

# MedTech STRATEGIST

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CAMBRIDGE MA

## CONTACT

Contact: Jonathan Thon, PhD, (Co-founder, CEO & CSO)

jthon@plateletbiogenesis.com

## YEAR FOUNDED

2014

## WHO'S BEHIND IT

Jonathan Thon, PhD; Sven Karlsson, Co-founder, COO/CBO; Joseph Italiano, PhD, Co-founder, chair of scientific advisory board

## UNMET CLINICAL NEED

Platelets are critical to hemostasis and coagulation. Transfusion is the most effective way to increase their count in patients with certain disorders, but the blood supply chain faces chronic shortages, due to the fragility of *ex vivo* platelets, which have a very short half-life, require careful handling, and may be contaminated with pathogens from donors

## SOLUTION

A system for manufacturing platelets that mimics conditions inside the bone marrow, where human platelets are normally produced, and is independent of the availability of human donors. This system must be scalable, inexpensive, and compliant with cGMP regulations

## FUNDING TO DATE

\$20 million, from grants issued by Massachusetts, NIH and the DOD, as well as a \$10 million Series A that closed in June 2017

## Platelet Production

# PLATELET BIOGENESIS: GETTING PLATELETS TO PATIENTS ON TIME AND AT COST

*Using recently discovered cell culture techniques and an innovative bioreactor, Platelet BioGenesis is closing a weak link in our blood supply chain by offering on-demand production of platelets at affordable prices.*

Platelets are essential for blood clotting and hemostasis, and their variable quality and availability can lead to deadly complications or disorders for vulnerable patients, particularly those undergoing cancer treatment, who are thrombocytopenic or victims of traumatic injury.

These anucleate cells, however, are the weak link in our blood supply chain, due to their frustratingly short half-life and exacting storage requirements. Ever wonder why blood shortages are such a problem globally, despite ongoing blood drives and availability of donors?

Unlike red blood cells, which are comparatively sturdy and can be stored *ex vivo* in the fridge for up to 42 days, or plasma, which in a frozen state lasts for years, platelets must be incubated at room temperature and have an *ex vivo* maximum lifespan of five days. Access to them, therefore, requires continual replenishment from human donors and an infrastructure geared to careful coordination between delivery and utilization. Their fragility is the chief culprit behind blood shortages and in fact the reason most of the world exists in a "platelet desert," which is not equipped to manage their limited shelf-life and the resulting need for on-demand delivery.

That clinical challenge has led to decades of research on making platelets more durable and easier to obtain. It was the primary motivation for Jonathan Thon's passionate interest in platelet storage and the driver of his ascent to become one of the world's leading experts in the field. "Platelets are the *Band-Aids* of the blood stream," says Thon, who has a PhD in biochemistry and molecular biology from the University of British

Columbia in Vancouver. "Yet, most places in the world do not have the infrastructure to collect and store them."

Almost from the start of his academic career in the lab of Dana Devine, PhD, the chief medical and scientific officer at Canadian Blood Services (analogous to the American Red Cross), Thon was aware of the constant shortage of platelets for use in surgery and wound care. He focused on finding ways to extend the useful life of platelets in his doctoral work, and switched to finding alternatives to the unrelenting reliance on human donors during his post-doctoral work. This passion led him to move to the lab of Joseph Italiano, PhD, an expert in *in vivo* platelet production at Harvard-affiliated Brigham & Women's Hospital in Boston, eventually becoming an assistant professor at Harvard Medical School in charge of his own lab.

During his career trajectory, several key innovations in the scientific world fell into place that have made advances toward this goal possible. In 1994, scientists discovered and purified thrombopoietin, the growth factor that regulates production of platelets from stem cells. In 1998, Italiano and John H. Hartwig, a renowned platelet biologist, now retired, demonstrated that platelets are formed by megakaryocytes (MKs, parent cells to platelets) through long arms called proplatelets, which extend into blood vessels in the bone marrow. In 2006, Shinya Yamanaka, MD, PhD, and his team at Japan's Institute for Frontier Medical Sciences showed they could generate induced pluripotent stem cells (iPSCs) from adult mouse cells, a technique later applied to human cells. While that fundamental discovery has broad implications for

by  
WENDY DILLER



regenerative medicine in many clinical areas—Yamanaka subsequently won a Nobel Prize in Medicine for this work—one of its most promising clinical applications is platelet production.

All of these discoveries helped Thon make what he says is his single biggest contribution to the field—something hardly conceivable only five years ago: large-scale production of functional human platelets outside of the human body for therapeutic and commercial use. The realization that this was feasible and could lead to a viable company came when Thon and Italiano developed a microfluidic platelet bioreactor to produce human platelets *ex vivo* that could be scaled to support clinical use. Once Thon and Italiano validated these claims, in 2014, **Platelet BioGenesis Inc.** was born.

Thon, who has resigned from his academic post but retains an academic affiliation with Harvard as a lecturer, is now CEO and CSO of the company. While Italiano continues to run a lab at Brigham & Women's Hospital, he is also chair of the company's scientific advisory board; in addition, the pair brought in Sven Karlsson, a former analyst and venture capital investor as a co-founder and president.

