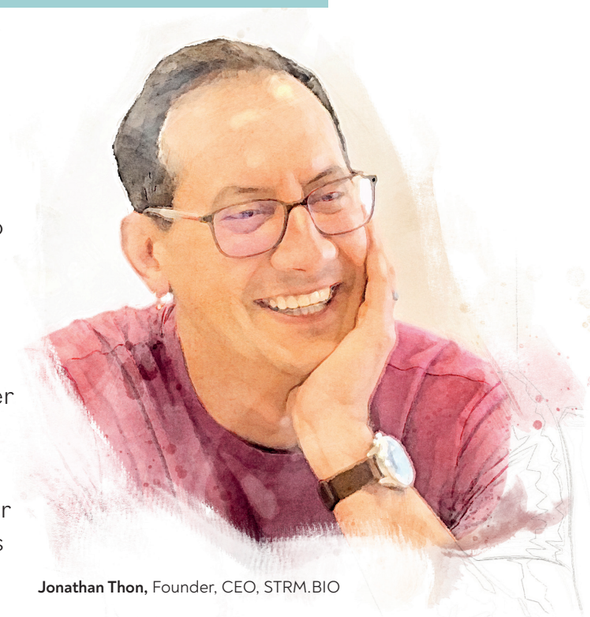
A&A

ASKED & ANSWERED

Bringing Gene Therapy to Life

A serial biotech entrepreneur, Jonathan Thon, is the founder and CEO of STRM.BIO, a pre-clinical, VC-backed biotechnology company that is leveraging extracellular vesicles (EVs) to deliver gene therapies. Prior to launching STRM.BIO, he founded and served as CEO / CSO of PlateletBio where he helped develop next-generation allogeneic cell therapies for the treatment of human diseases. Today, he has an audacious goal–to democratize gene therapy by developing a simpler, safer, and more affordable way to deliver treatment.

Dr. Thon describes to *Inside Precision Medicine* the need for next generation delivery vehicles for gene therapies and how the use of microvesicles offers differentiated advantages over both viral- and exosome-based approaches.



Jonathan Thon, Founder, CEO, STRM.BIO

Doherty: The concept of gene therapy is intuitive but not easy to execute. What is needed to unleash its full potential?

Thon: Undoubtedly, this modality is elegant in its simplicity and yet a remarkable advance in healthcare. With gene therapy, we can now reverse a particular type of blindness and treat spinal muscular atrophy. While these are impressive achievements, the field has run headlong into an obstacle limiting its application – the requirement for successful in vivo delivery, which is the linchpin for success. These limitations arise from the use of viral vectors and include broad versus targeted tissue biodistribution, the risk of immunogenicity which prevents repeat dosing, the limited payload capacity of the vector, and difficult purification shared by viruses and lipid nanoparticles.

I like to draw a parallel between the state of the gene therapy field and what the microprocessor did for personal computing. Before the invention of the microprocessor in the late 1960s, computers filled whole rooms. The ability to rapidly transfer data between different memory locations on increasingly tiny and cost-effective microprocessors revolutionized the field and brought computing technology into every home, democratizing the personal computer, and creating a new industry.

Credit: STRM.BIO

Gene therapy needs a similar breakthrough. The once-laborious process of identifying the genetic variants responsible for inherited disorders is now relatively straightforward, and innovations such as CRISPR–Cas9, base editing, and prime editing mean that the gene editing process itself is no longer the technical bottleneck. Multiplexed therapies that can edit multiple genes in parallel have the potential to expand the applications of gene therapy beyond relatively rare single-gene disorders for the first time. And yet the list of approved gene therapies remains short, while the cost and the risks of the current therapies remain high. The principal obstacle now limiting the widespread application of this lifesaving technology is the safe and efficient in vivo transfer of the editing constructs into the right cells. Solving this delivery problem would reinvigorate the field and help bring new treatments and cures for diverse diseases into every hospital.

Given the potential for gene therapy, there is significant interest in the field to identify better routes of delivery. That's the focus of STRM.BIO and we envision a future where gene therapies are capable of treating many more diseases and many more patients than is currently possible.

Doherty: What sparked your entrepreneurial spirit in the life sciences?

Thon: I've always been most interested in the intersection of scientific fields—particularly physics, biology, and medicine. Interestingly, this reflects my upbringing at the intersection of several cultures–I was born in Argentina, grew up in Canada, and now work in the US.

Biotech was a natural fit for me as it presses at the boundaries of what we know and what is possible. The thirst for a greater understanding and better tools to answer our most important questions drives me.

I began my undergraduate career at McMaster University in Ontario, Canada by specializing in biotechnology and genetic engineering, and then earned my PhD in biochemistry at the University of British Columbia. During my academic career, I became exposed to the blood transfusion space and recognized that the key problem was not in the storage time or sterility of products, but in our dependence on a volunteer donor blood system. The question of whether we could disconnect product from donor by making human cells/tissues for transplant led me to pursue a post-doctorate fellowship at Harvard where my work focused on making blood cells from pluripotent stem cells in culture. This idea that we could leverage existing biology to solve clinical manufacturing and delivery challenges became a central theme of my research and the foundation of my lab when I became a faculty member. At Harvard my team began developing platforms for commercial manufacture and scale up of cell-based therapeutics. This was the genesis of Platelet Bio, my first biotech startup, which served as a translational vehicle for this technology. I ran Platelet as its chief executive officer and chief scientific officer for nearly seven years before stepping away in 2019 to found STRM.BIO.

Doherty: What is the origin story of STRM.BIO?

