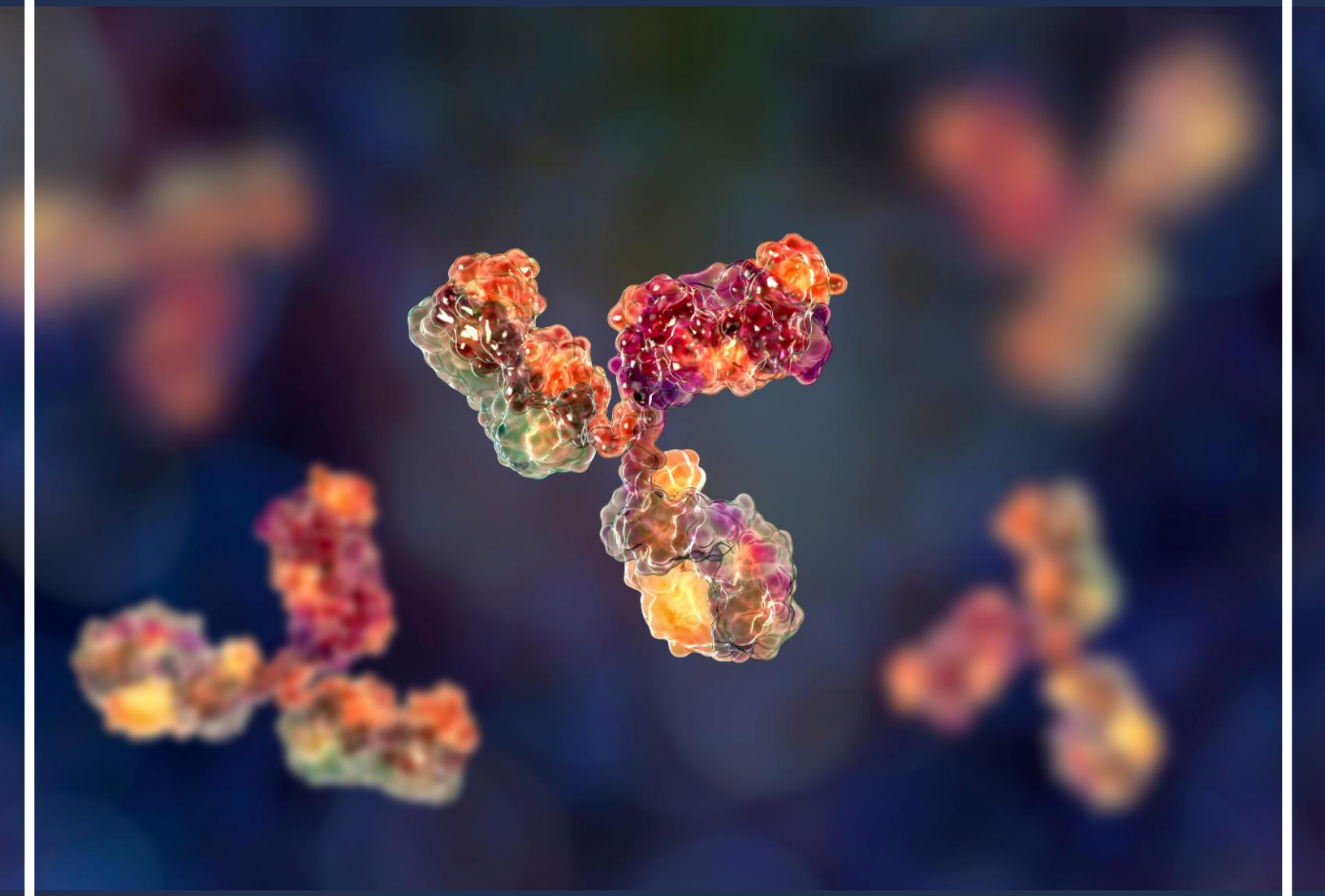
LYRIC

Next generation manufacturing for complex therapeutics



WHITE PAPER

SUMMARY

Complex Therapeutics are a class of life-saving drugs that are sourced exclusively from human donors. The inability to manufacture these therapeutics has led to supply constraints that limit patient access, increase costs, and stifle development of emerging therapies.

