Osteopore®

In-vitro and in-situ tissue engineering

Are you aware of the two approaches in tissue engineering?

Why Osteopore® is fast tracking in-situ tissue engineering using 3D printing technology as the enabler

The tissue engineering challenge

There is a lot of hype around in-vitro tissue engineering, because 'growing an organ in a lab' appears futuristic; presenting 'exhilarating' opportunities to help cure the seriously ill. To most people, this seems like an exciting concept.

Like space travel, it is something we have only considered in movies until this point – growing something in a box, then putting it in your body to change your life – it seems unreal but it is becoming reality.

However, in many cases it is also expensive, time-consuming and under-developed – just because something is pushing scientific boundaries doesn't mean it should. It takes time to grow cells and tissue; and there is no guarantee the cells and tissues grown are viable and not mutated.

At Osteopore®, we are looking at a more direct way of applying tissue engineering concepts to achieve clinical impact. In-situ tissue engineering is a more cost-effective and reproducible alternative to in-vitro tissue engineering because of quality control and we can consistently repeat the same desired results.

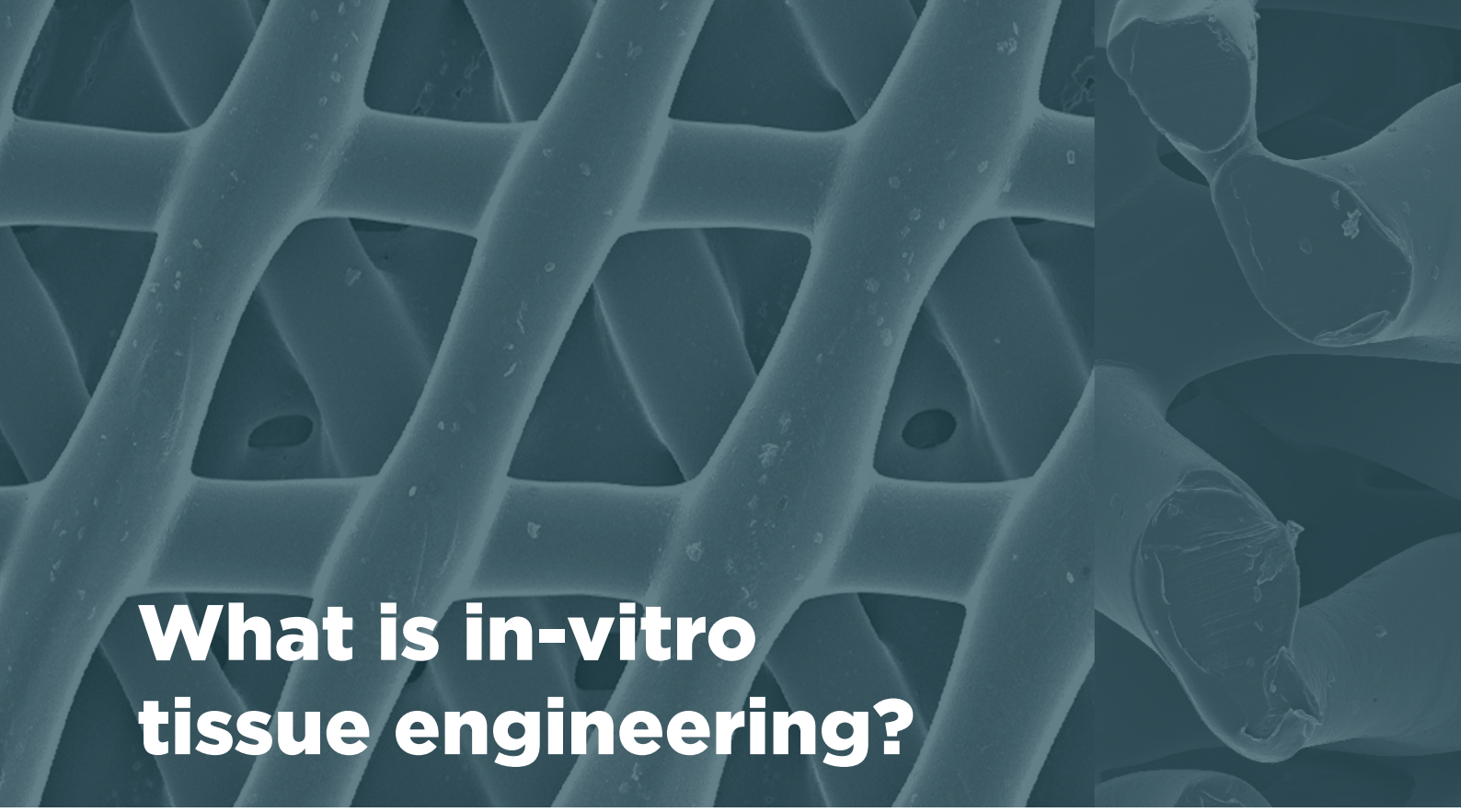
In-situ tissue engineering

With in-situ tissue engineering, we are looking at medical products that interface with blood, blood vessels and cells – working in proposed harmony with how your body already functions.

