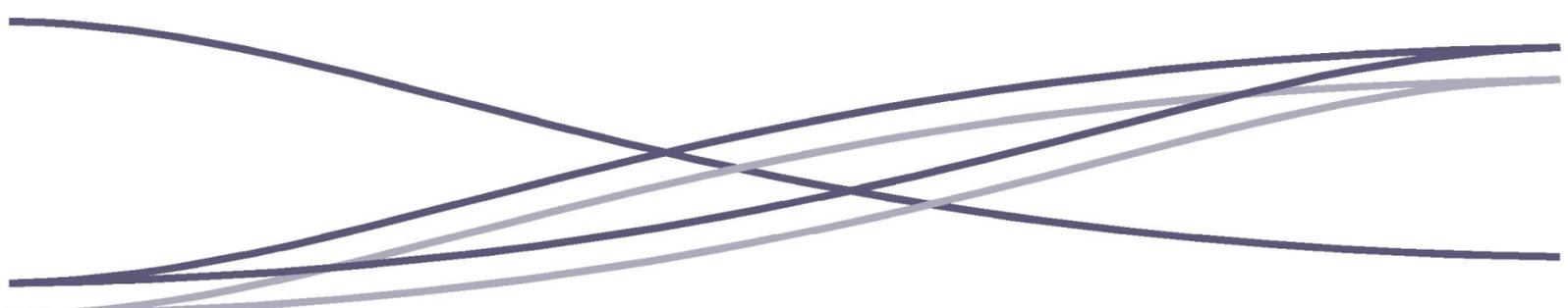
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Authorship

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EXECUTIVE SUMMARY

This Innovation Dynamics report is submitted in response to a Request for Tender (RFT) from Research Infrastructure Support Services (RISS) Ltd for a “Cellular Therapies and Cell Manufacturing Industry Benchmark Analysis”.

Key findings of the report are now being made publically available for informational purposes so that all stakeholders in the industry may benefit. For confidentiality purposes, all individual responses, appendices and raw data have been removed

This report looks at key healthcare drivers (ageing population, obesity epidemic, organ donation statistics and personalised medicine emergence) and their interrelationships with cell therapy R&D targets.

The approach taken included the identification and survey of, key opinion leaders and researchers in the cell therapy and support services sectors. Thirty face-to-face and eight telephone interviews were undertaken with key opinion leaders. A comprehensive internet based survey was designed and distributed to around 260 stakeholders.

Eighty respondents began the survey entitled “Review of Cell-Based Therapeutics and Manufacturing Infrastructure”. Thirty five completed all 47 questions, with the remaining forty five respondents exiting at various points throughout the questionnaire. This equates to an impressive response rate of 38%, and a completion rate of 16.7%, to the internet survey. Such a significant response rate is attributable to diligent follow up with stakeholders, as well as the sector’s general interest in helping shape future assistance programs.

Significant findings from the survey included:

- 82% (n=50) of respondents are undertaking research with the aim of developing therapeutics, with 83% (n=42) targeting human and 16% animal applications;
- 71% (n=62) are targeting autologous applications and 52% are investigating both autologous and allogeneic human therapeutic applications;
- 29% (n=62) are performing xenogeneic transplants;
- 65%(n=54) undertake collaborative R&D with other organisations to access equipment, infrastructure and leverage funding;
- 51% (n=53) currently have in-house access to cGLP, cGMP or clinical trial facilities and/or services , with 44% (n=50) having utilised contract service providers to access services, equipment or infrastructure over the previous 18 months;
- 73% (n=52) will require additional access to facilities and services in the near future – the infrastructure and services most required over the next five years will be clinical trials centres (required by 60% of respondents, n=35) and clinical research organisations (57%);

-
- 29% (n=48) of respondents stated that their organisation has development plans for establishment of in-house infrastructure, equipment or services, to be utilised for cell therapy R&D, within the next 18 months;
 - the majority of respondents (59%, n=41) agree that cell therapy services, equipment and infrastructure should be centrally located at no more than a few strategically chosen national sites;
 - 25% (n=32) of respondents are very dissatisfied with the current availability of translational R&D support, 29% (n=28) are dissatisfied with the level of service and only 38% (n=29) are in any way satisfied with the breadth of support service provided;
 - less than one third of respondents (32%, n=28) have considered the potential models for commercialisation of their technology in any detail, with a further 18% having given the process some general thought only; and
 - emerging trends that respondents' perceive to have a potential impact on the development of cell and cell-based therapies for commercial application primarily relate to the changing Australian regulatory environment, including its current uncertainty and development of the new TGA tissue code, as well as the sector specific knowledge of regulators.

The report reviews the current Australian research environment and discusses the regulatory environment, extent of collaboration, funding sources and support services. Australian cell therapy companies have been identified and described, and an analysis of the stage of industry development is included. In addition, key international cell therapy companies have been identified and tabulated with a descriptor of their activity and current contact information.

The sector is commercially immature in Australia with the majority of therapeutic research work being undertaken in medical research institutes, universities and hospitals. New therapeutic clinical data, both in Australia and internationally has to date been generally characterised as being stronger in safety than efficacy. The regulatory environment has been confusing for stakeholders and so benchmark therapies have not been effectively challenged to date. Such characteristics have hampered therapeutic commercialisation from the private sector; however alternate support sectors including banking, screening and consumable / instrumentation supply have evolved. Veterinary applications are emerging in the companion and production animal sectors, due in part, to a perceived accessible regulatory environment.

The ability to secure translational research funding in Australia for cell based therapeutics is both limited in source and quantity, yet is critical for sector development. Current funding models allow limited clinical trial assessment only, often with small patient numbers. Australian institutes are developing strategic relationships for information sharing, infrastructure and funding access.

Existing Australian cell therapy R&D infrastructure and plans for expansion have been identified in each relevant State. The extent of existing and planned certified good manufacturing practice (cGMP) and PC-2 infrastructure is believed to exceed current demand, given the level of currently underutilised infrastructure. The reason for this is likely a combination of generous (State and

Federal) government and philanthropic funding for medical research infrastructure over recent years, an under-estimation of the cost of operating cGMP facilities, altered research directions and unsustainable business models. There are no fully self-sustainable cGMP contract service business models currently in operation, with all having an affiliated supporting entity and the ability to cherry pick staff and/or support services on an as needs basis. The current TGA interpretation of such business models is unlikely to remain the same in the future, with increasing regulatory hurdles and consequential on-costs expected.

Emerging trends have been separated into social and technical aspects. Typical social observations discussed include the sector's need for public engagement, cell therapy tourism, the regulatory environment, funding and the emergence of animal and cosmetic cell therapies. The technical trends discussed include induced pluripotent adult stem cells (iPS), high throughput screening, cell expansion technologies including robotics and bioreactors, as well as the development of initiatives to supply cGMP and AQIS approved *in vivo* reagents for use in both R&D and cGMP manufacture.

Current and future demand for cGMP facilities, preclinical testing services, biomaterials laboratories and clinical research organisations (CRO's) has been reviewed with input from both service providers and clients. Preclinical service providers are currently under-utilised, and suggestions are offered to explain why this situation exists within the Australian context. It is believed that the reasons are not necessarily competence or infrastructure based, but likely commercial. Suggestions for infrastructure consideration are made. Analytical testing services, particularly TGA approved laboratories for Mycoplasma, NAT and viral testing have been identified as limiting, as has the necessity for centralised, expert cell banking services. Stakeholders identified the availability of CRO's as a primary concern, particularly those with cell therapy experience.

Areas of concern for sector stakeholders include Good Clinical Practice (GCP) and CRO accessibility, with less focus on Good Manufacturing Practice (GMP) capability. It is expected that regulatory compliance for cGMP facilities will continue to increase beyond currently acceptable "virtual" models in associated institutions.

Recommendations to facilitate the cell and tissue therapies sector in Australia include:

- Support of indirect Salaries and Wages (S&W) associated tasks and/or software with increased cGMP or GCP regulatory compliance in the translational setting as these are currently not captured through existing funding mechanisms. These may be considered soft infrastructure elements;
- Support services including preclinical, analytical and cell banking which are as necessary to effective translational research, and are a comparable service model as good manufacturing practice; and
- Facilitate formal GXP training with a cell therapy focus. Training is considered a critical soft infrastructure element.

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1. Background to this Review

This Innovation Dynamics report was originally undertaken in response to a request for tender from a key stakeholder in the cell therapy and support services industry. Key findings of the report are now being made publicly available for informational purposes so that all stakeholders in the industry may benefit. For confidentiality purposes, all individual responses, appendices and raw data have been removed.

The UK Department of Trade and Industry (DTI) reviewed the landscape for regenerative medicine in Australia in November 2006.¹ The objective of the current report will be to complement and expand the scope of the DTI study, to include a wider net of respondents (both publicly funded and commercial interests) and specifically focus on current and perceived future research infrastructure needs.

With reference to terminology adopted in this report, the terms “cell therapy” and “cell therapy support services” include the following sectoral activities:

- cell and tissue isolation and processing – includes stem cells, progenitor cells, differentiated cells, gene therapy, immune cells, skin (epithelial) and muscle / cartilage (for example, chondrocytes);
- both therapeutic and non-therapeutic applications;
- human and animal therapeutic transplant targets;
- interfacing technologies to cell therapies – loosely described as “regenerative medicine” and including the use or incorporation of cells and tissues to matrices, devices etc; and
- a “support service” sector – typically provides analytical services, reagents and consumables, equipment and professional services.

The terms “cell therapy” and “regenerative medicine” are often loosely interchanged within the scientific community, the former likely derived from the cell transplant community and the latter from the tissue and biomaterials sector. Buckler (2009)² argues that cell therapies are a subset of regenerative medicine, as according to the definition proposed by Mason and Dunnill (2008)³ “cell therapy is always about the replacement or regeneration of human cells, tissue, or organs, to restore or establish normal function”. Regenerative medicine may or may not use cells as the vehicle for achieving the same, with small molecule activators, non-cell-based gene therapy and/or non-cellular biomaterials as alternative options.⁴ Innovation Dynamics contends the inclusion of “human cells” only in the above definition of cell therapy, to the exclusion of the emerging veterinary industry.

¹ DTI Global Watch Mission Report, “An Assessment of regenerative medicine and stem cell technology – a mission to Australia”, November 2009, UK DTI and EESC.

² Buckler, L (2009). Cell Therapy <<http://knol.google.com/k/lee-buckler/cell-therapy/2tn18yspf7o31/2>> Viewed 2 July 2009

³ Mason C & Dunnill P (2008). A brief definition of regenerative medicine. *Regen Med* 3(1); 1-5

⁴ Buckler L (2009). *op cit*

1.1. Cell Therapy Context

1.1.1. Healthcare Trends

The following healthcare trends of ageing populations, increasing obesity, decreased organ donation and the emergence of personalised medicine represent key drivers for growth of cell therapy technologies and regenerative medicine.

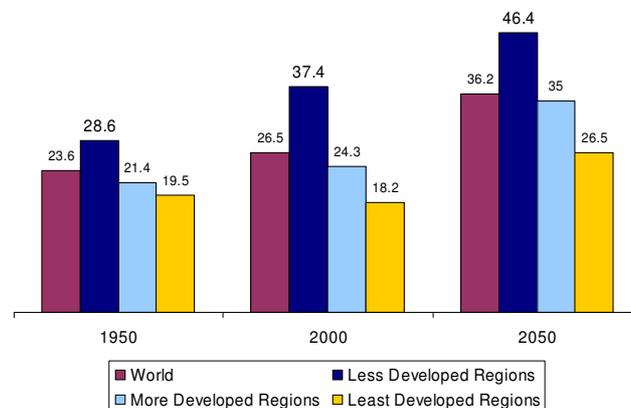
1.1.1.1. Ageing

According to the United Nations,⁵ the worldwide population reached 6.5 billion in 2005, with an annual growth rate of 1.2%. The demographic that has been experiencing one of the fastest growth rates is “older people” (those aged 60 years and over). Growth of 2% per annum in this segment is considerably higher than that of the world population. The proportion of older people is expected to reach 22% of the total population by mid-century, compared to just 10% in 2005. This trend is universal, with the average age of the population worldwide increasing from 28 years in 2005 to an expected 36.2 years in 2050 (Figure 1). Within the demographic of older people, the oldest old (80 years and older) is the fastest growing age group in the world, with an annual growth rate of 4.2%.

Resulting from this demographic trend, there is a demand for improved healthcare options and a noted increase in healthcare costs as a percentage of most western government’s GDP (gross domestic product).

Associated with increased longevity is an increased incidence of age related illnesses, including but not limited to cancer, orthopaedic conditions and neurodegenerative diseases such as dementia and Alzheimer’s.

Figure 1: Median age of population: world & developmental regions, 1950-2050



Source: United Nations. (2005) *Population Challenges and Development Goals*

1.1.1.2. Obesity

Another looming world health issue is obesity. Apart from the physical stress on bones and joints from being obese, it is also recognised that considerable stress is typically placed on organs such as the heart, liver, pancreas and kidneys, and serious chronic illnesses such as diabetes and heart disease can result. The

⁵ United Nations (2005). *Population Challenges and Development Goals*. Population Division, Department of Economic and Social Affairs.

number of people classified as obese has reached near-epidemic proportions, following significant increases in recent decades. Worldwide, there are over 1 billion people who are overweight and over 300 million who are clinically obese.⁶ In Australia, 32.6% of adults were reportedly overweight in 2004/2005, which is a dramatic increase from the 29.5% overweight adults recorded in 1995.⁷

The steady increase in both the obese and the ageing population has significant potential to impact on the size of the joint replacement market. Older people are at a higher risk from diseases such as osteoarthritis and osteoporosis, where there is a higher incidence of partial or full joint replacements. Osteoarthritis is one of the most common joint diseases and represents one of the most significant problems for the ageing population. Joint problems in younger generations tend to be attributed to secondary causes; one of the largest secondary causes is obesity. Obese people have twice the rate of hip and knee arthritis, approximately 32% compared to 16% of adults with a normal body weight.⁸ The market for hip and knee replacements was valued at more than \$5 billion in 2006,⁹ representing a significant cost to patients and healthcare systems.

