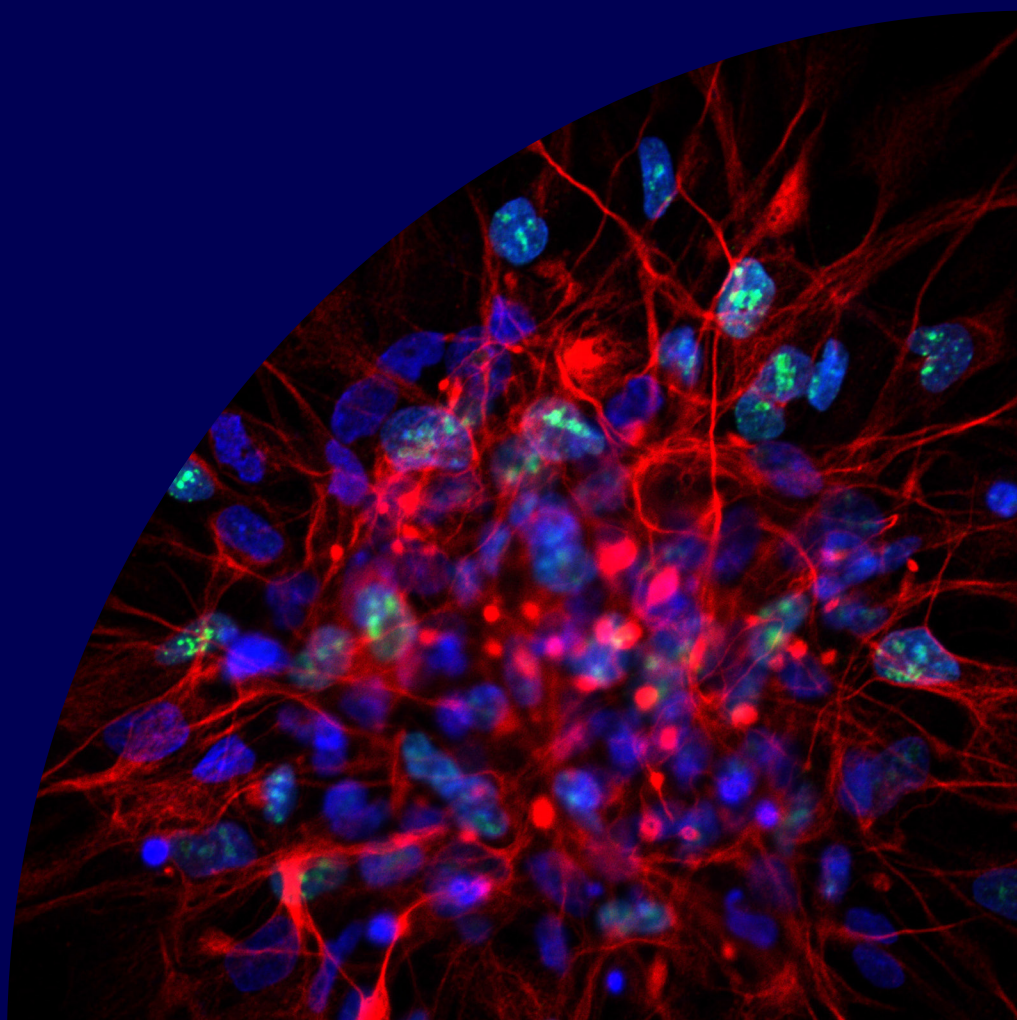
RMIT UNIVERSITY

Insight Series

# Biofabrication and Tissue Engineering

New solutions for long-standing health issues



## Authors

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Advanced Manufacturing and Fabrication, Advanced Materials, and Biomedical and Health Innovation Enabling Capability Platforms

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## Key Terms ^

**Biomanufacturing –** the design, development and production of functional assemblies that focus on restoring biological functions and/or machines, devices and processes associated with delivering these aims. This encompasses the optimised production of biofabricated structures to restore the function of hard tissues such as bone, soft tissues such as skin, muscle and nerves, and implantable devices that monitor and regulate dysfunctional tissue to restore normal function. Biomanufactured structures and devices can also be applied to the modelling of functional versus dysfunctional tissue and organ systems.

**Biofabrication –** the application of appropriate materials, including biologically-active molecules that are able to effectively integrate into living tissue systems. This includes the incorporation of biologically-appropriate cells into biologically-compatible gels and the processing of these and/or biologically active material scaffolds (without cells) into structures for functional remodelling of failing or otherwise dysfunctional tissue systems.
Technologies such as wet-spinning, hot-melt extrusion, reactive gelation, electrospinning and drop and cast moulding are some of the main methods used for biofabricating materials into biologically active and compatible structures. Additive Biofabrication (AdBioFab) technologies utilise additive technologies such as 3D printing or laser particle welding for the formation of structures to be used for biological applications in living systems (*e.g.* neo-genesis of bone, muscle and other tissues).

**Tissue engineering –** the design and production of biological structures as ex vivo implantable structures or as implantable biological constructs that mimic the structure and function of tissues. These constructs are used to restore functional tissues in situations where tissue and/or organ failure occurs due to loss or degeneration of endogenous tissue.

**Regenerative medicine –** the replacement of failing, dysfunctional or lost tissue by applying biofabricated constructs that restore function by re-instating the production of new tissue by introducing appropriate cells within the construct or through biomimetic properties of the implanted material scaffold.

**Additive manufacturing –** the process of additive layer-by-layer deposition and construction of materials into defined structures rather than by ablative/subtractive (e.g. milling) processes. This includes laser-mediated particle welding of metals, the extrusion of biologically active polymers into hard structures, or bio-printing cells within hydrogels into soft biologically active structures.

**Bioprinting –** the process of Additive Biofabrication using computer/software controlled reactive extrusion, piezo or a combination of these to deposit biomaterials, cells and biofactors organised into bio-inks to create micro-tissue-like structures that emulate native tissues.

**Bioassembly –** the coordinated assembly of biofabricated multiple-component biological or synthetically constructed bio-structures into complex multi-functional organ-like structures.

**Autologous –** cells or tissues derived from an individual for the purpose of reintroducing those cells into the same individual to mediate in re-building dysfunctional tissue.

**Biomimicry/Biomimetics/Bionics –** characterising and incorporating functionality into the design and production of materials, structures and systems that is modelled on existing biological structures, processes and interactions.

**Neogenesis –** the new formation of a functional biological structure, tissue or other biofunctional system that closely emulates, but with restored structure or function, the original dysfunctional biological structure.

**Tissue-on-a-chip/Organ-on-a-chip –** Model tissue-like structures that are constructed ex vivo to emulate native tissue for the purposes of studying the structure and function of disease and health in various biological settings and situations.

^ The definitions of key terms tend to evolve as rapidly as the fields and activities they are attempting to describe.

## Abbreviations

| | |
|---|---|
| **ACMD** | Aikenhead Centre for Medical Discovery |
| **BTE** | Biofabrication and tissue engineering |
| **CNS** | central nervous system |
| **ECP** | Enabling Capability Platform. RMIT has established eight ECPs to bring the University's multidisciplinary research expertise together under thematic umbrellas to facilitate and support collaborative research and research translation |
| **iPSCs** | induced Pluripotent Stem Cells |
| **MPC** | muscle precursor cell |
| **NMDs** | neuromuscular disorders |

**Cover photo:** Human neural stem cells. Courtesy: Dr Anita Quigley, RMIT

# Overview

The world's population is ageing and the associated burden of age-related diseases and degenerative disorders is rising accordingly. Similarly, the impacts of road trauma, global conflict, cancer, diabetes and many other causes of personal injury, death and disability are placing increasing pressure on health and welfare systems.

Several traditional research fields have converged in the last 20 years to create a perfect storm of opportunity for the medical and healthcare sectors to rapidly evolve to address these major global health challenges. Emerging biofabrication and tissue engineering technologies have the potential to generate step-change transformative solutions for managing human health and wellness.

Biofabrication opens up immense opportunities for engineering and manufacturing fully functional, biocompatible tissue constructs and devices for repairing or replacing lost human body tissue functions. The science behind biofabrication is advancing rapidly in research laboratories worldwide, however translation of this research to provide community benefits is challenging.

Why is this the case and what can be done to speed up the process of translating biofabrication capabilities into medical devices, products and practices that benefit the wider population? And why do health sector organisations, clinicians and other end-users need to be involved in helping to create this watershed? This white paper explores these questions.

The paper identifies five priority clinical targets for emerging biofabrication technologies:
- treating major physical trauma
- replacing lost muscle tissue
- helping people age well
- repairing nerve damage, and
- creating personalised diagnostics.

Several scientific and engineering challenges are examined, which need to be overcome before the potential flood of benefits from biofabrication technologies can be successfully delivered to the Australian and global health communities:
- limited choice of materials suitable for biofabrication
- restoring complex biological structure and function
- achieving full bio-integration
- optimising the sourcing, development and management of cells
- creating standardised procedures
- expanding the suite of fabrication and manufacturing techniques, and
- establishing ethical, regulatory, public acceptance and translational pathways.

The paper also raises the importance of:
- adopting a broader cross-disciplinary approach to delivering innovative healthtech solutions
- establishing viable biomanufacturing processes to ensure rapid research translation, and
- embracing human-centred design to deliver new products and devices that are highly functional while also responding to the specific needs, likes and dislikes of end users.

> **When the full potential of these new biofabrication technologies is realised, millions of people with common age-related and general disabilities will be able to live better-quality lives and feel more positive about themselves and their future.**
>
> **The adverse impact of age-related dysfunction disorders will be mitigated because these new technologies will effectively address deteriorative processes that are currently underserved by existing technologies.**
>
> **Our medicines and diagnostic methods for serious conditions such as cancer, diabetes and neurological disorders will be vastly improved using new, personalised biofabricated human tissue models and constructs.**
>
> - Professor Mark Cook, Head of Neurology, St Vincent's Hospital Melbourne

# Unprecedented healthcare benefits evolving from biofabrication technologies

The history of medicine is dotted with pivotal breakthrough developments. Biofabrication is destined to join the historical record as one of these game-changing advancements.