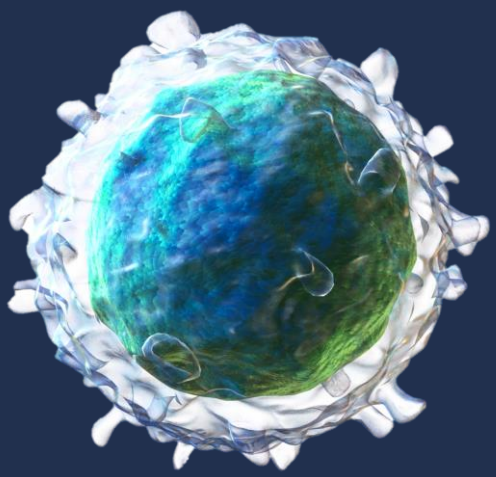
Using proprietary tissue engineering technology licensed from Prellis Biologics, Inc., Lyric Bio is developing ultra-high-density bioreactors for commercial production of complex therapeutics.

Examples of Complex Therapeutics include:

- **Human stem cells**
- **Red blood cells**
- **Human Immunoglobulin (Ig) therapies (IvIg and ScIg)**

Each of these therapies represents a multi-billion-dollar market that is currently supply restricted. Our mission is to provide high-efficiency, scalable, next-generation manufacturing to produce Complex Therapeutics. Our vision is to address the drug markets left behind in the biotechnology revolution, by offering higher consistency products with improved supply stability at a lower cost.

Lyric Bio, Inc. has chosen immunoglobulin (Ig) therapies as our first product for next-generation complex therapeutics manufacturing.



INTRODUCTION

The ***biotech revolution*** created a 1.5 trillion-dollar industry that has fundamentally changed how we treat disease. With advancing technologies like CRISPR, CAR-T, and gene therapy it is easy to overlook what enabled modern medicine. Simply put, it was advances in biomanufacturing.

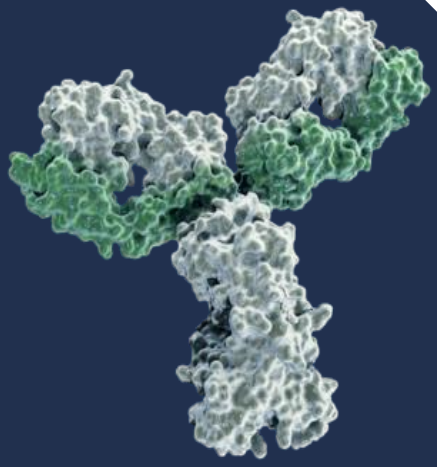
By the mid-1980's protein therapeutics had been used for several decades, but their supply was completely dependent on donors (often animals). This severely limited availability and product consistency, not to mention commercial attractiveness. The biotech giants of today, companies like Eli Lilly and Genetech who partnered to produce insulin and Amgen who developed epoetin alpha, were made possible by the simple discovery that scientists could 'program' nearly any cell type to produce endless copies of the same human protein. Recombinant protein engineering allowed large scale production of therapeutic proteins in bioreactors, enabling companies to scale biologic therapies to meet global demand at a fraction of the cost. An explosion of growth ensued, and this new manufacturing approach ensured the consistent production and distribution of single protein therapeutics. In the age of CRISPR and AI driven protein development, it easy to forget that 50 years ago manufacturing of drugs that enable cancer survival, autoimmune disease remission, and diabetes management was simply not possible.

But, modern protein manufacturing left many life-saving drugs behind.

'Complex Therapeutics' are medicines that consist of mixtures of proteins (human polyclonal immunoglobulin) or cells (red blood cells and stem cells) that ***can not*** be produced using standard manufacturing processes. Today, we still rely on human donation to meet need, but this is not guaranteed and rationing of these products is routine. Dependence on human donation has created a landscape of high-costs, reduced access and looming bottlenecks in future therapeutics development. This presents a significant opportunity: development of the next-generation manufacturing technologies that uncouple production of complex therapeutics from dependency on human donation.

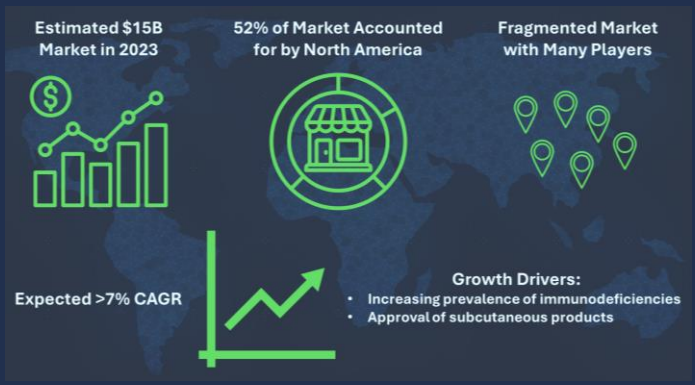
Lyric Bio is developing the technology to manufacture complex therapeutics, starting with therapeutic human immunoglobulin (IvIg and ScIg).