Obesity is a driving force behind type 2 diabetes, which has cardiovascular and other complications. These include renal failure and blindness, and diabetic ulcers are a major cause of amputations and patient suffering. A 2002 study found that the prevalence of diabetes in Australia had reached 7.4%, with an additional 16.4% of the population aged over 25 years suffering from an impaired glucose or fasting tolerance.¹⁰ It is the sixth most common problem managed by General Practitioners, and in 2000 Australian health system expenditure on type 2 diabetes was around \$686 million, or a cost of \$42 to every Australian.¹¹

1.1.1.3. Organ Donation

Organ (heart, lung, liver, kidney, pancreas), eye and tissue (heart valve, skin, musculoskeletal tissue) transplants are well established procedures in Australia. They can save lives, restore health and improve quality of life. Australia has had a pioneering role in international transplant surgery; medical teams at Princess Alexandra Hospital (Brisbane) performed the world's first successful living donor liver transplant (1990) and first single segment liver transplant on a baby,

⁶ World Health Organisation (2003). Global Strategy on Diet, Physical Activity and Health. Obesity and Overweight

<<http://www.who.int/dietphysicalactivity/publications/facts/obesity/en/>>

⁷ Biggs.M. Parliament of Australia. Overweight and obesity in Australia. E-brief 05/10/06

⁸ Wallis.C, Joint replacements expected to soar, Time (Online), 06/03/2008,

<<http://www.time.com/time/health/article/0,8599,1720041,00.html>> Viewed 30/04/08

⁹ Whitney.J. (2007) Opportunity in Motion: Advances in spinal and other small-bone implants round out an already robust market. Orthopedic Design & Technology.

¹⁰ Dunstan DW, Zimmet PZ, Welborn TA, De Courten MP, Cameron AJ, Sicree RA, Dwyer T, Colagiuri S, Jolley D, Knuiman M, Atkins R, Shaw JE (2002). The rising prevalence of diabetes and impaired glucose intolerance: the Australian Diabetes, Obesity and Lifestyle Study. Diabetes Care, May 25(5); 829-834

¹¹ Australian Medical Association (2006). Counting the Cost of Diabetes. 10 July 2006

just 24 days old (2002). Additionally, the world's first kidney / liver / pancreas transplant was performed at the Royal Prince Alfred Hospital (Sydney) in 2006.¹²

The number of deceased organ donors in Australia is fairly constant at 10 per 1 million population, with rates varying from a low of 7 donors/million in NSW to a consistently higher South Australian rate of 23 donors/million (2006 figures).¹³

Australia's low donation rates translate to an organ transplant waiting list of 1858 patients between 1999 and 2007, of which 1391 of those were waiting for a kidney transplant. In 2006, the average waiting time for a kidney transplant was 3.79 years from a deceased donor and 1.38 years from a live donor. Liver transplant waiting time was 205 days (192 patients waiting as at 3 December 2007); 145 days for a heart transplant (93 patients waiting as at 3 December 2007); 187 days for a lung transplant (136 patients waiting at 3 December 2007); 1.9 years for a pancreas transplant (47 patients waiting as at 3 December 2007; and 1.4 years for islets (15 patients waiting as at 3 December 2007).

Low organ donation rates in Australia have been exacerbated by many factors, including (i) reduced road accident fatalities, (ii) complex approval processes with family veto at death, (iii) disjointed State based jurisdictions, (iv) ethnic and indigenous population reluctance to donate based on religious and/or cultural beliefs, (v) poor broader community awareness, and (vi) an "opt in" donor system where one must actively seek to donate, as opposed to the default "opt out" position of some countries (e.g. Spain).¹⁴ The profile of organ donors is thus changing from young road accident victims to older cardiovascular and other induced co-morbidities, where transplanted organ life may be reduced.

Other emerging trends have been the increasing proportion of transplants from living donors for some organ types, particularly kidneys / liver, and a greater number of retrieved organs per donor.¹⁵ Both of these trends are driven by the low donor population in Australia.

1.1.1.4. Personalised Medicine

Personalised medicine refers to the use of molecular analysis of genes, gene expression and metabolites to tailor medical treatments to the individual characteristics of patients. Such customisation for specific subpopulations will, now and even more in the future, allow clinicians to achieve optimal medical outcomes for patients, and effective management of predispositions to disease.

The major promises of personalised medicine are to shift the focus of medicine to prevention, reduce trial and error prescribing and adverse drug reactions, and to decrease the overall cost of healthcare. Current applications of the technology include genetic profiling to guide breast cancer treatments (Herceptin and HER2), analysis of individual patients' metabolism of blood thinner warfarin and testing for enzyme mutations to select the most effective colon cancer treatment.

¹² National Clinical Taskforce on Organ and Tissue Donation – Final Report 14th Dec 2008, <<http://www.health.gov.au/internet/main/publishing.nsf/Content/organ-donation-nctf-final-report.htm>> Viewed 3 September 2009

¹³ *ibid*

¹⁴ *ibid*

¹⁵ *ibid*

The global market for personalised medicine technology has been estimated to be US\$14.4 billion in 2009, growing at a compound annual growth rate of 15.2% to reach US\$29.2 billion by 2014. The largest sub-sectors within this market are pharmacogenomics contributing 28.7% (US\$4.1 billion in 2009 and US\$9.5 billion by 2014), and point-of-care, contributing 18.9% (US\$2.7 billion in 2009 and US\$5.1 billion by 2014).¹⁶

The rapid growth of this market is being driven by technological advances, increasing healthcare costs, decreasing analytical costs, and support from regulators and legislators. The advent of affordable genome sequencing is key to widespread use of personalised medicine, and with these costs dropping from around US\$20 million in 2006, to US\$2 million in 2008, and expected to be under US\$1000 by 2009-2010,^{17,18} this is fast becoming reality. Other key requirements include large scale studies to link genetic variation to disease and response to therapy, suitable healthcare information infrastructure, and reimbursement.

Evidence of the trend towards personalised medicine includes the emergence of education programs and dedicated personalised medicine practices across America; drug R&D incorporating genetic variation testing; broadening applications beyond cancer to cardiovascular, infectious and psychiatric diseases; integration of genetic testing onto pharmaceutical product labels; reimbursement by some insurers of certain genetic tests identifying pre-symptomatic high-risk populations; and U.S. governmental support and legislative changes including the *Genetic Information Non-Discrimination Act* and *Genomics and Personalized Medicine Act* (introduced to American Congress by Senator Barack Obama , 2006).

1.1.2. Technological Environment

Cell therapy technologies have the potential to impact the human and veterinary healthcare sectors through direct *in vivo* delivery of cells to affected tissues, or direct transplantation of *in vitro* engineered organs or tissue with the potential of reconstituting lost, damaged and/or degenerated parts of the body aiming for a return to stasis or normal functioning.

The direct delivery of *in vitro* expanded cells to replicate specific extant cell numbers is currently well established, for example with chondrocytes for cartilage repair. This application is aligned with the identified market trends of increased orthopaedic needs due to the ageing and obese population trends.

The direct delivery of autologous bone marrow (consisting of hematopoietic stem cells, mesenchymal stem cells, endothelial and precursor progenitor cells and growth factors) to oncology patients following chemotherapy, irradiation and/or immune suppression is a well established transplant procedure to re-establish the immune system. The International Bone Marrow Transplant Registries estimate that 30,000 autologous (own bone marrow) haemopoietic and 17,000 allogeneic

¹⁶ BCC Research (2009). *Personalized Medicine: Technologies and the Global Market*, Published July 2009

¹⁷ Personalized Medicine Consortium (2009). *The Case for Personalized Medicine*. Published May 2009

¹⁸ Oberweis J (2009). *The Next Big Thing: Personalized Medicine*. The Oberweis Report, Forbes Magazine, 28 May 2009

(donor bone marrow) haemopoietic stem cell transplants are performed annually.¹⁹ Whilst autologous bone marrow transplantation is now being explored in “healthy / non-severely immuno-compromised patients” for other indications (e.g. osteoarthritis, gastrointestinal tract, diabetic ulcers), it is oncology treatment which remains the primary transplant application. At current Australian incidence rates, one in three men (33%) and one in four women (25%) will develop cancer by the age of 75. This risk will increase by age 85, to one in two for men (50%) and one in three for women (33%).²⁰

Stem cells can be derived from wider sources than bone marrow, with other common sources including circulating (peripheral) blood, umbilical cord blood and adipose (fat) tissue.

The need for organs is an increasing unmet need in healthcare, and one for which stem cell based therapeutics may play a practical remediation role. Currently, organ tissue may be grown *in vitro* as a nucleation patch. Typically, more simple structures such as blood vessels, skin, bladder, breast and bone have provided foundational learning, however more complex fully engineered solid organs remain as challenges. Organs of interest are those such as the heart, liver, pancreas and kidneys and are consistent with those stressed organs resultant from obesity and ageing. Of particular interest is the application of nucleated organ tissue patches for children, whereby the new cells / organ may grow with the patient and circumvent the need for repeated surgical interventions.²¹

The interfacing of cells with medical devices to develop bioartificial organs has been explored for a number of applications. Such devices may be either an interim or bridging solution until a full organ transplant may occur, or an acceptable destination therapy for less severe complications and where a normal lifestyle may be possible. The development of extracorporeal Bio Artificial Liver (BAL) systems has progressed considerably due to the global shortage of donor livers and the high reject rate (20%) before transplantation.²² The device gives patients time for liver regeneration, as does a hepatocyte transplant. Both human and porcine hepatocytes and stem cells are being explored to charge the BAL devices.

Other potential therapeutic applications of cell therapy are the treatment of autoimmune diseases, genetic disorders and indications related to cancer. Specifically, stem cell based therapeutics may be considered for the regeneration of depleted cells and tissues lost due to infection. These could include immune response cells and/or remediation of damaged tissue such as may occur in HIV, hepatitis B, hepatitis C, or the autoimmune disease lupus. Stem cells may be utilised in gene therapy – specific genes are transferred to stem cells which, once transplanted, replicate and populate the body with a corrected gene and gene

¹⁹ Steenblock, D (2007). Bone Marrow Stem Cell Therapy; Lecture delivered SENS-3 Conference, Queen’s College, Cambridge, England 6-10 Sept 2007

²⁰ Cancer Australia (2009) Website: Overview

<<http://www.canceraustralia.gov.au/about-cancer/overview.aspx>> Viewed 3 Sept 2009

²¹ Munevar, S (2008). Stem Cell Technology: Current Applications and Future Directions, BCC Research, July 2008.

²² Bacarani U, et al (2006) “State of the art on human hepatocytes: isolation, preservation and clinical use” Current Opinion in Organ Transplantation, 11:643-647

product (e.g. enzyme). Genetic disorders such as cystic fibrosis, in time, may be treated in such a manner. Aside from carrying specific correctional genes, stem cells have been considered as possible vehicles for delivering therapeutics.²³

Still further applications associated with stem cells are in non-therapeutic areas, or those with indirect therapeutic application. For example, used in cellular assays and diagnostic tools, or as models for disease and the drug discovery process. Academic investigation of human cellular development and growth has led to intense research into stem cells over the last decade. High self renewal and differentiation capability of stem cells have led to the development of differentiated cells which may be used as toxicity models for new pharmaceutical compound screening or testing, prior to clinical use. For instance, stem cells differentiated into hepatocytes may be used for *in vitro* studies of a new pharmaceutical's probable impact on the liver. A number of big pharma companies, such as Pfizer, GlaxoSmithKline and Roche currently utilise stem cell technology in new compound screening. Indeed, coupled with somatic nuclear transfer technology, stem cells may be used to create disease specific cell-based models for a variety of disease types. This may ultimately lead to the development of new drugs more tailored to disease at a cellular or tissue level, with less unwanted side effects and perhaps better tailored to specific patient subpopulations. Such developments will potentially see a move away from the current high volume, low price, mass manufactured big pharma drugs and their associated litigation risk from adverse reactions and off-label (unproven) market application, to more segmented, lower risk, lower volume drugs at higher individual prices. It drives pharmaceutical commercialisation to the perennial marketing issue of globalisation versus segmentation. This latter segmentation is foundational to more personalised medicine.

The population at large, both healthy and ill, is beginning to explore the banking of stem cells, either publicly for future allogeneic transplants or privately for own / family use. These people are 'investing' with the expectation that in the near future the potential of stem cell technology will be proven and therapies will be available to benefit their loved ones, should they require medical intervention. The banking sector is growing, with emerging specialist cell therapy support services ranging from companies who store or bank cells and tissue, to the many media, reagents, consumables and plastic ware companies, to the generic and highly specific equipment and software service providers. The development of sophisticated aseptic, robotic technologies, cell sorting, high speed throughput array and microscopy systems are becoming *de rigueur* infrastructure for the cell therapy R&D laboratory.

1.1.3. Regulatory Landscape

A significant difference between R&D in therapeutic and non-therapeutic applications of cell therapy is the regulatory landscape. The therapeutic application of cell therapy products requires a higher level of regulatory risk management due to the need for clinical trials in humans. In Australia, the human cellular and tissue therapies (HCT) regulator, the Therapeutics Goods

²³ Munevar, S (2008) *op cit*

Administration (TGA), has proposed a new framework to clarify the current confusing array of exemptions and inclusions across various codes. Initial implementation of the new framework is planned for 2010, with the transition being completed over the following three years.²⁴ The framework excludes assisted un-manipulated reproductive tissues and organ transplants, and will also initially exclude haematopoietic progenitor cell transplants until further sector consultation is concluded. The HCT framework will not cover blood, blood components or products, secreted or excreted human products such as hormones, breast milk or urine, and other potential articles yet to be defined. Four classes of biologicals are proposed, classified by increasing levels of risk, from Class 1 (low) to 4 (high), associated with increased levels of manipulation, and /or altered homologous function. Classes 2 to 4 will require adherence to Manufacturing Principles in a TGA inspected facility with a current Manufacturing Licence; in essence, adherence to the current Code of Good Manufacturing Practice (cGMP) - Human Blood and Tissues.

