INNOVATIVE DRUG-ELUTING ADHESIVES: APPLICATION IN CHRONIC RHINOSINUSITIS

In this article, Maria Pereira, PhD, Chief Innovation Officer, Elise DeVries, Head of Innovation & Strategy, and Camille Legros, PhD, Head of Formulation, all of TISSIUM, introduce novel applications in the treatment of chronic rhinosinusitis for the company's programmable synthetic polymers and an associated delivery device.

TISSIUM is developing fully synthetic, biomorphic, programmable polymers, which can be used in several ways – to seal or adhere to tissue, as 3D-printed scaffolds, and for localised drug delivery.

The technology at the foundation of TISSIUM's polymer platform was developed at The Massachusetts Institute of Technology (Cambridge, MA, US), Harvard Medical School (Boston, MA, US), and Brigham and Women's Hospital (Boston).[1] The first product based on TISSIUM's polymer platform (SETALIUM) received CE mark approval in 2017 for use as an add-on to sutures during vascular surgery.

The polymer technology is based on the combination of safe, naturally occurring compounds (glycerol and sebacic acid) to form a viscous pre-polymer that can be applied to internal tissues during surgical procedures, both open and minimally invasive. The high viscosity of the pre-polymer allows it to be precisely applied with minimal displacement by body fluids.

Once applied to the target location, the viscous pre-polymer is activated (polymerised) using an external blue light. The resulting bond is both adhesive and elastic, allowing the polymer to comply with the underlying tissue while remaining strongly adhered. Furthermore, this biocompatible polymer biodegrades over time. The properties of the polymer technology, precise delivery and on-demand activation, give the surgeon full control over the procedure.

TISSIUM is currently expanding the range of applications for its core polymer platform. The unique ability of TISSIUM's polymer platform to be leveraged in many different ways is due to the modular platform design: each use case leverages a targeted polymer formulation, distinct delivery device and specific activation technology (Figure 1).

> "The polymer can be loaded with drugs and deployed potentially anywhere in the body, including through minimally invasive procedures, to create a drug depot that delivers drugs locally for extended periods of time."

In addition to being applied as a sealant or adhesive, where the polymer is activated on demand inside the body, the pre-polymer can be used as a 3D-printing resin to build high-resolution 3D printed scaffolds. This is being applied by TISSIUM, for example, in the design of nerve guides to promote the repair of peripheral nerves. Furthermore, the polymer can be loaded with drugs and deployed potentially anywhere in the body, including through minimally invasive procedures, to create a drug depot that delivers drugs locally for extended periods.

> "TISSIUM is leveraging the adhesive and drug delivery properties of its polymer platform for its first drug-device indication to address chronic rhinosinusitis."

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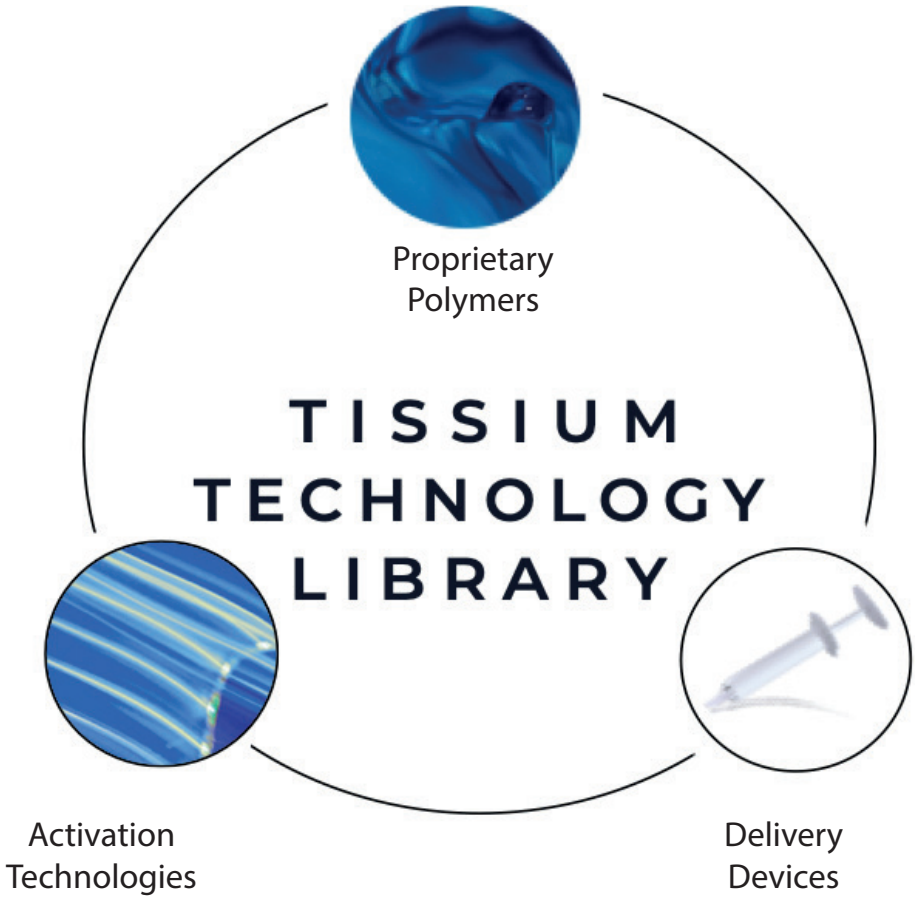

Figure 1: TISSIUM's modular platform design, comprising the polymers, delivery devices and activation technologies, enables products for different clinical indications.