A recent study by the Biomedical Engineering Society (www.bmes.org) looked closely at the differences between in-vitro and in-situ tissue engineering, finding in-situ tissue engineering represents a promising new avenue of regenerative therapy research.

The Society's study explains in-situ tissue engineering will continue to provide important solutions to the clinical problems we are facing today. We agree.

This whitepaper will explain the pros and cons of the two tissue engineering types, supported by this study.



What is in-vitro tissue engineering?

In-vitro tissue engineering creates functional tissue that can be used to replace tissue in the body and has a number of practical uses in terms of studying biological processes – leading to many significant advances in the area of regenerative medicine.

In-vitro tissue engineering aims to recreate tissue structures that are functionally mature in a bioreactor, which creates a template for how that tissue will behave inside a living organism.

As an example, cardiac tissue can be created in an in-vitro environment by building a scaffold and applying electrical stimulation to recreate how that tissue would operate in the cardiac natural biological system.

In-vitro tissue engineering has also been used successfully in the creation of the artificial bladder.

In this example, bladder biopsies taken from patients were grown in culture, seeded onto an artificially created scaffold (made of collagen and PLGA (poly-lactic-co-glycolic acid) and combined in a bioreactor.

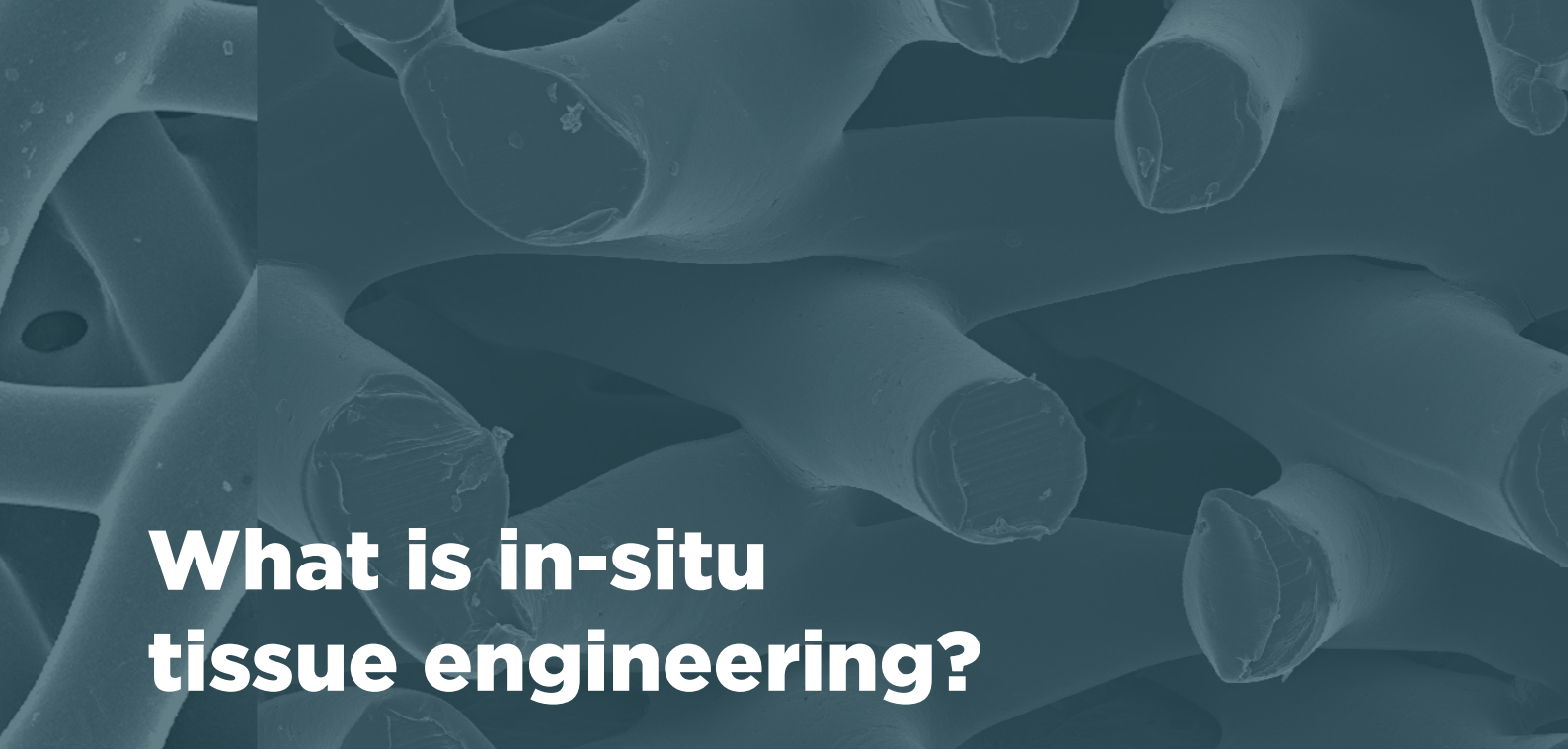
Once those structures had grown to the appropriate size, they were implanted into patients and served the same purpose as a bladder, allowing those patients to regain the use of their bladders.