Since 2003, all facilities and individuals engaged in, or responsible for, retrieval/collection, processing, storage, labelling and packaging, product testing or release for supply of human tissue and cell based products for therapeutic purposes, or for the screening of cell or tissue donors in Australia, must register their facility with the TGA.

The significance of the current and proposed regulatory framework for HCT in Australia is that infrastructure with TGA cGMP licensed facilities and systems will become a necessary part of human clinical cell therapy development.

²⁴ TGA (2009). Website: Biological Framework Implementation
<<http://www.tga.gov.au/bt/hct.htm>> Viewed 10 August 2009

2. Approach

This study is intended to address, as a minimum, the following broad themes:

- Australian Industry Overview
- Emerging Technologies
- Sector Needs
- Pricing
- Benchmarking

Australian Industry Overview, Emerging Technologies and Sector Needs are addressed in here, with Pricing and Benchmarking addressed in a secondary report.

Information was secured through a combination of research tools, including face-to-face and telephone interviews with Key Opinion Leaders (KOLs) and industry stakeholders, an internet based survey, constructed and implemented for broader stakeholder involvement, and extensive desk research.

2.1. Interviews

Some 340 industry stakeholders were identified from publicly available information. Separately, suppliers of both consumables and equipment servicing the Australian cell therapy sector have been identified

Approximately thirty face-to-face interviews were undertaken with key opinion leaders and industry stakeholders in Brisbane, Sydney and Melbourne. Not all requests for interview were acknowledged or granted. In part, this was due to factors such as alignment of visit schedules, or perceived benefit by the targets.

Telephone interviews were undertaken with those stakeholders who were not available to meet or with whom Innovation Dynamics was already familiar. Eight telephone interviews were completed.

2.2. The Internet Survey Design

An internet based survey tool (SurveyMonkey.com) was designed to elicit information from stakeholders regarding their affiliation, cell therapy activities, perceptions and experience of the sector, as well as future plans and outlook. Questions were designed to be both qualitative and quantitative, with a mixture of multiple answer tick boxes, scaled matrices and short answer commentary. The survey was designed to minimise required respondent time to less than 30 minutes, and therefore participant drop out / non-completion. Following positive feedback after beta testing, the survey link was sent to approximately 260 stakeholders for response over a period of 3 weeks. Brief, weekly reminder emails were also sent to encourage response.

In an effort to elicit greater penetration of the survey to allied cell therapy stakeholders, requests were made to certain professional societies to notify their members of the survey or send to their members directly. The societies contacted included:

- The Australasian Society for Stem Cell Research (ASSCR)
- Australasian Gene Therapy Society
- Australasian Leukaemia and Lymphoma Group (ALLG)
- NSW Stem Cell Network
- Haematology Society of Australia and New Zealand (HSANZ)
- Australasian Wound and Tissue Repair Society (AW&TRS)
- Australasian Society for Biomaterials and Tissue Engineering

3. Cell Therapy Internet Survey Results

Eighty respondents began the survey entitled “Review of Cell-Based Therapeutics and Manufacturing Infrastructure”. Thirty five completed all 47 questions, with the remaining forty five respondents exiting at various points throughout the questionnaire. The email link to the survey was sent to a total of 259 email addresses, however due to old or incorrect contact details, the estimated number of actual survey recipients is 210. This equates to a response rate of 38%, and a completion rate of 16.7% to this internet survey. Such a significant response rate is impressive and attributable to the weekly reminder emails sent in follow up to the initial link, as well as the sector’s general interest in helping shape future assistance programs.

The majority of respondents were participating on their own behalf (51.5%, n=66). There were 21.2% responding on behalf of their Department, and the other 27.3% were responding on behalf of their organisation as a whole. Of these 32 respondents participating on behalf of a larger group, 13 were associated with companies, 8 with hospitals, 3 with public sector R&D institutes, 6 with universities and 2 with the Blood Service. The location of respondents was concentrated around the five major Australian cities, with 32.3% from New South Wales, 24.6% from Victoria, 23.1% from Queensland, 12.3% from Western Australia and 7.7% from South Australia.

Primarily researchers involved in cell therapy R&D responded (45.5%), with another 10.6% of respondents providing support services to the sector and 13.6% providing manufacturing and/or distribution. A notable 30.3% of respondents claim to participate in all of these activities.

Respondents were mainly cell therapy researchers based on the East Coast of Australia.

3.1. Cell Therapy Interests and Applications

Of the 50 respondents with R&D activities, most (82%) are pursuing therapeutic uses for their research. Only one-respondent stated their focus as non-therapeutic applications, however 8 respondents chose the ‘other’ response, and answers varied from exploratory interest only to animal reproduction and basic translational research. The majority of R&D activities (83.3%, n=42) are focussed on human applications, with the other 16.7% targeting animal applications. Almost a third (29.5%, n=62) of respondents’ work involves gene transfer.

Autologous human cell transplantations are the target application of 71% (n=62) of respondents’ R&D, with 51.6% also targeting allogeneic human transplants. Allogeneic animal cell transplants are an aim for 27.4% of respondents, with xenogeneic transplants (animal to human, human to animal or animal to different species animal) are being worked towards by a combined 29%.

Whilst most respondents do not focus on non-therapeutic applications of their research and technology, most perform some such activities (57 of 66 noted at least one non-therapeutic area of work). Many (68.4%) are involved in basic research, 42.1% use processing technologies, 36.8% perform analysis, 29.8% participate in cell banking, 28.1% have activities relating to biomedical devices, 21.1% perform diagnoses and 12.3% are working on media development.

3.2. Current Situation

Currently, there are 31 discovery projects, 28 preclinical studies and 33 clinical trials ongoing by 56 respondents participating in therapeutic R&D. Of the clinical trials, 17 are in Phase I, 10 are in Phase II, 5 are in Phase III and one is in Phase IV trials. Almost two thirds undertake collaborative R&D with other organisations involved in cell therapy (64.8%, n=54). Around half of these respondents (48.6%) undertake such collaborative R&D to access equipment or infrastructure not available within their own organisation. This includes NATA accredited cell therapy facilities, GMP facilities for manufacturing clinical trial product, GMP recombinant protein manufacturing, Fournier transformed infra red spectroscopy, magnetic resonance imaging (MRI), fluorine MRI coil, nuclear magnetic resonance imaging (NMR), atomic force microscopy, flow cytometry, heart function monitoring equipment, equipment for electrical mapping within the endocardium, cardiac catheters and devices, veterinary services, genomic platforms, biomaterials expertise, proteomics expertise, sequencing, specialised immunology and antibodies, and general equipment, laboratories and staffing needs.

Approximately half of all respondents (50.9%, n=53) currently have in-house access to cGMP, cGMP or clinical trial facilities and/or services. Over the past 18 months, 44% (n=50) have utilised contract service providers to access services, equipment or infrastructure.

Many researchers participate in collaborative R&D to access equipment or infrastructure, and around half have contracted service providers recently.

Future Needs

The current or immediate future operations of 73.1% (n=52) of respondents will require additional access to facilities and services.²⁵ The infrastructure and services most required over the next five years will be clinical trials centres (required by 60% of respondents, n=35) and clinical research organisations (57.1%). Other important resources include cGMP training services (45.7%), GMO

²⁵ Reasons for not requiring additional access included working outside R&D, not yet being far enough down the development pathway, having sufficient internal or collaborative partner access to facilities and services in the near term, and "diagnostic value".

certified cGMP facilities (37.1%), access to analytical testing facilities (37.1%), imaging (34.3%), access to cGLP testing facilities (28.6%), access to a cGMP contract manufacturing organisation (22.9%), non-regulatory compliant capability (14.3%) and cGLP training services (11.4%). Additionally, 3 respondents noted requirements for TGA licensed microbiological testing facilities, manufacturing software, cGMP testing services, contract services (not access only) for analytical testing, preclinical testing and cGMP contract manufacturing. .

The majority of respondents (38%, n=50) will require additional infrastructure within 1-3 years, 16% have requirements in less than one year, 12% see a need in 3-5 years and 4% can foresee needs beyond 5 years (30% of respondents could not estimate a timeframe for further infrastructure and support services requirements).

Equipment valued over \$100,000 that would benefit respondent's R&D includes microscopy and imaging equipment, fluorescence activated cell sorter (FACS) and PCR machines, automated cell isolation, sorting, processing, characterisation, expansion, incubation and cryostorage machines, low oxygen cabinets, manufacturing software for tracking and traceability, dynamic cell and tissue culture systems and robotics, NMR and MRI imagers, confocal and atomic force microscopy, flow cytometry and HPLC instrumentation, clean room facilities, high throughput gene expression analysis equipment, microarray scanner, protein production and purification equipment (microbial fermentation and chromatography), platform arrays, spray drying and freeze drying equipment, live cell imaging capabilities, microcomputer aided tomography, mass spectrometers, liquid nitrogen storage, laser capture micro-dissection system and injecting catheters and monitoring devices. One respondent noted that their key need is staffing.

Almost three quarters of respondents will require additional facilities / services in the near future, primarily CRO and trial centres. There is much equipment valued under \$100,000 that would benefit researchers.

3.3. Development Plans

Fourteen respondents plan to establish in-house infrastructure, equipment or services, the majority within the next two years.

There were 14 respondents (29.2%, n=48) who stated that their organisation has development plans for in-house infrastructure, equipment or services to be utilised for cell therapy R&D, in the next 18 months. Of these 14 responses, 11 specify an establishment timeframe within two years, and a further 2 expect establishment within three to five years. Support Services

The majority of respondents (58.5%, n=41) agree that cell therapy services, equipment and infrastructure should be centrally located at no more than a few strategically chosen national sites. They do however note that this only makes

sense due to the cost and limited funding available, and clarify that this system will only work if sites are appropriately staffed and easily accessible. Another 31.7% would rather a distributed network of regional, key research centre or hospital based locations, and 4.9% believe a mixture of centralised and distributed infrastructure is the best option. The remaining 4.9% are in favour of such resources being restricted to individual organisations, as a function of therapy type.

Respondents' levels of satisfaction with typical support services and products for cell therapy R&D in Australia were surveyed based on current availability, level of service, breadth of service and spend impact on R&D budget. Some stand-out results show that 25% (n=32) of respondents are very dissatisfied with the current availability of translational R&D support, 28.6% (n=28) are dissatisfied with the level of service and only 37.9% (n=29) are in any way satisfied with the breadth of service. The availability of preclinical testing services, TGA accredited cGMP +/- PC2 facilities and clinical trial facilities is also less than satisfactory to over half of the respondents, with >10% very dissatisfied with current availability and >15% very dissatisfied with the current breadth of service of each. The breadth of service of cGMP facilities is of particular concern, with only a third of respondents (n=30) in any way satisfied, as well as 18.2% (n=22) of respondents being very dissatisfied with the spend impact of these facilities on their R&D budget.

Some internationally available support services that respondents' are aware of, which are not currently available or require improvement in Australia include affordable cell manufacturing and cryostorage, RCR testing for vector safety, bioreactors for cell expansion, gene vector production facilities, CMV and EBV vector safety, better cell bank resources, GMP facilities for hESC and iPS cell , oligoclones for treating viral reactivation post transplant, clinical grade gene transfer formulations and manufacturing facilities, TGA registered transport media (including collagen and human thrombin), and NAT testing facilities. International facilities or operations that respondents see as best in practice in these areas or would like to see emulated locally include MPI Research, ATCC, UK Stem Cell Bank, Innovotech (preclinical testing, Canada), Bioreliance (analytical and development services, USA and Edinburgh) and ToxTest Inc (multispecies toxicology, USA).

Australian support service providers that respondents view as offering international best practice include Cell Therapies Pty Ltd in Melbourne (recognised by four respondents as the Australian leader in the field), BD Biosciences in Sydney (due to speed of service), and the Australian Red Cross Blood Service (for their licence support, experience and contacts).

In choosing a TGA accredited cGMP facility and contract service provider, the majority of respondents ranked all criteria except for two as very important. Specific instrumentation (specified by respondents to include cell processing hardware, reliable cryostorage facilities, cell sorters and cell expansion technologies appropriate for patient care) was rated by almost 40% of respondents as important (almost 50% if N/A answers excluded) and the same time zone rating was mainly spread between 'of little importance' and 'very

important'. The most important considerations appear to be regulatory compliance of facilities, followed by experience of facility staff and cost. Other high importance criteria include intellectual property protection, physical access to the facility, ability to audit the facility and its location within Australia.

3.4. Funding & Commercialisation

Less than one third of respondents (32.1%, n=28) have considered the potential models for commercialisation of their technology in any detail, with a further 17.9% having given the process some general thought only. This leaves 42.9% of respondents participating in cell therapy R&D with no clear idea of how they will turn their technologies into commercially sustainable propositions. Emerging trends that respondents' perceive to have a potential impact on the development of cell and cell-based therapies for commercial application primarily relate to the changing Australian regulatory environment, including its current uncertainty and development of the new TGA tissue code, as well as the sector specific knowledge of regulators and the length of time to receive approvals. Other key factors identified include cell expansion and manufacturing scale-up, technology developments in the automation / robotics and manufacturing arenas and Australia's competitiveness (particularly with Asia) in attracting private investment.

One fifth of respondents' operating and capital budgets are sourced from private investment. Less than a third of respondents have considered their technology commercialisation model.

4. Overview of Cellular Therapies & Manufacturing

4.1. Australian Research Environment

The cell and cellular therapies sector is an active area of biomedical research in Australia. The majority of research is being undertaken within either universities or medical research institutes where the freedom to explore such “public good” is more viable due to accessible government funding.

There has been a strong historical linkage in Australian cell therapy R&D from a number of sources. These include:

- The Australian Red Cross with blood donation, processing, banking and research;
- Bone marrow transplantation for treatment of oncology patients in the public and private hospital sector;
- University and medical research co-affiliations with academic / clinically qualified staff;
- Clinical trial research facilitation through hospital linkages; and
- General scientific expertise in cell culture and optimisation.

