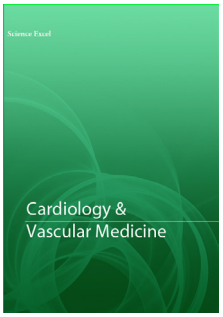
Cardiology and Vascular Medicine

Original Article




# Tissue Stents (Bio Stents): Search For Non-Metallic Stent And Can It Be A Game Changer In Cardiovascular Interventions?

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## Abstract

Coronary and Vascular stenosis poses great challenge in terms of cardiovascular disease burden. Evolution of metallic stents has been key in treating Coronary Artery Disease both acute and chronic and has met challenges successfully. The last 2 decades have seen substantial reform in technology, bringing second and third generations of coronary and vascular stents mainly metallic drug-eluting stents (DES). Though stent related stenosis is big challenge, DES has met relatively much success especially during initial years. DES are found to be associated with good first-year outcomes but subsequent risk of stent-related adverse events like thrombosis, myocardial infarction, restenosis usually appear after 1 year following implantation. The pathogenesis of these late events is related to the permanent presence of the metal stent frame or polymer within coronaries. Besides intimal hyperplasia, late stent thrombosis, and noncompliance with DAPT are still major issues leading to stent failure and often the need for reintervention. As an effective alternative to metallic stents, Bioresorbable scaffolds were developed to provide drug delivery and mechanical support functions similar to metallic drug-eluting stents (DES), followed by complete resorption with recovery of vascular structure and function, potentially improving very late clinical outcomes. A first-generation bioresorbable scaffold demonstrated to be no inferior to a contemporary metallic drug-eluting stents for overall 1-year patient-oriented and device-oriented outcomes. However, increased rates of scaffold thrombosis and target vessel-related myocardial infarction were noted subsequently at 5 year follow up. Tissue/Bio Stents can present as a path breaking alternative approach to avoid intimal hyperplasia. They are characterised by presence of biodegradable struts with tissue mesh and complete absence of metal preventing ingrowth of the neointimal tissue into the lumen. Currently used stent materials include mainly metals and synthetic polymers. Their main limitation is lack of hemocompatibility, which can induce thrombosis and ultimately reocclusion, thus impairing the long-term performance of these devices. We are proposing use of biologically derived material to overcome this issue with the aim of enhancing the biocompatibility and the capability of this type of stents to support endothelialilzation. The aim of this article is to give a comprehensive overview of the manufacturing and applications of Tissue or Bio Stents as well as the different strategies followed for their development from the perspective of the material selection, fabrication approaches, and logical validation of the different concepts into animal and clinical trials.

## Bioresorbable stents and what actually went wrong

Bioresorbable stents (BRS), also referred as bioabsorbable or biodegradable stents, refer to coronary stents that could fully dissolve in the body. The main advantage of using a BRS was that it will clear out of the body within a few years, thereby theoretically reducing the long-term adverse effects normally seen with conventional metallic stents (Figure 1).The first and the most extensively studied BRS device, Abbott's Absorb, was approved for use by the FDA in 2016. The device was quickly adopted by many cardiac centers. However, since then, multiple studies, including the ABSORB clinical trials, have shown that Absorb had little or no competitive advantage over commonly used drug-eluting stent (DES) devices. In 2017, the FDA issued a warning for the use of BRS, and the European Society of Cardiology (ESC) concluded that there was not enough data to support the superiority of BRS stents to DES. Instead, the ESC recommended that physicians use of BRS should be discouraged until further data on Absorb became available. Abbott removed Absorb from the market in September 2017 due to unprecedented adverse events in BRS implanted patients. The idea of being able to clear the body of a foreign object after the treatment of a blockage still remains attractive, especially considering the growing aging population and the fact that people are expected to live longer after a PCI procedure.