The field of biofabrication leverages the collective expertise embodied within disciplines such as Materials Engineering, Biological Sciences, Additive Manufacturing, Nanotechnology and Biomedical Health Technologies (Fig. 1).

The field presents unprecedented step-change possibilities for tissue engineering, particularly for repairing and replacing defective body organs, performing human tissue-based diagnostics and modelling, developing personalised medicine, and testing drug efficacy and toxicity.

This relatively new and exciting field of study provides tools for designing multi-component biomaterial structures that can be used to replace lost or dysfunctional tissues in the human body. Biofabrication techniques will enable us to restore, modify and improve the structure and function of bones, muscles, brain, nerves, joints, connective tissues and many other body tissues. For the first time, biosynthetic human tissue constructs can be made that come close to mimicking the true and phenomenal complexity of the native systems they are being designed to repair, replace or regenerate.

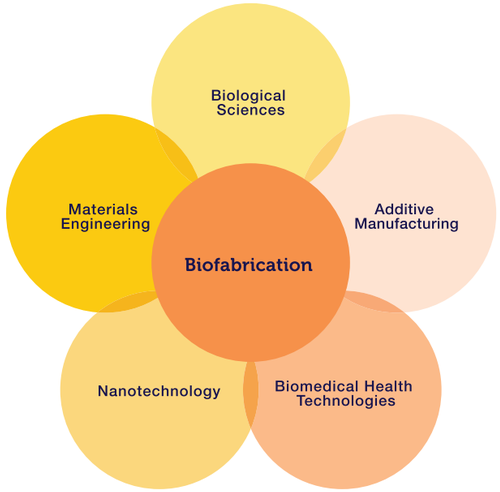


Figure 1. Traditional research disciplines contributing to the field of biofabrication

**When the full benefits of biofabrication technologies are finally flowing into the community at the clinical level, the health and wellbeing of billions of people worldwide will be transformed.**

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The potential applications in medicine and health care are limited only by our imagination and attention. For example, personalised, biofabricated, regenerative 3D constructs made using autologous cells and manufactured into devices, implants and 'tissue-on-a-chip' diagnostics can be used to:

- repair deteriorating bone, cartilage and muscle in the elderly
- enhance amputees' quality of life by developing next-generation prosthetic limbs that communicate directly with the brain and nervous system
- implant new biocompatible muscles and tissues into people who have had soft tissue cancers removed or who have lost tissue due to trauma or disease processes
- give people with diabetes a customised, self-regulating artificial pancreas
- supply fully biocompatible replacement skin for burns, cancer and trauma victims
- repair or replace damaged peripheral nerves, and
- enable clinicians to conduct patient-specific diagnostics and drug response tests using tissue models built from an individual's own cells.

A paper published in the journal Biofabrication in 2009 (its founding year), described biofrabrication as *'having the potential to emerge as the leading manufacturing paradigm of the 21st century'*.[1]

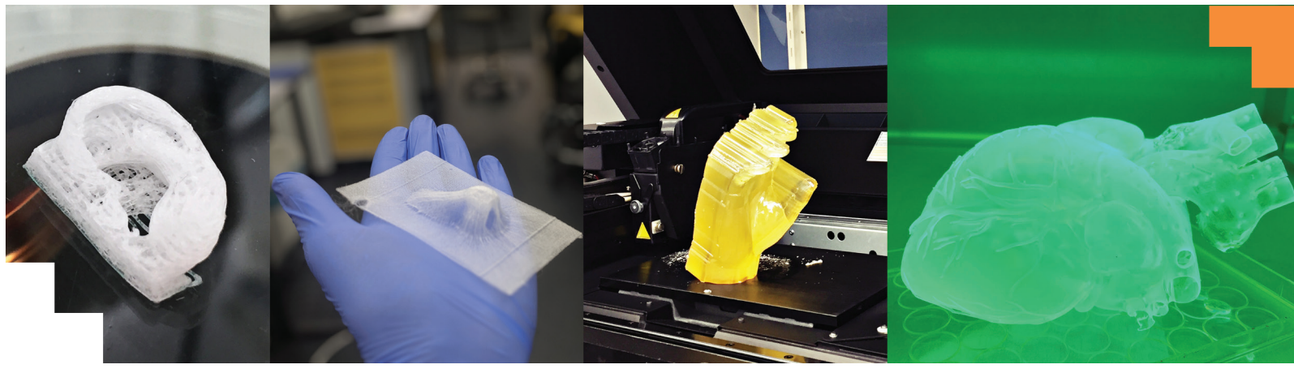
Biofabrication technologies continue to evolve, particularly for biomedical advancements towards clinical application. However, little of this immense potential impact has translated to the wider community in the form of tangible improvements in medical treatments, devices and products. Despite a surge of over 100,000 research articles and 9,000 patents involving biofabrication and tissue engineering during the past 20 years, comparatively fewer products have been delivered for clinical use.[2] These few to date include scaffolds for wound management, bone healing, nerve grafts and small vessel grafts. More recently, the modelling of surgical target sites and 3D disease tissues for advanced therapy has been facilitated through evolving biofabrication technologies such as 3D printing.

## Building up to new, high-impact solutions

The application of biofabrication in health care is experiencing a pre-emptive 'build-up' phase. There have been a few promising but isolated cases of new technologies and products that have filtered through to clinicians and patients. However, in real terms, the floodgates holding back the design, development and translation of biotechnology products and processes for clinical use have yet to open. This presents vast opportunities for research institutions and research and development (R&D) consortiums with relevant cross-disciplinary capabilities to impact on this growing field. In Australia, we have the technological, manufacturing and commercial skills needed to contribute. Australia's integrated R&D infrastructure and innovative research training programs are internationally recognised. Despite this, however, our ability to translate biofabrication technologies into market products currently lags behind that of many other countries.

There is, therefore, an urgent need for new, biofabrication-based healthtech solutions to old existing problems to be rigorously pursued by the Australian research sector in partnership with corporate, health and government sectors. Only then can the true potential embodied in biofabrication technologies finally penetrate into our hospitals and throughout our healthcare infrastructure to benefit the community.

> The research world has been in the laboratory focussing on developing biofabrication and tissue engineering capabilities for long enough. The time has arrived for us to deliver viable, high-impact health solutions back to the community.
>
> - Distinguished Professor Adrian Mouritz, Executive Dean, School of Engineering, RMIT



Images courtesy of Dr Cathal O'Connell

# Biofabrication: New solutions to old problems

Many disabling health conditions that affect the global human population can benefit from biofabrication technologies, which open up possibilities for new, emergent solutions to long-existing problems. These solutions can deliver paradigm shifts in the diagnosis, treatment, management and even (potentially) eradication of disability and degenerative disease, chronic pain and physical and mental deterioration in the human body.

## Ageing population

The ageing global population is already generating significant healthcare challenges and these will only increase in coming decades. In 2019, 703 million people were aged 65 years and over worldwide. That figure is projected to double to 1.5 billion by 2050, or around 1 in 6 people globally (up from 1 in 11 in 2019). Future generations of older citizens will also be living longer than previous generations.[a]

With this shift in human life expectancy comes an associated rise in the incidence of age-related diseases and degenerative conditions, placing further pressure on the health, disability and aged care sectors, and the wider community. At the same time, in the decades to come, older members of society will be working longer before qualifying for full retirement.

They will have greater expectations than previous generations around the importance of staying active and ageing well. This intensifies the need for innovative new solutions for treating the diseases and degenerative tissue conditions most prevalent in old age.

## Rising disability rates

More than 4.4 million people in Australia are living with some form of disability. This equates to 1 in 5 people in this community. These disabilities may be caused by accident, trauma or disease.[b]

Table 1 lists the categories of disability where biofabrication and tissue engineering technologies provide relevant strategies for novel therapies. The people in these common disability groupings represent almost three quarters (71%) of the years lived with disability (YLD) in Australia. Reducing the physical and mental health impacts of such conditions will go a long way to lessening the disability burden on Australia's healthcare and welfare economies. Millions of Australians with disabilities – and billions worldwide – will be able to participate more fully and productively in day-to-day life due to new biofabrication-based therapies.

| Disability grouping | % of total YLDs |
|---|---|
| Trauma-related tissue loss/dysfunction | 24% |
| Specific organ/tissue systems dysfunction | 19% |
| Neurological disorders and dysfunction | 18% |
| Dementias and mental disorders | 6% |
| Cardiovascular disease and dysfunction | 2% |
| Cancers and cancer-related dysfunction | 1% |
| % Total YLD that can be addressed by BTE activities | 71% |

Table 1. Percentage of total years lived with disability (YLD) in Australian males and females, all ages, all causes (2017). Figures relevant to conditions able to be treated by biofabrication and tissue engineering solutions.

Source: Global Burden of Disease 2017 data visualisations [c]

[a] https://www.un.org/en/development/desa/population/publications/pdf/ageing/WorldPopulationAgeing2019-Highlights.pdf
[b] https://www.and.org.au/pages/disability-statistics.htm
[c] http://vizhub.healthdata.org/gbd-compare



## Alleviating the after-effects of cancer treatments

Cancer is the second leading cause of death in the world, behind cardiovascular disease. Although cancer survival rates have vastly improved in the past 30 years, the treatments still cause considerable pain, discomfort and disability due to tissue damage and loss.

There were 17 million new cases of cancer worldwide in 2018 and by 2040 that number is expected to grow to 27.5 million cases annually. Australia has the highest cancer rate in the world of 468 cases per 100,000 people.[d]

Biofabrication technologies will provide new solutions for these old health issues through their ability to provide regenerative constructs that integrate into sites where cancers have been removed from tissues such as muscle, brain, skin and bone and, later, even complex organs such as the liver.