Hospitals, be they public or private, have provided a significant infrastructural base for cell therapy research and development both in Australia and internationally. In Australia, a perceived lack of TGA regulatory jurisdiction in the hospital environment has been of significance. The TGA currently advise that one-off human products that remain under clinical supervision will be excluded from oversight by the TGA.²⁶ Additionally, the Clinical Trial Notification (CTN) scheme circumvents direct TGA approval in lieu of an in-house/hospital Human Research Ethics Committee (HREC) approval process for clinical trials. The cumulative effect of these regulatory conditions has been internationally recognised clinical trial accessibility in Australia.

According to some key findings of the internet based survey, which characterise the Australian R&D sector and researchers activities:

- 82% (n=50) are undertaking therapeutic research and development;
- 83% (n=42) are targeting human and 16% animal therapeutic applications;
- 71% (n=62) are targeting autologous and 52% are investigating both autologous and allogeneic human therapeutic applications; and
- 29% (n=62) are performing xenogeneic transplants.

Australian researcher’s who responded to the survey are investigating the broad areas of oncology, neurology, inflammation and musculoskeletal disease, degeneration or injury. Again, these indications are consistent with the prevalent conditions associated with an obese and ageing population.

²⁶ Smith, G (2009). Presentation: Implementation of HCT/Biologicals Regulatory Framework <<http://www.tga.gov.au/bt/presentation-atbf090505.pdf>> Viewed 7 September 2009

Of significance from this survey was the level of activity identified in cell and tissue therapies. Responses from 56 researchers in therapeutic R&D revealed 31 discovery projects, 28 preclinical studies and 33 clinical trials ongoing. Of the clinical trials, 17 are in Phase I, 10 are in Phase II, 5 are in Phase III and one is in Phase IV trials (bone marrow cord blood). As a benchmark comparison, Australian listed and unlisted companies in December 2007 were known to be conducting 122 Preclinical, 61 Phase I, 80 Phase II and 18 Phase III clinical trials.²⁷

Almost two thirds of Australian researchers who responded to the survey undertake collaborative R&D with other organisations involved in cell therapy (64.8%, n=54), with half of these respondents (48.6%) undertaking such collaborative R&D to access equipment or infrastructure not available within their own organisation. Typically, the partners are Australian medical institutes and hospitals, with few reported corporate partnerships. The Australian Stem Cell Centre (ASCC), a predominately federal and Victorian State government funded (\$100 million and \$11 million respectively for the period 2002 -2011) initiative, is reflective of the academic centric relationships predominating in the Australian cell therapy sector. The institute has nine collaborative member institutes, all of which are university or medical research institutes. Established as a National Centre of Excellence, the ASCC has had a problematic history in establishing and consummating commercial relationships, however recent initiatives in both structural and strategic change seek to redress this issue.²⁸

Collaboration for access to equipment, infrastructure is also complemented by access to capital. The majority of funding received by survey respondents for cell therapies research is divided almost equally between competitive grants from the National Health and Medical Research Council (NHMRC) and Australian Research Council (ARC), institute discretionary grants, State government grants and shareholder funds. Some Australian institutes have sought international partners to broaden not only their technical relationships but also to broaden their funding opportunities. The University of Queensland's Australian Institute for Bioengineering and Nanotechnology (AIBN) cited these reasons upon recently signing a Memorandum of Understanding with Cornell University's Nanobiotechnology Centre.²⁹ The Victorian Government and the California Institute for Regenerative Medicine (CIRM) recently announced the co-operative funding of joint programmes between the ASCC and the Scripps Research Institute, La Jolla; the ASCC and the University of California, Irvine; the Florey NeuroScience Institute and the Burnham Institute of Medical Research, La Jolla; and Monash University with Novocell Inc, San Diego.³⁰ CIRM is charged with directing US\$3 billion for stem cell research funding with US\$68 million for translational projects in addition to the US\$600 million awarded to basic research, training and facilities over the last 3 years. Such relationships, if well managed, will not only provide Australian scientists and managers with valuable

²⁷ Innovation Dynamics Pty Ltd proprietary ANZ Pharma Product Pipeline Database

²⁸ Evans, N (2009). ASCC moves in new direction. *BiotechnologyNews.net*, 24 July 2009

²⁹ BioSpectrum Asia (2009). Australia, US institutes join hands for nanobiotech research. 21 July 2009

³⁰ Victorian Government (2009). Press Release: International Collaboration Funds Stem Cell Research, 21 May 2009

technical and infrastructural access but also important insight, potential awareness raising and access to international commercialisation models for these technologies.

Announced late in 2008 was the Australia-China NanoNetwork, forged between two university networks: the Australian Technology Network (ATN) with its 5 member universities and the Chinese International Strategic Technology Alliance, which includes 24 of China's top universities. The two networks have agreed to work together in one of the most promising current scientific areas - nanoscience and nanoengineering. Its overarching aim is to coordinate the collaboration of member universities in academic exchange, research, knowledge dissemination and knowledge transfer for commercialisation.³¹

A common sentiment amongst those working in cell technologies for therapeutic purposes is the lack of funding for translational support and/or clinical trial scale-up. Whilst it is recognised that the NHMRC funds cell therapy research, and indeed clinical trials, there is a perception that very early stage and part funding of late stage clinical trials have most success in NHMRC funding rounds. It is generally considered that the scale-up of cell technologies, required for larger clinical trial at Phase II, do not constitute adequate research merit. This of course represents a significant dilemma in terms of funding for technical translation and an impediment to the commercial and/or societal expectation of medical research funding. Some 25% (n=32) of survey respondents are very dissatisfied with the current availability of translational R&D support, 28.6% (n=28) are dissatisfied with the level of support service and only 37.9% (n=29) are in any way satisfied with the breadth of translational support services. The availability of preclinical testing services, TGA accredited cGMP +/- PC2 facilities and clinical trial facilities is also less than satisfactory to over half of the respondents, with >10% very dissatisfied with current availability and >15% very dissatisfied with the current breadth of service of each.

The breadth of service of cGMP facilities is of particular concern to survey respondents, with only a third of respondents (n=30) in any way satisfied, as well as 18.2% (n=22) of respondents being very dissatisfied with the spend impact of these facilities on their R&D budget.

Australian Cellular Therapy Companies

The cell and cellular therapy sector is considered to be in its commercial infancy. There are a number of reasons for this, including:

- public concern regarding the ethical issues surrounding embryonic stem cell research has impacted regulatory and technology momentum;
- technical issues remain unanswered regarding long term cell line purity, cell expansion and cell rejection regarding certain therapeutic initiatives;
- significant lead times will be required to demonstrate cell technology performance against current benchmark therapies and encourage clinician uptake;
- the cost of therapies will initially be expensive and widespread adoption by the public will be dependent upon both government and/or private health

³¹ Australian R&D Review , September 2009.

insurance reimbursement – such reimbursement models are unlikely to appear until there is compelling evidence that cell therapies are cheaper, more efficacious (and safe) compared to the current relevant standard (of course, there is greater prospect of earlier cell therapy adoption where there is no benchmark therapy – cell therapies involved in neural illnesses such as dementia and Parkinson’s disease where there are no existing cures are of particular interest in an ageing world, as are injuries where full remediation to stasis is a potential outcome rather than long term or permanent disability);

- regulators have not provided a definitive position on the regulatory landscape, thus creating uncertainty for stakeholders in regards to regulatory risk and expectation; and
- organ transplants are predicted to continue to be the preferred modality for organ replacement – any initiatives to increase organ donation within the wider community will impact the opportunity for broader uptake of specific organ cell therapies.

The net result of these factors is the relative commercial infancy of the therapeutic cell technology sector in Australia (and elsewhere), plus a reduced profile and low public awareness of the sector potential. As any intellectual property associated with this technology will predominately reside within hospitals, medical research institutes and/or university research groups, the technology must be presented with a clear commercialisation model to attract venture capital funding, noted in the survey results as significantly low. Commercialisation issues specific to this sector may include unencumbered IP, scientists and clinicians preparedness to enter the private sector with associated funding risks and diminished recognition, infrastructure access agreements, lack of proven, commercially-oriented management teams, controlled clinical trial data demonstrating efficacy as well as safety, and appropriate corporate structures. Whilst universities have developed varying levels of experience and competence at commercialisation and private sector interfacing, it is likely that government funded hospitals and medical research institutes may be presented with new challenges in this context.

There are a few mainstream cellular therapy companies in Australia. Table 1 identifies (and provides brief overviews and websites for) Mesoblast Ltd and Living Cell Technologies Ltd, both ASX listed companies with international profiles. Mesoblast has a current market capitalisation of \$143 million, trading at \$1.05 per share and Living Cell has a market capitalisation of \$42 million, trading at \$0.16 per share (as at 9 September 2009).

The Chinese State Food and Drug Administration (SFDA) has given Avita Medical Ltd, an ASX listed company, regulatory approval for its ReCell® Autologous Spray-On Skin product. ReCell has been issued an unrestricted import license by the SFDA into the key Chinese market where ReCell seeks to address the growing demand for cosmetic surgery, scar revision and burns treatment.³²

³² Australian R&D Review (Sept 2009) *op cit*.

A number of private Australian companies and lesser known public firms are performing human cell and tissue therapy research and/or processing. Examples include Australian Biotechnologies Pty Ltd, BioNova International Pty Ltd, Colltech Australia Ltd, Celxcel Pty Ltd, Cytomatrix Pty Ltd, Dendright Pty Ltd, Nephrogenix Pty Ltd, Orthocell Pty Ltd, Prima Biomed Ltd, Sydney IVF Stem Cells and Tissue Therapies Ltd.

Verigen Pty Ltd, located in Western Australia, is a subsidiary of the US firm Genzyme. Verigen processes autologous chondrocytes for transplantation. It recently announced the establishment of an expanded cGMP facility in Perth, which will service the region and provide numerous skilled workforce opportunities in the State.

As characterised in other countries, Australia has a number of support service companies who offer cryogenic storage and retrieval services for cord blood and other tissues. These companies include Australian Stem Cell Healthcare Pty Ltd, Cellsense Pty Ltd, Cordlife Ltd (BioCell Pty Ltd) and Cryosite Ltd.

CordLife has recently signed an agreement with China's largest cord blood bank, Beijing China Cord Blood Bank (BCCBB), whereby CordLife will help BCCBB align its protocols with blood processing and storage standards required for international accreditation; the first in China to receive international accreditation.³³

The area of animal cell and tissue therapy is an emerging area in Australia. Two companies are known to be involved in transfer of animal tissue into humans – Living Cell Technologies Pty Ltd, who are exploring the use of encapsulated porcine cells for treatment of diabetes in humans, and CelXcel Pty Ltd, who are trialling the use of a bovine pericardial patch in humans.

Vet Biotechnology Pty Ltd is licensed with the Australian Pesticide and Veterinary Manufacturers Association (APVMA) for the use of stem cell therapy for tendon and ligament injury in horses, whilst Sydney based Regeneus Animal Health Pty Ltd has commercialised an adipose tissue based stem cell procedure (AdiCell™) for the treatment of arthritis in dogs.

Private company BlueChiip Pty Ltd is developing and trialling unique technology with specific application in cryogenic storage data and management and retrieval.

Other Australian and international companies associated with clinical trial design and delivery, as well as contract testing and manufacturing service provision, are discussed in section 5.1

4.2. International Market Participants

Internationally, cell therapy technologies have primarily been developed through academic research laboratories, or in association with such institutes. The model is the same within Australia. The reasons for this are multiple, and may include

³³ *ibid*

patient access, clinical trial infrastructure availability, less expensive regulatory compliance models, or no obvious commercial model for specific illness or injury.

In a review of US patent trends in stem cell technology from 2000-2008, 218 patents were reviewed and 74% of all patents were assigned to US entities. Canada held 4.6%, Japan 3.2% and Israel 2.8%. Australia represented 0.9% of US stem cell patents during this time.³⁴

For this same period, only 17 companies were assigned 2 or more stem cell patents in the US. Of these companies, Geron Corporation (16 patents) and Osiris Therapeutics (25 patents) have developed the most significant intellectual property portfolios and are active in clinical applications. Other companies with significant IP holdings developed during this period were Advanced Cell Technology, Anthrogenesis Corporation, Neurosphere Holdings Ltd, PharmaStem, and ViaCell Therapeutics.

Table 1 identifies some key international companies pursuing cell therapies and/or associated technologies. The majority of companies seeking to commercialise cell therapy and supporting technologies are located in the USA and are primarily small to medium size enterprises. Very few companies are publicly listed at this time. Whilst this table is not a comprehensive list of all global cell therapy firms, websites such as www.stem-cell-companies.com and www.stemcellresources.org offer updates of emerging firms and brief overviews.