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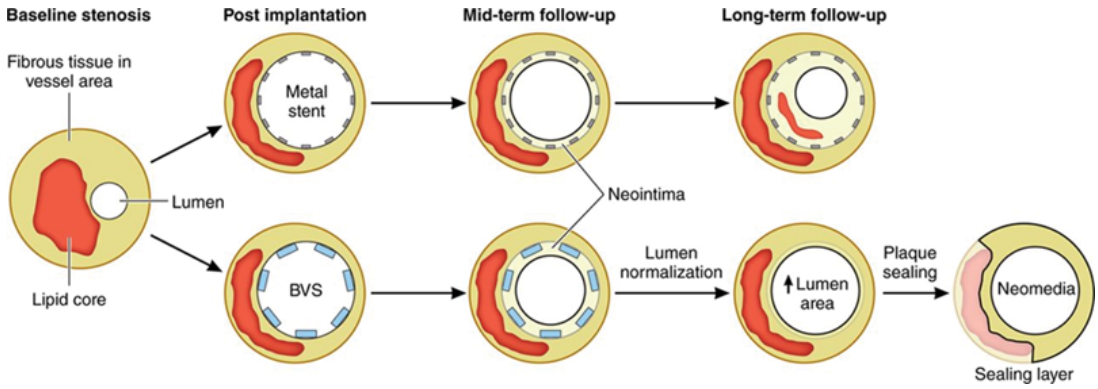



***Figure 1***

There has been no shortage of interest in bioresorbable stent technologies; however, there was noticeable apprehension about what the future of the technology will be. During the period there was even focus away from traditional metallic drug-eluting stents (DES) to these bioresorbable scaffold technologies as the next possible step in stent evolution.

However, since trial data, especially from the ABSORB III Trial, and the first commercial bioresorbable stent being pulled off the market on Sept. 14, 2017, this view is dampaned. Subsequent trial data for the Abbott Absorb everolimus-eluting bioresorbable vascular scaffold (BVS) shed light on why the company announced it was pulling the stent off the market. Though data from several ABSORB trials statistically showed good performance compared to the market-leading Xience everolimus-eluting metallic stent, there was signal in the data for slightly poorer outcomes, negating any long-term benefits the stent might offer. Experts involved in the trials said Absorb saw a very low usage rate, with estimates of U.S, usage of less than 5%.

It was known that the bioresorbable stent had its limitations, but the goal with the new technology was its expected late benefits when the stent dissolves after three years. However, these benefits have not been demonstrated yet in the ABSORB III Trial, while the device carries several disadvantages, including demonstrated poorer outcomes. Earlier clinical data on the scaffold showed late benefits such as the return of vasomotion to treated vessels, the elimination of a metallic implant to preserve future surgical options, the elimination of a vessel prosthesis that could cause late stent thrombosis or restenosis, target lesion stent thrombosis and myocardial infarction. The ABSORB III trial two-year results were presented first at the ACC-2017 meeting and showed mixed results for Absorb, which may have made some clinicians more apprehensive about its use earlier in 2017. This 2,008-patient trial showed Absorb had results comparable to Xience, but had a slightly higher percentage of poor outcomes. This raised concern about Absorb's slightly higher rates of target lesion failure, poor outcomes in 2.5 mm or smaller vessels, and a few cases of late-stent thrombosis. With the ABSORB II and ABSORB Japan studies, there were findings of late scaffold thrombosis. This was the key safety signal that researchers paid more attention to in the ABSORB III and IV trials. In ABSORB III, there were four patients out of 1,300 who received the Absorb stent that had late-stent thrombosis.

One of the issues after releasing Absorb stent into market was that many operators thought it could be used just like the metallic stents they were used to implanting. Many of the ABSORB trial operators felt this way too. One of the mechanisms by which metallic drug-eluting stents work is that they can actually score the vessel. It's a little bit like stepping on snow with a cross-country ski as opposed to a snow shoe. But, you cannot embed the Absorb as easily into the vessel wall, and the device is thicker, so it tends to protrude significantly into the lumen, and which inherently induce thrombogenic milieu. Vessel sizing also was more critical with BRS, because BRS would not over expand as easily or as well as metallic stents. Also, the Absorb did not perform well in smaller vessels < 2.5 mm and cannot as easily be snaked through tortuous vessels like its metallic DES counterparts. Both issues are related to the thick stent struts. It was associated with higher rates of target lesion failure and device thrombosis than current metallic DES. The Absorb, being made of a pliable plastic as opposed to metal, means it has limitations on how much it can be expanded before the struts break. Besides, it also can recoil after expansion. If the device is not well apposed to the vessel wall, when the vessel wall heals, it does not heal around the device to encompass it, the device is hanging into lumen.