**The ability to replace damaged tissue, such as that excised when removing soft tissue cancers, with healthy, biocompatible, biosynthetic tissue is an area where biofabrication technologies can have a major impact.**

## Rising demand for high-tech implants

Rapidly growing populations in countries such as China and India, combined with the expanding economies and increasing individual wealth in those countries, have increased global demand for effective ways of managing tissue and organ dysfunction or loss. Alongside this, recent advances in biofabrication technologies have kindled expectations within the global community for new-format medical technologies based on biofabrication to deliver implants capable of managing these medical problems better than existing technologies.

Even though they have yet to realise their full delivery potential, biofabrication technologies are being carried forward as a result of this expansion in global demand for biofabrication-compatible solutions. As such, the global market in 2018 for 3D bioprinting was around US$965 million, with an ongoing compound annual growth rate (CAGR) of 19.5% forecast to drive this value expectation to US$4.1 billion by 2026 (Fig. 2). Such rapid expansion has been attributed to progressive increases in the incidence of chronic disease, the ageing population and the resulting need for functional tissue and organs. This rapidly expanding market is expected to gain further momentum as biofabrication and associated technologies and industrial entities continue to evolve.[e] In particular, the global biomaterials industry is expected to burgeon from a US$105.2 billion market in 2019 to a US$206.6 billion market by 2024, with a CAGR of 14.5%.[f] The rapid ongoing expansion of these markets provides strong foundation platform for consolidating biofabrication as a newly emergent industry, underpinning advancements in regenerative medicine and tissue engineering on a global scale.

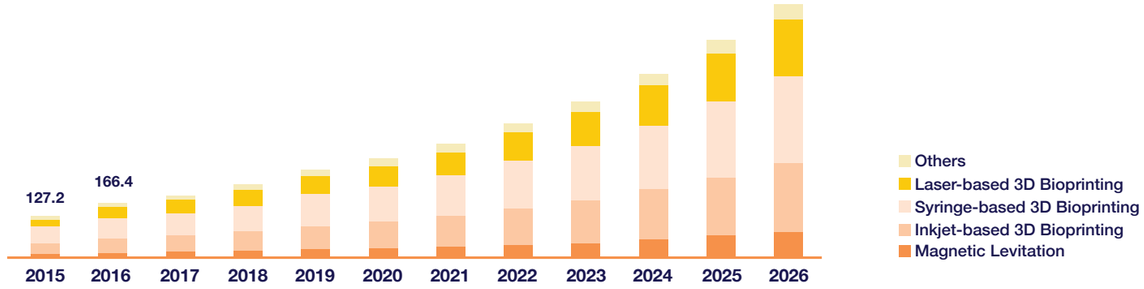



Figure 2. U.S. 3D Printing market size by technology 2015 - 2016 (USD Million)
Source : www.grandviewresearch.com

## An increasing focus on research impact

The Australian Government and other major funding bodies around the world are increasingly recognising the importance of ensuring that government-funded research delivers outcomes that benefit the community. As such, translational research and scientific innovation are acknowledged by funding bodies such as the Australian Research Council and the National Health and Medical Research Council as being major contributors to long-term economic growth for the Australian economy. [g]

Funding opportunities on a global scale are therefore geared towards activities with immediate to short-term capacity to translate into viable solutions for the paying stakeholders. This will become increasingly important as competition for the available funding becomes more intense and funders become more focussed on achieving demonstrable returns in the form of high-impact environmental, economic and social outcomes.[h]

## Moving away from animal testing

Animal testing of disease pathologies and novel drugs has been essential for advancing applied medical research. However, the perception of this activity within the wider community is poor and generally accepted as unethical. The process of animal testing also often fails to predict human responses because traditional animal models do not always accurately mimic human pathophysiology.[i]

Biofabrication technologies enable the generation of 3D human tissue constructs that accurately mimic the functions and responses of the in vivo environment. This opens up enormous scope for improving the efficacy of new drugs and treatments while also reducing reliance on traditional animal testing.

[d] https://www.wcrf.org/dietandcancer/cancer-trends/data-cancer-frequency-country. [e] https://www.grandviewresearch.com/press-release/global-3d-bioprinting-market
[e] https://www.grandviewresearch.com/press-release/global-3d-bioprinting-market
[f] https://www.globenewswire.com/news-release/2019/06/24/1873102/0/en/Global-Biomaterials-Market-Outlook-2019-2024-206-Billion-Opportunity-Analysis-Driven-by-Increasing-Demand-for-Implantable-Devices.html
[g] https://www.arc.gov.au/policies-strategies/strategy/research-impact-principles-framework
[h] http://pandora.nla.gov.au/pan/131022/20111216-0901/ReviewAdvicePaper.pdf?
[i] https://wyss.harvard.edu/technology/human-organs-on-chips/

Prosthetic limbs designed to effectively integrate with the nervous system will provide enhanced function and sensory feedback to the individual.

# Priority clinical needs for biofab solutions

Biofabrication technologies will revolutionise the diagnosis, treatment, recovery and ongoing support provided to people with a wide range of medical conditions, including many common disabilities. However, there is an urgent need to close the gap between the continuing scientific inquiry in this field and its ability to deliver on clinical needs. Five areas of particularly high clinical need are described below. Focusing intensive cross-disciplinary expertise on developing viable solutions in these areas will enable them to be rapidly transitioned from concepts to prototypes and then into commercial products that benefit clinicians and the wider community.

## 1. Treating major physical trauma

Limb loss after physical trauma is a major cause of disability in the global community. In 2010 (the last readily available census in this area), 5.3% of all workers experienced work-related injuries, of which 25% involved major impact or penetrating injury.[3] In addition, 12% of Australians experience long-term effects from injuries annually. These injuries mostly arise from falls (~4% of the total Australian population) and collisions (~2.3% of Australians). Global warfare and terrorism, along with natural disasters can also inflict major physical trauma on individuals. Similarly, bone cancers often necessitate limb removal.

Motorised prosthetic devices play an important role in the rehabilitation process and improving an individual's level of independence post-trauma. However, existing electronic interfaces between motorised prostheses and their recipients' nervous systems have limited functionality.

Motorised prosthetic limbs currently use electrodes to record electrical activity directly from nerves to drive the limb and may also be used to send nerve signals back to the brain to facilitate the feeling of key sensations such as pressure and heat from the prosthetic. While some approaches have been proposed for sending motor signals to the prosthetic, no effective solutions currently exist for sending sensory signals back to the brain to monitor and control the prosthetic's movement.

A second key issue with implantable electrodes for driving motor and sensory signalling in prosthetics is post-implant electrode fouling, often caused by fibrosis, resulting in a loss of connection between the electronics in the prosthetic and the neural circuitry.

A significant clinical need therefore exists to develop interfaces that enable bio-mechatronic prosthetic limbs to communicate directly with the brain and nervous system. It is only a matter of time before concerted R&D focus in the biofabrication arena addresses this need.

Interfacing between tissues and electronic systems (for bio-mechatronic purposes) requires the fabrication of biocompatible, non-fouling electroactive surfaces that can be used in the body over the long term. Creating an integrated fibrotic-free interface between a living electrode and the surrounding tissue is a critical step in ensuring the efficacy of these devices. The aim will be to develop an autologous cell-based interface between electrodes and tissues that stabilises the interaction between neural tissues and electrodes to achieve a more reliable connection between mechatronic prostheses and neural circuitry.

The underlying principle of the living neural-electrode interface is that cells that normally interface with the nervous system are grown from the person with the amputation and biofabricated as part of an electrode array. In the robotic hand example illustrated in Figure 3, these bio-mechatronic structures are then incorporated into a contained arterio-venous fistula (shown in frames A and B), implanted into the recipient (frame C), where they connect with the mechatronic prosthetic device, allowing brain impulses to control its movement. All aspects of this system are subject to biofabrication and tissue engineering technologies, from the soft robotics that generate the prosthetic device to the cells within the bio-ink that generate the electro-neural connection.

## 2. Replacing lost muscle tissue

The muscle engineering electrode-interface principle described in the preceding section can also be refined for treating cases of muscle loss or dysfunction resulting from:

- the surgical removal of tissue when treating cancers such as soft tissue sarcoma and melanoma
- accidental trauma (ablation) caused by an industrial, road or other accident, or
- a degenerative muscle disease/disorder such as muscular dystrophy.

**Muscle-tissue loss due to surgery.** Around 1% of all cancers worldwide are soft tissue sarcoma and affect up to 5 people in every 100,000, with 24% of these involving muscle tissue.[4] The need to excise sarcomas from the muscle of affected people presents long-term cosmetic and functional challenges. This type of cancer affects 1,000 Australians annually, with consequential loss of muscle structure, mass and function.

**Muscle-tissue loss due to trauma.** On average, 1 in 300 Australians will be involved in a motor vehicle accident each year. About 40% of the collision injuries these people will suffer are penetrating wounds that require surgical intervention that results in the loss of associated muscle tissue.[5] Casualties of war, terrorism and natural disasters are also high on the list of people who suffer muscle trauma that can result in life-long disability.