FIRST PRODUCT



Ig therapy (including IvIg and ScIg), is a polyclonal antibody mixture derived from human serum and a $15B growing market. For existing products, production involves isolating immunoglobulins (antibodies) from thousands of healthy donors. The antibody mixture is then purified and concentrated to create a therapeutic.

Ig products are currently FDA-approved for seven (7) indications but are used off-label to treat over 100 different diseases, and for many patients, they are a life-saving medicine. Broadly, Ig is used to treat diseases that fall into 2 categories: 1) Immunodeficiencies where Ig provides a protective mixture of antibodies to patients unable to make enough of their own antibodies, and 2) Autoimmune diseases where Ig is linked to multiple mechanisms of action that reduce inflammation and suppress autoimmune responses. Ig therapies are also being explored in numerous ongoing clinical trials including Alzheimer's Disease and Long COVID.



Because Ig therapy is a mixture of thousands of different antibodies, it cannot be manufactured with existing techniques. Producing Ig with current processes would require sequencing thousands of antibodies, transfecting DNA coding for each antibody into CHO cells, and then maintaining thousands of cell lines to produce the product. Even if this was feasible, Ig therapy is meant to represent a snapshot of a patient's immune system which co-evolves with diseases in circulation. This process would need to be repeated at a regular cadence to truly match the effectiveness of current Ig products.

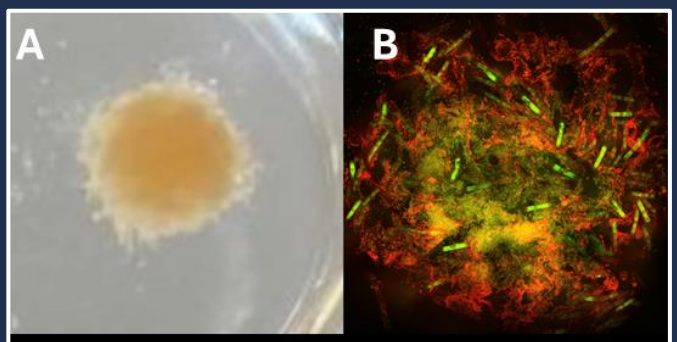
As a result, we are completely reliant on human plasma donations for supply. Donations must be collected at centers around the world, then millions of liters of plasma must be shipped to centralized processing facilities and purified. Once there, it takes ~7-10 donations just to produce a single dose of Ig therapy. The result is an expensive product that routinely faces market shortages, further limited by a process that is too expensive to scale to meet growing demand.

However, there is an alternative: collect and culture antibody-producing B-cells from donors instead of the antibodies themselves. This process can produce an Ig product similar to those on the market, while reducing dependency on donors.

SOLVING CURRENT LIMITATIONS

Human B cells naturally produce the immunoglobulin used in IvIg and ScIg. These specialized immune cells spend most of their life as tissue resident cells, closely packed together in high density niches in the bone marrow, lymph nodes, and spleen. Cell densities in these tissues can approach 3-5 billion cells per cubic centimeter. Although a viable manufacturing processes has not been developed, several academic groups have shown that B cells can be cultured ex-vivo to produce immunoglobulins suitable for Ig therapy *(Neron, S. et al. PLoS ONE. 2012, Pinna, D. et al. Eur J. Immunol. 2009, and Muir, L. Wellcome Open Res. 2017)*. Based on Ig secretion rates from this research we estimate that to cost effectively manufacture Ig with human B cells it would require cell densities of >1 B cells per milliliter (mL).

Current manufacturing technologies for antibodies and other biologic therapeutics rely on suspension cell lines cultivated in large vat bioreactors which do not support primary B cell culture. Even if it were feasible to culture B cells in these systems, most bioreactors only reach a maximum cell density of 10 million per mL *(Jyothilekshmi, I. and Jayaprakash, J. Microbiol Biotechnol, 2021)* which does not support cost-efficient production of Ig. Hollow fiber bioreactors can support cell culture at densities higher than suspension bioreactors. However, none exceed 100 million cells per mL of media which is not cost effective for production of human Ig. This coupled with the high media use of hollow fiber bioreactors, expensive consumables, and that our team was unable to find any examples of primary B cell culture in hollow fiber, strongly indicates that hollow fiber bioreactors are not a suitable solution.