This understanding had put us into the journey of developing an alternative technique and a stent delivery system that should be sustainable with both early and long-term outcomes.

## Tissue/Bio Stents

As late lumen loss and restenosis is one of the most devastating and costly problems in coronary intervention today, there is eventually an increasing demand to find alternatives to bioabsobable stents for stenting atheromatous vessels. In an effort to meet this considerable challenge, we designed Tissue Stents using current, advanced and available technology.

Tissue Stent Delivery system has 2 elements-

1. Inner Biodegradable scaffold similar to bioabsorbable stent (though using different polymer) that provides

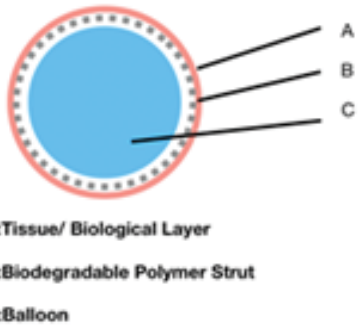



***Figure 2.*** *Tissue Stent delivery system*

1. tensile and recoiling strength and actually acts as a vehicle to deliver tissue layer to atheromatous vessel.
2. Outer Tissue layer that remains in contact with endothelium and covers the plaque after ballooning.
3. Entire system can be placed on a balloon and can be delivered like any other stent system. (Figure 2)

Let's consider how this stent can be manufactured using various advanced technology.

## A. Scaffold

Scaffolds are materials that have been engineered to cause desirable cellular interactions to contribute to the formation of new functional tissues for medical purposes. Cells are often 'seeded' into these structures capable of supporting three-dimensional tissue formation. Scaffolds mimic the extracellular matrix of the native tissue, recapitulating the in vivo milieu and allowing cells to influence their own microenvironment (Figure 3).They usually serve at least one of the following purposes: allow cell attachment and migration, deliver and retain cells and biochemical factors, enable diffusion of vital cell nutrients and expressed products, exert certain mechanical and biological influences to modify the behaviour of the cell phase. Scaffold of design, space and morphology used in metallic stents can well be manufactured using biodegradable material that provides platform for tissue growth.

Scaffold can be manufactured by using following technology:

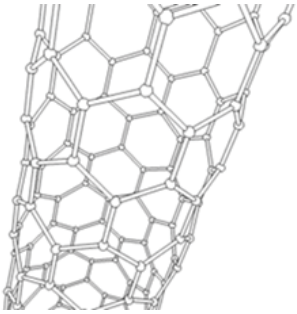


***Figure 3***

***Figure 4***

### 3D Precision Microfabrication Technology

3D Precision Microfabrication Technology fabricates porous structures of intricate shape and/or patterns with precisely controlled pore size and porosity. The application of this novel technology in biomedical fields is endless. Both degradable and non- degradable polymers, such as polycaprolactone (PCL), poly(lactide-co- glycolide) (PLGA), poly(DL-lactide) (PDLLA), polyglycolide (PGA) and polystyrene (PS), can be used to develop scaffolds for tissue engineering research, as well as for creating normal and diseased in vitro tissue models. Based on the 3D Precision Microfabrication Technology platform, a Rapid Stent Fabrication (RSF) System is developed which can be used to fabricate bioabsorbable porous tubular structures for blood vessel regeneration and cardiovascular stent applications. Porous tubes and stents for cardiovascular applications have been successfully fabricated using biodegradable polymers such as PCL, PLGA and PGA. The world's first CAD-based RSF System has the capability to quickly and reproducibly fabricate bioabsorbable polymer stents directly from polymer pellets/ powders. Moreover, this fabrication system makes very efficient and cost-effective use of expensive polymers, and can therefore accelerate the product development process and reduce the overall R&D cost.This RSF System introduces a new method for the fabrication of tissue/bio stents (Figure 4).