**Muscle loss due to disease.** Neuromuscular disorders (NMDs) are life-long degenerative muscle diseases caused by primary defects of muscle tissue or by defects in the nerves controlling the muscles. These conditions collectively affect more than 1 in 1000 people worldwide. The dystrophic process involves a more rapid than usual loss of muscle fibres, which over-burdens and depletes the body's available pool of muscle precursor cells (MPCs) needed to replace the lost tissue.[6]

Regenerative cell replacement (particularly targeting restoration of the MPC niche) is the best option for restoring muscle tissue structure and function. Studies have revealed the key biological criteria required to achieve this. However, muscle engineering strategies have generally failed due to poor i) delivery to/migration in host muscle, ii) post-implant donor cell survival, and iii) inherent myo-regenerative capacity of donor cells.[7-10]

MPCs are not feasible as an autologous cell source in muscle loss situations due to their depleted numbers in myodegenerative muscle disease and bulk muscle loss. To account for this, it is necessary to develop non-muscle sources of regenerative cells for muscle engineering, such as Induced Pluripotent Stem Cells (iPSCs), which can be used to facilitate sustainable and personalised re-engineering of damaged or lost muscle tissue.[10-15]

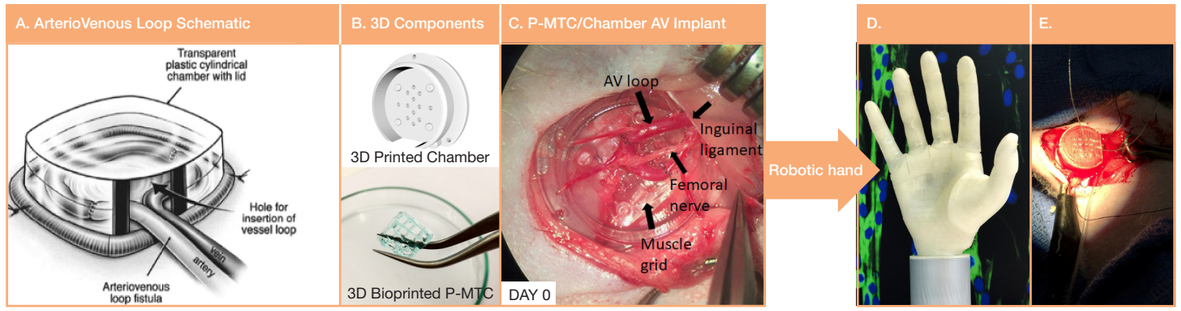



Figure 3. Design process and stages for living electrode systems in biomechatronic robotic prosthetic limbs. A. Arterio-venous loop (AVL) system schematic for vascularised tissue at electrode interface. B. Pre-assembly 3D printed chamber (MED610) and 3D printed muscle construct. C. Assembled chamber/muscle/AVL implant connected to rat casculature and peripheral nerve as a living electrode implant. D. Mechatronic robotic hand designed to integrate with the living electrode to process and translate nerve signals to actuation of digits in the hand. E. Living electrode implant after 4 weeks' implantation in a rat with electrode (wires) in place to read nerve signals from the attached peripheral nerve. Figure courtesy of Dr Catherine Ngan

## 3. Helping people age well

As the global population ages, the prevalence of age-associated conditions such as osteoarthritis and diabetes is also increasing. Innovative biomedical solutions are urgently needed that enable clinicians to support people to age well and maintain active lifestyles for longer.

**Musculoskeletal conditions** affect around 30% of the Australian population, representing almost one quarter of the non-fatal disease burden in this country.[j] About two million people (~10% of Australians) are affected by osteoarthritis, a dystrophic condition that causes progressive loss of bone cartilage. Age-related arthritic conditions affect up to 20% of all people over the age of 60.

Biofabrication and tissue engineering technologies can deliver new personalised solutions to address osteo (bone), osteochondral (bone/cartilage interface) and chondral (cartilage) defects that occur with ageing, injury and disease. Stem cells from the person with the osteochondral defect can be converted to precursor components of the osteochondral interface and fabricated within a compliant matrix that supports the appropriate development of functional cartilage tissue (Fig. 4).

**Diabetes** is a major condition that compromises the ability of many older Australians to age well. Australian Bureau of Statistics (self-reported) figures from 2017–18 show that more than 1.2 million (>6% ) Australian adults over the age of 18 are living with Type 1 or Type 2 diabetes. The incidence in older Australians (65–75 years old) is three times higher than for people aged between 45–54 and 1.5 times higher than for those aged 55–64, and affects 13 in every 100 Aboriginal and Torres Strait Islanders.[k]

This highlights diabetes as a major condition that compromises ageing well within the wider Australian community.[l]

These statistics translate on a global scale, with the American Diabetes Association reporting that 9.4% of Americans (30.3 million people in 2015) live with diabetes, generating a national annual cost burden of more than US$245 billion per annum.

The clinical need has never been greater for the creation of an artificial, living pancreas that will enable a person with diabetes to produce their own insulin. Having an implanted, self-regulating artificial pancreas will remove a diabetic individual's reliance on drugs and minimise the many downstream issues associated with diabetes. Biofabrication and tissue engineering approaches can develop personalised 3D constructs containing autologous Islet of Langerhans cells derived from non-islet stem cell sources. These active matrices can be implanted as living 'synthetic pancreatic tissue constructs', using a similar technique to the living electrode arterio-venous fistula illustrated in Figure 3 for improving prosthetic devices.

> Stem cells from a person with the osteochondral defect can be converted to precursor components of the osteochondral interface and fabricated within a compliant matrix that supports the appropriate development of functional cartilage tissue.

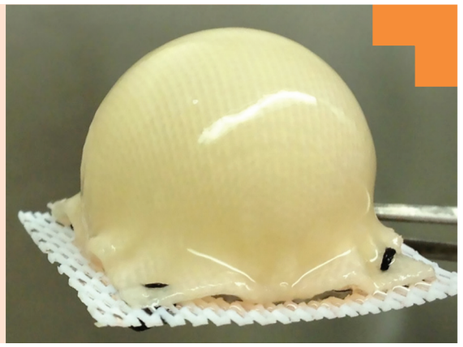


Figure 4. A biofabricated 3D scaffold moulded to the shape of a hip joint. Fabricated from fat-derived stem cells turned into cartilage cells and biodegradable polymers, this scaffold may lead to treatments for hip osteoarthritis. Source: Creative Commons.

## 4. Repairing nerve damage

Peripheral nerve damage can be caused by external factors such as trauma or internal processes such as neurological disease, soft tissue injury or non-neurological disease (e.g. cancer).[16, 17] It can result in the loss of sensation and function in target organs and cause mild to severe incapacitation. The most prevalent peripheral nerve injuries occur in the upper extremities of young males,[18,19] imposing a high cost burden on the community through lost productivity and psychological trauma.[20, 21]

Estimates from retrospective studies indicate that every year more than one million people in the USA suffer serious peripheral nerve injuries arising from lower limb trauma.[16] It is estimated that more than 50,000 procedures are performed per annum in that country, costing more than US$7 billion,[22] to correct problems associated with such injuries. Neuropathies or nerve dysfunction due to other pathological processes, such as diabetes, further the socio-economic impact of peripheral nerve injury.[23]

Minor nerve injuries can usually regenerate on their own and most short gaps (up to 2 cm) can be repaired by suturing.[24] Larger or more severe injuries need to be treated surgically and are commonly treated by procedures using autologous nerve grafts harvested from elsewhere in the body. The use of such grafts is far from ideal and can result in suboptimal function, the formation of neuroma, and/or sensory loss in the tissue innervated by the harvested nerve.[25]

Tissue scaffolds based on allografts, xenografts and various bio-resorbable or non-resorbable polymers have been proposed for repairing defects in the peripheral nervous system (PNS).[26-28] However, it is noteworthy that despite their inherent drawbacks and significant activity in developing synthetic nerve repair conduits, allografts remain the gold standard for neurosurgeons.

Biofabrication and tissue engineering science is capable of developing a bio-optimised nerve repair conduit that addresses the shortfalls in current repair devices. Sheath and core matrix components will be made using additive technologies with materials that comply physically and biologically with the damaged peripheral nerve milieu. Controlled release biomolecules will further condition the recipient damaged nerve towards a regenerative state, while internal lumen materials will biomimetically support functional cells and prevent fibrosis post implant.

These pro-neural materials and accessory technologies can also be applied to the generation of 3D central nervous system (CNS) constructs containing iPSC-derived neural precursor cells for repairing gross defects in CNS tissue.

[j] Australian Institute of Health and Welfare (AIHW). The Burden of Biofabrication Conditions in Australia: A Detailed Analysis of the Australian Burden of Disease Study 2011. Canberra: AIHW; 2017.
[k] https://www.diabetes.org/
[l] AIHW (Australian Institute of Health and Welfare) 2015. Cardiovascular disease, diabetes and chronic kidney disease—Australian facts: Aboriginal and Torres Strait Islander people. Cardiovascular, diabetes and chronic kidney disease series no. 5. Cat. no. CDK 5. Canberra: AIHW. ABS (Australian Bureau of Statistics) 2018. National Health Survey: First Results, 2017–18. ABS cat. no. 4364.0.55.001. Canberra: ABS. Viewed 30 April 2019.



## 5. Creating personalised diagnostics

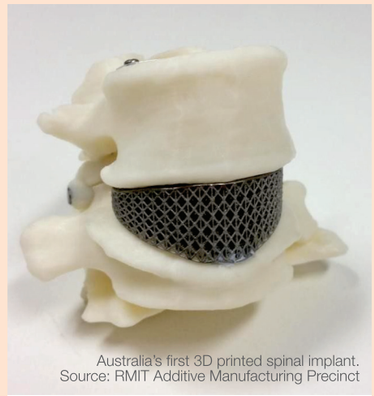
Another significant clinical need exists for better patient-specific screening approaches to help clinicians determine appropriate drug treatments, particularly when treating people with neurological diseases such as epilepsy.

The combination of advanced engineering, materials, fluidics and manufacturing technologies is already generating benchtop disease models that mimic the natural tissue behaviours and responses in human organs (e.g. 'organs-on-chips' and 'tissue-on-chips' devices). Advanced microfluidic-based diagnostic systems based on these principles will enable clinicians to precisely evaluate a person's response to various drug regimes.

For example, a 'CNS drug evaluation chip' can be created using a patient's stem cells to generate functional 3D neural cultures that replicate functional epileptic activity. These three-dimensional cultures can be integrated into electrophysiological fluid platforms developed for evaluating disease function development and testing the person's functional response to drug treatment.

