Bioengineering to Improve Cardiovascular Health for All Australians

Mission Statement

To deliver technologies that have **clear and proven** clinical relevance, which form a substantial contribution to the science community and are potentially **marketable**. At our core will be a research culture that embraces **discovery**, **innovation** and **entrepreneurship** in everything we do. We feel that the interest of the patient is best served by applying a **business approach** in device and technology development.

Vision

A shared national vision for bioengineering targeted towards the improvement of cardiac healthcare through the development of new technologies and devices. **Australia has internationally leading programs in bioengineering that are currently fragmented in different silos**. This sector has now matured over the past decade to a point where it is now poised to make a big impact on healthcare if we put the right framework and strategy in place. Our vision is to strengthen this community by both supporting this sector and facilitating a nation-wide approach. By **bringing together a national program** we will be able to share devices, modelling approaches and algorithms, coding expertise, tissue engineering approaches, and data across the sector. This will facilitate novel interactions yielding innovations not possible in single labs and enable us to compete with the resource rich European and North American research sectors.

Rationale

Our goal is to improve the understanding of the mechanisms of cardiovascular disease to deliver practical solutions leading to health improvement for individuals, communities and populations. Working together, we aim to translate research between the laboratory and the clinic, with fundamental research themes being informed by the most important clinical problems facing our community.

Our Strategy

Much of the world's leading medical research originates from outside Australia; we remain followers rather than leaders in much of the advanced cardiovascular research in which we take part. While Australia ranks impressively with cited research in STEM fields, we rank relatively poorly according to the Thompson Reuters list of global innovators (http://top100innovators.com).

In the current climate, single labs in Australia will struggle to compete with the "brute force" of large well-funded labs in North America and Europe (which each have ~100X the funding for cardiovascular research in comparison to Australia). Therefore we propose a strategy to have a complete national framework, whereby Australia as a collective is competing against our international competitors. This strategy will facilitate unique cross-disciplinary fertilization of bioengineering approaches to yield new devices and technologies not possible to achieve in single lab environments. Thus achieving new bioengineering solutions for cardiovascular disease to improve the health of Australians.

Underpinning Principles

A national framework of applied research programs targeted to improve cardiac healthcare through bioengineering.

Scope

New engineering strategies are poised to improve the precision and cost of diagnosis and treatment people with or at risk of cardiovascular disease (both heart and stroke focussed). Our program is targeted at reducing hospitalisation time and clinician burden via: 1) improving clinical phenotyping to reduce number of tests and

increased diagnosis power, and 2) developing new treatments for those who go on to develop cardiovascular disease. This program of research is targeted at developing these new devices and technologies which will be leveraged via commercialisation and industry partnerships to ensure widespread implementation in the healthcare system both nationally and internationally.

Improving Diagnosis **–** for example new bio-devices for the analysis and better phenotyping of patients. This will ensure the right patients get the right and most effective treatments. In Silico modelling of the cardiomyocyte contraction and heart function are providing important insights and improved data analysis for patient diagnosis. These new approaches may unlock the potential of existing clinical tools such as imaging or electrocardiogram, cardiomyocyte contraction cycles or even integration of the two. These may prove powerful in more accurate phenotyping will also dovetail into the other Mission Flagships including precision medicine. These approaches may also lead to better design of devices or identification of new therapeutics for patients with cardiovascular disease. These technologies will also dovetail into the other Mission Flagships including precision medicine.

New Treatments **–** for example approaches using bioengineering to develop new treatments such as innovative bio-devices including implementation of new biomaterials to improve current devices, targeted cardiac cell/drug/therapeutic delivery, tissue engineering for drug discovery models or as cellular therapies. This will improve the treatment of patients. These technologies will also dovetail into the other Mission Flagships including drug discovery.

