Submission
2016 National Research Infrastructure Roadmap
Capability Issues Paper

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Data for Research and Discoverability

Question 1: Are there other capability areas that should be considered?

Of particular note, while advanced physics, chemistry, mathematics and materials are identified as a capability focus area, biology is only identified in the context of enabling the health and medical science capability focus area and the combination of biology, materials science and information technology is not referenced at all.

Question 2: Are these governance characteristics appropriate and are there other factors that should be considered for optimal governance for national research infrastructure.

Question 3: Should national research infrastructure investment assist with access to international facilities?

Question 4: What are the conditions or scenarios where access to international facilities should be prioritised over developing national facilities?

Question 5: Should research workforce skills be considered a research infrastructure issue?

Question 6: How can national research infrastructure assist in training and skills development?

Question 7: What responsibility should research institutions have in supporting the development of infrastructure ready researchers and technical specialists?

Question 8: What principles should be applied for access to national research infrastructure, and are there situations when these should not apply?

Question 9: What should the criteria and funding arrangements for defunding or decommissioning look like?

Question 10: What financing models should the Government consider to support investment in national research infrastructure?

One of the major challenges for any research infrastructure is financing the initial capital cost. Government cost of capital (whether own funds or through public-private partnerships which can reduce the burden of ongoing maintenance on public funding if structured correctly) is significantly lower than private sector. On the other hand, operation using private sector commercial discipline will typically be more efficient. A plausible operating model is therefore for capital infrastructure costs to

be met with government or public-private funding that then garners rent from a fully commercial operator.

Research, public sector and early stage local companies are often unable to afford the fully loaded cost recovery of access to such facilities. Rather than attempt to make additional lower cost/subsidised facilities available, providing vouchers to enable access to larger, commercially viable and sustainable facilities at lower effective rates is likely to be a more efficient way of allocating public funds to support proof of concept research. The Victorian government's Market Validation Program voucher system is just one example of how this model could work.

Question 11: When should capabilities be expected to address standard and accreditation requirements?

In the capability focus area of Health and Medical Science, and consistent with the aspiration of maximising the benefits of research by enhancing and emphasising translational research, it is vital that assets and infrastructure involved in manufacturing products for clinical trials be built, maintained and operated to appropriate standards of Good Manufacturing Practice (GMP). There should be a requirement for ongoing demonstration, through regulatory agency licensure or independent audit, of compliance with GMP and funding should allow for this. Delivering this requirement cost effectively would suggest concentration of infrastructure in a smaller number of facilities of varying scale rather than a larger number of facilities of similar (small) scale, enabling the facilities to operate on a full commercial basis with a voucher system or similar to facilitate research access rather than subsidised operating costs.

Question 12: Are there international or global models that represent best practice for national research infrastructure that could be considered?

Maximising translational research outcomes and productivity requires a collision and concentration of science, skills, industry and capital, with industry need and early input being a critical component. Creating these concentrations is not easy. In the field of cell and gene therapies however, several countries have adopted novel approaches to achieve this. Two examples that might be applicable in Australia in the cell and gene therapy sector, but also perhaps in other sectors include:

A. *Canada's Centre for Commercialisation of Regenerative Medicine (CCRM) that has brought together sector focussed basic research, clinical research and translation, industry projects, capital and skills under a structured but intellectual property framework that promotes polling and combination of intellectual property to create solutions to industry led problems. In five years, CCRM have raised more than $150m in public and private funding and are now raising a dedicated VC fund, assessed over 200 technologies, completed 30 projects, built an industry consortium of more than 45 companies, launched 10 co-development projects with these companies, created 5 new companies and established linkages with leading translational centres around the world, including in*

Australia. This model is a significant extension in scope and scale of our already successful CRC model and warrants detailed review and consideration