Advanced fabrication facilities, such as the MicroNano Research Facility at RMIT University's Melbourne City Campus, provide state of the art technical resources and expertise for designing and manufacturing these new-era chip-based diagnostic devices.

Modelling human organs and diseases in vitro in this manner will also help to accelerate the development of new drugs and reduce the need for using laboratory animals for tissue function diagnostics and evaluation.



Australia's first 3D printed spinal implant. Source: RMIT Additive Manufacturing Precinct

### Biofabricated scaffolds for tissue replacement

RMIT researchers collaborated with a medical device company and neurosurgeons to successfully deliver a tailored, 3D-printed vertebral cage to a patient with severe back pain.

Bespoke scaffolds such as this are designed to specifically fit into the individual patients by 3D modelling, providing a 'best fit' implant.

Custom-printed bone implants such as these will precisely fill the space left after removal of a section of diseased bone. Source: RMIT University

### Advanced implants for treating bone cancer

3D implants and robotic surgery are radically advancing the way physicians surgically treat bone tumours and cancer. A project led by RMIT's Professor Milan Brandt in collaboration with Professor Peter Choong (St Vincent's Hospital Melbourne) combined 3D printing, robotic surgery and advanced manufacturing to create tailored implants for people with bone cancer.

In collaboration with international industrial surgical entity Stryker, this highly innovative process represents a major shift in the way implants are designed, manufactured and supplied to repair bone lesions in people.

> By combining specialised imaging techniques, 3D printing and the accuracy of robotic assisted surgery, we are aiming to deliver a personalised implant in time for the surgeon to remove the cancer and repair the patient's bone in the one operation.

- Professor Peter Choong, Orthopaedic Surgeon, St Vincent's Hospital Melbourne

# Challenges to be met by biofabrication research and industry

Significant effort is required to deliver a fully optimised process for translating robust biofabrication and tissue engineering technologies into tangible and valid applications in human healthcare. The singular aspect of biofabrication that will realise translatability, commercialisation and, ultimately, the delivery of biofabrication solutions to the community, lies in the cross-disciplinary integration of numerous key established disciplines.

Established disciplines such as Materials Engineering, Mechatronics, Biological Science, Advanced Manufacturing and Fabrication, Biomedical and Health Innovation and other biofabrication-relevant technologies provide a stable platform from which to develop a strong translational pathway for biofabrication solutions for human health issues (Fig. 5).

There is a lack of in-depth understanding within the industry of the variety of next-generation technologies capable of handling, mimicking and supporting the unimaginable natural complexity of living organisms

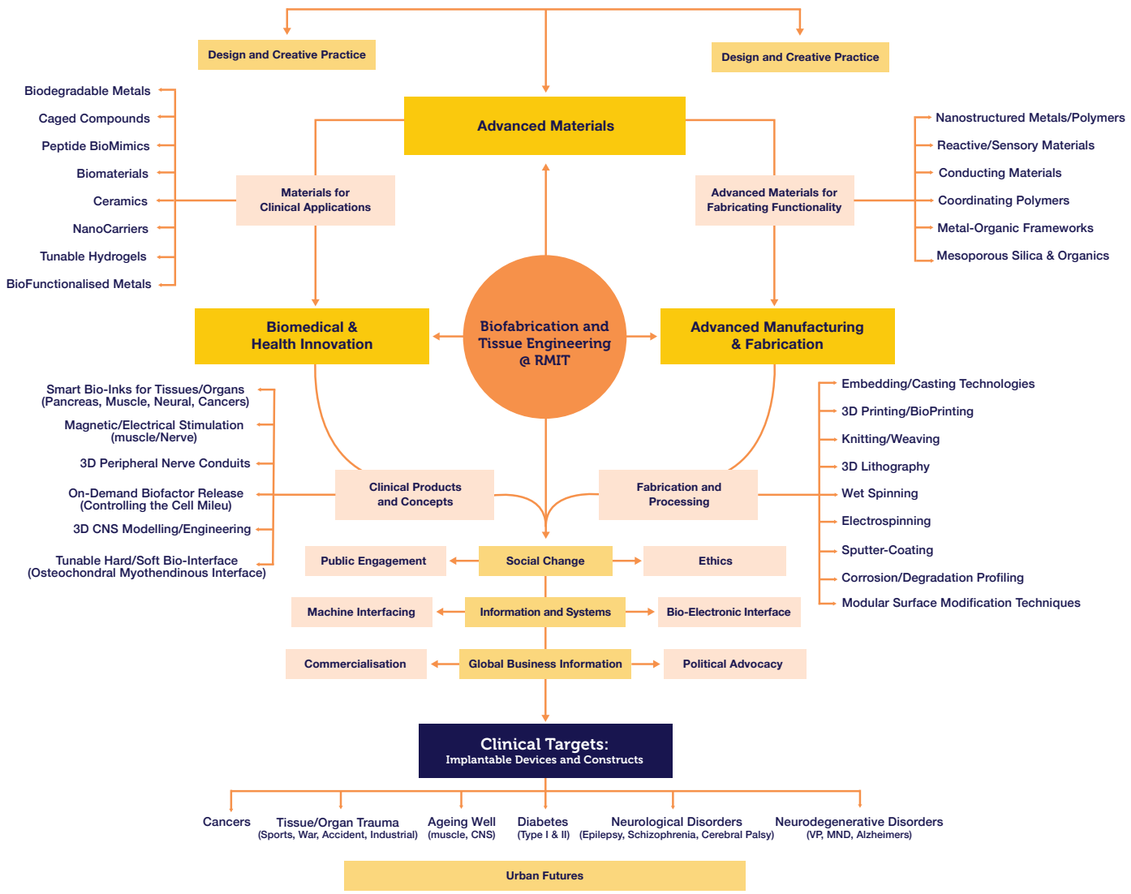



Figure 5. Integrational schematic for the cross-disciplinary development of biofabrication products for use in clinical applications. Based on RMIT University's internal Biofabrication and Tissue Engineering research focus area and its key interface disciplines.



Rapid, innovative progress is being made within experimental research settings and among pioneering collaborations involving researchers and clinical entities such as the collaborative BioFab3D@ACMD hub based at St Vincent's Hospital in Melbourne.

Integrating such centres within a practising hospital environment provides a clinical focus for participating research institutions and their collaborative activities.

In the global biomanufacturing industry, the ability to translate biofabrication research into commercial outcomes follows a structured pathway that traverses technical; production; and regulatory, promotional and logistical issues, as shown in Figure 6.

As such, several critical areas of challenge can be identified that need to be met before the biomanufacturing industry consistently delivers fully functional tissue assemblies and organs capable of successfully replacing or supporting the regeneration of damaged body parts or functions.

## 1. Limited choice of materials suitable for biofabrication

The choice of materials suitable for constructing synthetic tissues is currently very limited. It is therefore necessary to compromise when selecting materials for specific biofabrication applications to ensure their processability while minimising their impact on cell viability. Thus at best, currently achievable biofabricated construct configurations still fall short of satisfying the full requirements of the post-implant cellular and tissue environments.

New sources of materials will alleviate some of the current compromise and enable biofabricated configurations to be developed that effectively remodel failing tissue systems.

It is also essential to develop more effective reactive biomolecular components (e.g. growth factors) and biocomposites to better control and influence cells' development and behaviour to enable desired functions within the bio-construct to be restored. These new-generation bioactive systems need to be developed under a cross-disciplinary feedback loop, where biological evaluation supports materials and process engineers to develop specific modular features and properties within complex biomolecular constructs.

These considerations are within reach of current technologies and necessitate the building of deeper knowledge around how bioactivities are affected by and interact with the physicochemical properties of scaffold materials and constructs. As such, better understanding and control of inherent material factors such as viscoelasticity, stiffness, porosity, and degradation and corrosion rates will deliver more functionally dynamic structures that integrate more effectively into dysfunctional tissue systems.

This challenge within the field of biofabrication is highlighted by multitudes of existing patents based on a very limited number of materials and techniques for constructing imperfect, but nevertheless functional structures.

**There is a lack of in-depth understanding within the industry of the variety of next-generation technologies capable of handling, mimicking and supporting the unimaginable natural complexity of living organisms.**

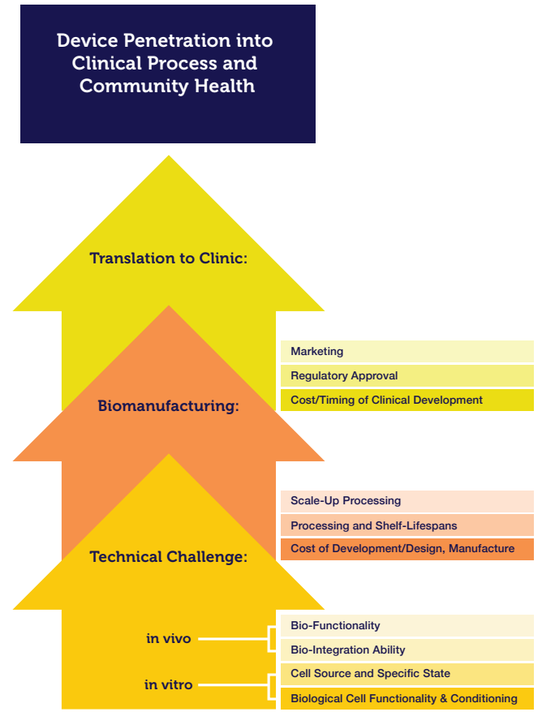



Figure 6. Developmental milestone pathway for translating biofabrication technologies from research to clinical application

## 2. Restoring complex biological structure and function

Many gaps remain in the scientific understanding of how complex tissue and organs develop and function at cellular and molecular levels. There is still much to be learned about how these complex (dysfunctional) biosystems interact with biofabricated constructs and implants in order to restore native tissue function.