PCL, PLGA, PDLLA, PGA, and PS scaffolds are engineered using 3D Precision Microfabrication Technology. Uniquely, fibre diameter is controlled by nozzle diameter and spacing between fibre is controlled by a motion control system. The struts of each layer are oriented relative to the struts of the layer immediately below. Before use, scaffolds are plasma treated (PS only) and sterilised.

### Rapid Stent Fabrication Technology

Using PCL, PLGA, and PGA, tubular structures are engineered using 3D Rapid Stent Fabrication Technology which uses Precision Microfabrication Technology as its platform. Biodegradable polymers PCL (Figure 5A) and PGLA (Figure 5B)can be precisely engineered into complicated, yet precise shapes and patterns.

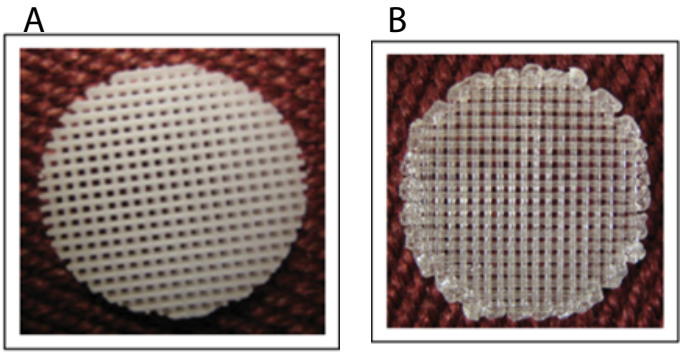



***Figure 5.*** *A : Scaffold made from Biodegradable Polymer PCL . B : Scaffold made from Biodegradable Polymer PGLA.*

## B. Tissue Layer

Developing Tissue layer over scaffold is next step in the process (Figure 6).

### 3D cell culture

3D cell culture technique offers a better cell culture environment because it is one step closer to the in vivo cell growth environment( Figure 7) However, because 2D culture is easy to carry out and there are no satisfactory 3D cell culture devices available, 2D cell culture is still the predominately used cell culture technique. As a publication in the journal Nature pointed out, "Awareness of the potential of 3D tissue culture among scientists is far too low (Figure 8).But the benefits of the technique are so self-evident that little marketing will be needed to persuade the uninitiated to move up one dimension.

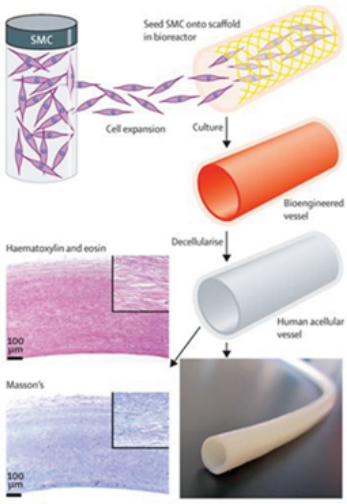



***Figure 6***

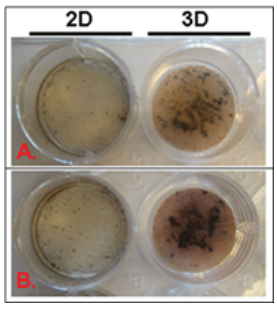



***Figure 7***

**3D Insert-PCL**

Polycaprolactone (PCL) is a biodegradable polymer used in many FDA approved implants, drug delivery devices, sutures, as well as for a wide variety of applications in tissue engineering research (Figure 9). These applications include: Bone/Cartilage, Cardiovascular, Nerve, Skin, Tendon/Ligament, Liver.

Benefits-

***1. Pre-Sterilized and Ready to Use***

3D Insert-PCL scaffolds are prepackaged into wells of tissue culture plates and terminally sterilised using γ-radiation. Currently PCL Scaffolds are available in prepackaged tissue culture plates ranging from 6-well to 96-well plates.

***2. 100% Connectivity***

The pores of the products are 100% open, making it easy for cells to be seeded throughout the porous scaffolds and the nutrient and cell metabolic waste to be exchanged.This feature makes it especially useful in conducting dynamic cultures where the medium can perfuse through the 100% open porous structure.