These structures were not rejected by the immune systems of the patients thanks to the use of autologous tissue (tissue obtained from the same patients the devices are implanted into).

In addition, in-vitro tissue engineering is also being used to develop prevascularized constructs, although that work still has a number of obstacles to overcome.

While in-vitro tissue engineering has a number of practical uses, it also faces a number of concerns before successful standard-of-care implementation in humans. Finding enough cells that are acceptable to the immune system is not simple, and there are also challenges in terms of the availability and scaling-up capability of in-vitro tissue engineering. Cost-effectiveness, preservation and handling also present problems.

There is a growing amount of research that suggests that in-situ tissue engineering may present the answers to these challenging questions.



What is in-situ tissue engineering?

In-situ tissue engineering essentially harnesses the native regenerative potential of the body to regenerate tissue, as opposed to creating it wholesale in an in-vitro environment.

Rather than implanting cells into a body from an external source, in-situ tissue engineering looks to recruit endogenous stem cells (cells created within a living organism) to the site of an injury by using biomaterial with 3D microarchitecture and/or growth-factor-based cues to enhance healing.

When it comes to in-situ tissue engineering, any construct that is implanted into the body is not a fully-functional, full-size replacement of the lost tissue – rather, the constructs look to grow with and enhance the pre-existing regenerative capabilities of the human body.

Biomaterials are an important factor in the in-situ tissue engineering process. They can be used to facilitate interactions that the tissue microenvironment is comprised of – and many have been approved by the FDA. Biomaterials can be synthetic and naturally derived and many are able to assist the body's physiology. It is only recently that apart from biochemical cues the microarchitectures and mechano-induction cues are also very important.

In terms of in-situ engineering, they can be used in methods of bioengineering that incorporate signals that enhance native regeneration.

The microstructure of these biomaterials is an important element of in-situ tissue engineering because their structure can be used to mimic the in vivo environment, guide cell growth, growth and infiltration. Recruiting and providing a home for the right cells to the site of injury is a key focus in in-situ tissue engineering. The interconnected porosity and microstructure of biomaterials can assist the regulation of cell-cell communications aid nutrients and waste transport.

One of the major benefits of the ideal in-situ biomaterial is the ability to provide the maximum tissue engineering support while also ensuring that the material is also efficiently cleared by the biological system – meaning any foreign body response will be minimised. Thus, we can ensure that in-situ tissue engineering occurs only where necessary and does not exist in the body beyond the completion of the regenerative process.

The in-situ approach has several advantages— in-situ tissue-engineered products offer improved off-the-shelf availability of the finalized products, because in-situ tissue engineering often does not involve extensive manipulation of cells and materials outside of the body to create functionalized tissue. Because in-situ tissue engineering often relies on extracellular components to stimulate native regeneration, this approach offers the opportunity to apply state of the art regulatory controls while simultaneously realizing tissue engineering concepts in the clinics.

A comparison of in-situ and in-vitro tissue engineering

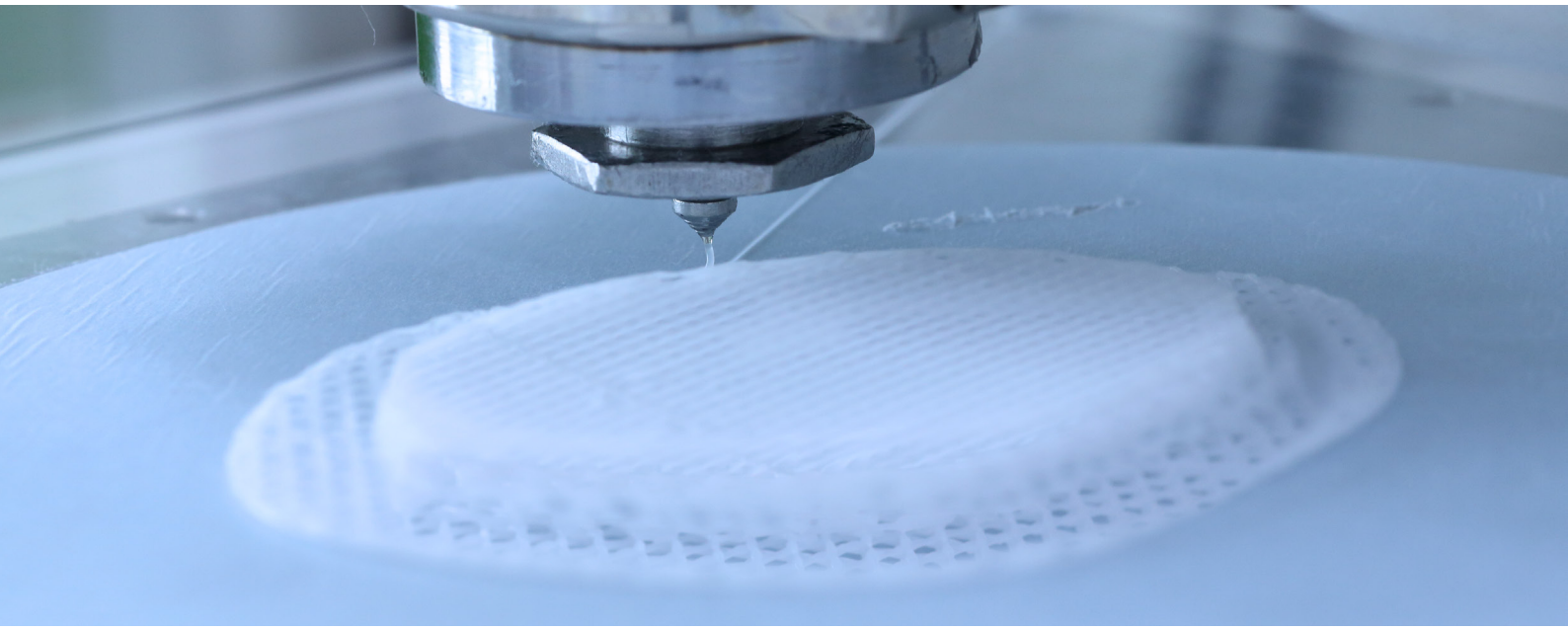
A variety of in-situ techniques exist, which complement existing in-vitro tissue engineering methods. In addition to in vivo therapies, in-vitro tissue engineering will be an invaluable tool for models of tissues and organs for mechanistic studies and drug screening.