In particular, further study is needed to determine how biofabricated implant design can promote complex and controlled functional outcomes in tissues. Existing knowledge of biofabricated

constructs' abilities to influence cell differentiation and integrity is limited to very few cell types that compose target tissues. The ongoing challenge lies in perfecting cells' rapid, coordinated development and organisation within the recipient tissue to form all viable sub-tissue compartments required for restoring healthy tissue function.

## 3. Achieving full bio-integration

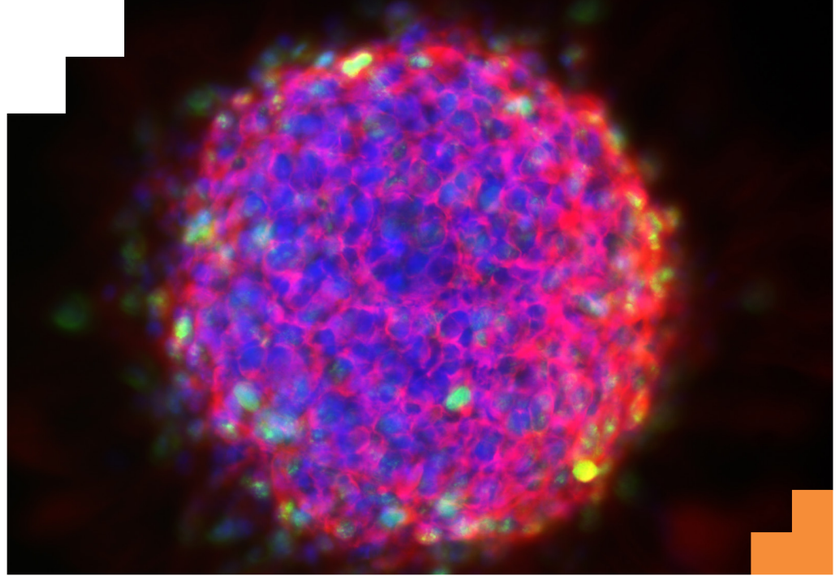
There is a disconnect between biofabricated materials and structures in terms of their ability to completely integrate into target tissues. This is largely because the limited choice in materials and techniques constrains the level of sophistication in functionality that can be successfully incorporated into biofabricated structures. This process fails to include specific sub-structures required to achieve fully integrated, matured and functional tissue, such as innervation, vascularisation, immune system reactivity or forming functional tissue interfaces (e.g. osteochondral, neuromuscular, myotendinous). These need to be incorporated as secondary functionalities independently engineered into biofabricated constructs.

Such applications require much greater fine-tuning of materials formulation and construct composition than is currently available from existing technologies and knowledge. Addressing these areas will deliver highly defined, multi-modal implants that achieve appropriate neogenesis of functional tissue by coordinated, reciprocal interaction with the regenerating tissue environment.

## 4. Optimising the sourcing, development and management of cells

The sourcing of cells to be used in biofabricated constructs, and good manufacturing protocols for cultivating, developing and maintaining them, needs to be addressed. Specific integrative and regenerative cell states need to be better understood to establish constructs that promote controlled development of a fully integrated functional tissue.

Specific cell state needs to be matched to specific tissue applications for more comprehensive and integrated tissue remodelling outcomes. Better understanding of bioreactor technologies



Three-dimensional spheroid culture of human neural stem cells. These can be used for characterisation of human neural behaviour ex vivo. Courtesy of Dr Anita Quigley, RMIT

will enable fine control of cell state and allow their expansion to numbers sufficient for applied biofabrication outcomes. In particular, cells that promote functional rather than non-function or otherwise inhibitory (e.g. fibrotic) post-implant responses can be selectively cultivated using bioreactor technologies.

There is a highlighted need for prioritising cell protocols for ubiquitous as opposed to personalised applications. For ubiquitous applications where the cells are used primarily for generic scaffold and construct development, universal cell line resources are required. In contrast, more complex applications may require autologous stem cell-derived cells (e.g. derived from induced pluripotent stem cells) to promote regenerative effects in tissue systems exposed to the host immune environment. Integrating these applications into biofabrication protocols will improve delivery time, logistics and costs. This will facilitate the most effective penetration of new, highly effective cell-based biofabrication technologies to the masses rather than to a privileged few.

## 5. Creating standardised procedures

Standardised procedures for evaluating the biological effects of material-cell interactions within a biofabricated construct context need to be established and universally adopted at the molecular level. This will introduce effective comparability within the global biofabrication community that in turn, will facilitate the rapid development of highly effective products for the growing biofabrication market.

The demand for personalised health solutions calls for highly complex diagnostic and monitoring techniques to assess their efficacy, which at present do not exist. This creates another layer of R&D opportunity, while also expediting the development of viable new devices and products.

## 6. Expanding the suite of fabrication and manufacturing techniques

Protocols for using multiple different materials will be required in order to rebuild complex tissue interfaces such as osteochondral, myotendinous and neuromuscular junctions. This requires better engineering of desired mechanical, resolution, bioactivity and elasticity profiles than is generally possible with current biofabrication protocols.

Thus, a more comprehensive and encompassing suite of fabrication and manufacturing technologies is needed to produce market-ready biomaterial devices and products. This will improve repeatability, resolution and multi-material handling capabilities.

These new technologies will also draw out new properties and capabilities from existing materials by fabricating, manipulating and configuring them in ways beyond current methods.

Innovative additive biofabrication hardware solutions (from printheads to bioreactors) generated as new mechatronic devices and procedures will enable diversity and specificity in choices of material for new generation biofabrication products.

## 7. Establishing ethical, regulatory, public acceptance and translational pathways

The degree of complexity and innovation inherent in biofabricated technologies and the novel products and devices they generate are likely to be met with natural resistance, wariness and scepticism in some sections of the market. This highlights the importance of creating effective public engagement protocols to bring industry and end users along on the journey of discovery.

The necessity to raise understanding, socialise concepts and ensure end-user requirements are embedded in product development processes are an often under-estimated imperative for delivering successful new technologies to stakeholders.

Ethical considerations arising from step-change biofabrication solutions for the healthcare sector include ensuring the sustainability of the materials and processes being used, and making sure the benefits are universally available to all rather than to only those who can afford them. These considerations need to be addressed by engaging proactively with the wider global community, industry and government stakeholders and, in particular, with appropriate sub-sectors of the community that are directly relevant to the specific biofabrication technologies being proposed.

Regulatory approval processes relating to biomaterials, biofabricated devices and constructs, and the protocols for their assembly, are currently in a state of under-developed transition. There are few regulations covering 3D-printed tissue constructs or point-of-care manufactured organs. They mostly come under the US FDA 510(k) – medical devices pre-market notification protocol and ISO 13485 quality management standard, which are more relevant to mechatronic implants and do not adequately accommodate the biofunctional nature of biofabricated constructs for implanting into human tissue systems.

A lack of adequate regulatory standards leads to variability in the application and format of quality control and good manufacturing protocols for biofabricating implantable constructs. This especially relates to the standardisation of reliable, reproducible and biocompatible protocols for cell generation, material sourcing and synthesis, and tissue-informed requisites for safety and efficacy. Significant effort in this area will result in the production of highly effective, reproducible constructs that can be used safely in people to ameliorate defective tissue function.

The current focus on developing personalised and custom-made solutions requires a combined approach that involves both generic and individual-specific components for establishing safe and effective applications for biofabricated solutions. Current protocols relating to quality assurance, quality control, clinical evaluation and regulatory procedures are not readily available in the personalised biofabrication space.

As such, obvious and well-defined gaps exist that need to be addressed in relation to fundamental life sciences, R&D, fabrication and manufacturing technologies, as well as the peripheral regulatory and further lifecycle support of tissue-engineered products. These need to be resolved before a systematic approach to clinical trials can be established for translating biofabricated solutions for human health issues.

Figure 7 indicates some of the key checkpoints along the pathway to developing and translating biofabricated constructs for clinical use.

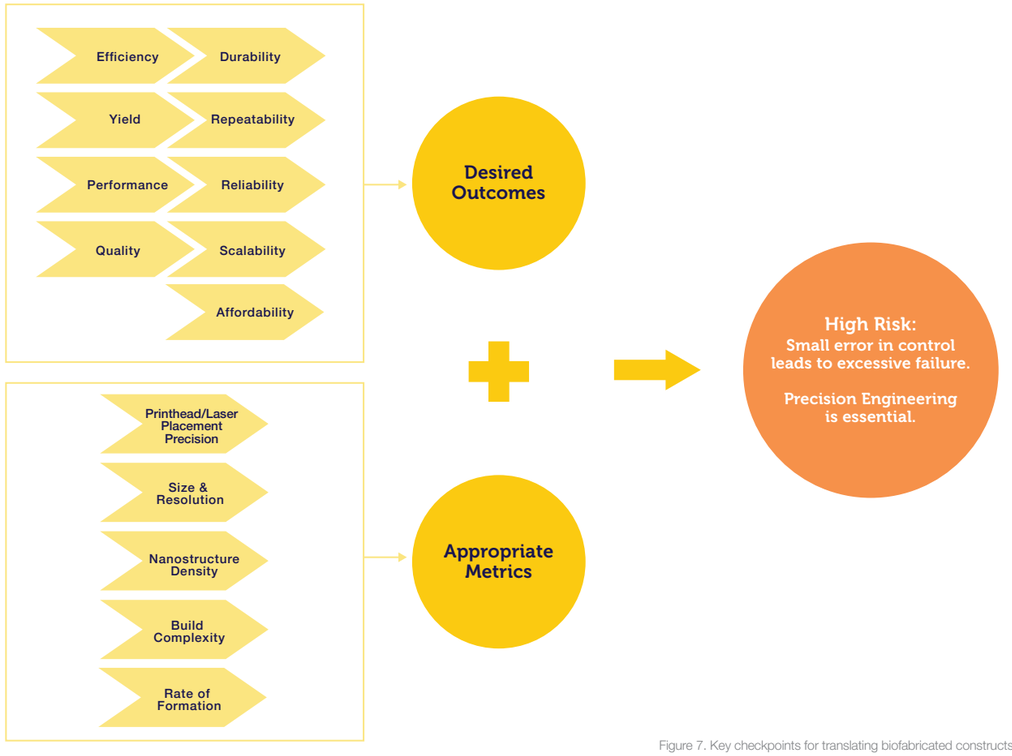



Figure 7. Key checkpoints for translating biofabricated constructs


# Further areas for consideration

## Expand cross-disciplinary research

The journey from conceptualising innovative healthtech solutions to creating clinically and commercially viable products that reach people at the community level is a long and bumpy one. This is where drawing on extensive cross-disciplinary resources, particularly those with applied research capability, is invaluable.