***3. Well Defined Pore Size and Porous Structure***

Microfabrication technology produces a well-defined pore size and ensures the reproducibility of the porous structure from batch to batch.

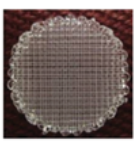
***4. Improved Cell Culture Efficiency***

Increased surface areas as compared to 2D cell culture plates. Therefore, more cells can be cultured using the same size cell culture dish/plates/flasks/bioreactors.

***5. Easy Separation of Cytokines and Growth Factors Secreted by Cultured Cells***

3D cell culture scaffolds will not absorb cytokines and growth factors. Therefore, cytokines and growth factors, which are secreted by cultured cells during 3D culture, can be easily

| 3D Insert™-PCL | |
|---|---|
| Stem Cells | • Human Mesenchymal Stem Cells (hMSCs) (including adipocytic and osteoblastic differentiation) |
| Hepatocytes | • HepG2<br>• Huh-7 |
| Keratinocytes | • HEKn |
| Osteoblasts | • 7F2<br>• hMSCs-derived osteoblasts |
| Fibroblasts | • NIH-3T3<br>• L929 |



| 3D Insert™-PS | |
|---|---|
| Stem Cells | • Human Mesenchymal Stem Cells (hMSCs) (including adipocytic and osteoblastic differentiation)<br>• Mouse bone marrow stromal stem cells (mBMSSCs) |
| Cancer cells | • MCF-7<br>• MCF-7:WS8<br>• ECC1 |
| Hepatocytes | • HepG2<br>• Huh-7 |
| Keratinocytes | • HEKn |
| Neuronal Cells | • CHP212 and SY5Y |
| Osteoblasts | • 7F2<br>• hMSCs-derived osteoblasts |
| Cardiomyocytes | • H9c2<br>• Rat primary cardiomyocytes |
| Fibroblasts | • NIH-3T3<br>• L929 |

***Figure 8***

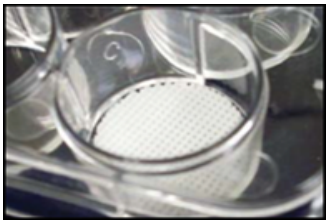


***Figure 9***

***Figure 10***

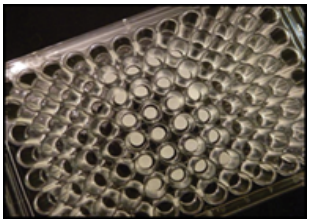


***Figure 11***

separated or recovered from the culture medium without going through any extra separation steps.

***6. Organic Solvent Free***

Cytotoxic organic solvents, such as chloroform and methylene chloride, are often used in fabricating PCL scaffolds. Precision micro-fabrication technology is a solvent-free manufacturing process. Therefore, the 3D Insert- PCL is free of organic solvent.

***7. Fit Into Various Bioreactors***

The size and configurations of 3D Insert - PCL can be customised to fit into the bioreactors of choice.

**3D 100MM DISH**

3D Insert PCL scaffolds for large scale 3D cell expansion, in comparsion with traditional 2D culture, more closely resembles an in vivo environment. Cells expanded on 3D scaffolds have more physiological-like morphology and function, thereby providing with higher quality cells to use in research. Combine 3D Insert PCL quality with the time, money and space will save with this technology. Ultimately, the 100 mm compatible 3D Insert PCL will save money on expensive media and supplements. It reduces handling time, and save s space in tissue culture incubator (Figure 11)

**3D Bioreactor**

***CAD model of chamber/scaffolds assembly***

Numerous studies have proven that cells grow better under dynamic culture condition, simply because both nutrition supply and metabolic waste removal are better under dynamic culture conditions. Additionally, in some instances, the shear force produced by the flowing medium can act as a mechanical

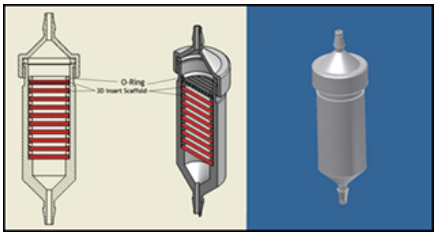


***Figure 12***

***Figure 13***

stimuli signal that will further promote stem cell differentiation toward certain cell lineage, such as osteoblast (Figure 12) Combined with our proven 3D Insert scaffold technology, a novel 3D Perfusion Bioreactor can be used for our purpose.