It is of note that big pharma have maintained both an interest and an active involvement in the emerging cell therapy space. A common participation model has been through drug screening with collaborative specialist cell technology organisations. GlaxoSmithKline donated US\$25 million to the Harvard Stem Cell Institute in July 2008; Pfizer have announced collaborations with the University of Wisconsin Alumni Research Foundation (use of human embryonic stem cells), University College London (stem cell ophthalmic conditions) and US\$100 million for a new Pfizer Regenerative Medicine institute in Cambridge, England, as a sister to their existing regenerative medicine facility in Massachusetts, USA, all during the past two years; in 2008 Roche announced a collaboration with Cellular Dynamics International (USA) for cardiotoxicity testing of compounds as well as a formal collaboration with the UK Stem Cell Consortium (SC4SM). Those big pharma companies involved in cell therapy activity have considered it necessary to make corporate position statements regarding their strategic involvement in the technology whilst acknowledging potential broader community concerns regarding ethical issues.^{35, 36}

Table 1: Some Key Global Cell Therapy Companies

Company	Cell Products / Technology	HQ	Website
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³⁴ Munevar, S (2008). *op cit*

³⁵ Roche (2009). Roche Position on Human Stem Cells and Cloning, May 12, 2009
<http://www.roche.com/stem_cell_research_position_paper_09.pdf>

³⁶ Pfizer (2009). Pfizer's Stem Cell Research Policy
<www.pfizer.com/responsibility/research_clinical_trials/stem_cell_research.jsp>

Aastrom Biosciences Inc	Platform manufacturing technology enabling production of autologous stem cell products for tissue regeneration from a small sample of bone marrow.	USA	www.aastrom.com
Celgene Corporation	PDA001 is a novel culture expanded stem cell population with therapeutic potential in oncology, immunology, inflammation and hematology. Biovance and Acelagraft are wound coverings derived from amniotic membrane. Celgene owns LifebankUSA.	USA	www.celgene.com
Advanced Cell Technology Inc	Research into blastomeres, cellular reprogramming and stem cell differentiation. Retinal pigmented epithelial cell, hemangioblast cell and myoblast programs underway.	USA	www.advancedcell.com
BeFutur Biotechnologies SA	Developing novel autologous stem cell culture mediums and methods with initial focus on cosmetic market (keratinocytes).	Switzerland	www.befutur.com
BioTime Inc	Sell human embryonic progenitor cells and media. Subsidiary Embryome Sciences has proprietary vector free iPS technology.	USA	www.biotimeinc.com
Cellartis AB	Human embryonic stem cells for drug discovery, toxicity testing and regenerative medicine. Aim to develop hepatocytes and cardiomyocytes from these cells. Key products: mesenchymal progenitors, cardiomyocyte clusters, hepatocyte like cells and stem cell antibodies.	Sweden / United Kingdom	www.cellartis.com
Cellerix SL	Ontaril - expanded mesenchymal stem cells obtained from adipose tissue for treating perianal fistulas. Cx501 - allogeneic fibroblasts and autologous keratinocytes for treating epidermolysis bullosa.	Spain	www.cellerix.com
Cellerant Therapeutics Inc	Developing cell-based medicine (Myeloid Progenitors / CLT-008) as a treatment for chemotherapy- and radiation-induced neutropenia and Acute Radiation Syndrome. Applying expertise in hematopoietic ontogeny to identify novel drug targets and therapeutic antibodies aimed at cancer stem cells.	USA	www.cellerant.com

CellGenix Technologie Transfer GmbH	Develops, manufactures and markets cell and protein therapeutics for cancer & orthopedic patients. Owns CellGro Ex Vivo Cell Processing Tools (Kits, Cytokines, Media, Bags); CartiGro ACT (Autologous Chondrocyte Transplantation); and Metreon UCB (Umbilical Cord Blood Banking Services).	Germany	www.cellgenix.com
CellResearch Corp Pte, Ltd.	Provides primary cell strains, culture media and contract research services. Includes umbilical cord stem cells, and normal skin, keloid scar and hypertrophic scar derived cells.	Singapore	www.cellresearchcorp.com
CellTran, Limited	Myskin™ is a cultured autologous epidermal substitute for the treatment of burns, ulcers and other non-healing wounds and contains autologous cells expanded from a small skin biopsy. Lyphoderm consists of a total lysate derived from cultured human keratinocytes providing a natural complex of growth factor activity.	United Kingdom	www.celltran.com
Cytori Therapeutics Inc	Family of products designed for the extraction and concentration of stem and regenerative cells from adipose tissue, including Celution®, computerised medical devices and cell processing reagents. Sponsoring heart disease and reconstructive surgery trials in Europe.	USA	www.cytoritx.com
EmCell	Performed more than 5,000 transplantations of embryonic stem cells for various diseases.	Ukraine	www.emcell.com
ES Cell International Pte, Ltd.	Development of manufacturing processes for hES cells and their progeny. Owns 6 of the 21 hES cell lines currently listed on the US National Institutes of Health. Subsidiary CellCure Neurosciences (Israel) involved in development of neural technology derived from hES.	Singapore	www.escellinternational.com
Gamida Cell Ltd	Haematopoietic progenitor cell expansion technologies and therapeutic adult stem cell products, from umbilical cord blood and bone marrow. Targeting leukaemia / lymphoma, metabolic diseases, myocardial infarction recovery and peripheral vascular disease.	Israel	www.gamida-cell.com
GE Healthcare	Range of cell culture products, including WAVE Bioreactor.	USA	www.gehealthcare.com

Genzyme Corporation	Epicel® cultured epidermal autografts for severe burns; Carticel® autologous chondrocyte cell therapy for knee cartilage repair; MACI® matrix-induced autologous chondrocyte implantation for cartilage repair. Research into cell and gene therapies, initially cardiac.	USA	www.genzyme.com
Geron Corp.	Biopharmaceutical & hES therapies. GRNOPC1 glial cells for spinal cord injury; GRNCM1 cardiomyocytes; GRNIC1 islets; and chondrocytes, osetoblasts and hepatocytes. Also cellular assay products derived from hESCs for use in drug discovery, development and toxicity screening (partnered with GE Healthcare).	USA	www.geron.com
GlaxoSmithKline	Use adult, foetal, embryonic and iPS stem cells in own research and in collaboration with external partners. Donated US\$25m to Harvard Stem Cell Institute.	United Kingdom	www.gsk.com
Histogen Inc	Newborn fibroblasts placed in simulated embryonic environment so fibroblasts produce an Exceltrix™ material with proteins and growth factors used to make up ReGenica™ (for skin care) and Hair Stimulating Complex. BioNuesis - all-human soluble extracellular matrix, culturing kit for stem cell growth.	USA	www.histogeninc.com
Histostem Co., Ltd.	Stem cell provider, specialising in Multi-Lineage Progenitor Cell research, treatment of disease and injury, and banking of stem cells.	South Korea	www.histostem.co.kr
Intercytex Group plc	VAVELTA® - suspension of human dermal fibroblasts for skin rejuvenation; ICX-SKN - <u>allogeneic</u> human dermal fibroblasts for skin graft replacement and hair regeneration; cyzact® - <u>allogeneic</u> human dermal fibroblasts for topical woundcare; developing retinal implant to treat macular degeneration - retinal pigment epithelium cells derived from human embryonic stem cells mounted on a synthetic membrane.	United Kingdom	www.intercytexas.com
Lonza	Process development, manufacturing & commercialisation services for cell-based therapeutics.	Switzerland	www.lonza.com

Living Cell Technologies Ltd	Encapsulated porcine islet cells for diabetes treatment (DIABECCELL®). Choroid plexus cells for degenerative diseases (NTCell®). Encapsulated porcine liver cells to produce Factor 8 in haemophiliacs (Fac8Cell®).	Australia	www.lct.com.au
Mesoblast Ltd	Adult stem cells for regeneration of bone, cartilage and discs. Part owns Angioblast Systems Inc, targeting cardiac, vascular and eye conditions. Both using proprietary mesenchymal stem cell isolation technique.	Australia	www.mesoblast.com
MediStem Inc	Adult stem cell extraction and manipulation for use in treating inflammatory and degenerative diseases - developed a novel type of stem cell, the Endometrial Regenerative Cell. Initially targeting critical limb ischemia & angiogenesis.	USA	www.medisteminc.com
Multicell Technologies Inc	Holds unique cell-based technology for use in drug discovery screening applications and production of therapeutic proteins, and is producer of immortalised human hepatocyte cell lines.	USA	www.multicelltech.com
Neuralstem Inc	Technology for isolation of human neural stem cells from tissue, expansion <i>in vitro</i> up to a billion billion times, and controlled differentiation into mature human neurons and glia. Aim to create cures for diseases of the CNS.	USA	www.neuralstem.com
Novathera Ltd	Licensed novel process technology enabling rapid and defined scale-up of stem cell culture and controlled and directed differentiation of both murine and human embryonic stem cells into Type II Pneumocytes.	United Kingdom	www.novathera.com
Novocell Inc	Cell encapsulation technology to protect transplanted cells. Use directed differentiation to engineer human embryonic stem cells and generate therapeutic cell types, including endoderm and insulin-producing cells. Exploring cancer stem cells to create good targets for discovery of novel cancer drugs. Drug discovery assays for regenerative medicine and drug ADME/ toxicity prediction using liver and intestinal cells.	USA	www.novocell.com

NsGene A/S	EC Bidelivery™ – drug delivery technology using genetically modified encapsulated cells to secrete therapeutics directly into the brain over a prolonged period of time.	Denmark	www.nsgene.dk
Odontis Ltd	Developing a biological replacement tooth product using stem cells (BioTooth™).	United Kingdom	www.odontis.co.uk
Organogenesis Inc	Maintain cell bank; developed automated closed bio-reactor system for advanced cell manufacturing; Apligraf® technology is contracted collagen gel matrix with living keratinocytes and fibroblast cells for skin healing; VCT Cellular Matrix for surgical repair and regeneration applications; CellX™ is a cellular construct designed to deliver living cells to regenerate oral soft tissue.	USA	www.organogenesis.com
Osiris Therapeutics	Use adult mesenchymal stem cells from bone marrow – Prochymal for GvHD, Crohn’s, cardiac, COPD, diabetes and ARS; and Chondrogen for osteoarthritis of the knee.	USA	www.osiristx.com
Pfizer	Opened regenerative medicine units in USA and England and announced US\$100m investment into stem cell research. Has collaborations with cell therapy developers.	USA	www.pfizer.com
PharmaStem Therapeutics Inc	Pioneer in development of umbilical cord and placental blood preservation for therapeutic use. Licenses technology to cord blood banks and promotes R&D.	USA	www.pharmastem.com
Pluristem Therapeutics Inc	Allogeneic cell therapy products, derived from human placenta, for the treatment of ischemic & autoimmune disorders. PluriX™ 3D Bioreactor - system of stromal cell cultures and substrates.	Israel	www.pluristem.com
Progenitor Cell Therapy LLC	Supports the development of cellular therapies by providing cG(x)P-compliant cell manufacturing and consulting services.	United Kingdom	www.progenitorcelltherapy.com
ReNeuron Group plc	Stem cell expansion and screening technology, <i>c-mycER</i> . Encapsulation technology, <i>micmac</i> ®. ReN001 neural cell therapy initially for stroke. Cell lines for non-therapeutic research licensed to Millipore - <i>ReNcell</i> ®VM neural cell line derived from ventral mesencephalon region of the brain; <i>ReNcell</i> ®CX is derived from the cerebral cortex.	United Kingdom	www.reneuron.com

Hoffman - LaRoche	Collaboration with UK Stem Cell Consortium to create stem cell repository for toxicology testing and high throughput platforms. Collaboration to test candidate drugs for cardiotoxicity using cardiomyocytes derived from hES.	Switzerland	www.roche.com
SinoCells BioTechnologies Co. Ltd	Cord blood stem cell processing & banking and related laboratory testing services. Also researching ex vivo expansion of HSC and directed differentiation of MSC.	Taiwan	www.sinocell.com.tw
Stem Cells Inc	Cell based therapeutics targeting CNS and liver. HuCNS-SC® cells (purified human neural stem cells), specialty cell culture media products (SC Proven®), and developing cell-based technologies for use in drug discovery and development.	USA and United Kingdom	www.stemcellsinc.com
Stem Cell Therapeutics Corp.	Developing agents to stimulate patients' neural stem cells in situ to proliferate and differentiate to regenerate lost, damaged or diseased tissue. NTx-265 to treat stroke, NTx-428 for traumatic brain injury and NTx-488 for multiple sclerosis.	Canada	www.stemcellthera.com
Stemride International Ltd	Offers human Embryonic Stem Cell lines and provides training and consulting. Has a bank of more than 100 ordinary lines and more than 80 lines with genetic or chromosomal abnormalities for 23 conditions. Closely affiliated with the Reproductive Genetics Institute.	United Kingdom	www.stemride.com
TheraVita Co, Ltd.	Currently using VesCell™ adult stem cell therapy to treat patients with heart disease and peripheral artery disease, but trials for wide range of chronic and acute illnesses. Cells expanded from blood sample.	Thailand	www.theravita.com
Thermogenesis Corp.	Systems for processing, preparation, and preservation of cord blood and stem cells, including automated platforms. Subsidiary Vantus Inc. provides veterinary stem cell laboratory service.	USA	www.thermogenesis.com
TriStem Corporation	Retrodifferentiation technology offers potential to prepare large quantities of autologous stem cells. Initially evaluating clinical potential in aplastic anaemia, thalassemia and leukaemia.	United Kingdom	www.tristemcorp.com

ViaCell Therapeutics	Cord blood banking service. Separate institute researching increasing cell count and yield, emerging stem cell therapies (diabetes & cerebral palsy), maternal / neonatal genetic screening, and improved cell transplant outcomes.	USA	www.viacellinc.com
VistaGen Therapeutics	ES cell technologies for discovery and validation of disease- drug targets and pathway-specific proteins that are potential biological drug molecules. Focusing on high-throughput drug discovery screens in the diabetes and neurological disease markets. Technology provides predictive human heart and liver cell assay systems for pharmaceutical toxicity testing.	USA	www.vistagen.com

5. Australian Infrastructure

5.1. Cell Therapy and Related Research and Production Infrastructure

There are approximately 70 institutes working in the Australian cell therapy sector, characterised by their activities in biomaterials, nanotechnology, cell/tissue banking, clinical trials (including preclinical), medical research, manufacturing and/or screening.

A discussion of significant current infrastructure in each State is discussed in the following section relating to new and recent development.

5.2. New Facility Development and Plans

There are a number of recently established, work-in-progress and approved cell therapy facilities across Australia.

The following list includes information obtained through both the survey and interview, however it should not be considered exhaustive.

5.2.1. *Western Australia*

Western Australia's health infrastructure is in a state of flux, given the review undertaken by the incumbent government when recently elected. The former State Government had initiated a reform of health infrastructure in Perth, with the closure of Royal Perth Hospital and relocation of entities to either the newly approved Fiona Stanley Hospital adjacent to Murdoch University, or to the Charles Gairdner Hospital campus in the city. The current government has reviewed aspects of the rationalisation with parts of the Royal Perth Hospital now remaining in place. Significantly, the Cell and Tissue Therapies cGMP laboratories at Royal Perth are unclear of their destination. Provision has been made in the footprint of the proposed Fiona Stanley Hospital. Until plans at Royal Perth are finalised, it is possible Cell and Tissue Therapies may end up with a bigger footprint at their current site. This would be a preferred scenario so as not to impact cGMP facility licenses and associated infrastructural commissioning. Some facility support services such as pathology will be relocated.