For example, applied research teams working in this field need to either include or have ready access to experts working in fields such as bioinformatics, ethics, intellectual property, business development, research translation, industrial design, global business networks, marketing and product commercialisation.

## Viable biomanufacturing processes

Well thought-out biomanufacturing processes are critical for enabling the rapid development of biologicals and medical devices to market. Establishing Good Laboratory Practices and adherence to Therapeutic Goods Administration requirements (for biologicals and medical devices) at all process levels will ensure rapid translation. The focus needs to be on developing sustainable, socially conscious manufacturing techniques.

## Embrace human-centred design

Many medical technology products created using biofabrication techniques will be attached to or implanted into the bodies of individuals. These new products and devices will be more acceptable and beneficial to the market if the entire R&D process incorporates human-centred design.

Healthtech developers therefore need to be cognisant of not assuming they already know what end users want and 'inflicting' products on the market that ultimately receive low user acceptance. The needs, likes and dislikes of end recipients need to be understood as early as possible and considered throughout the entire R&D process. For example, the aim would be to develop prostheses that people feel better about wearing, implantable devices and tissue constructs that adapt seamlessly into a person's body, and diagnostic tools that are both clinician and patient-friendly.

Ensuring these products match recipient expectations supports a rapid and successful translation to market while also enhancing the physical and mental wellbeing of the people who use them.

**Ensuring these products match recipient expectations supports a rapid and successful translation to market while also enhancing the physical and mental wellbeing of the people who use them.**




3D-printed titanium covered with the diamond coating. Source: RMIT University

## A diamond-coated solution

RMIT research headed by Associate Professor Kate Fox is set to radically improve the way human bodies accept biomedical implants. The project has developed technology to coat 3D printed titanium implants with diamond as a first step toward 3D-printed diamond implants for biomedical uses and orthopaedic applications.

Titanium is currently the gold standard for medical implants. However, although the metal offers a fast, accurate and reliable material for medical grade and patient-specific implants, human bodies sometimes reject this material. Coating titanium implants with synthetic diamond obviates this issue.

The research team used detonation nanodiamonds to create the coating, which are cheaper than the titanium powder. The diamond enhances the integration between the living bone and the artificial implant, and reduces bacterial attachment over an extended period of time.

> Not only could our diamond coating lead to better biocompatibility for 3D-printed implants, it could also improve their wear and resistance. It's an exceptional biomaterial.
>
> – Associate Professor Kate Fox, RMIT

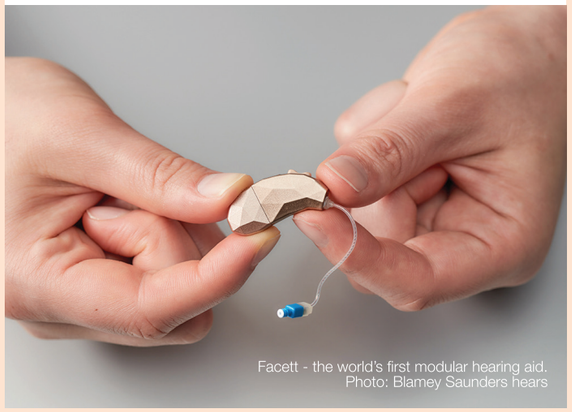
## Designing a device that people want to wear

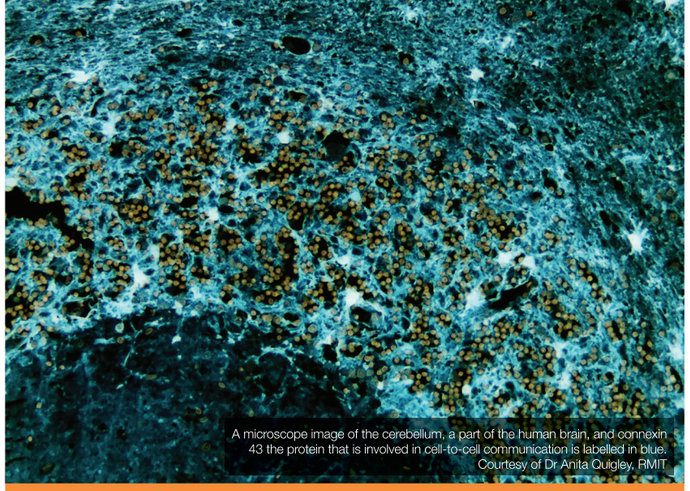
Human-centred design is at the heart of the world's first modular hearing aid, developed through a deep design collaboration between RMIT and industry.

The perceived stigma of wearing a hearing aid is a significant barrier for millions of people who have untreated hearing loss. However, the revolutionary, multiple award-winning Facett hearing aid is not only highly functional, it is also designed to look like a beautifully facetted piece of jewellery.

A lecturer from RMIT's School of Design spent almost nine months embedded in the company developing the device. She joined engineers and audiologists during R&D discussions and kept end users' needs and preferences at the forefront of the development team's mind. The RMIT design specialist then spent days studying specimens in Museum Victoria's mineralogy collection and assisted in developing 130 iterative prototype designs to achieve a final market-ready design.

Facett's development reflects RMIT's approach to creating applied health solutions in partnership with industry that are perfectly aligned with end users' needs.


Facett - the world's first modular hearing aid. Photo: Blamey Saunders hears



A microscope image of the cerebellum, a part of the human brain, and connexin 43 the protein that is involved in cell-to-cell communication is labelled in blue. Courtesy of Dr Anita Quigley, RMIT

> We're already living in the world of tomorrow with this game-changing new field of biomedical science ... It's time for the clouds to finally burst and the deluge of step-change medical and healthcare solutions to flow out into society.
>
> - Dr Erol Harvey, Head Strategy and Translation, Bionics Institute

# Conclusion

It is inevitable that cross-disciplinary research will ultimately deliver biofabrication and up-scaled biomanufacturing technologies that will yield step change improvements in healthcare management applications. This will provide unprecedented availability of products and processes that allow full reparation of dysfunctional body tissues and improve life expectancy and quality of life for billions of people worldwide.

For people who face having to endure disability for their remaining lifetimes, biofabrication and tissue engineering technologies represent freedom from the pain, incapacity and psycho-social impediment that will otherwise afflict their lives.

It is time for scientists, technologists and engineers to partner with industry, clinicians and other end-users to deliver what people in the community need

**It is time for scientists, technologists and engineers to partner with industry, clinicians and other end-users to deliver what people in the community need.**

Collaborative cross-disciplinary research will overcome the challenges described in this white paper to achieve translational biofabrication outcomes that satisfy critical clinical needs. This will open the floodgates of opportunity for biofabrication technologies and deliver transformative outcomes for long-standing human health issues.

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# RMIT at the frontier of healthtech innovation

## Internationally recognised research capability

RMIT has demonstrable capability to deliver highly innovative, cross-disciplinary solutions for treating human conditions such as diabetes and other metabolic diseases; cancers; tissue injury, dysfunction and disease; and for addressing disorders of the central and peripheral nervous systems.

Expertise and resources within and outside RMIT's colleges, schools and eight research-oriented Enabling Capability Platforms (ECPs) coalesce to provide a broad cross-disciplinary capability that integrates research, clinical practice and education. RMIT is therefore well-positioned to deliver clinically and biologically-informed transformative education, research and translation in fields such as biofabrication and tissue engineering, to benefit industry partners, research collaborators and the wider community.

## Pioneering biofabrication research collaborations

RMIT has well-established, integrated partnerships with major clinical entities and complementary research institutions. These pioneering relationships are giving RMIT ground-floor influence in developing rapid, iterative 'clinic to lab to workshop to community' translation approaches to delivering high-impact biomedical solutions.

For example, RMIT is a founding partner, with St Vincent's Hospital and several other institutions, in the BioFab3D centre – Australia's first hospital-based biofabrication lab. Established in 2016, this state-of-the-art robotics and biomedical engineering facility brings together researchers, clinicians, engineers and industry partners to collaboratively build biological structures such as cartilage, muscle, bone, nerves and organs.

A new $210 million healthtech research centre planned for St Vincent's Hospital, the Aikenhead Centre for Medical Discovery (ACMD)[1], will expand on the BioFab3D multi-institutional partnership model. ACMD will serve as a hub fusing medicine, engineering, science and industry. The new centre is being established through a unique partnership between several of Australia's best universities and medical research institutes and a leading health services provider.