Thon: Interestingly, the ideas upon which STRM.BIO was founded pre-date Platelet Bio by a number of years—and while the vision was there, the science was still developing. Imagine a gene delivery platform before there were gene therapies to deliver. Fortunately, the gene therapy field made tremendous strides on non-viral gene delivery throughout the decade I was working at Platelet. Pivotal proof-of-concept studies by many academic labs, including our scientific advisors and collaborators, demonstrated that extracellular vesicles could be used to deliver gene therapies in vivo. The field still had to progress significantly before we could realistically start a company to realize this opportunity, but we arrived there a few years ago and suddenly the window to solve a major bottleneck in gene therapy opened. STRM.BIO was founded to help accelerate this vision the rest of the way through.

We founded STRM on a hybrid-virtual operating model. The idea was to avoid reinventing infrastructure and recreating pre-existing expertise when we could leverage them instead to accelerate programs and keep our focus where it matters–our research. When we first began pitching the operational idea behind STRM

in the fall of 2019 (pre-COVID), it was met with little enthusiasm. Frankly, it was very hard to get investors to return our calls. A couple months later, in February 2020, COVID became our new reality. The premise that we could leverage existing infrastructure and work remotely suddenly became a lot more exciting and attractive. It also turned out to be true! This approach made it possible for STRM to move a lot faster than any of us expected in our first year of operation and accelerate while others were slowing down during a global pandemic.

STRM turned out to be the right company built at the right time under the right operating model.

Doherty: Why are microvesicles such a promising vehicle for delivery of gene therapies?

Thon: Exosomes, which originate inside cells, have garnered quite a bit of attention as a possible delivery mechanism for gene therapy. Unfortunately, they have a very small carrying capacity and no inherent tissue targeting capabilities, and therefore suffer from all the same limitations in targeting as previous approaches.

Microvesicles offer differentiated benefits. They are a larger class of extracellular vesicles, with a carrying capacity similar to that of adenoviruses. As such, they can be used to deliver a diverse range of cargos, including combination constructs required for multiplexed gene editing applications and next generation base/prime editors that are increasingly becoming larger and more difficult to package otherwise. As part of the body's intercellular communication network, microvesicles have an innate ability to encapsulate RNAs, DNAs, and proteins and to efficiently deliver this cargo into other cells. Because they bud from the cell surface membrane, microvesicles inherit the complex combination of surface proteins expressed by their source cell which can be modulated, making them a highly tunable option for diverse gene therapy applications. Microvesicles have more immune privilege than lipid nanoparticles and viruses, allowing for repeat dosing. As microvesicles are naturally secreted into the blood and other bodily fluids from multiple cell types, they have been present in every blood transfusion and organ transplantation ever performed, beginning long before their formal discovery and characterization; they're also present in other blood and biological products. This long history demonstrates their safety.

Doherty: Which applications of gene therapy is STRM.BIO focused on?

Thon: STRM.BIO is initially focused on the major unmet need which resides at the intersection of gene therapy and rare blood diseases. Our proprietary microvesicles have an innate tropism to long-term hematopoietic stem cells in the bone marrow (the earliest progenitors, desired for durable correction), offering the prospect of long-lasting in vivo treatments and cures for a range of inherited hematopoietic disorders, without the need for prior immune system ablation. In addition to their natural tropism and preferential targeting, STRM.BIO's platform is further differentiated in that it allows tunable loading that supports protein and nucleic acid cargo delivery in vivo, and repeat dosing–both of which will be game-changing attributes for the field.

Doherty: What are some of the notable milestones STRM.BIO has achieved thus far?

Thon: To date, we have established important proof points including consistent and scalable production, tunable loading of diverse cargo, hematopoietic stem and progenitor cell targeting, and successful cargo delivery. The company's lead programs reflect the breadth of their platform and are designed to establish pre-clinical proof-of-concept across multiple cargo modalities in well-defined monogenic disorders. Programs currently in preclinical development include bone marrow failure syndromes, oncology, and hemoglobinopathies such as sickle cell disease. We are also exploring the ability to broaden our platform and enable directed tropism to other tissues, which would enable us to pursue other diseases.

Doherty: What was the inspiration for the name STRM.BIO?

Thon: The acronym STRM stands for "Some Things Really Matter".

At the core of gene therapy is the fundamental idea that one can cure a disease as opposed to treating its symptoms. The final bottleneck is delivery. It is critical to the future of the field that the next generation of gene therapies be implemented as simple injections in standard clinical settings. The current ex vivo approach, in which a patient's cells are edited in culture and then re-transfused, is not a sustainable model. The patient must undergo immune system ablation before receiving an ex vivo gene therapy treatment, which can have severe side effects or even be fatal. These treatments require specialized facilities and training and are too expensive to be supported by payers as a routine option. A solution that meets all these criteria will democratize gene therapy by providing a simpler, safer, and more cost-effective way to deliver treatments and cures as standard of care for diverse diseases. The ability to make gene therapies a viable therapeutic option for people. This is an area that is ripe for disruption and the remaining challenge that needs to be overcome to realize the promise of curative therapies. STRM.BIO is that solution.

Doherty: What keeps you motivated as you develop your venture?

Thon: The vision of what the world could look like if we're successful. The idea that we could democratize gene therapy. That we can do for gene therapies what the microprocessor did for the personal computer–that is, enable gene therapies to become viable therapeutic options for people, is transformative. For many, it's going to change the landscape of medicine by curing diseases and offer the possibility of effective, life-changing treatment where none are currently available. And that's just the beginning.