Goals

- Develop novel cardiac bioengineering strategies
- Integrate different approaches in a national framework
- Promote commercialisation and industry partnerships to leverage a sector with limited funding
- Develop approaches that will go on to transform cardiac healthcare nationally and internationally
- Develop a strong sector that will support the Australian economy and healthcare sector after the 10 year Mission funding period
- Position Australia as an international leader in cardiac bioengineering
- Develop new intellectual property and R&D opportunities including new advanced manufacturing platforms for novel technologies

Investment Considerations

We have carefully thought out different strategies and scenarios. Our funding approach has been specifically devised to:

1) develop a strong and collegial cardiac bioengineering community,
2) support the researchers and clinicians within cardiac bioengineering
3) focus on innovation and cross-fertilisation of ideas through a supporting and national framework with a flat hierarchy
4) as bioengineering is an emerging field in cardiovascular disease we will support both early and late stage researchers and clinicians with a focus on innovation for impact in the healthcare sector

Governance

The Bioengineering Flagship will be independent board set up with leading business, academic and commercialisation experts and the 2 flagship directors (A/Prof James Hudson and Prof Peter Barlis), together with a scientific advisory board consisting of national and international bioengineering leaders.

KPIs

Publications – Research publications in high quality journals provide a research check via peer review and as industry wants to work with the best and most innovative researchers this also serves as an essential pathway to industry partnerships for translation into the clinic.

Patents – While many Bioengineering Flagship researchers will already be up to speed with commercialisation processes, we will also run workshops to ensure that strong and appropriate patent positions are outcomes of our funding program. This is essential for commercialisation and translation.

Translational Outcomes – The translation of bioengineering research to impact cardiovascular health care requires the licensing, industry partnering and/or commercialization of the technology if it is to be successfully implemented. Therefore, these different avenues of translation are the critical long-term KPIs for this proposal. Different projects will have different time-frames and we will have a full pipeline in action whereby this support will further aid the technologies we are currently translating and also develop new technologies for future translation.

An Integrated National Community – conference some funding to dedicated stream at CSANZ, invitation of international speakers, etc

Implementation

We will reserved funding to support the network: a national co-ordinator, funding for travel of the international advisory board, funding for the national conference stream at CSANZ, and funding for workshops “eg. commercialisation”.

Funding – A “Research Support Package” will be given to members after successful application to the national cardiac bioengineering flagship to support personnel, consumables and equipment. If additional leveraged funding becomes available over time or if there are changes to the membership we will also release additional rounds of application over the funding period. Additional funding can be leveraged from the host institutions, industry partnerships, or commercialization strategies without restriction. We will also leverage an additional 20% of funding from institutions from where the bioengineering members are employed.

Integration – As commercialisation is an important aspect of this flagship IP must be protected appropriately and will be owned by the host institution to ensure a streamlined and effective avenue for commercialization. However, the researchers entering this cardiac bioengineering flagship will make their IP and knowhow developed as part of this flagship available to the other members. This will facilitate the cross-fertilisation of ideas which will lead to more innovation and novel ideas.

Reporting – Continued funding will be subject to bi-annual reporting of progress reviewed by the governance committee and signed off by the international advisory board. As different research topics will have different time-lines and project milestones these will be taken into account rather than a “one size fits all” approach. The governance committee reserve the right to eject members if satisfactory performance or integration into the national framework is not being achieved.

Meetings – We will have an annual meeting as part of a conference stream at the annual CSANZ cardiology conference. In this we will give early, emerging and established researchers the opportunity to present their work. We have decided to do this as part of this conference as it is the premier cardiac conference attended by Australian biologists, physiologists, bioengineers, industry representatives and cardiologists at the same time, and will ensure the most effective cross-fertilization of ideas and help with translation to the clinic through partnerships.

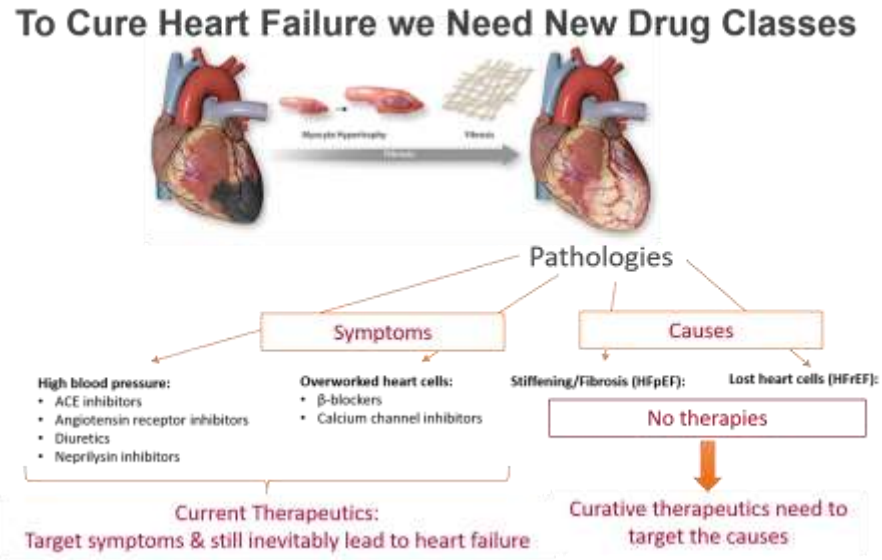
Application to the Bioengineering Program