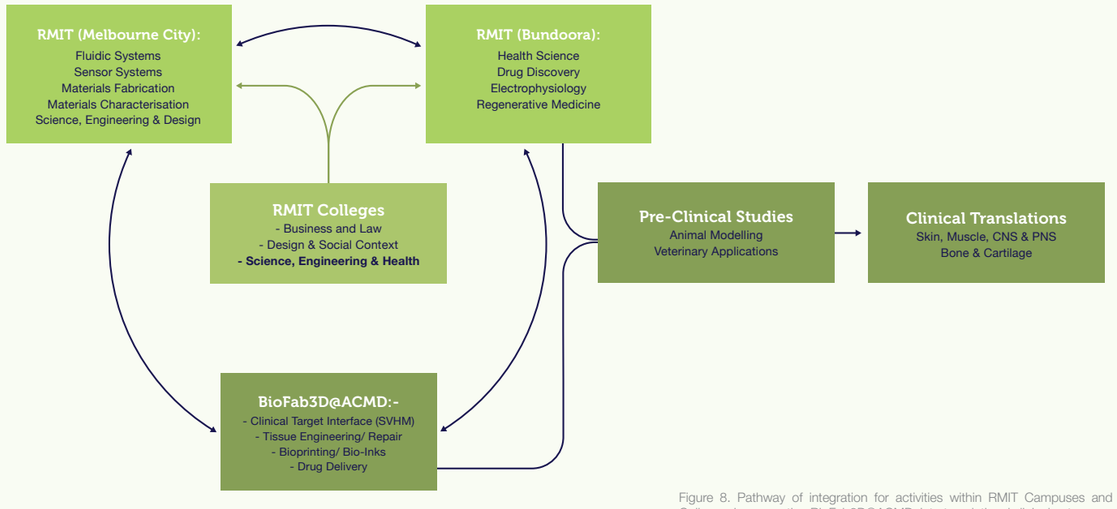


Figure 8. Pathway of integration for activities within RMIT Campuses and Colleges, incorporating BioFab3D@ACMD, into translational clinical outcomes.

[1] Aikenhead Centre for Medical Discovery (ACMD), named after the Sisters of Charity founder, Sister Mary Aikenhead, will house researchers, clinicians, educators, and students from the following partner organisations in addition to RMIT: St. Vincent's Hospital Melbourne (SVHM); St. Vincent's Institute of Medical Research (SVI); Bionics Institute (BI); Swinburne University of Technology (SUT); Australian Catholic University (ACU); and University of Wollongong (UoW).



## Enabling Capability Platforms

As a modern multi-centre University, RMIT's cross-disciplinary capacity in biofabrication and tissue engineering is harnessed and amplified by its eight ECPs. Unlike conventional discipline-based research structures, RMIT's ECPs connect researchers from multiple disciplines and across RMIT's schools and colleges infrastructure under eight interconnecting thematic umbrellas.

RMIT's biofabrication capability is shared across three ECPs: Advanced Manufacturing and Fabrication, Advanced Materials, and Biomedical and Health Innovation. Expertise from other ECPs is available to contribute to biofabrication and tissue engineering projects as required, as indicated in the table below.

Significant scientific capabilities exist within disciplines dealing with Materials Engineering, Biological Sciences, Manufacturing and Fabrication, and Biomedical Health technologies. Collectively, these capabilities can generate biofabrication technologies to address key clinical issues that existing medtech has been unable to resolve within the global community. RMIT's social, economic and business centres add deep expertise in Design, Ethics, Social Science and Business Innovation disciplines to help translate these new technologies to the people who need them.

**RMIT Enabling Capability Platforms' contribution to biofabrication and tissue engineering research activities**

| Contribution | Advanced Manufacturing and Fabrication | Advanced Materials | Biomedical and Health Innovation | Design and Creative Practice | Global Business Innovation | Information and Systems (Engineering) | Social Change | Urban Futures |
|---|---|---|---|---|---|---|---|---|
| Core | ✓ | ✓ | ✓ | ✓ | | | | |
| Strategically Aligned | | | | | ✓ | ✓ | ✓ | |
| Contributing as needed | | | | | | | | ✓ |

## New biofabrication research focus

RMIT is intensifying its focus on developing innovative, high-impact biofabrication and tissue engineering solutions to address the key clinical needs identified in this white paper. The University is establishing a cross-disciplinary, collaborative research focus area to drive and integrate its research, clinical practice and education activities and outcomes in these fields. The core 'ecosystem' of this new focus area is indicated in Figure 8.

The intention is to translate RMIT's research in this area into unprecedented clinical outcomes of major significance to the scientific and higher education community, the healthcare sector and, most importantly, the wider global community. By coordinating RMIT's internationally recognised capabilities, forging new clinical and surgical partnerships and engaging with health sector industries, the research will support the development of highly effective new solutions to long-standing health issues such as those mentioned in this white paper.

The new research area will have two primary streams:

**1. Tissue regeneration and functional repair:** New biomaterial formulations will be developed for specific clinical target applications and used to generate implantable autologous tissue constructs and develop innovative biofabrication processes. The aim will be to progressively address structural and compliance aspects of materials with target tissue systems. Biomechatronic implants with advanced tissue interfacing capabilities will address communication of tissue systems with electronic monitoring or actuation devices to restore tissue dysfunction. These new interfacing technologies will also be used to promote tissue–tissue interfacing as sub-functions of regenerative implants that optimise implant integration into target tissue.

**2. Tissue modelling for screening and diagnostics:** Bio-informed, multi-dimensional 3D and 4D synthetic tissue constructs that accurately reflect the processes taking place within the human body, will be developed for use in modelling, screening and diagnostics.

RMIT researchers will target muscle, nerve, skin and ovarian cancers; disease and trauma-induced tissue damage; musculoskeletal disorders; diabetes; and neurological and neurodegenerative disorders such as epilepsy. In addition, RMIT's collaborative research teams will work on finding solutions in areas of age-related tissue dysfunction, such as muscle wasting, arthritis and dementia.

## Access to major research funding opportunities

RMIT's new biofabrication and tissue engineering research focus aligns with Australia's National Health Priority Areas of: arthritis and musculoskeletal disease, injury prevention and control, mental health, cancer, cardiovascular disease and diabetes. It also addresses the Victorian Health Priorities Framework 2012–2022: Metropolitan Health Plan, which aims to expand Victoria's role as a national leader in health and medical research.
The direct relevance to national and state health priorities opens up numerous opportunities for RMIT and its industry partners to secure government funding for collaborative research projects. The strong focus among government funders on research translation and commercialisation also positions RMIT and its collaborative research partners to tap into capability and impact-focused funding initiatives.

## Ongoing commitment to applied research

RMIT has a long history of delivering practical solutions for industry through applied research. The University's researchers are committed to supporting their partners to create and capture value through tailored approaches for small business through to leading research programs in large consortiums.

The University's research teams are working with a wide range of industry partners and research collaborators, large and small, to rapidly unlock the practical applications of biofabrication, tissue engineering and associated biomedical technologies. Biomaterials, biofabrication, biomanufacturing, biofactor delivery, sensor, tissue engineering and commercialisation technologies emerging from RMIT's ECPs, Colleges, Schools and new research focus areas will deliver high-impact solutions for addressing clinical needs that existing technologies have been unable to resolve.

## Key RMIT facilities for high-impact biofabrication

### Advanced Manufacturing Precinct (AMP)

Unique in Australia, the AMP houses some of the most advanced manufacturing technologies available worldwide. RMIT has the capability to build final products direct from a computer model in both polymers and high-tech metal alloy powders. The available state-of-the-art additive manufacturing technologies include:

- Selective laser melting (metal-based technology)
- Direct laser metal deposition (metal-based technology)
- Fused deposition modelling (polymer-based technology)
- Objet machines (polymer-based technology)
- Multi-Dimension bioprinting (GeSim), and
- U Print machines (polymer-based technology).

### MicroNano Research Facility (MNRF)

A $30 million, 1200 $m^2$ building that drives cutting-edge advances in micro- and nanotechnologies, supporting projects across the traditional disciplines of physics, chemistry, engineering, biology and medicine.

The world's first rapid 3D nanoscale printer was installed in this facility and is capable of producing thousands of structures – each a fraction of the width of a human hair – in seconds. It also offers more than 50 cutting-edge tools, including focused ion beam lithography with helium, neon, and gallium ion beams to enable imaging and machining objects to 0.5 nm resolution – about 5 to 10 atoms.
The facility has nine state-of the-art laboratories, including:

- Gas sensors laboratory
- Metrology laboratory
- Novel fabrication laboratory
- PC2 mammalian cell laboratory
- Photolithography laboratory
- Physical vapour deposition laboratory
- Polydimethylsiloxane and nanoparticle laboratory
- Wet etch laboratory, and
- Support laboratory.

### RMIT Microscopy and Micro analysis facility (RMMF)

This facility is equipped with high-quality electron microscopy and microanalysis equipment, which supports a broad range of research activities and can handle everything from chocolate to aluminium, fabrics, and biological and plant materials. The facility enables imaging of materials, organic components and micro-organisms over magnification levels up to x10,000,000 from as small as 1 nm.

### BioFab3D@ACMD

BioFab3D@ACMD, based at St Vincent's Hospital in Melbourne, is a collaborative hub that brings together researchers, clinicians, engineers and industry partners to build biological structures such as cartilage, muscle, bone, nerves and organs: almost anything that requires repair through disease and physical trauma.

RMIT is a key stakeholder in BioFab3D@ACMD, which contains state of the art stem cell, 3D printing, materials characterisation and molecular analysis capabilities that complement and focus RMIT's internal biofabrication capabilities towards translational clinical outcomes.



# Contact RMIT to partner for a better future

Reach our Research Partnerships and Translation Team on:
research.partnerships@rmit.edu.au

Find further information and examples of our success stories at:
https://www.rmit.edu.au/research/research-expertise/our-focus/enabling-capability-platforms

**... the universities can often support and provide a 'thinker' to come into a team who is able to represent a clear, often challenging view, backed by a wealth of knowledge, support and broader thinking as gained in the university space.**

**It's this convergence of commercial strategic development and specialist university-supported global thinking that creates a cutting edge view, with a real passion for delivery motivated by different drivers.**

**Indeed this could present strong possibilities for both industry and universities in delivering innovations through collaboration.**

Dr Elaine Saunders, Co-founder, Blamey Saunders hears, discussing how the company developed the multiple award-winning Facett modular hearing aid in collaboration with RMIT

Insight Series

# Biofabrication and Tissue Engineering

New solutions for long-standing health issues

RMIT UNIVERSITY