**3D Perfusion Bioreactor**

The bioreactor consists of multiple independent, autoclavable polycarbonate chambers (4 chambers as shown in the picture). The chambers are interchangeable and are specially designed to take the advantage of 3D Insert scaffolds with various sizes ranging from 24-well, 12-well and 6-well. Cell culture media is perfused through the open porous structure of scaffolds using a peristaltic pump. The entire unit is autoclavable (except pump, of course) and can be used as a single-use bioreactor system (Figure 13).

**3D Insert Technology**

Porous polymer scaffolds were engineered using 3D Precision Microfabrication Technology. These scaffolds are available in both biodegradable (polycaprolactone, PCL) (Figure 14). and non-biodegradable (polystyrene, PS) polymers. Struts of each layer of the scaffolds are oriented 90° relative to the struts of the layer.

## 3D Cell Expansion System-A Novel Integrated 3D Perfusion Bioreactor/Incubator System

The 3D Cell Expansion System (3D-CES) is an integrated system designed for large scale expansion of anchorage-dependent cells in a 3-dimensional (3D) microenvironment. Culture and expansion of a large quantity of cells by the traditional two dimensional (2D) method is difficult and known to have many challenges. The 3D-CES is designed to lift this inherent limitation of 2D cell culture and expansion methods. With the 3D-CES, cells are grown and expanded on 3D polystyrene (PS) scaffolds. The unique dynamic system circulates media throughout the system using a peristaltic pump providing an efficient exchange of nutrients and waste between media and the cells. With minimum hands-on time, this innovative technology is more efficient and significantly

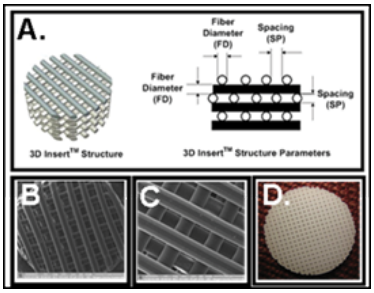



*Figure 14*

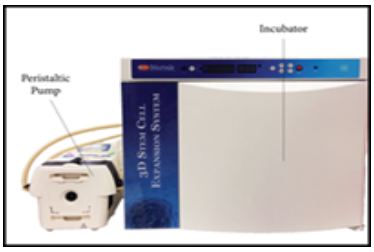



*Figure 15*

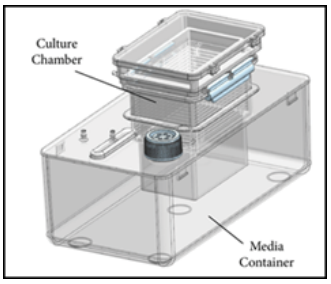



*Figure 16*

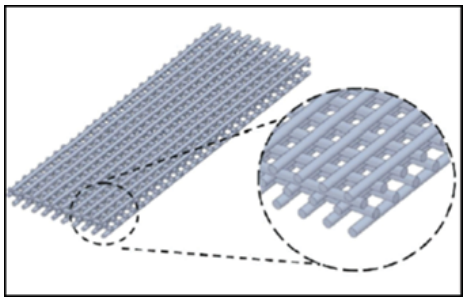


*Figure 17*

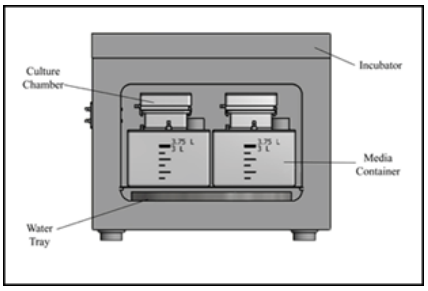



*Figure 18*

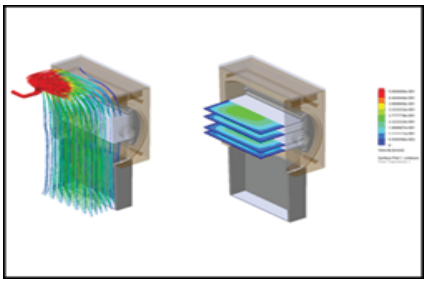


*Figure 19*

space, and labor needed to achieve the desired number of cells in a shorter amount of time compared to other methods.

