Submission
2016 National Research Infrastructure Roadmap
Capability Issues Paper

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Note: Responses to template questions begin on Page 4.

The National Biologics Facility is pleased to read in the National Research Infrastructure Capability Issues Paper that biologics is listed as a current and emerging capability need, and included within the desired new capability of 'Bioengineering Solutions for Precision Medicine'.

Biologics (or biopharmaceuticals) are complex molecules hundreds of times the size of traditional small molecule drugs and require production in a biological system. The success of the biologics as a class of therapeutics is such that **six out of the world's ten top selling drugs are now biologics**, the majority being monoclonal antibodies. The process from research-level discovery and validation of a target biomarker and antibody pair, or vaccine candidate, to clinical trials testing safety and efficacy is a demanding, expensive and lengthy process. Whilst Australian researchers have an excellent track record in discovery of biomarkers and candidate biologics, **translation into the clinic needs cost-effective manufacture of sufficient quantities of high-quality biologics** suitable for pre-clinical and clinical validation. Australian companies do not usually have the capital to construct in-house biologics production capacity, and so are heavily dependent on external protein production and development work.

Australia has a large-scale cGMP mammalian biologics contract manufacturing plant located in Brisbane (Patheon Biologics). However, any potential product needs to have had sufficient cell line and bioprocess development to be ready for cGMP production. Therefore, this facility is generally only accessible to researchers or companies who have already completed pre-clinical validation and attracted investment towards the development of their biologic.

The National Biologics Facility (NBF, located at AIBN, University of Queensland and CSIRO, Melbourne) was established under the NCRIS scheme, to assist Australian academic and industrial researchers **bridge the gap between research discoveries of potential biologics and the bioprocesses required to produce material** for pre-clinical and clinical trials. Funding through NCRIS, QLD and VIC state governments, CSIRO and University of Queensland, and the EIF and Super-Science initiatives, established a suite of state-of-the-art equipment for the production of biologics. NCRIS funding has contributed towards the salary costs of core technical staff to operate this equipment and provide expert knowledge in the areas of biologics manufacture, analytics and regulatory affairs.

NBF at AIBN currently have a core team of 12 technical staff who have an **integrated range of skills, which is unique in the Australian context**. This number of staff are required to provide the full

range of skills to take a biologic lead protein through to a clinically ready bioprocess, including: antibody discovery and engineering, molecular biology, cell line development, high-throughput clonal isolation, bioreactor operation in batch, fed-batch and perfusion cultures, downstream bioprocessing, protein purification and protein characterisation.

Although **NCRIS funding is currently only sufficient to cover ~50% of NBF-AIBN staff costs**, the Facility still operates a pricing structure under NCRIS guidelines such that Tier I clients (publically funded universities, research institutions and hospitals) are only charged consumable costs without any labour charges, whilst Tier II clients (small Australian biotechnology companies) are charged labour and consumables at cost-recovery. This is a model that is essential to maintain affordability for Australian researchers to access this service, but is not sustainable for the Facility long-term with the current level of NCRIS funding, as ~50% of clients are from the public sector.

Projects undertaken at NBF are generally labour-intensive and long-term relative to many other NCRIS facilities. The shortest projects may take up to 2 months for transient expression and purification of a recombinant protein, whilst projects such as cell line development can take up to 18 months to complete. Large scale manufacture of high-quality material, such as the production of the anti-Hendra virus antibody for compassionate therapeutic use can take 6-12 months with a high labour demand for quality control and documentation, followed by ongoing stability studies with associated quality documentation.

The national need for continued NBF funding is best captured by the extent of our client base, both public and private; **on a yearly basis, NBF collaborates with over 20 publically funded universities, research institutions and hospitals, and over 25 private biotechnology companies**. Over the last eight years, the NBF has completed over 700 projects, and produced and purified over 13,000 litres of cell cultures, representing kilograms of purified proteins.

NBF-AIBN has seen a recent increase in demand for services in cell line development. Generation of a stable clonal cell line producing a candidate biologic and an optimised bioprocess is a prerequisite towards large-scale cGMP manufacture by a CMO such as Patheon Biologics. **NBF is the only service facility is Australia which can offer these services**, with sufficient documentation for subsequent cGMP manufacture, but our current demand for cell line generation is exceeding our ability to deliver this service.

Another area where NBF provides a unique service is in therapeutic antibody discovery and engineering. NBF has access to external as well as internally developed human antibody phage display libraries, which collectively cover a diversity of close to 10^{11} antibody specificities. **Recently, there has been a surge in interest in using antibodies for precision targeting of nanoparticles** laden with cytotoxic drugs to cancer cells, and NBF has assisted industry clients and academic researchers in this area. NBF have trained close to thirty users in phage display methodology using these libraries (including staff and post-graduate students).