Prevascularized tissue constructs, decellularized organs and organ-on-a-chip will be further developed for these applications. On the other hand, bioactive and tuneable materials with incorporated adhesion molecules, growth factors and drugs present a bright future for in-situ tissue engineering, especially for the regeneration of connective tissues.

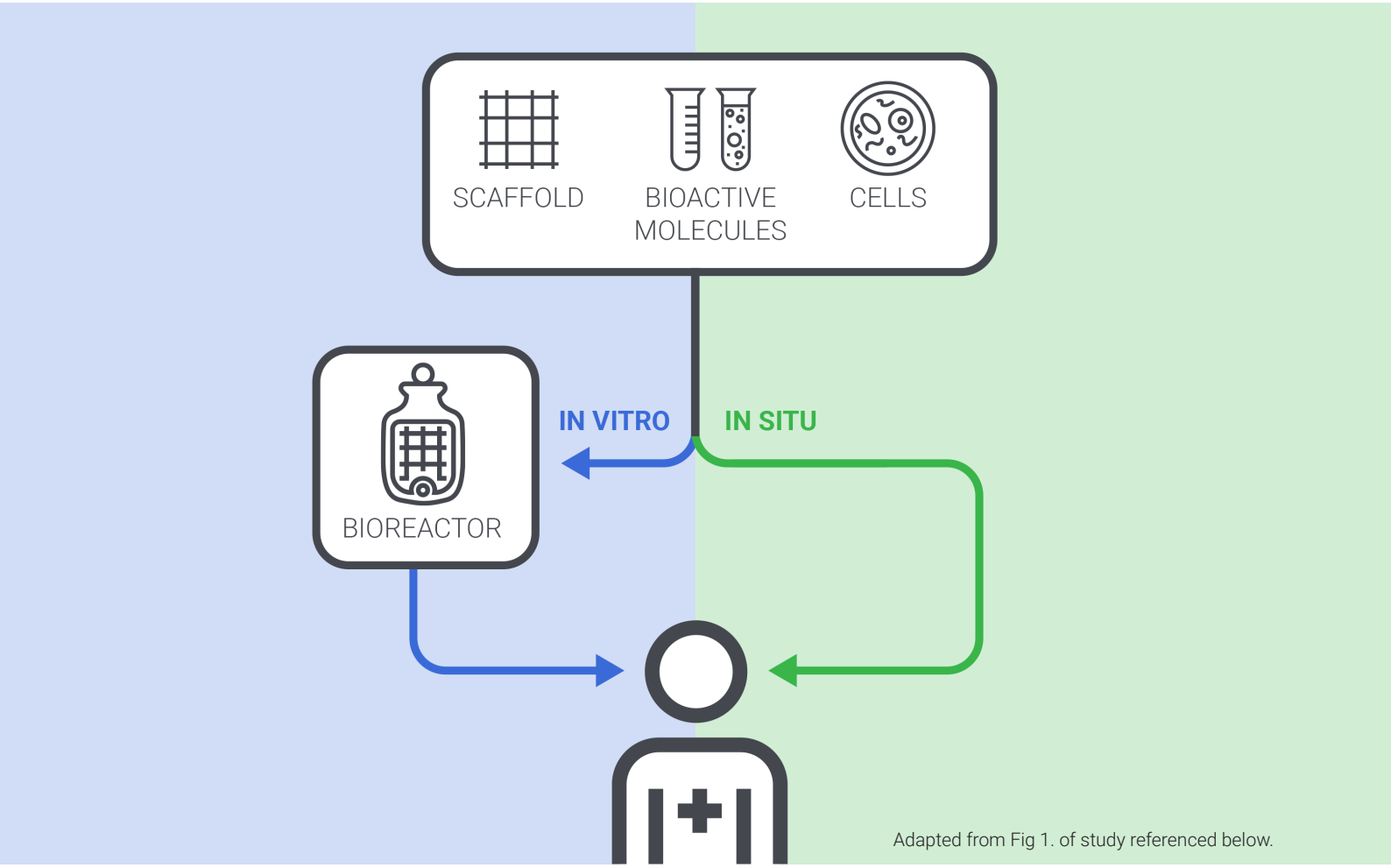
The advancement of micro- and nano-fabrication technologies will provide the platforms to engineer biomaterials structures at resolutions never achieved previously. The development of smart materials is also important for future research.