A feasibility study on the construction of a regenerative medicine and contract manufacturing facility was undertaken in recent years for the former State Government. The strategy paper is under reconsideration by the new government.

Of significance to the State has been the announcement by Verigen Australia, a subsidiary of Genzyme, that they will expand their cGMP manufacturing activity to a new greenfield site with commissioning expected in late 2010.

The former State Government was instrumental in funding the Orthocell cGMP

facility, adjacent to Murdoch University. It is unclear if the facility has retained its cGMP status and is still available for contract service activity.

5.2.2. South Australia

The University of Adelaide Robinson Institute's Centre for Stem Cell Research was opened in September 2008. It is a collaborative initiative comprising 18 mature research groups located in the Faculties of Sciences and Health Sciences, the Hanson Institute, the Women's and Children's Hospital, the Institute of Medical and Veterinary Sciences, the Queen Elizabeth Hospital and the Royal Adelaide Hospital. The focus of the centre is on translating basic research into clinical and commercial outcomes via collaboration with external partners.

Its members undertake internationally recognised research in bone marrow, neural, periodontal, ovarian and cord blood stem cells and their potential applications in stroke repair, cardiac repair, tissue repair (dental, muscle, cartilage), cystic fibrosis, lysosomal storage and other inherited disorders, as well as transplantation medicine, developmental biology, immune diseases and leukaemia.

The BioSA Incubator, was opened in June 2008 to fast-track the growth of local bioscience companies. The state-of-the-art, purpose-built building provides modular office and laboratory space to accommodate 6 early stage bioscience companies.

In June 2007, the South Australian Government announced its commitment to invest \$1.7 billion over the next decade to build a new state-of-the-art central city hospital to replace the ageing Royal Adelaide Hospital. The hospital will also house some of the more complex services from the Queen Elizabeth Hospital and is expected to bring opportunities for other developments, including research and education. It is currently unknown if the hospital will house any direct or indirect cell therapy infrastructure.

5.2.3. Victoria

The Victorian Government is an active supporter of medical research and has invested some \$3 billion in State innovation programmes since 1999.³⁷ In addition to capital infrastructure, the government recognises the importance of operational infrastructure support as evidenced by the August 2009 announcement of a disbursement of \$25.7 million in grants to 13 Victorian medical research institutes.

On 3 September 2009, the Victorian Minister for Innovation, launched the \$25 million Victoria's Science Agenda (VSA) Strategic Project Fund. This new program will support the acquisition of world class research facilities and equipment, the advancement of high level skills and the development of next generation technologies. The Strategic Project Fund will provide a competitive round of funding aimed at establishing new science and technology capabilities to solve major challenges faced by Victoria in the

³⁷ Evans, N (2009). "Vic grants \$25.7 m to medical research". BiotechnologyNews.net, 27 August 2009

areas of health, sustainability, and productivity. Applications are invited from universities, research institutes, co-operative research centres and government agencies. Partnerships with technology companies are also welcomed.³⁸

Significant recent infrastructure developments in Victoria also include the establishment and opening in April 2009 of the Australian Regenerative Medicine Institute (ARMI) at the Science Technology Research Innovation Precinct (STRIP) of Monash University's Clayton campus. ARMI is a \$153 million facility, established through a joint venture between Monash University and the Victorian Government, with allocated funding from the federal government. The Institute claims, at full capacity, to be one of the world's largest regenerative medicine and stem cell research centres with an objective of pursuing rapid commercial transfer for its technologies.

Over recent years a significant amount of cell therapy and associated infrastructure has been located at Monash University's Clayton campus (www.bioplatforms.monash.edu.au). This includes the Australian Stem Cell Centre, the Monash Immunology and Stem Cell Laboratories (MISCL), Monash Institute of Medical Research, the Flow Cytometry Core Facility (FlowCore), the FishCore Facility (part of ARMI), the Monash Animal Research Platform (MARP) and Monash Micro Imaging (MMI). This strategic location, adjacent to the CSIRO Division of Molecular Health and Technologies (MHT) at Clayton, has led to the facilitation of a number of alliances including the South East Melbourne Alliance for Regenerative Therapies (SMART), and a new co-joint facility to be built on the Monash campus, the Melbourne Centre for Nanofabrication (MCN). The MCN has been designed to be an open access, world class bio-nano fabrication capability focused on health and environmental applications. It will comprise a national facility, integrated with local sub-node facilities housed within the MCN partners - CSIRO, RMIT University, MiniFAB (Aust) Pty Ltd, Swinburne University, Small Technologies Cluster Pty Ltd, La Trobe University, the University of Melbourne and Monash University. Its funding will be provided by NCRIS, the State Government and the project proposal partners. The facility will include cGMP and PC2 clean room capability.

The federal government has recently announced the funding of \$71 million for a new Translational Research Facility at the Monash Health Research Precinct in Clayton with partners Monash University, Southern Health, Prince Henry's Institute and Monash Institute of Medical Research. The facility, designed to expedite laboratory to clinic research is to be completed in 2012.

Additionally, non-cGMP cell culture and processing capability is being established through the NCRIS facilitated CSIRO MHT and Monash University Centre for Green Chemistry at Clayton.

Current construction at the Murdoch Children's hospital in Melbourne has revealed the potential availability of redundant cGMP clean room capability due to an alteration in research focus.

³⁸ Biotechnology Victoria e-bulletin, September 2009

It is noted that the Small Technologies Cluster at the Caribbean Park, Scoresby (near Clayton), where MiniFAB are located, also has redundant laboratory and clean room capability.

Of specific interest in Victoria is the development of a \$1 billion world class Comprehensive Cancer Centre at Parkville, bringing together the Peter MacCallum Cancer Centre, the Ludwig Institute for Cancer Research, the Royal Melbourne Hospital, the University of Melbourne, the Walter and Eliza Hall Institute of Medical Research and the Royal Women's Hospital in co-located facilities. The complex, planned for completion in 2015, will see the total relocation of the Peter MacCallum, and associated Cell Therapies cGMP processing capability. The new Cancer Centre is expected to have 194 in-patient beds, 110 same day beds, and a clinical trials facility with 24 treatment places. The site will include 30,000 metres² of research space capable of accommodating up to 1,400 researchers.³⁹

Work has begun on constructing the Austin Neuroscience Facility at the Austin Hospital in Melbourne. The \$45 million neuroscience building is the first stage of the \$225 million Australian Centre for Neuroscience and Mental Health Research that will bring together recognised world leaders in epilepsy, stroke, Alzheimer's disease and brain-imaging. It will house staff from the Florey Neuroscience Institutes, the University of Melbourne and the Mental Health Research Institute. The Victorian Government is contributing a total of \$53 million to the centre with the Australian Government committing \$77 million.⁴⁰

RMIT University's Advanced Manufacturing Precinct has been recently launched and will deliver cross-disciplinary training to meet whole-of industry needs by incorporating teaching in engineering and advanced manufacturing technologies, applied design, development, production, marketing and management. Activities will include rapid prototyping and manufacturing, computer integrated manufacturing including automation and systems integration, computer numerically controlled manufacturing and testing of products and materials.⁴¹

5.2.4. New South Wales

Macquarie University in North Ryde, Sydney is close to opening its on-campus private hospital (150 beds). The facility is expected to be a combined patient care, research and teaching hospital with specialisations in cognitive neuropsychology, telemedicine and teleradiology, speech therapy and audiology. The hospital is expected to enhance the capabilities of spinal research with a new Centre for Spinal and Medical Imaging.⁴² Whilst there is currently limited cell therapy capability at Macquarie, the new facility is likely to increase local support services in medical imaging and neurological disease / injury. ASX listed

³⁹ Victorian Government (2009). Press Release: World Class Cancer Centre to be built in Parkville, 7 May 2009

⁴⁰ Australian R&D Review (Sept 2009) *op cit*

⁴¹ *ibid*

⁴² Macquarie University (2006). Press Release: New Hospital on Campus, October 2006

audiology devices company Cochlear Ltd is relocating to the site. Cochlear are actively involved in biomaterials R&D for their implantable medical devices.

The Prince Alfred Hospital's Cell and Molecular Therapies facility has licensed aphaeresis and bone marrow transplantation services. A GMP laboratory is under construction and due for completion in early 2010. It is expected to include cleanrooms with PC2 (recombinant technology level) to support clinical trials and will be dedicated to selection, expansion, transduction and other aspects of human cell manipulation.

The Australian Red Cross Blood Service has announced the planned development of a more modern and larger facility to house all its New South Wales services under one roof, including the supply and testing of blood and blood product, as well as organs and tissues for transplantation. The organisation will relocate from its Clarence Street operations to a new four storey laboratory and office building with warehouse and distribution facilities at O'Riordan Street, Alexandria. An initiative to establish centralised cell therapy facilities within this new complex for Sydney based stakeholders failed to gather support.

The Millenium Institute at Westmead Hospital is planning a potential expansion. Any associated expansion is likely to incorporate a new cell therapy capability in support of those current node facilities located at Westmead for gene therapy and separately, pancreatic islet processing and transplantation.

The University of New South Wales' recombinant products facility has been the recipient of NCRIS funding and has a cell culture capability which is non cGMP associated.⁴³

5.2.5. Queensland

Along with Victoria, Queensland has seen a rapid increase in medical research infrastructure investment in recent years. New facilities located at the University of Queensland and actively involved in cell and tissue therapy R&D include the Institute for Molecular Bioscience (IMB) founded in 2000, the Queensland Brain Institute founded in 2003 and the Australian Institute for Bioengineering and Nanotechnology (AIBN) founded in 2007 as a \$70 million multidisciplinary facility, funded by both philanthropic, State Government and university funds.

The Griffith University, Nathan campus is home to the Eskitis Institute for Cell and Molecular Therapies, a \$30 million facility funded by State and Federal government funding and established in 2003. The National Centre for Adult Stem Cell Research, the Queensland Compound Library (reputedly Australia's largest collection of bioactive compounds), and the Queensland node of the Co-operative Research Centre for Cancer Therapeutics are all located at the Eskitis.

Queensland University of Technology has recently established the Institute of Health and Biomedical Innovation (IHBI), located at the Herston Campus.

Over the last two years the Orthopaedics and Trauma Queensland group of IHBI have rapidly developed a significant team of orthopaedic regenerative and

⁴³ UNSW Recombinant Products Facility (2009). Website <www.proteins.unsw.edu.au> Viewed 10 September 2009

biomaterials researchers, international industry collaboration and international benchmark infrastructure. Significant experience resides in 3D cell culture biomaterials. Facility infrastructure includes the commissioning of the Medical Engineering Research Facility (MERF) in late 2008 at the Prince Charles Hospital, Chermside, which incorporates large scale animal, imaging, surgical implantation and testing capability.

Scientists at QUT's IHBI, the Mater Medical Research Institute, the University of Queensland and Prince Alfred Hospital will join one of the southern hemisphere's largest medical research institutes, a \$354 million Translational Research Institute (TRI) to be built at Princess Alexandra Hospital, Brisbane. Funding sources have included the Commonwealth Government (\$140 million), the Queensland State Government (\$100 million) and a US based philanthropic group (\$50 million). The proposed seven storey institute will be 32,000m², with four storeys of laboratory space, housing up to 700 researchers. The facility is considered to be one of the few international facilities capable of taking new biopharmaceutical discoveries through production, clinical testing and manufacture. A cGMP manufacturing facility is expected to be built adjacent to the main building. The TRI is expected to focus on the areas of cancer, traumatic injury and wound healing.^{44,45} Relocating to this new facility will be the Mater Medical Research Institute's haemopoietic stem cell transplantation team.

Queensland Institute of Medical Research (QIMR) has recently signed contracts for the construction of a new 13 storey research facility, the Smart State Medical Research Centre (SSMRC). The facility will house 20 new research laboratories and increase staff by more than 60% to near 1200 researchers at QIMR. It is expected the new capability will be focussed on mental illness including neurodegenerative disease, indigenous health, tropical health, cancer and genetics research. The facility is located on the QIMR campus at Herston and will be commissioned in 2012.

⁴⁴ Queensland University of Technology (2009). New Institute fast tracks research to patients, Inside QUT, August 2009, 296; 3

⁴⁵ PA Foundation (2009). PA to become home of Australia's flagship medical research facility. PA Foundation Newsletter, 2;3

6. Emerging Industry Needs

6.1. Emerging Trends and Technologies

6.1.1. *Social Observations*

There are a number of drivers associated with the direction and speed of adoption of emerging cell therapy technologies. These include public awareness, the regulatory landscape, translational research funding, infrastructural access and overcoming the technology challenges.

Cell therapies and associated regenerative medicine represent an exciting area of scientific endeavour with immense potential to remediate illness from genetic disorder, disease and/or injury. There has been considerable community support and expectation of the benefits of these technologies, especially stem cells. Yet, there has also been significant debate about cell therapies associated with the use and misuse of human embryonic cells and international governments have legislated to curtail aspects of cell therapy R&D due to ethical concerns from influential political, cultural and religious pressures. The human therapeutic applications of gene therapies have also been stalled over a number of years due to concerns about safety. A significant boost has been given to embryonic stem cell research with the new US Obama administration's recognition and approval for federal government funding for such research.

The debate has been divisive. Cell therapy technologies must engage with the general public or risk alienation through ignorance. The majority of the Australian population will have completed their scientific education by 16 years of age, and left school before learning about the scientific principles behind modern biology and biotechnology - yet these people and their families are the ones the sector must seek to invest in the technology with their funds, faith or even their lives. The technology developments are exciting and the circumvention of ethical issues have inspired scientific endeavour. The community must be engaged through informed debate and information. The genetic modification of food crops is a case example where public opinion was not adequately engaged and this has stalled the technology progress. It is interesting to observe the many approaches taken to inform and reposition public opinion with regard to current medical technologies; reality television programmes such as RPA and The Gift have provided powerful communication vehicles to the general public with a candid technical transparency.