B. *Most regulatory agencies globally are seeking to address the significant lag in translation and adoption of new medical technologies, particularly in fields such as regenerative medicine and orphan indications where data generation can be difficult with specific regulatory structures. US FDA and EU EMA have orphan drug, breakthrough therapy, accelerated review and adaptive licensing regimes and Japan has introduced conditional approval pathways for regenerative medicine – all to help remove barriers to development and access to novel, niche and complex therapies. While regulatory reform is not strictly "infrastructure", it does enable maximal use of translational research infrastructure and importantly is underpinned by infrastructure-like investment in regulatory science and learning. By contrast, Australia's TGA lacks even the most basic accelerated approval pathway for biologics addressing orphan conditions and breakthrough therapies that exist not only in Japan but also in Europe and USA. Infrastructure investment in advanced regulatory science is recommended to enhance translation of breakthrough technologies in health science.*

Question 13: In considering whole of life investment including decommissioning or defunding for national research infrastructure are there examples domestic or international that should be examined?

Question 14: Are there alternative financing options, including international models that the Government could consider to support investment in national research infrastructure?

Health and Medical Sciences

Question 15: Are the identified emerging directions and research infrastructure capabilities for Health and Medical Sciences right? Are there any missing or additional needed?

CTPL strongly supports the identified need for research infrastructure capabilities in the field of stem cell therapies (which we define to also include cell and gene therapies and regenerative medicine). We believe that Australia is justified in investing disproportionately in this field based on our scientific track record, the growth of the sector and the impact it will have on the health of our own population. Two specific focus areas are suggested below.

Investing disproportionately makes sense. Cell based therapeutics are poised to realise the promise of two decades and transform health outcomes in a range of intractable acute and chronic conditions. According to the US based Alliance for Regenerative Medicine, and other sources, clinical trials in the field of cell based therapies have grown 25-30% per year for the past four years to more than 600 active trials world-wide. Funding raised by the industry has grown at similar rates with more than US$11b raised in 2015. Big pharma (including Novartis, Pfizer, GSK) and big biotech (including Amgen, Celgene, Biogen) are now investing heavily. The resulting clinical data from late stage clinical trials is demonstrating transformational

results, particularly in cellular immunotherapies and gene therapies where greater than 90% complete remission rates in paediatric leukaemia and single dose cures for genetic diseases such as thalassemia are becoming "expected".

Australia has genuine research leadership in this field, from the earliest days of mobilised apheresis to improve stem cell transplants in haematology, through pioneering efforts in IVF and the isolation of the first breast cancer stem cells. It has created more than 15 companies, supports 25-30 clinical trials and has demonstrated ability to support global clinical translation efforts. For example, Peter McCallum Cancer Centre has achieved some of the highest ex-US recruitment rates into an international multi-centre CAR-T trial and has successfully licensed its own CAR-T therapy to a significant international biotech company.

Triple benefits of investment in translation research infrastructure, particularly in manufacturing and supply chain. Translational research infrastructure offers the potential to improve the volume and velocity of company creation and improve retention of intellectual property in Australia longer. The same manufacturing and supply chain infrastructure is critical to enabling offshore developments to be deployed here (since the required supply chain is small batch, just in time) and so without it Australia risks missing out on access to these breakthrough therapies from any source. And finally, this infrastructure creates high value manufacturing jobs that are difficult to move offshore but at the same time can create exports for Australia into SE Asia, as well as spill-over jobs in clinical trials and component manufacture.

Cellular therapy infrastructure focus areas:

A. ***Build on existing centres of research, clinical and manufacturing excellence by facilitating a co-ordinated, national collaborative translation and commercialisation eco-system modelled on Canada's CCRM (as described in our response to question 12)***

B. ***Facilitate a small number of existing centres of manufacturing excellence with strong clinical linkages to support late stage clinical and commercial scale cellular therapy manufacturing. These centres require both scale/capacity and the ability to aggressively develop production processes to demonstrate commercial viability.***
Globally, the cellular therapy industry is facing a capacity crisis – there simply is not sufficient capacity to meet the demand that will emerge if even a fraction of the current pivotal clinical trials are successful. Additionally, and contributing to this shortage, is limited investment in automated, scalable manufacturing processes (which is also a significant disincentive to investment in new products).