"The intimate contact between the adhesive polymer and the mucosa is expected to result in a high drug concentration for passive diffusion to the inflamed tissue."

MODULAR PLATFORM DESIGN

This modular platform design enables the extension of the technology for applications with different tissue types and therapeutic indications. To support this growth, TISSIUM has scaled up its own manufacturing capabilities, with a 1,300 m^2 manufacturing site in Roncq (France) equipped with clean rooms (totalling 300 m^2) and an analytical laboratory extending over 140 m^2.

TISSIUM is leveraging the adhesive and drug delivery properties of its polymer platform for its first drug-device indication to address chronic rhinosinusitis (CRS). In this scenario, the polymer, loaded with a drug, is delivered through minimally invasive endoscopic techniques to the sinonasal cavity. A later phase of this project will address the use of this solution in other procedures and therapeutic domains where targeted local delivery of bioactive agents is of critical need.

CASE STUDY: ADDRESSING THE BOTTLENECK OF STEROID DELIVERY IN CRS PATIENTS

CRS is defined by the chronic inflammation of the paranasal sinus. Despite the simple definition, this is a complex disease that incorporates many different conditions and endotypes that impact the treatment outcomes.

Regardless of the underlying etiology, all CRS patients endure a long treatment pathway which often does not provide effective treatment or long-term palliation of their disease (Figure 2). The combination of repeat medical management, office visits, sinus surgery and maintenance therapy costs the US a total of US$12 billion (£10 billion) per year in direct costs alone. While functional endoscopic sinus surgery (FESS) provides the most targeted therapy, it does not have long-term efficacy for up to 65% of patients, with 20% of them opting to undergo repeat surgery to "treat" their disease.[3]

A common denominator in the treatment of all CRS conditions is the use of corticosteroids to control the inflammatory processes. Systemic corticosteroids are used in selected patients but widespread

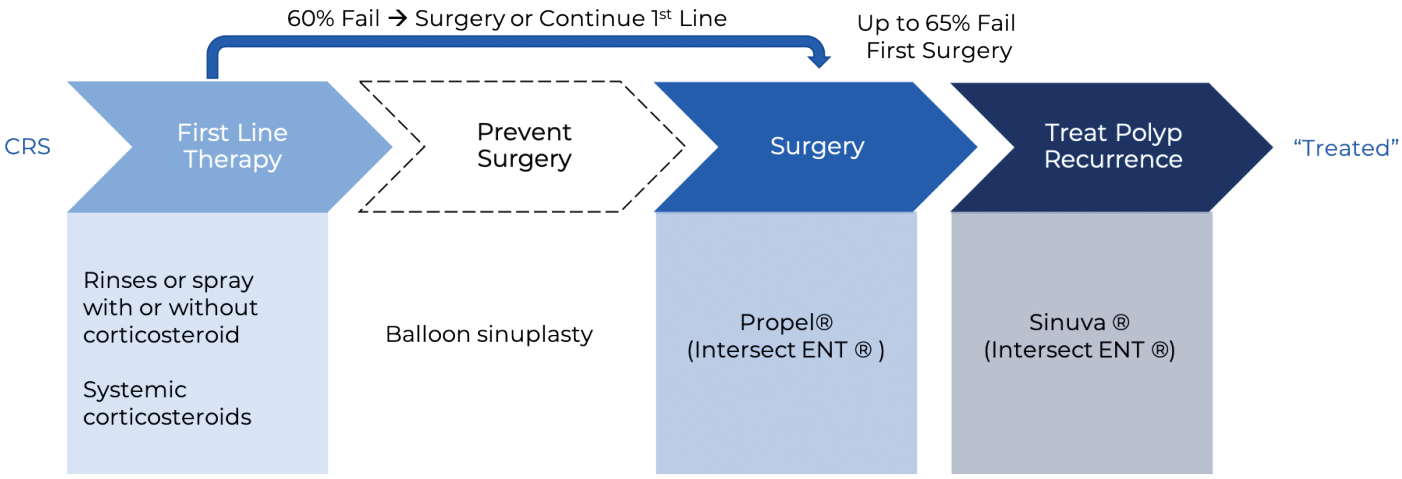

Figure 2: Patient treatment pathway and opportunities for innovation in CRS.

use is limited due to the systemic toxicity of such drugs. Instead, administration of topical corticosteroids is almost universal, and often performed through the use of nasal sprays and rinses. However, the bioavailability in the most critical locations (e.g. sinus) is limited, especially in patients that have not undergone FESS. Up to 60% of the spray or rinse washes away in the first 15 minutes,[4] leaving patients untreated between doses. Furthermore, as with many self-administration products requiring repeated use, patient compliance is a challenge.