On the flip side of low awareness are those, still often ignorant of the technical issues, who are confronted with life threatening or altering illness and who are keen to embrace any opportunity or hope for remediation. The internet advertises opportunities for cell therapy treatments claiming a range of remedial benefits, thus spawning the growth industry of "therapy tourism". Annually, many Australian therapy tourists visit regions including China, Eastern Europe, South and North America for promised treatments either as part of clinical trials, or on a fee for service basis. Unfortunately, not all such facilities understand or explain their technology fully, or maintain acceptable levels of good clinical or

manufacturing practice. More specifically, those patients receiving allogeneic treatment of cells or tissue from poorly characterised sources may receive more imminent or compounding life threatening illness to that for which they were seeking treatment. Such therapy tourists, as with most clinical trial patients, have undertaken extensive state of the art western therapy with resultant challenged immune systems. The scientific outcome for such therapy tourists can be unclear, with the psychological benefit of more value. Poor outcomes and prognoses from therapy tourism have the ability to alienate public opinion and cast the technology in a poor light. It is important that the sector develops credible, media spokespeople that are knowledgeable of the sector and its broader issues.

6.1.2. Regulatory Issues

Australia has adopted a cautious approach regarding the regulation of cell therapies, noting the position of other international state entities. The US FDA has focussed on the safety and communicable disease risk elements of cell transplant, de-emphasizing the product identity and efficacy standards associated with traditional pharmaceutical.⁴⁶

The protracted decision making by the TGA in providing clear guidance for cell and tissue therapy regulatory expectation, both at a development and a commercial level, has led to apparent sector confusion. Those researchers working with blood and bone marrow raw materials have greater clarity through historical experience. Researchers are concerned with the lack of regulatory and ethical guidance when it comes to helping define adequate preclinical models before seeking human Phase I/II safety and efficacy clinical trials. Most preclinical work is performed in rodents, where there are some very good mouse models of some human illnesses and for which NCRIS is funding resource development. The advised requirement for larger animal studies in dogs, pigs and/or primates has left some researchers confused about the likely technical value, resource availability and funding source.

Further, it is noted that many of the facilities which claim to have cGMP capability do not have a TGA licence, and some that do, appear to operate a business model which is not consistent within cGMP for the pharmaceutical and biotechnology sector. This may be due to the TGA having physically separate inspection groups – one located in Canberra for pharmaceuticals and one located in Melbourne for blood and tissue products. Sector experience of staff and code interpretation are undoubtedly different for each group. It is doubtful that a “virtual” cGMP facility model would be accepted internationally to be cGMP compliant, yet we see this model in the cell and tissue sector. A virtual model is considered to have little direct investment, making use of contracted staff and services. Such virtual cGMP facilities may have appropriate documentation, perhaps a Quality Manager and operating staff who are project seconded on an as needs basis from other (associated parent facility) responsibilities. Such a model does not allow for establishment of appropriate training and core cGMP cultural development; particularly if such staff primarily fulfil R&D functions where the focus on prescriptive adherence to written instruction, extensive

⁴⁶ Preti, R (2005). “Bringing safe and effective cell therapies to the bedside” *Nature Biotechnology* Volume 23, No.7, July 2005.

documentation, repeat training, extensive traceability, acknowledgement of deviation, and extensive validation of process/ equipment/facility are not characteristic work qualities. The argument for maintaining a virtual cGMP facility model, “that staff are too difficult to get in the public healthcare, or medical research sector”, is neither plausible nor consistent with those requirements for corporate cGMP contract service providers.

It is likely that the TGA are taking a developmental approach to the sector in their cGMP awareness raising; clinical trials, particularly early stage trials, being less prescriptive and recognising the deficiency of certain infrastructure or practice, with remediation timeliness as a function of risk. It is important that those current cell therapy facilities with cGMP licences, and those seeking manufacturing licences, understand that regulatory expectations and hurdles will likely significantly increase. It will be necessary for the TGA to ensure that no perceived expectation gap exists between “blood and tissue products” with other “pharmaceutical” cGMP facility operations, despite the obvious risk differences from personalised, low volume processing. One could expect pharma seeking reach back of expectations, and Australia’s TGA being perceived as not fulfilling its international reciprocal cGMP treaties; something the organisation and industry have both worked hard to achieve. If one extrapolates the thinking that Blood and Tissue Product cGMP facility requirement increases, then it is likely that appropriate full time quality teams (management, assurance, validation, documentation, training, environmental monitoring, release) and production staff will be required, with commensurate workflow to justify the expense and overheads. Such a development may lead to more centralised cGMP facilities than even currently exists. It should be noted that nearly 60% (n=41) of survey respondents preferred a centralised model of services, equipment and infrastructure into strategic national sites.

There will be instances where facility centralisation may not be feasible and hospital co-location is imperative. The TGA has delegated clinical trial regulatory compliance to hospital Human Research Ethics Committees. It is unclear if such committee’s have an obligation to maintain a cGMP manufacturing professional on their committee or as an advisor. One would expect such an initiative should become introduced.

6.1.3. Funding of R&D and Market Access

It was recently reported that there is a one in five chance of being successful in receiving an ARC Discovery Project grant, and that if one is successful in receiving any type of competitive grant, be it ARC or NHMRC, it will cover about two thirds of the research costs only, with no funds for indirect costs of research. Whilst the federal government is seeking to partially redress this issue, it is recognised that the UK and USA fully fund indirect costs.⁴⁷ The cell therapy R&D sector’s almost sole reliance on such grants is disconcerting. Putting aside the competitiveness and completeness of funding issues, of particular concern is the availability of funding for translational clinical trial development. One quarter (25%, n=32) of survey respondents were very dissatisfied with the

⁴⁷ Symonds, A (2009). Win a grant..but lose money. The Australian Financial Review, 31 August 2009

current availability of translational research support. This must be addressed for cell therapy technology development to thrive. Additionally, research groups may need to become more creative in their funding options; for example by establishing spin out companies housing technology and IP, and so becoming vehicles for broader funding options (e.g. Innovation Investment Fund).⁴⁸ Institutes could also develop more targeted philanthropic capital raising. Of course, this does mean that researchers who choose a commercial path will be required to give or contribute to far greater thought regarding commercialisation models. The survey suggested less than one third of respondents (32.1%, n=28) have considered the potential models for commercialisation of their technology in any detail, with a further 17.9% having given the process some general thought only. This leaves 42.9% of respondents participating in cell therapy R&D with no clear idea of how they will turn their technologies into commercially sustainable propositions.

Two emerging trends, borne from commercial drivers in a currently developing regulatory environment, are those of animal stem cell therapy and cosmetic stem cell therapy. Animals, such as dogs and horses, are being treated and are able to take advantage of reduced clinical trial regulatory hurdles; both representing reduced time and cost to market with tangible commercialisation models. At least two significant, national research groups indicated an interest in pursuing a veterinary stem cell therapy direction.

AgResearch, in NZ have been working in production animal stem cell research for some years, exploring such desirable traits as increased muscle mass, increased wool follicles, lactation yield and deer antler development. Current work is focussing on optimising conditions for induced pluripotent bovine cells.⁴⁹ CSIRO are also involved in gene therapy for bovine species improvement.

Cosmetic surgery applications are emerging through the use of cosmetic reconstruction and /or tissue sculpting. The autologous redirection of adipose tissue from one body site to another, with or without processing, has the ability to be captured in cell therapy technologies and regulations. Similarly, the insertion of sterile injectable hydrocolloid matrices with subsequent cell adherence and tissue growth could be complicated by similar legislative hurdles.

6.1.4. Technologies

Trounson (2009)⁵⁰ recently highlighted the precarious state of human stem cell therapeutic research when noting the considerable data supporting safety of bone marrow and mesenchymal stem cell transplants, but variable efficacy data being of mixed benefit. He optimistically speculated on the increased flow of clinical trial data, in part being driven by the Obama administration's review and adoption of embryonic stem cell research, yet still cautiously predicting 5-10 years before suitable efficacy data would be available for therapeutic

⁴⁸ AusIndustry (2009) Website

<[http://www.ausindustry.gov.au/VentureCapital/InnovationInvestmentFundIIF/Pages/InnovationInvestmentFund\(IIF\).aspx](http://www.ausindustry.gov.au/VentureCapital/InnovationInvestmentFundIIF/Pages/InnovationInvestmentFund(IIF).aspx)> Viewed 11 September 2009

⁴⁹ InTouch (2009), AgResearch Issue 50, August 2009.

⁵⁰ Trounson, A (2009). "New perspectives in human stem cell therapeutic research" BMC Medicine 2009, 7: 29.

applications. Such caution was warranted as September 2009 was a reflective month for international stem cell research with clinical studies by embryonic stem cell company Geron halted by the US FDA following the detection of spinal cysts in laboratory animals, and Osiris Therapeutics announcing its stem cell treatment Prochymal found to be no more effective than the placebo in a late stage trial.⁵¹ Such results reinforce the technical challenges still to be addressed in the sector.

6.1.4.1. Induced Pluripotent Cells

Compared to embryonic stem cells, which are pluripotent, adult stem cells are multipotent and have a more limited capacity to differentiate into varying cells of the body. However, recent research has demonstrated that under certain conditions of induced pluripotency, adult stem cells may be reprogrammed to a more primitive, less differentiated state. Such induced pluripotent cells (iPS) have a greater ability for longer lasting self renewal and the capacity to differentiate into differing cells of the body. The implications of this technology are multiple and it has the potential to circumvent the perceived advantages of embryonic stem cells and associated broader community ethical concerns. In addition, there are logistical, technical and economical advantages of sourcing adult stem cells from anywhere in the body and being able to expand cell numbers in sufficient quantities for therapeutic use.

The reprogramming of iPS cells is still very early in the research phase and the technology may have associated downsides which have yet to be determined. These include long term function and storage.

6.1.4.2. Drug Screening

An emerging local trend, yet one which has been internationally prevalent with big pharma participation, has been the use of cell technologies in drug screening. The infrastructural equipment associated with such activity is expensive and relatively complex. Screening technologies, by virtue of their repetitive high throughput, make extensive use of robotic technologies. The Eskitis Institute at Griffith University is possibly the most significantly equipped Australian facility from both an infrastructural equipment perspective, as well as being home to a database of around 200,000 pre-fractionated extracts of drug-like compounds isolated from 40,000 samples of regional plant and marine origin. Additionally, the group has an established bank of approximately 200 adult stem cell lines derived from patients with neurologic disease. Neurologic disease strongly correlates with an ageing western population. Other national high throughput screening capabilities exist, including the Monash Institute of Medical Research's High Content Cell Discovery and Screening Facility (HCSF) which uses genome-wide RNAi libraries coupled with robotics. Such facilities as these are of national significance and it would be counterproductive to see new additional facilities established without reviewing current occupancy and appropriate cost benefit.

⁵¹ Australian Life Scientist (2009). "Trial failures a setback to stem cell therapies", 21 September 2009.

6.1.4.3. Drug-Cell-Device Products

Cell therapies lend themselves to many applications that involve other technologies. Such technologies have differing modes of delivery, from implantable devices to potentially inhaled nano-therapies. The regulatory framework for how such multi-modal developments will be handled is to be determined in Australia, given that cell therapies and medical devices have separate TGA regulatory bodies with differing expectations and modes of approval. One can assume that rigorous risk analysis will be a critical feature of regulatory submissions that should also embrace the regulator's input rather than seeking CTN approval vehicles. It is also likely that such pioneering products will incur higher regulatory costs in meeting undetermined regulatory expectations. One can also safely assume that any implantable or inhaled device will require full cGMP manufacturing capability.

6.1.4.4. Manufacturing Operations

Of specific interest to cell technology commercialisation has been the infrastructural implications from large scale uptake of these technologies. Some companies have been dedicating time to exploring how current skilled, labour intensive cell processing methodologies would occur within cGMP compliant clean room facilities under a highly escalated scale-up and scale-out scenario. A solution is closed system robotic processing within closed HEPA environment cabinets, with multiple independent cabinets each processing separate patients, and all housed within the one HEPA filtered room; what may currently require 20 clean rooms can be done with twenty cabinet units in one room.⁵² Along similar lines is the exploration of bioreactors as a mechanism to replace plastic ware flasks. Such large scale cell growth is not new technology, with significant cell culture scale having occurred in Australia at a number of contract service providers utilising low sheer tower bioreactors. The inevitable risk with bioreactors is the high cost of medium and high risk of contamination in slow growing cell lines. Bioreactor design is currently being revisited internationally and locally at AIBN, particularly given improved aseptic instrumentation and disposable connection devices developed since the early 1990s.

6.1.4.5. Traceability

A significant but little realised issue within cGMP processing is the traceability and origin of reagents, particularly those which represent risk. These include reagents of protein origin, particularly animal, and those reagents which come in contact with the active ingredient (i.e. cells). Thus, the use of animal derived culture media, such as bovine sera, represents significant risk unless procured and demonstrated to be unblended and sourced from Australia or New Zealand only. This is due to the risk of Transmissible Spongiform Encephalopathy (TSE) from European, Canadian and USA herds. The use of protein (enzyme) reagents, typically from bovine or porcine sources, is now considered to represent significant risk for *in vivo* application. It is a common mistake of scientists to buy and develop processes for *in vivo* application using *in vitro* specified reagents. The Australian Quarantine and Inspection Service (AQIS), who are responsible for approved import by suppliers, often approve imports with an "*in vitro* or lab

⁵² James, D (2009). Profit by Design. AusMedtech (Sydney) presentation, 27 May 2009

animal use only” application. The supplier is responsible for ensuring customer knowledge and adherence. Requests must be made to and granted by AQIS for *in vivo* approved use through the importer, and following extensive desk and/or physical reagent manufacturer audit. This is often an inordinately slow, expensive and cumbersome process with rejection more likely than approval. The outcome for researchers, usually at their cGMP contract facility, is to seek and use alternate reagents, which may not provide the level of cell growth expected. One international reagent company (SAFC) has attempted to circumvent this issue for its cell culture clients in Australia by initiating the manufacture of its key protein reagents locally. It is likely that other suppliers could follow, or alternatively develop and offer acceptable protein free or plant protein based reagents and media. The current regulatory environment requires such reagents to be listed as medical devices with listing on the ARTG. Ultimate risk group and requirements under the new TGA framework is to be determined.