Since its founding, the company has attracted more top-tier talent as outside collaborators, including world-class scientists such as Cedric Ghevaert, PhD, a senior lecturer in transfusion medicine at the University of Cambridge in the UK, and Robert Flaumenhaft, MD, PhD, Chief, Division of Hemostasis and Thrombosis and Professor, Harvard Medical School. Ghevaert has expertise in the transformation of stem cells into megakaryocytes and Flaumenhaft is a leader in the study of how platelets release their payloads from internal pockets called secretory granules.

With the engagement of some of the world's top platelet researchers, the

company has created a 'platelet platform' that can scale and standardize the *ex-vivo* production of platelets for transfusions. Beyond that, it is working on enabling the use of platelets for drug delivery. Down the road, the hope is to eventually use these technologies to create a new class of therapeutics.

Platelet BioGenesis is using human induced pluripotent stem cells (hiPSCs) as a source for its platelets, starting with a cell line that is qualified specifically for clinical-grade differentiation of tissue, derived by the National Institutes of Health more than five years ago. Yamanaka's work has led to an explosive interest in regenerative medicine, but one of the big challenges for stem cell technology is the risk of uncontrolled growth (see *"Regenerative Medicine—Cornell's Lawrence Bonassar's Efforts to Scale 3D-Printed Biomaterials,"* MedTech Strategist, March 13, 2019). Platelets are an attractive prospect for early commercialization of regenerative technologies because they are anucleate and lack DNA, so they cannot reproduce, Thon explains. That said, he observes that the company's innovations around platelets are based on cell culture advances that enable cells to grow externally, and not regenerative medicine, which refers to growing cells within the body.

A key competitive advantage is the company's ability to scale inexpensively, made possible by the bread-box-sized bioreactor that Thon and Italiano invented at Harvard. Platelet BioGenesis has optimized the geometry and conditions for production of platelets within the bioreactor and successfully built in multiplexing capabilities, resulting in a platform that is flexible enough to match any production needs. It is preparing to transition the technology to meet cGMP manufacturing requirements.

The bioreactor is designed to replicate the architecture of human bone marrow, enabling megakaryocytes, to

produce platelets. A millifluidic design helps reduce costs by requiring minimal amounts of media, the most expensive component of cell culture, to grow vast volumes of MKs—a series of parallel channels comprising cellphone sized "blades" that can be stacked to produce multiples of between  $1 \times 10^8$  and  $1 \times 10^9$  platelets.

The key to all of this is the bioreactor's ability to expose the megakaryocytes to the same tightly regulated biophysically relevant pressures as they are under in the human bone marrow and recreate only components needed to trigger the process, says Thon. These platelets have the same characteristics as natural platelets in all respects, but they have tremendous handling and durability advantages because they can be manufactured on demand, says Karlsson. They also will be safer because they are produced under sterile conditions, he adds.

Natural platelets have a roughly 10-day lifespan, but by the time they arrive at providers, their shelf life is on average two days, due to time-consuming testing for pathogens and the fact that donated platelets are a mix of new cells and older ones nearing the end of their lifespan, explains Thon. Manufactured platelets have a known production date, potentially extending their shelf life to the full 10-day lifespan of platelets in the body.

The competitive landscape is wide open, leaving plenty of room for innovators. According to scientific journals, one potential commercial competitor, **Megakaryon Corp.**, is also working to develop platelets from iPSCs, but it is still in the early stages of creating a bioreactor system to trigger platelet production and questions linger around its cost and quality of results. Some academics are also working on this problem, but they appear to be far from commercial solutions.

Despite the limited attention the field is currently receiving, the market opportunity is huge. The global annual market for platelet transfusion is \$12 billion, of which the US market is \$2 billion (based on a \$1,000 cost per unit of platelets). That number is conservative, however, because many surgeries are postponed due to lack of

adequate platelet supplies, and many cancer patients who depend heavily on platelet transfusion, receive suboptimal volumes because of inadequate supplies, says Karlsson.

For commercial applications, the company plans to rely on a centralized production process that will enable

it to produce and deliver platelets directly to providers on demand, as opposed to the current system, which relies heavily on donors to voluntarily donate platelets 2-3 days in advance of when they are needed. Hospitals want better access to platelets, not new machines or manufacturing responsibilities, says Karlsson.

The bioreactor also has other cell production uses, so the company is considering options for enabling access to the technology for non-platelet applications. "Our cell-culture technology is a true platform with applications well beyond platelets," says Thon.

And beyond that, there are plans to design bioengineered platelets to deliver oncology drugs. Platelets are natural transporters of materials within the body and could be loaded with anti-cancer drugs to deliver targeted therapies. Validation work on that project should take 1 to 2 years.

Platelet BioGenesis has raised \$20 million to date through angel and VC investors, including a \$10 million Series A that closed in June 2017, led by Qiming US Healthcare Fund and joined by Vivo Capital, VI Ventures, Nest.Bio Ventures, eCoast Angels and others, as well as grants including \$2.1 million from the NIH and more recently, a DOD grant for \$3.6 million awarded in July 2018 to develop a mobile version of the bioreactor. It is planning an additional financing round this year. 



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