Commercial enterprise ability to raise the capital necessary to support rapid capacity expansion is limited due to current low returns. For example, investment bank Maxim Group say of leading US cellular therapy contract manufacturer Caladrius PCT "we believe it is quite misleading for Caladrius to make claims

regarding commercial commitments that we believe require significant upfront capital beyond Caladrius' reach". At product level, investment in manufacturing optimisation is often a lower priority than investment in clinical development leaving successful products unscaleable.

A direct consequence of this capacity crisis will be a shortage of supply to Australia and an inability to transition local early stage clinical products through the "second valley of death" because the manufacturing processes cannot scale. We are aware of clinical trial sites in Australia with pent up patient demand for cellular therapies that could not be supplied because scarce capacity was allocated to US and EU. Our own experience confirms that process development lags behind clinical development such that inefficient processes cannot be changed for fear of having to repeat clinical trials.

Australia's current cellular therapy translational infrastructure is too fragmented and as a result is sub-optimally funded and skilled. Australia has a network of approximately 7 early stage translational cell processing facilities across the major capital cities that are "open access". These have been established over the past 15 years in no small part with the support of NCRIS investment. Five of these continue to receive funding under the Translating Health Discovery program administered by Therapeutic Innovations Australia and part funded by NCRIS, however the funding is spread very thinly, is insufficient to make a material difference to individual projects, and competes with four other clinical areas. In addition there is at least one small captive facility dedicated to its own development programs. Several other laboratories aspire to episodic clinical supply of a single product type, often under special access or physician exemption criteria.

This infrastructure has several limitations:

a. *Most of the facilities are sub-scale with limited capacity and probably only two have capacity to manufacture commercial quantities of cellular therapy product for extremely limited/ultra-orphan indications.*
b. *Only half (including only two of the NCRIS supported facilities) can point to TGA accreditation for GMP and most of the others are, by their own admission, challenged to achieve the levels of GMP required for any production beyond a pilot study or Phase I clinical trial.*
c. *Almost all are not profitable, relying on grant funding for continued operation and/or not being able to maintain full GMP accreditation.*
d. *None of the facilities have the capability to manufacture large volumes of product for late stage clinical trials or commercial autologous therapies in large indications or for allogeneic product. As a result, all Australia's allogeneic cell therapy companies are currently manufacturing off-shore and Australia has no special advantage when competing to be an Asian autologous therapy hub with markets such as Singapore.*

e. *None of the facilities are optimised for automated production processes and few have the capabilities to assist researchers to functionally close, scale and automate their processes – again limiting them to early stage trials and not supporting research to demonstrate the process viability at scale necessary to attract further funding.*

To overcome these limitations, future investment in translational research infrastructure for cellular therapies should focus in the short term on strengthening and improving access to existing centres of excellence that can operate on a financially sustainable full cost recovery basis (rather than creating new, subsidised small scale infrastructure) and in the longer term on establishing a national commercial scale cell processing capability. This will ensure that local technologies can be developed through to later clinical stages with data and processes capable of further scale-up and of a quality acceptable to multinational licensing partners. It will also ensure that Australia has the necessary infrastructure in place to ensure Australian patient access to international innovations.

Strengthening and improving access to existing centres of excellence can be achieved by:

- *Ensuring a subset of existing facilities are identified as centres of excellence. These will have the largest capacity, deepest experience, demonstrated quality credentials, extensive commercial linkages and deep clinical integration; in other words the capacity and skills to advance products and processes beyond initial human pilot studies*
- *Ensuring these facilities, which should operate commercially, are equipped with, or have access to, the necessary advanced processing technologies necessary for scale-up so that they can function as an effective test-bed and process innovation hub for product development*
- *Providing additional access to these facilities through a voucher system or similar to ensure that researchers can access the facilities at or after first in human clinical trials without compromising the financial viability of the facility or its ability to price commercial and international clients appropriately. These vouchers need to be substantial (of the order of $2-5m) to ensure robust scale process development and could be made available for the centres to administer or be linked to research grant funding.*

In the longer term, there is a strong case for a single, shared access, multi-product cell processing facility that can cater for:

- *Process development and automation of clinical stage cellular therapy processes (enabling local companies to increase the value of their technology and attract international process development work)*

- *Later stage clinical trials and commercial production of large indications (for both Australian and international companies, improving access for Australian patients), and*
- *Scale-up and production of large scale allogeneic cell culture.*

The GMP mammalian cell culture facility constructed in Brisbane by BioPharmaceuticals Australian and operated by Patheon Biologics is a successful example of a model that could be applied. Such a facility could be linked to the CCRM ecosystem described at question 12. There might be only one or two such facility in Australia. Design/construction and (separately) operations could be competitively tendered. The facility is likely to support several hundred high value manufacturing jobs at a minimum and an ecosystem of advanced manufacturing support companies, secure access to a supply chain for advanced cellular therapy products for the benefit of Australian patients, export cellular therapy products to Asia, and provide a basis for capturing more value from Australian intellectual property.

Question 16: Are there any international research infrastructure collaborations or emerging projects that Australia should engage in over the next ten years and beyond?

Question 17: Is there anything else that needs to be included or considered in the 2016 Roadmap for the Health and Medical Sciences capability area?

CTPL notes that ancillary infrastructure also needs to be supported to maximise returns on cellular therapy investment: big data, next generation dual modality imaging and structural biology are also needed.

Environment and Natural Resource Management

Question 18: Are the identified emerging directions and research infrastructure capabilities for Environment and Natural Resource Management right? Are there any missing or additional needed?

Question 19: Are there any international research infrastructure collaborations or emerging projects that Australia should engage in over the next ten years and beyond?

Question 20: Is there anything else that needs to be included or considered in the 2016 Roadmap for the Environment and Natural Resource Management capability area?

Advanced Physics, Chemistry, Mathematics and Materials

Question 21: Are the identified emerging directions and research infrastructure capabilities for Advanced Physics, Chemistry, Mathematics and Materials right? Are there any missing or additional needed?

Question 22: Are there any international research infrastructure collaborations or emerging projects that Australia should engage in over the next ten years and beyond?

Question 23: **Is there anything else that needs to be included or considered in the 2016 Roadmap for the Advanced Physics, Chemistry, Mathematics and Materials capability area?**

Understanding Cultures and Communities

Question 24: **Are the identified emerging directions and research infrastructure capabilities for Understanding Cultures and Communities right? Are there any missing or additional needed?**

Question 25: **Are there any international research infrastructure collaborations or emerging projects that Australia should engage in over the next ten years and beyond?**

Question 26: **Is there anything else that needs to be included or considered in the 2016 Roadmap for the Understanding Cultures and Communities capability area?**

National Security

Question 27: **Are the identified emerging directions and research infrastructure capabilities for National Security right? Are there any missing or additional needed?**

Question 28: **Are there any international research infrastructure collaborations or emerging projects that Australia should engage in over the next ten years and beyond?**

Question 29: **Is there anything else that needs to be included or considered in the 2016 Roadmap for the National Security capability area?**

Underpinning Research Infrastructure

Question 30: **Are the identified emerging directions and research infrastructure capabilities for Underpinning Research Infrastructure right? Are there any missing or additional needed?**

Question 31: **Are there any international research infrastructure collaborations or emerging projects that Australia should engage in over the next ten years and beyond?**

Question 32: **Is there anything else that needs to be included or considered in the 2016 Roadmap for the Underpinning Research Infrastructure capability area?**

Data for Research and Discoverability

Question 33: **Are the identified emerging directions and research infrastructure capabilities for Data for Research and Discoverability right? Are there any missing or additional needed?**

Question 34: **Are there any international research infrastructure collaborations or emerging projects that Australia should engage in over the next ten years and beyond?**

Question 35: **Is there anything else that needs to be included or considered in the 2016 Roadmap for the Data for Research and Discoverability capability area?**

Other comments

If you believe that there are issues not addressed in this Issues Paper or the associated questions, please provide your comments under this heading noting the overall 20 page limit of submissions.