6.1.4.6. Product Tracking and Storage

All facilities engaged in cell therapies have to contend with secure sample identification and tracking at low temperatures. Cell banking is now sophisticated and routine for larger biotech organisations that have multiple cells in storage as master and working banks. Specialised cell banking companies will have invested in competent tracking and isolation systems for doing this but the process can still be labour intensive, cumbersome and costly to maintain and ensure compliance. The smaller facilities have particular problems in secure storage and may benefit from contract storage with specialised companies. Newer labelling and tracking devices are being developed that function at low temperature to ensure accurate item identification.

6.2. Current Demand for R&D Infrastructure

6.2.1. *Available cGMP Infrastructure Capacity*

There are a significant number of cGMP licensed facilities nationally, with a minimum of one in each State.⁵³ In addition, within each State there are a number of facilities which are seeking cGMP approval, or have infrastructure built to adhere to cGMP.

It is clear that a significant amount of cGMP and PC2 infrastructure has been incorporated into most new life science research infrastructure over the last decade. As previously noted, such infrastructure has been generously supported by federal and State governments as well as philanthropic initiatives. cGMP and PC2 infrastructure is easy to incorporate and design into the overall initial capital cost. However, the operating costs of running a cGMP facility are quite severe and unless full use is made of the infrastructure, it is simply more cost effective to close it and use as non designated laboratory space.

⁵³ Tasmania and the Northern Territory are not included nor is there significant cell therapy R&D in these locations.

Current approved cGMP facilities in every State except Western Australia appear to have surplus capacity. The under capacity of Western Australia may be associated with a number of factors, including the smaller facility footprint, high local activity and the lack of a commercial contractor operating model. Q-Gen at QIMR in Queensland is in an uncertain cGMP state, with the facility having only three managers, and the company having notified the TGA of restrictions to its cGMP licence. This facility is currently the largest and best equipped cGMP/PC-2 cell culture facility in Australia, yet it is essentially vacant at present.

For note only, and by no means a comprehensive list, facilities visited and enquiries made revealed the following vacant capacity: the Eskitis facility has a vacant cGMP / PC-2 laboratory in Queensland; a vacant cGMP laboratory was noted at the Sydney Cord Blood Bank, New South Wales; the Murdoch Children's Research Institute and the Small Technologies Cluster in Victoria also have vacant cGMP capacities.

The survey reflects this current situation well. Approximately half of respondents (n=53) currently have in-house access to cGLP, cGMP or clinical trial facilities and/or services. Over the previous 18 months, around 40% (n=50) have used contract service providers. The breadth of services by cGMP service providers was of concern with only 33% (n=30) in any way satisfied, and 18% (n=22) very dissatisfied with the spend impact of these facilities on their R&D budget.

6.2.2. Preclinical Service Providers

Interviews were held with three pre-clinical service providers in Australia, RDDT (Melbourne), ICP Firefly (Sydney) and Q-Max (Brisbane), as well as companies who utilise local and international service providers. ICP Firefly is a private company, with RDDT and Q-Max being university spin-outs and utilising associated RMIT and University of Queensland infrastructure respectively.

All companies considered that they were working under their capacity, with one seeking to actively explore the international market. The companies offer toxicology and pharmacokinetic services with differing levels of capability in delivery of bioanalytical services, histology and animal species testing. All have NATA registrations. From certain contractors' perspectives, the Australian preclinical market has few products being developed and they do fail at the preclinical phase. It is understood that early stage preclinical work may be performed locally, including analysis development. It represents local control and reasonable cost for clients. However, from a client perspective, when product registration is sought overseas along with clinical trial data, companies do not wish to undertake technology transfer issues. So, they seek larger international Contract Research Organisations (CRO) who are capable of performing the full service from preclinical to clinical, can design trials for maximum effect with minimum dollars (if managed), and importantly may utilise global experts, such as in histology, who are already recognised by the regulators as having requisite experience and competence in their fields.

In addition to the above Australian firms, New Zealand's Trinity Bioactives and their partners Valley Animal Research Centre and ESR Pharmaceuticals offer comprehensive preclinical non-rodent and clinical animal studies (non-primate)

for human and veterinary products. They also service Australian companies' preclinical needs.

Stakeholders identified MPI Research (www.mpiresearch.com) and Bioreliance (www.bioreliance.com) as US based, full service CROs offering safety, toxicology, cell bank characterisation, animal testing and clinical product manufacture. Canadian firms Innovotech (www.innovotech.com) and Toxtest (www.marsdd.com) offer specialist analytical services in biofilms and animal toxicology testing respectively.

6.2.3. Biomaterials

There are a number of facilities developing specific skills and infrastructure in biomaterials for interaction with cells and tissue. Nationally, these include the AIBN at the University of Queensland in Brisbane, the IHBI at Queensland University of Technology in Brisbane, CSIRO at Clayton, Monash University's Clayton campus in Melbourne, Deakin University's Geelong campus in Melbourne, the Graduate School of Biomedical Engineering at the University of New South Wales in Sydney and the Mawson Institute in Adelaide. Whilst some groups, such as IHBI and CSIRO Clayton have commercial linkages, it is not believed that infrastructural demand is exceeded. Because of the extreme interdisciplinary elements of this area, groups have extensive cross linkage across institutes. The IHBI group are keen to implement specific infrastructure for rapid prototyping to complement their current facility needs.

6.3. Conclusion

Future demand for cell therapy infrastructure cannot be projected beyond the next five years, however it is known that major global healthcare drivers underpin the sector; these include the ageing population, obesity, personalised medicine and the organ transplant supply chain.

A review of the current situation can provide some indicator of the short to mid-term demand within Australia. The following indicators are suggested along with possible solutions for addressing these:

- There appears adequate cGMP infrastructure currently in place, and or being planned in the major cities performing cell therapy R&D. There appears to be considerable under-utilised cGMP infrastructure in Australia. The latter is associated with speculative cGMP/PC-2 laboratory construction through generous capital support from federal and State governments as well as philanthropic entities. The lack of commissioning of such laboratories and full potential use is due to a number of factors including; no internal in-house demand, unanticipated high operating costs and poorly conceived model of cGMP activity in R&D infrastructure. The lack of a clear TGA regulatory environment has also made cGMP for those not familiar with the area, a barrier to entry.
- There is no adequate model of sustainable contract cGMP manufacturing for cell therapy products currently in Australia. The current lack of financial transparency is currently masking the true financial position of

each cGMP licensed facility. This, together with a likely increase in regulatory conformance of cGMP cell and tissue culture facilities will see the emergence of a few strategically located facilities only. One can assume that state governments may fund one, but not multiple facilities in each State.

- The type of infrastructure and services over the next 5 years that respondents to the survey identified in decreasing priority:
 - clinical trial centres advised by 60% (n=35)
 - contract research organisations advised by 57%
 - cGMP training advised by 46%
 - GMO certified cGMP facilities by 37%
 - analytical testing facilities by 37%
 - imaging facilities by 34%
 - cGLP test facilities by 29%
 - cGMP contract manufacture facilities by 23%
 - non-regulatory facilities by 14%
 - cGLP training by 11%

This data is consistent with the perceived availability of cGMP contract manufacture facilities and does not identify non regulatory compliant laboratory access as a major infrastructural concern. Specifically, it is clinical trial centres and Contract Research Organisation access identified as most crucial. It should be cautioned that whilst all scientists assume their technologies arising from proof of concept discoveries actually work, the percentage that does actually make it to Phase I and succeed at Phase II is quite low. Thus, one can discount this demand significantly.

- Australia has been positioning itself as a location to perform international clinical trials in recent years. This has been successful due to a strong scientific and clinical research sector, an often less expensive western location of mixed ethnicity, the presence of major CROs, and importantly, the relative ease and timeliness of the clinical trial approval process compared to other western countries (i.e. CTN). The downside to Australia is the relatively small population and time it may take to recruit anything other than highly prevalent medical indications. Nevertheless, there has been a premium on clinical trial beds in Australia.
- Preclinical service provision in Australia appears to currently exceed demand. Early stage analytical development, toxicology and pharmacokinetics are performed by all organisations. Most have access to a range of animal models and contract small animal imaging. Some services such as inhalation models are recognised as deficient. Some organisations do not utilise Australian preclinical service providers believing it better to deal with CROs from the desired market, and have the whole technology transfer package in the one location. The “market” noted in the previous sentence refers to the “clinical trial and licence” business model used by most organisations, where the target market is usually US companies seeking a regulatory / IP / clinical trial package

with which they are familiar. Such organisations will not use an Australian preclinical company as the purchaser will often discount negotiated terms, believing they will undoubtedly have to repeat the work in the US for the benefit of FDA compliance. As such, the Australian preclinical organisations will struggle to find strong local support unless; the product is destined for the Australian marketplace; preclinical companies develop linkages with recognised international advisors; preclinical companies develop specific in-house technical expertise or can leverage local technical expertise; Australian organisations move away from the trial and license business model, which is unlikely. Analytical services were highlighted as a concern for a number of researchers. Specifically, TGA licensed microbiological testing facilities were noted; nationally there is only one licensed Mycoplasma testing laboratory. This is currently inadequate. Viral testing capability in Australia is also considered inadequate however it is also recognised that the low demand for such testing would be uneconomical for local providers. International service providers would offer greater expertise due to the experience from routine throughput. This situation may be reviewed based upon the success of relevant gene therapy clinical programmes.

- Equipment which researchers have identified as requiring in the near future has been outlined; items range from the expensive to the routine. Access to large expensive equipment is an issue for many scientists, and whilst ready access through laboratory ownership would seem ideal, it is also an unrealistic expectation. The default mechanism for institutions has traditionally been the parochial accumulation of infrastructure and equipment; some groups have become incredibly adept at a State government level to elicit funds. The cell therapy sector requires strategic thinking at a national level to ensure the best use of critical funds.
- The cell therapy R&D sector is seeing the emergence of areas with critical mass; arguably Clayton, Brisbane and Perth. Within these areas we are seeing critical infrastructure sharing through positive attempts toward collaboration. Witness also the collaboration theme at the heart of the re-invigorated ASCC.
- It is desirable that all funding requests for infrastructure are considered in light of the pre-existence of alternate national facilities with current occupancy or utilisation rates, as well as other quantitative and qualitative metrics; such as likely return on investment, stakeholder cost – benefit analyses, transforming technology etc. Granting bodies require mechanisms to prioritise the relative merits of grant applications which have both subjective and objective elements, and thereby deliver improved transparency for all stakeholders. One area identified by researchers for centralised infrastructure has been that of cell banking. Experienced researchers recognise they do not have adequate resources for the appropriate qualification of cell lines, yet it is fundamental to their research that this be achieved. A number of regional cell banks with trained staff, equipment and infrastructure appear to be unfolding. These include the Eskitis Institute in Brisbane, the ASCC in Melbourne and

CellBank Australia at the Children's Medical Research Institute, Sydney. It is likely that increased focus on cell line qualification, expansion and storage condition development in cGMP qualified in-vivo reagents has the potential to halt commercialisation momentum.

- People and people skills, as well as infrastructure, appear most concerning to cell therapy development. The sector has developed operating models to circumvent low staff levels, yet it is to be determined if this will be compatible with true regulatory compliance. Funding grants rarely support indirect Salary & Wages (S&W) costs in the translational setting; co-ordination and collection of samples between clinical and research groups, the clerical demand of clinical trial administration are cited as examples.
- In addition to numbers of people, it is also the availability of specific skilled staff that is an issue. As the future demand for clinical trials is raised, it is suggested there is little in the way of experienced clinical associates working within the cell therapy area. This was highlighted by a major Australian CRO. It is noted that one company, Nucleus Network Education, part of the not-for-profit clinical research and education company, Nucleus Network, offers accredited classes in conjunction with the Association for Clinical Research Professionals (ACRP). The Nucleus Network is wholly owned by the Baker IDI Heart and Diabetes Institute.

7. Recommendations

This report has characterised the cell and tissue therapy sector in Australia as enjoying considerable infrastructural support over recent years, to the extent that it may be considered there is adequate cGMP/PC-2 capability, either in existence or being planned.

The sector is commercially immature in Australia with the majority of therapeutic research work being undertaken in medical research institutes, universities and hospitals. New therapeutic clinical data, both in Australia and internationally has to date been generally characterised as being stronger in safety than efficacy. The regulatory environment has been confusing for stakeholders and so benchmark therapies have not been effectively challenged to date. Such characteristics have hampered therapeutic commercialisation from the private sector, however alternate support sectors including banking, screening and consumable / instrumentation supply have evolved. Veterinary applications are emerging in the companion and production animal sectors, due in part, to a perceived accessible regulatory environment.

The ability to secure translational research funding in Australia for cell based therapeutics is both limited in source and quantity, yet is critical for the sector development. Current funding models allow limited clinical trial assessment only, with often small patient numbers. Australian institutes are developing strategic relationships for information sharing, infrastructure and funding access.

Areas of concern for sector stakeholders include Good Clinical Practice (GCP) and Contract Research Organisation (CRO) accessibility, with less focus on Good Manufacture Practice (cGMP) capability. It is expected that regulatory compliance for cGMP facilities will continue to increase beyond currently acceptable “virtual” models in associated institutions.

Recommendations from the stakeholder survey to facilitate cell and tissue therapies sector in Australia include:

- Support of indirect S&W associated tasks and/or software with increased cGMP or Good Clinical Practice (GCP) regulatory compliance in the translational setting as these are currently not captured through existing funding mechanisms. These may be considered soft infrastructure elements;
- Support services including preclinical, analytical and cell banking which are as necessary to effective translational research, and are a comparable service model, as good manufacture practice; and
- Facilitate formal GXP training with a cell therapy focus. Training is considered a critical soft infrastructure element.