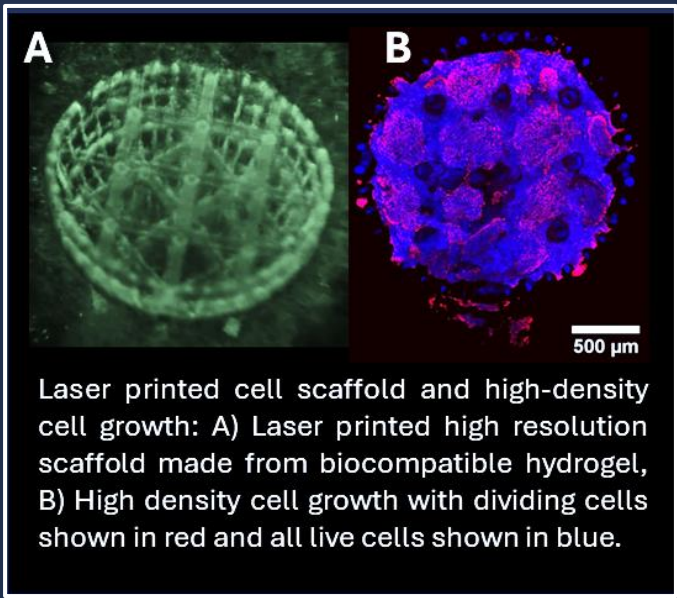


Large in vitro grown organoid: A) 1 x 1 x 0.2 cm primary human liver cells grown for 30 days in vitro, B) High resolution image of cell density (yellow and red) grow for 1 month under flow around scaffold material (green).

Lyric Bio is licensing technology from Prellis Biologics that has been used to create high-density tissue culture, routinely reaching 1-2 billion cells per cubic centimeter with minimal hypoxia (Prellis Biologics, unpublished data). By combining licensed tissue engineering technology with academically accepted approaches to primary B cell production of Ig, we believe Lyric Bio can develop bioreactors that produce 1,000 or more doses of human immunoglobulin from a single donation, significantly reducing reliance on donors.

TECHNICAL ADVANTAGE

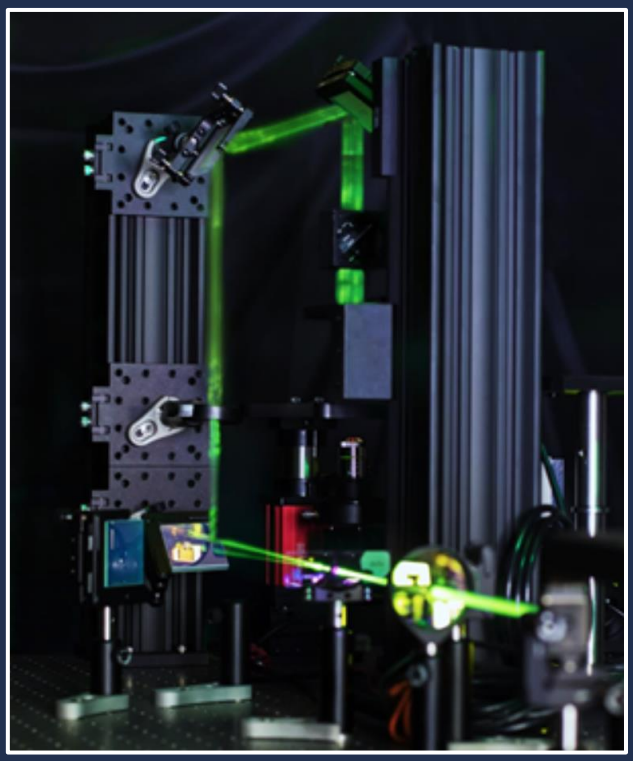
The key to Lyric's success is the internal surface area of our bioreactors, enabled by the world's fastest high-resolution bioprinter licensed from Prellis Biologics. Our technology uses lasers to print an internal bioreactor scaffold, with extremely fine features in biocompatible and oxygen-permeable polymers. This allows development of bioreactors with extremely high surface area to volume ratios, enabling a 3D culture that more closely resembles lymph node tissue and allows us to culture B-cells at much higher densities.



Laser printed cell scaffold and high-density cell growth: A) Laser printed high resolution scaffold made from biocompatible hydrogel, B) High density cell growth with dividing cells shown in red and all live cells shown in blue.

Higher densities of B cells means more Ig produced per liter of media consumed and greater cost efficiency for Ig production. We anticipate that our bioreactors will be capable of supporting hundreds of billions of cells in a compact lymph node-like niche in a volume less than 200 mL. This will allow Lyric to manufacture Ig for ~10-100X less than the current donor-derived process.