Biomaterials that are dynamically tuneable by chemistry, enzymes, light, mechanics etc. can be tailored for specific applications. An emerging and exciting area related to in-situ tissue engineering is immuno-engineering, where biomaterials can be used to regulate immune responses and used as vaccines or for therapies.

The combination of in-situ tissue engineering and immuno-engineering approaches may lead to more effective and new treatments to repair tissues and organs. In-situ tissue engineering represents a promising new avenue of regenerative therapy research and will continue to provide important solutions to the clinical problems we are facing today.



At a glance - in-situ vs in-vitro



Adapted from Fig 1. of study referenced below.

	In vitro tissue engineering	*In situ* tissue engineering
Availability off-the-shelf	Possible	More likely
Scalability	Difficult	Easier
Ease of clinical translation	Complex	May be easier
Biomaterials	Extensively used	Extensively used
Bioreactors	Used	Not commonly used
Chemical factors	Used	Used
Cells	Used	Not commonly used
Cost-effectiveness	Less	More
Disease modeling	Yes	N/A
Drug screening modeling	Yes	N/A

(Reference: From In-Vitro to In-situ Tissue Engineering - DEBANTI SENGUPTA, STEPHEN D. WALDMAN, and SONG LI, Department of Bioengineering, University of California, Berkeley, Berkeley, CA, USA; and Department of Chemical Engineering, Department of Mechanical and Materials Engineering, Queen's University, Kingston, ON, Canada)

Why is in-situ tissue engineering the future for Osteopore®?

Having comprehensively considered both in-vitro and in-situ tissue engineering and their respective benefits, in-situ tissue engineering represents the future for not only Osteopore® but potentially the medical devices industry as a whole – for the following reasons.

1 **In-situ tissue engineering is less onerous from a regulatory standpoint**

In a common in-situ tissue engineering process, the scaffold device is made separately, and the cells required to complete the process can be taken from a patient within an operating theatre. To produce the final product, the manufacturing process in accordance with Good Manufacturing Practice involves printing it in a clean room, sterilising it and bringing it into an operating theatre.

That makes the regulatory process more efficient because the individual components are already approved, and the cells required belong to the existing patient.

In-vitro tissue engineering, by contrast, faces significant regulatory barriers. The primary reason for this is that when you incubate cells taken out of the patient within a lab, cells in the incubation phase are extremely sensitive and can change in form depending on the material they have been incubated in (such as the glass or the incubation solution.)

2 **In-situ tissue engineering is a more scalable solution, and more cost-effective**

Largely as a result of this more efficient regulatory process, we feel that in-situ tissue engineering is at a point where the technology can reach more patients and have a tangible effect on more lives. That also means that in-vitro tissue engineering is likely to be a more expensive process.

In-situ tissue engineering allows us to leverage on our knowledge of biomaterials and various microstructure patterns to support tissue regeneration in a sustainable way. As the 3D printing technology evolves, we stand to benefit from an increasingly large pool of shared knowledge that drives process efficiency and quality, allowing us to bring higher quality products to patients in a sustainable way.