Criteria	Reasoning	Grading (Yes/No)
Demonstrated Knowledge and Expertise in Cardiac Bioengineering 2000 words	We are not looking for researchers that are chasing money. We are looking for researchers with intimate knowledge of cardiac/stroke biology and/or clinical management and bioengineering approaches to ensure the research teams are dedicated to this field of research and will spend the majority of their research time on this topic.	Applicants must provide examples and evidence of knowledge of cardiac/stroke AND bioengineering expertise
Criteria	**Reasoning**	**Grading (1-7, can give fractional grading)**
Area of work	We need to maintain a multidisciplinary approach so will not chose too many researchers within one area.	• 3D tissue engineering (delivery in vivo) • 3D tissue engineering (drug discovery) • 3D tissue engineering (surgical model systems) • Bioengineering stents • Biodevices for diagnosis • Improving diagnosis through bioengineered models • Improving treatment through bioengineered models • Other
Project (40%) 2000 words	This is to select for projects and groups that can provide the foundation to meet the Bioengineering Flagship Goals	Highest grades will be given to projects with transformative impact potential to cardiac healthcare.
Innovation (20%) 2000 words	In order to transform patients; lives the research programs must be internationally competitive. Many of the imaging, devices, treatments etc. come from overseas or multinational companies and in order for these to be commercialised and implemented through industry partnerships they must be competitive with the high quality innovations internationally.	Highest grades will be given to internationally innovative projects using novel approaches.
Integration into the National Framework (20%) 1000 words	Most bioengineering projects develop technologies and approaches that have the potential to be more broadly implemented across the discipline. This is one of the major goals of this national framework it is essential that this is one of the criteria for application to the program.	As this is one of the major goals of this national framework, a strong plan for how this will be disseminated will be graded highly.
Translational Potential (20%) 1000 words	For bioengineering to truly make an impact on patients' lives both nationally and internationally there must be potential for commercialisation and industry partnerships.	Strong plans for commercialization and translation will be graded highly. Demonstrated commercialization, industry partnerships and translation to the clinic will be looked upon favourably.

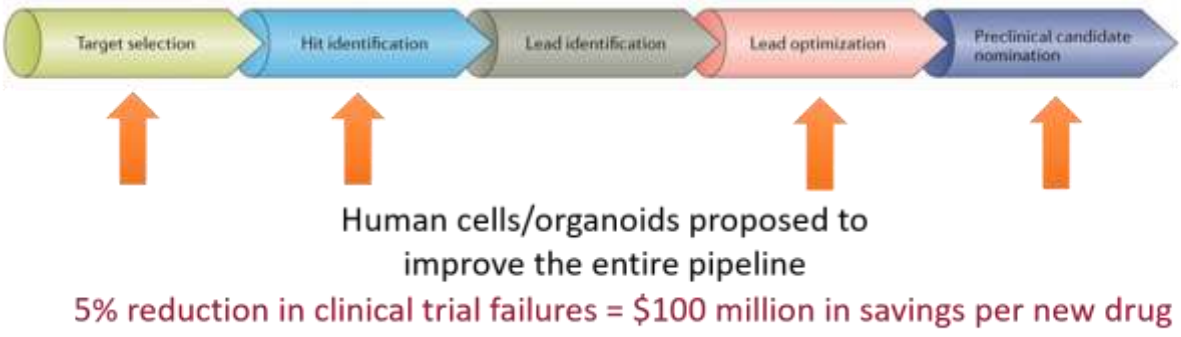
Co-Director – James Hudson- Case Study

A cure for heart failure (HF) would be a transformational in the care of heart patients but despite decades of research and billions in funding heart transplantation remains the only option for end stage disease. Whilst there have been major improvements in our management of patients and new therapeutic approaches for cardiovascular disease, the incidence of HF and its detrimental impact on society continue to increase. **Innovative new treatments for HF should therefore top of medical research priorities**.