As well as training researchers in phage display, **NBF has an excellent track record in training industry-ready personnel in the areas of biomanufacturing**. At least 11 staff of NBF-AIBN, since its establishment in 2007, have moved on to industry placements at Patheon Biologics (Australia and worldwide), Amgen, CSL and Biosceptre International. Training of industry-ready personnel will be further enhanced by the establishment of the ARC Industrial Transformation and Training Centre for

Biopharmaceutical Innovation, co-located with the NBF at AIBN. This centre will provide training to at least 14 PhD students and 5 early-career researchers, and its co-location with NBF and collaboration with industry partners CSL, Patheon, ARCBS and GE Healthcare, will ensure high quality, industry-ready personnel will be available for future recruitment into the Australian biotechnology industry.

The NBF, at both AIBN and CSIRO, has gained an excellent reputation in the Australian research community for its high quality work and services. Below are listed some quotations from various industry and academic users of NBF services.

"The entire field of therapeutic antibodies is an exploding area with great medical and commercial potential, and AIBN is well place to make a major contribution to Australia's efforts." - Sir Gregory Winter, Master of Trinity College, Cambridge, and pioneer of recombinant antibody technology

"The importance of having such high quality national research infrastructure was demonstrated very well to the Queensland Department of Health when we were faced with threats posed to public health by the Hendra virus." Dr Jeanette Young, Chief Health Officer, Queensland Health

"Without the subsidised support of the NCRIS programme, Circadian would be forced to consider relocating this work with overseas suppliers." Dr Michael Gerometta, Circadian Technologies Ltd

"Our relationship with NBF is a fine example of how the NCRIS concept has allowed an early stage Australian biotechnology company to keep their research within Australia, rather than relying on international partners, which ultimately will provide great benefit to the Australian economy and local biotechnology industry." Gavin Currie, CEO, Biosceptre International Limited

"(No other organisations…) within Australia are as fully integrated from cell line development through to scalable biologics production as the NBF-AIBN." Dr David Randerson, CEO, TransBio Ltd

"The facilities, equipment and expertise at NBF are an asset to the Australian biotechnology industry, and should be further funded to allow continued benefit from this investment". Dr Himanshu Brahmbhatt, Joint Managing Director, EnGeneIc Limited

"AIBN delivered a unique service that we could not be found anywhere else in Australia…. This unit is uniquely positioned to facilitate the difficult phase between laboratory scale and full production of our product." Dr Sharon de Wet, Director and CSO, Semexion

"It is crucial for our work that we have access to this type of capability in Australia and we hope that ongoing support of NBF under NCRIS2013 will retain the skill set here." Prof Derek Hart, Dendritic Cell Biology and Therapeutics, ANZAC Institute

Questions

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

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?

Only where the relevant infrastructure is not available in Australia, and the access to international facilities will further progress development of the work in Australia or have benefit to Australia.

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?

Yes. Skilled personnel are required to operate and maintain research infrastructure, and to assist with external researchers in the use of infrastructure. Skilled personnel have a knowledge base specific for the infrastructure or service that they are providing, and this expert knowledge is in itself an attractive capability to be offered to external researchers. For example, researchers or biotechnology companies require the knowledge of staff at NBF in developing a cell line or bioprocess for development of their product, as they do not have this capability or knowledge in-house.

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

Having national research infrastructure available which is accessible to students and other researchers is essential for training and skills development. An example of this the recent establishment of the ARC Industrial Transformation and Training Centre for Biopharmaceutical Innovation (CBI). This program will train 14 PhD students and 5 early career researchers to have the required skills for employment in the biopharmaceutical industry. As the CBI will be co-located with the National Biologics Facility at AIBN, the infrastructure available at NBF will be used to assist in this training, and the outcomes of the CBI will be industry-ready PhD graduates and early career researchers to contribute to the biotechnology industry in Australia.

As evidence of the skills training that NBF has already provided, at least 11 NBF staff have moved on from NBF to industry positions as Patheon Biologics (Australia and worldwide), Amgen (California), CSL (Melbourne) and Biosceptre International (Sydney), many in senior management positions. This is evidence of how collaborations between university staff operating national research infrastructure and industry clients, has helped to train personnel in the requirements of industry to become valuable assets in an area where there is shortage of skilled staff for industry.

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

Research institutes should have a responsibility to ensure that researchers are able to access national infrastructure. The use of research infrastructure for training, as well as by establihsed researchers, ensures the value of the infrastructure is maintained into the future.

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

Access should accessed in a meritorious manner to ensure the infrastructure is being utilised for beneficial work. Also access should be restricted to research institutions, publically funded institutions or small industry who may not have sufficient funding to access contract service organisations.

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?

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

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

Given the growing importance of biologics and the complexities inherent in the production of such large molecules as therapeutic products, many countries have established national research infrastructure in the field. The UK has established the 'National Biologics Manufacturing Centre' (https://www.uk-cpi.com/biologics) as part of their 'Catapult' initiative. In the US, plans are underway to establish NIMBL (a National Institute in Biologics Capability) to ensure that their bioindustry sector has access to the latest ideas and technologies.

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?

In the Biologics Capability, as well as a focus on the enhanced production of high quality recombinant proteins, there should be recognition of the services required to make a product ready for large-scale GMP manufacture. GMP contract manufacturers such as Patheon Biologics in Brisbane require a documented cell line producing the biologic of interest. NBF has seen increased interest in the last few years for services in cell line development, and this is the only facility in Australia that can provide this service.

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?

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.