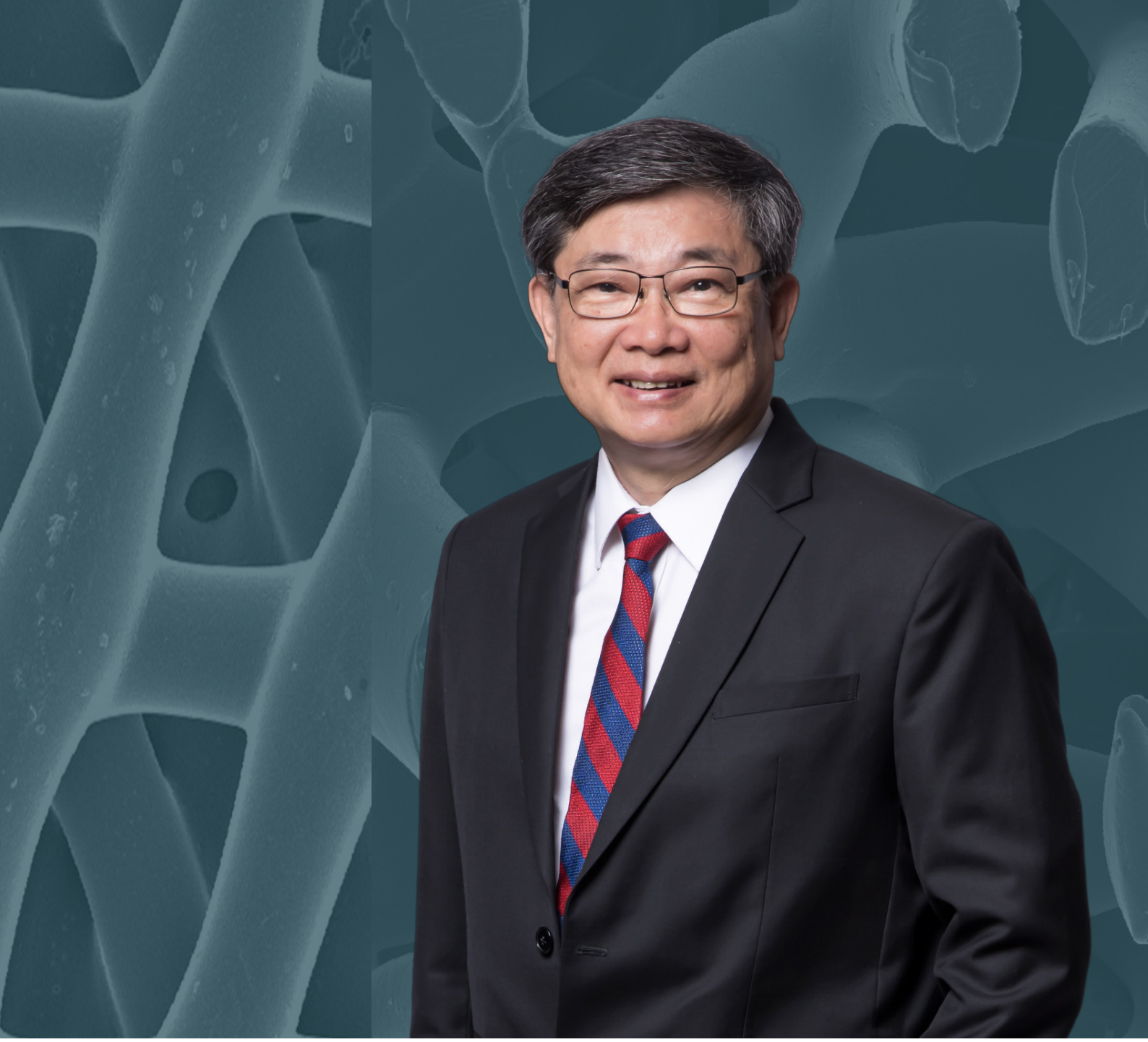
3 **In-situ tissue engineering is a more familiar process to the surgical community**

An in-situ tissue engineered scaffold is quite close to the type of product surgeons are already used to, meaning the chances of uptake within the medical community is higher.

For these reasons, and others, Osteopore® is pursuing in-situ tissue engineering with our vast experience in 3D printing as the enabling factor.

4 **In-situ tissue engineering has long-term, lasting impacts**

The biocompatibility, biochemistry and 3-D printed microarchitecture are a more sustainable, long-term outcome. So far, they have been found to have no observable ill effects in terms of immunological/inflammatory responses in more than a two-year period.



“The efficacy for patients is very important - they are mindful of the regulatory process. If you take any cells outside the body for more than six hours, that is classified as cell manipulation - even if it is your own body’s cells. That is why much surgery is limited to six hours… in-situ tissue engineering takes only 30 minutes to one hour.”

Professor Teoh Swee Hin

Non-Executive Director: Osteopore® development and clinical translation of 3D bioresorbable scaffolds.

Brodie's Story - In Situ Tissue Engineering In Practice

The in-situ tissue engineering medical procedure involving traumatic brain injury patient Brodie Ellis provides a first-hand example of how life-changing this type of surgery can be.

The 2019 world-first procedure with 3D-printed bone was pioneered by Brisbane's Princess Alexandra Hospital surgeon Dr Michael Wagels, using Osteopore's® 3D printed biocompatible and bioabsorbable implant, and ultimately gave Mr Ellis a second chance at life.

Dr Wagels used the implant to replace a section of Mr Ellis' missing skull. Prior to this, 27-year-old Mr Ellis had a different implant that had become the source of a life-threatening infection.

Mr Ellis was involved in a motorcycle accident in December 2018 that required parts of his skull to be removed and later replaced with synthetic implants.

Unfortunately, one of the implants became exposed and developed an infection. Because the implant had no blood supply, the infection kept worsening, so the implant had to be removed. This left Mr Ellis with headaches and a contour deformity of the skull.

The 11-hour procedure to implant the 3D-printed replacement bone, which has the ability to encourage natural bone growth, was performed on Mr Ellis in December 2019. This involved a team of plastic and reconstructive surgeons, anaesthetists, neurosurgeons, nurses, assistant surgeons and technicians.

Extensive planning was required prior to surgery to design and manufacture Osteopore's® implant, with the support of the Translational Research Institute (TRI) and the Australian Centre for Complex Integrated Surgical Solutions (ACCISS).

The massive team effort produced excellent post-operative results for Mr Ellis, with new bone infiltrating the device as well as integrating with surrounding native bone that it is connected to.

Mr Ellis' implant is completely absorbable, so it will disappear in tandem as the new bone forms within and integrate with surrounding native bone.