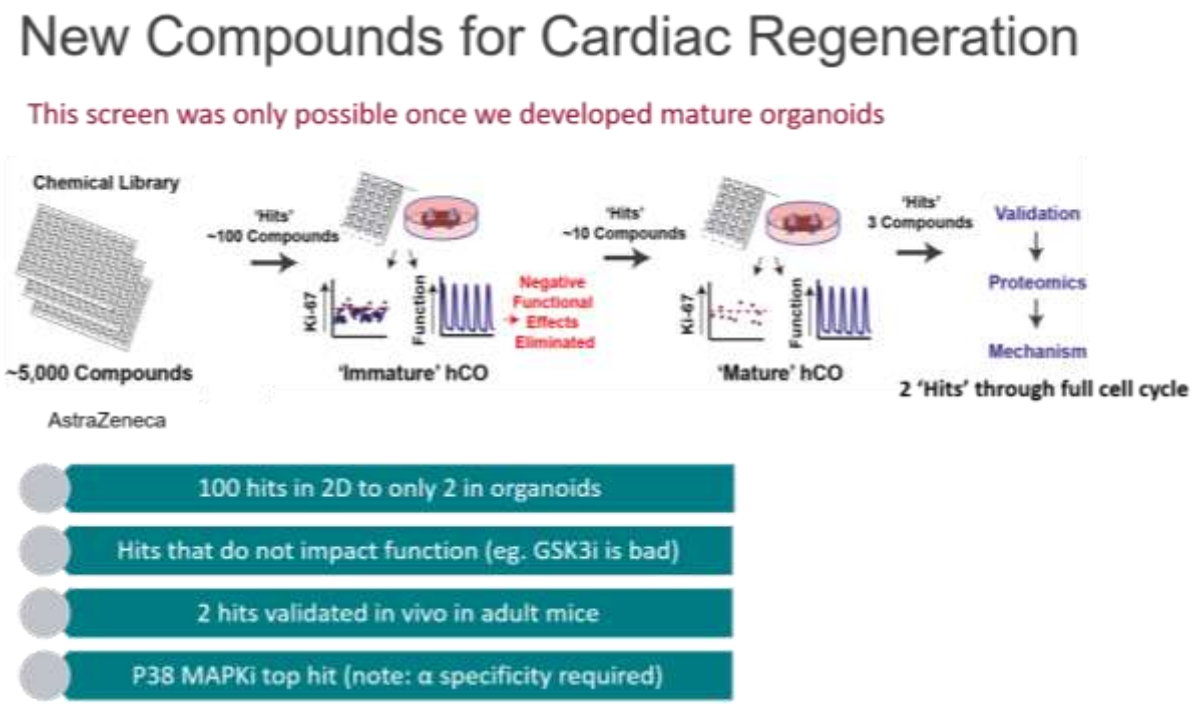
Relevance of Curing HF for the Public and Patients - Frontline HF drugs were all developed 2-3 decades ago and still primarily include beta-blockers, inhibitors of the renin-angiotensin-aldosterone system and ivabradine to slow down pacemakers. Neprilysin inhibitors are a newer addition to control blood pressure. These drugs have been very effective in reducing mortality, but survival rates are still only 50% within 5 years of onset and there are no cures. This **HF health burden is increasing with aging populations** worldwide but also as a result of long term survival of cancer patients treated with chemotherapeutics, which places many societies under economic and healthcare stress, **estimated to increase from $30 billion to $70 billion per year by 2030 in USA alone**. We therefore need new classes of therapeutics targeting the underlying causes.



Finding New Therapeutic Classes is a Challenge – We have failed to find new therapeutic targets for heart failure for many reasons, and typically **90% of drugs have failed in clinical trials**. In order to improve this pipeline new pre-clinical development pipelines have been proposed by the pharmaceutical industry and include the implementation of **human cells and organoids (see the industry expert piece at [1])**.



Human Cardiac Organoids to Discover New Drugs – The Hudson lab has generated human cardiac organoids (hCOs) from induced pluripotent stem cells, providing a potentially unlimited number of beating human cardiac tissues in a dish to do experiments, a "clinical trial in a dish". **The Hudson lab** has optimised conditions in >10,000 hCO to produce the most mature hCO to date [2]. This has facilitated screening for therapeutics [3], genetic disease modelling [4] and large scale omics approaches to decipher biology [2, 3] with yielding accurate results correlating to the *in vivo* heart [3, 5, 6]. Recently application has included finding **putative new drugs for heart regeneration together with big pharma company AstraZeneca** [3].