**Major Features**

Integrated Bioreactor/Incubator System for large-scale cell expansion (Figure 15)

- Optimised for Stem Cell (Adipose-Derived & Bone Marrow) expansion
- Cells are seeded and grown on 3D polystyrene scaffolds
- No need to change media in the entire expansion process
- Reduced human interaction to minimise chances of contamination
- Each culture chamber is capable of expanding up to 250 million cells in 14-18 days
- Two culture chamber design allows max expansion up to 500 million per production run
- Great potential for use in stem cell therapy and bio-banking
- Also suitable for use in protein production for cosmetic industry

**Culture Chamber and Media Container**

- The Culture Chamber and Media Container are placed inside a custom-made incubator which provides tubing connection through its side wall to the pump
- Culture Chamber can hold up to 15 pieces of polystyrene (PS) scaffolds (Fig. 16)
- Cells are seeded and expanded in the PS scaffold which provides a 3D micro-environment
- The capacity of cells for each culture chamber is about 200 - 300 million
- The Media Container can hold up to 3.5 litre
- For 200 - 300 million of cells, about 2.5 litre of media is needed
- Flow of media is from the Media Container in upward direction to the Culture Chamber through the PS scaffolds

**Polystyrene (PS) Scaffold**

- Fabricated by 3D micro-fabrication technology
- Its unique feature is 100% connectivity within its structure which allows effective exchange of nutrients and waste between the media and the cells
- PS scaffold is plasma-treated to enhence cell attachment
- The fiber and pore size are approximately 150 and 200 microns, respectively.
- The dimensions of each scaffold are approximately 105(W)x 66.5(D) x 0.6(H) mm

2-chamber design. It allows a max capacity of about 500 million of cells per single run.

**Computational Fluid Dynamics (CFD) analysis**

- CFD is used as a design tool for flow optimisation
- It provide important parameters such as flow rate and max shear stress
- Max shear stress is below critical value
- Media flow is fairly uniform through the culture chamber and the scaffolds

### Advantage over Bioresorbable Stent

Main concern that limited bioresorbable stent was the large strut width for coiling support and tensile strength, risk of increased vascular injury, hemodynamic disruption, blood particle deposition, and platelet activation. In addition, after complete absorption of stent, there was risk of plaque formation. Tissue Stent provides addition recoiling and tensile strength comparable to metallic stents. Besides tissue layer remains permanent covering the plaque and becomes part of stented vessel once endothelialisation.

### Advantage over Metallic Stents (DES)

Metallic Stents provides advantage of recoiling and tensile strength for better apposition. However this advantages limits its flexibility and make its application difficult in tortuous vessel or bridging besides creating metal load inside coronary arteries. Stent Fracture too is common phenomenon while used is such situation. Tissue Stent has distinct advantage of flexibility over metallic stents while having adequate recoiling and tensile strength via scaffold essential for proper apposition. Because of no metallic components, duration and need of dual anti platelet therapy can be revised/reduced with less consequent complications.

## Conclusion

Contemporary metallic DES are associated with very good 1-year outcomes but an ongoing hazard of very late device-related events thereafter, the pathogenesis of which is likely related to the permanent presence of a rigid metallic frame and polymer with associated incomplete healing, inflammation, neoatherosclerosis, and strut fracture. A variety of polymeric and metal-based BRSs have been developed to provide drug delivery and mechanical support functions similar to metallic DES during the first year after implantation, followed by complete resorption over 1 to 3 years with restoration of vascular structure and function. However, safety signals was emerged with the thick-strut first-generation device with respect to scaffold thrombosis and TVMI, especially when implanted in very small vessels. Tissue Stents offer a better and more sustainable alternative to both Bioabsorbable and Metallic Stents. It needs further study and trial to confirm if it can provide long term protection as effective alternative to DES and reduce DAPT burden on patients.

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The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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