To tackle this problem, steroid-eluting stents have been developed with the aim of improving sinus patency. Despite positive clinical studies, more data is still required to determine the cost-effectiveness of such solutions.[5] Furthermore, such stents have been associated with several downsides such as:

1. Low drug loading
2. Limited contact with mucosal tissue
3. Limited duration of release
4. Crusting of the device
5. Dislodgement
6. Delivery limited to locations that are easily accessible (i.e. approved devices are limited to post-surgery scenarios) and where mechanical anchoring is feasible.

Given the challenges in CRS treatment, where targeted steroid delivery is required in distinct anatomies, TISSIUM's polymer is uniquely poised to address this problem. Leveraging the adhesive and drug device properties of its polymer platform, TISSIUM is working on a novel device to enable precise drug deposition with extended steroid release to the sinonasal mucosa, independent of patient anatomy. The intimate contact between the adhesive polymer and the mucosa is expected to result in a high drug concentration for passive diffusion to the inflamed tissue.

Furthermore, by avoiding the need for anatomical anchors, TISSIUM expects to apply this concept not only for the treatment of post-surgery patients but also as a targeted solution between basic medical management and surgery. This approach may offer a solution to patients who have previously exhausted all options – those where medical management is ineffective but who are not eligible for, or elect not to undergo, surgery – thereby minimising the overall cost to the healthcare system and the burden on the patient.

Steroid Delivery for Chronic Rhinosinusitis
Antibiotic Delivery for Acute Sinusitis, Chronic Rhinosinusitis
Post-operative antimicrobial treatment to prevent infection
Pain relief for Septoplasty patients
Long Acting **Medical Therapy** for Rhinitis

Figure 3: Examples of use cases for TISSIUM drug delivery technology in ENT.

BREADTH OF OPPORTUNITIES IN NASAL DRUG DELIVERY AND BEYOND

For TISSIUM, CRS is just the first step in its drug-device platform, as the TISSIUM polymers can benefit treatment paradigms across other disease states as well. Due to the unique properties of the material – such as strong adhesion to both biologic and prosthetic tissues and the capacity to release small molecules in a controlled manner over time – this technology may be of great benefit to other surgical or office procedures where targeted local delivery of bioactive agents is of critical need.

A natural next step from CRS treatment is use of the steroid-loaded polymer for decreasing inflammation in allergic and non-allergic rhinitis patients. Similarly, loading of the polymer with antibiotics in place of steroids could introduce a new paradigm for targeted antibiotic delivery to the sinonasal cavity. Looking to the ENT space more broadly, there are myriad clinical needs that could be addressed by such a technology (Figure 3).

The polymer's versatile properties can be applied in other anatomic areas as well. In particular, local diseases involving inflammation, infection or pain could benefit from a technology that provides local therapy in lieu of traditional systemic dosing. Especially in the case of steroids and pain medication, the advantages of controlled drug delivery include a potential reduction in both the overall systemic dose and the associated side effects versus traditional systemic medications. Additionally, the ability to target the dose to specific anatomy using the adhesive polymer will allow for a localised therapeutic effect that does not depend on the patient – thereby eliminating the pervasive problem of patient compliance.

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ABOUT THE COMPANY

TISSIUM is a privately owned life sciences company based in Paris, France that is dedicated to the rapid development and commercialisation of a unique synthetic polymer platform to address clinical needs. The company's platform is based on a proprietary polymer family with properties including the ability to conform to, and integrate with, surrounding tissue to enable natural healing. Furthermore, the modular design of the polymers enables customisation to match tissue-specific requirements for different therapeutic areas. The company also develops delivery and activation devices for enhanced performance and usability of its family of polymers.

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ABOUT THE AUTHORS

Maria Pereira leads the Innovation Hub at TISSIUM. She co-invented TISSIUM's polymer technology while a PhD student at Prof Jeff Karp's Laboratories at Brigham & Women's Hospital (Boston, MA, US). She has been recognised for her research by *MIT Tech Review*'s "35 Innovators Under 35" in 2014, as well as *Forbes* in its "30 under 30" selection in healthcare in 2015. Dr Pereira holds a PhD in bioengineering from the MIT-Portugal programme and an MBA from INSEAD (Fontainebleau, France).

Elise DeVries is the Head of Innovation & Strategy at TISSIUM. Prior to TISSIUM, she attended the Stanford Biodesign Fellowship and worked for three years as an independent consultant in strategic marketing for a variety of medical device companies both large and small. She started her career as a Senior R&D Engineer and Project Manager for CareFusion (now Becton Dickinson). Ms DeVries also teaches classes on the biodesign process to aid companies in idea generation for new product development.

Camille Legros is Head of Formulation at TISSIUM, where she leads the formulation activities related to the company's drug-device programmes. Prior to TISSIUM, she worked at Saint Gobain as a Research Engineer, where she led and co-ordinated research projects for different business units, within a research group specialising in polymers and binders. Dr Legros holds a PhD in polymer chemistry from the University of Bordeaux (France).