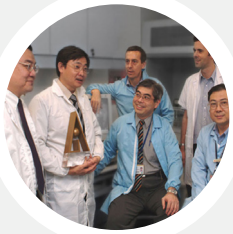
Our History

1992

First commercial 3D printing based on filament is commercialized by Stratasys Inc. It was called rapid prototyping.

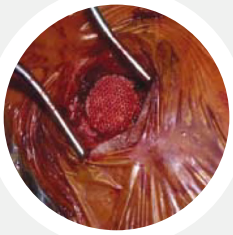
1996

On receiving news that Prof. Charles Vacanti was able to grow a ear on the back of a mouse, our founders embark on tissue engineering research and development.



1996

Inventors from National University of Singapore, National University Hospital and Temasek Polytechnic initiated research to identify the bioresorbable material, microarchitecture and manufacturing technique.

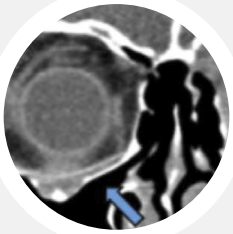


2002

First in-human procedure with Osteopore® technology. Osteopore's® implant carried out in a top hat configuration as a burr hole cover.

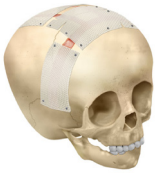
2003

After the success of the first in-human procedure for burr hole cover in 2002 and six years working on the technology, the team founded the company, Osteopore® International Pte Ltd.



2006

Prospective randomized clinical trial with Osteomesh® for orbital floor reconstruction successfully completed.



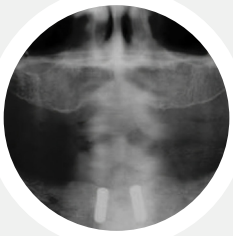
2006

The first in-human reconstruction for craniosynostosis with Osteomesh®. Researchers estimate that about 1 in every 2,500 births has craniosynostosis in the United States.

FDA 510(k)

2006

The Osteopore® technology for craniofacial application received the US FDA 510(k) clearance.



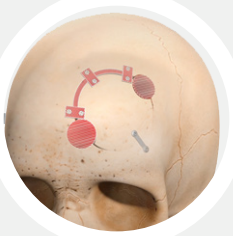
2007

First in-human 3D printed patient specific implant with polycaprolactone-tricalcium sulphate (PCL-TCP) microarchitecture for mandibular reconstruction.

International Organization for Standardization ISO 13485

2007

Osteopore® manufacturing for craniofacial application received ISO 13485 certification.

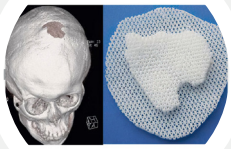


2008

First in-human implantation with Osteoplug® (plug and strip configuration) for craniotomy.

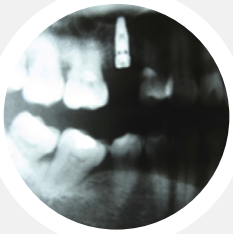
2009

In 2009, Osteoplug® and Osteomesh® were CE approved for cranial burr hole cover and orbital floor reconstruction respectively. Awarded MDD 93/42/EEC (Design Examination Certificate) CE Mark, TUV Rheinland.



2009

Successful first in-human craniofacial application with 3D PCL-TCP scaffold, a second generation material, in a child in Germany.



2015

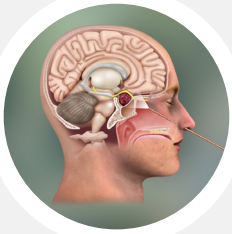
Osteopore® completed the first clinical trial for socket preservation in dental surgery. First in-human dental application with 3D printed PCL-TCP scaffold in Singapore.

2016

Osteopore® moved to a purpose-built medical technology hub, JTC MedTech Hub, to expand their production capabilities.

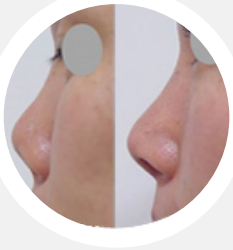
2017

Longest tibia reconstruction with Osteopore® regenerative implant performed by Dr Michael Wagels and team at the Princess Alexandra Hospital, Brisbane, Australia. 3-year post-operation results shows tibia bone successfully regenerated.



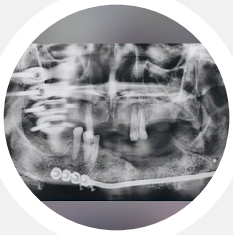
2017

First in-human skull base with Osteomesh®.



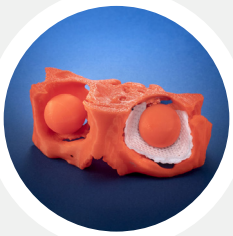
2017

First in-human rhinoplasty with Osteomesh®.



2018

First mandible reconstruction with Osteomesh® shaped tray to hold autologous bone grafts. Bony ingrowth and remodeling observed at 2 and 5 months postoperatively.



2019

First customized Osteopore® implant for orbital floor reconstruction.