Lyric Bio has been granted an exclusive license to the high-resolution bioprinting technology developed by Prellis Biologics. With recent advances in holographic laser printing technology, Lyric Bio can produce internal scaffolding for a bioreactor capable of supporting 100s of billions of cells in about three hours. Our bioreactors increase internal surface area to volume ratios by at least 10X relative to the densest existing commercial 3D cell culture technologies.



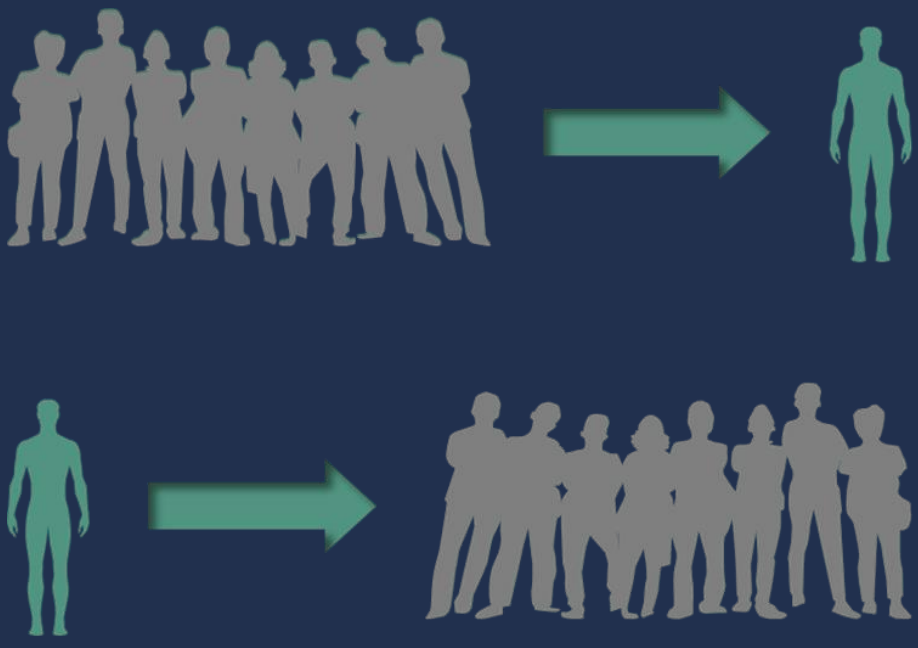
EXPANDING PATIENT ACCESS

Producing human Ig for a fraction of the cost is a great start toward commercial success, however, the real impact of Lyric's approach will be to expand access to Ig therapies. Routine supply shortages results in hospitals and physicians stockpiling the drug. Lack of access is compounded by increasing demand for Ig products in existing indications, a shift toward subcutaneous products, and continued research into new indications.

One of the most significant innovations in Ig therapy has been the recent approval and launch of subcutaneously administered products. Previously, all Ig was administered intravenously, requiring a trip to a clinic or hospital for each dose. Beyond being inconvenient for patients, this increases costs and limits which patients are likely to be prescribed or pursue treatment. Subcutaneous products allow for at home administration increasing convenience and expanding the eligible patient population.

However, there is a downside. Subcutaneous administration is significantly less efficient than intravenous, requiring 30-50% higher levels of antibodies to achieve the same effect. This has to potential to exacerbate supply shortages by exponentially increase demand for Ig, both increasing the number of patients and raising the required dosage.

Lyric's approach has the potential to dramatically increase global supply of Ig therapies. This will support market growth from expanding use cases and the launch of subcutaneous products, ensuring patients have access to the treatment they need.



CONCLUSION

Lyric's high-density tissue-mimicking bioreactors will enable unprecedented efficiency, supporting the manufacturing of complex therapies. Our first product will focus on B cell culture to manufacture human Ig, reducing costs and supply constraints. Manufacturing Ig therapies in bioreactors provides a much greater degree of product control, ensuring that each dose has desirable antibody characteristics. Introduction of manufacturing controls to human sourced products has the potential to improve quality and consistency across lots, while enabling the introduction of engineered improvements.

Lyric also has the potential to produce bioreactors to support other human cell types including human stem cells and red blood cell production by recreating bone-marrow like tissues. Reducing costs and securing supply across these markets will ensure patient access to life saving therapies while supporting innovation.

The next revolution in biotherapeutics, much like the first one, may come down to a revolution in manufacturing processes for new categories of biologic therapies. We believe that bioreactors replicating high-density tissues will unlock value across multiple life saving medicines and will support the development of next generation therapeutics.

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