Translation and Commercialization – While the **Hudson lab** has published these scientific findings (see references above), they have also ensured they have appropriately disclosed information to filed for patents on these technologies. This work has led to the application of 1 patent (now PCT) on the human cardiac organoid technology, and 2 on cardiac regeneration therapeutics (both now PCT). The Hudson lab is now working with the Sydney based company Inventia to commercialize the device technology to make this platform more widely available and also working with AstraZeneca in an industry partnership to develop the putative new cardiac regeneration drugs.

References

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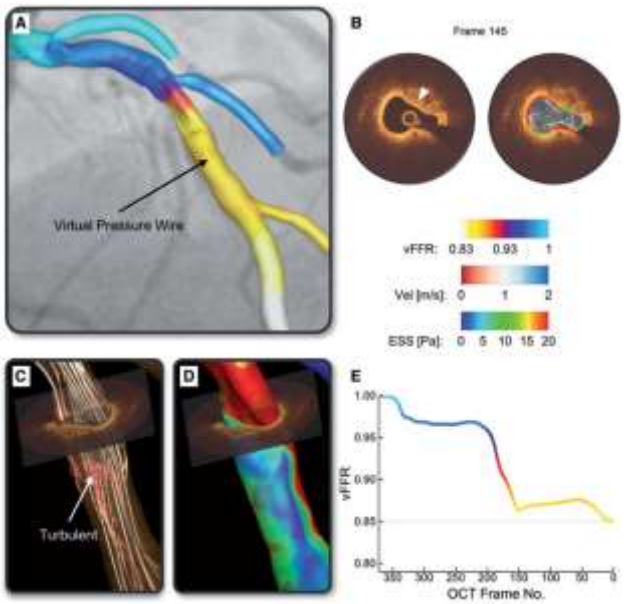
2. Mills, R.J., et al., *Functional screening in human cardiac organoids reveals a metabolic mechanism for cardiomyocyte cell cycle arrest.* Proc Natl Acad Sci U S A, 2017. **114**(40): p. E8372-e8381.
3. Mills, R.J., et al., *Drug Screening in Human PSC-Cardiac Organoids Identifies Pro-proliferative Compounds Acting via the Mevalonate Pathway.* Cell Stem Cell, 2019.
4. Anderson, D.J., et al., *NKX2-5 regulates human cardiomyogenesis via a HEY2 dependent transcriptional network.* Nat Commun, 2018. **9**(1): p. 1373.
5. Quaife-Ryan, G.A., et al., *Multicellular Transcriptional Analysis of Mammalian Heart Regeneration.* Circulation, 2017. **136**(12): p. 1123-1139.
6. Puente, B.N., et al., *The oxygen-rich postnatal environment induces cardiomyocyte cell-cycle arrest through DNA damage response.* Cell, 2014. **157**(3): p. 565-79.

Co-Director – Peter Barlis - Case Study

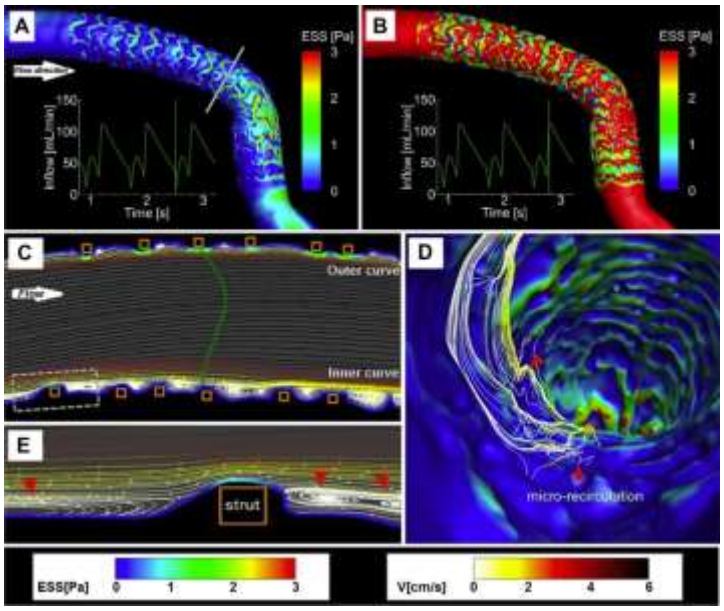
Heart disease is the No. 1 killer in the world and causes more than 17.9 million global deaths each year. Direct and indirect cost of heart disease is estimated at USD 329.7 billion per year. Despite highly effective and minimally invasive stenting treatments to heart disease, optimal patient care is often about early heart disease prediction and prevention to avoid patient suffering from long-term complications and loss of productivity. Furthermore, current technologies rely on patient's medical history and visual diagnosis of imaging data that can vary from clinician to clinician. Hence, **evidence-based predictive diagnostic device is the key to ease health and economical burdens on patient, families and society**.