2019

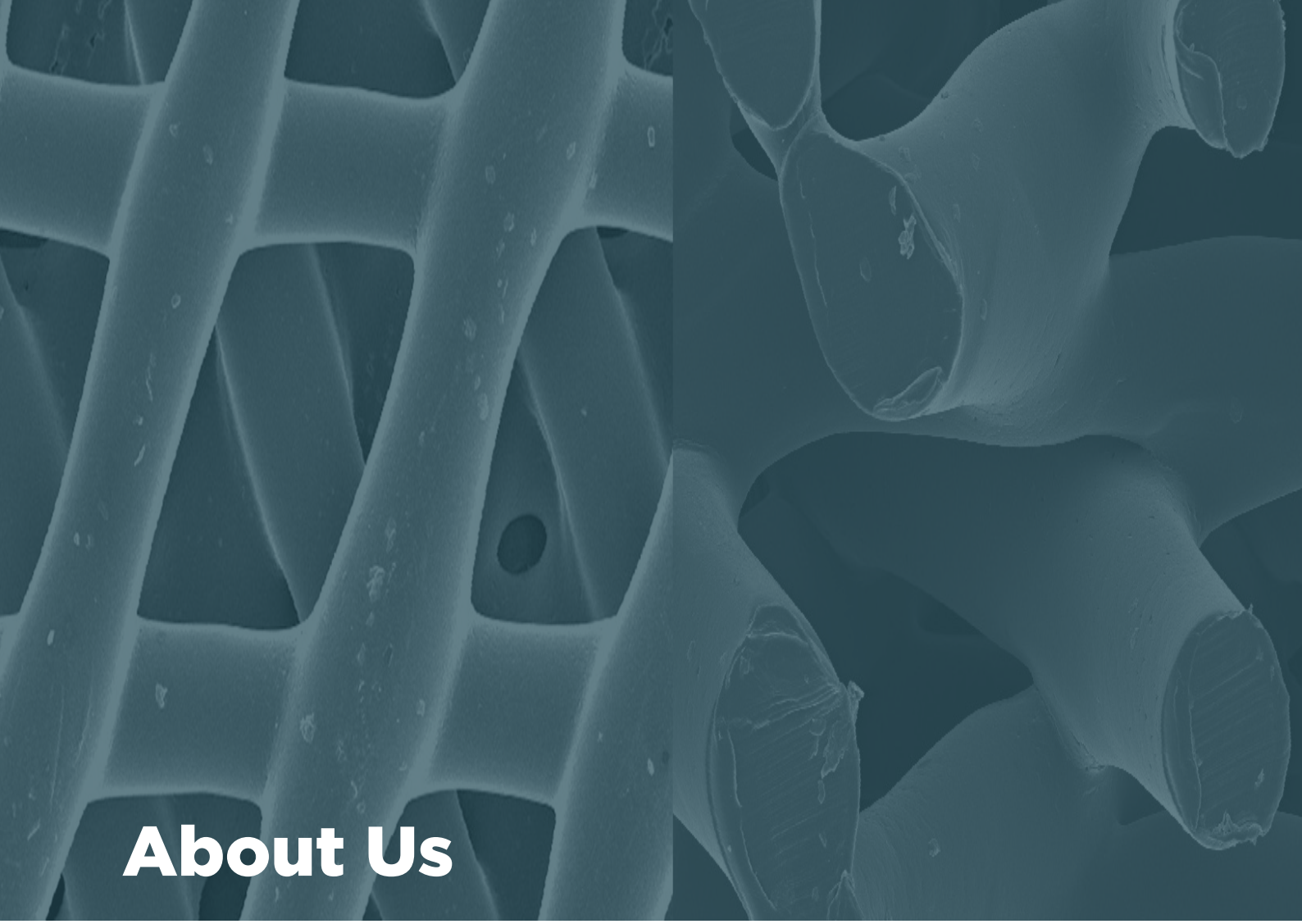
Osteopore® IPO on the Australian Securities Exchange took place on 23 September 2019.

2020

Primary products are CE Marked, have US FDA 510k and Australian TGA clearance and are available through an expanded global distribution network of 23 partners allowing for their safe and effective application in around 20,000 procedures globally.

2021

Osteopore's® CE Mark was extended to include 7 new designs, all sizes of Osteoplug®, Osteomesh® and Osteostrip®, and extended product shelf-life providing on-indication access to an incremental 100,000 craniotomy cases p.a.



About Us

Osteopore® Ltd, an Australian ASX listed company (OSX.AX) with R&D and manufacturing in Singapore, is the global leader in the manufacture of innovative regenerative implants at commercial scale.

We believe that the self-healing capacity of humans can be enhanced through technology.

Our technology mimics the healing process of tissue by providing a bioactive porous microstructure that recruits cells, growth factors and blood capillaries to create an active regenerative environment. By combining biomimetic tissue science with proprietary 3D printing and materials technology, Osteopore® produces medical implants to meet the needs of both tissue and bone reconstruction as well as restoration. These bioresorbable implants provide a scaffold for bone regeneration, dissolving predictably over time to leave only natural bone tissue.

In collaboration with clinicians and researchers, Osteopore® develops and manufactures implants that address unmet clinical needs which improve patient outcomes, enhances lives, and reduces healthcare costs.

Osteopore®

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