An enormous change is on the horizon. Government regulation on over stenting, budgetary pressure on healthcare system and the demand for personalised treatment pathway have constantly leapfrogged cardiovascular research in medical imaging, devices and diagnostic platforms. It is imperative for researchers/bioengineers to consider **early disease prediction and prevention that effectively reduce the incidence of acute and/or chronic heart disease**. Bioengineering technology research, translation and commercialisation will be **a national challenge that requires a united approach** to translate basic science research to early clinical adoption via scalable clinical trials.

Integrating Computer Modelling in Cardiac Imaging Diagnosis



<u>Virtual flow index to detect coronary artery disease</u> – current routine diagnostics are often a slow and time-consuming analysis of hundreds to thousands patient images, placing a heavy burden on clinicians. Abnormal haemodynamic environment has long been linked to disease detection and development. Our team has developed a unique 4D flow analysis. The advantage of this 4D method is **gaining physiologic information (e.g. fraction flow reserve, FFR) along with high-resolution anatomic imaging** through the marriage of advance medical imaging and computer modelling without having to rely on multiple invasive measurements [7]. The developed virtual FFR index can help quantify disease length and location that ultimately enable personalised treatments.



<u>Biomarkers to predict long term hard event</u> – endothelial shear stress (ESS), a haemodynamic force, affects proatherogenic and proinflammatory phenotypes. Our 4D flow analysis toolkit can predict the ESS patterns within the cardiovascular system (from Aorta to coronaries [8, 9]). In particular, as key opinion leaders, (together with Prof. Patrick Serruys and A/Prof. Frank Gijsen from Erasmus University, the Netherlands; Prof. Peter

Stone from Harvard Medical School; A/Prof. Alison Marsden From Stanford University, etc.) in a recently accepted expert consensus document in the European Heart Journal, entitled "Expert consensus on the assessment of wall shear stress in human coronary arteries: existing methodologies, technical considerations, and clinical applications" [10], we have articulated **global translational research strategies in coronary artery disease modelling, prediction and prevention**.

Artificial intelligence (AI) – it is of critical importance to speed up current modelling process, bringing the long and expensive computer modelling to the bedside. Applications of AI in clinical setting continuously gather interest from industries. **AI can be easily integrated into regional hospitals** and hence eliminates the disparity of cardiovascular health care in remoted areas.

Novel Biomaterials and Customised Devices

"No two arteries are shaped the same". We're all different, with arteries that have different branches and sizes, tapering from larger to smaller. Our team has closely collaborated with Prof. Gordon Wallace from ACES and Prof. Xiumei Mo from Donghua University, China in a bid to develop novel biodegradable materials for next-generation vascular scaffold. Biodegradable scaffold absorbed by our body **avoids long lasting effects of foreign object in our body**. As a result, reducing the health and economic burden in long term.

3D printed patient model can also be used to study blood flow and predict the best type of stent for a patient. All in all, the bench tests platforms in 3D printed arteries and devices represents the key step towards further device development and translation.

Translational Research Pathway

Our team has been at the forefront of cardiovascular disease management, research and development. We believe that **better patients' outcomes can only be achieved via research, innovation and commercialisation**. Over the past years, our team has proactively establishing partnerships with global industries. Our ties with the global industries are the main reason for our success in bioengineering product R&D [7], leading to a PCT application and further proof-of-concept supports from the Business Development team at University of Melbourne. Most importantly, the profit generated by integrating our research into both Australia and global health together with manufacturing industries might potentially help **creating a healthy, sustainable ecosystem to further fund basic science and translation research in CVD**. And hence continuously reduce the burden of heart disease and improve patients' quality of life.

Reference

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