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From Bench to Billions:

Facilitating Scale-up of Adherent Cultures for Cell and Gene Therapy Workflows

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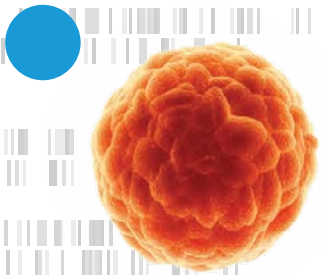
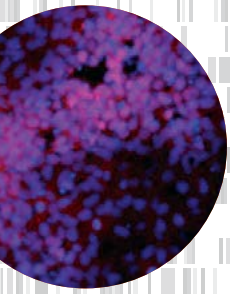
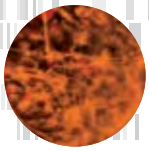






Cell and gene therapies (CGT) have changed what's possible in modern medicine. Since their advent, clinicians have gained access to more tools than ever for preventive and curative care, whether that care involves stem cells, viral vectors, vaccines, or other therapeutic formats.

Given the promise and potential of these emerging therapies across a variety of disease states, it's no secret that the market will demand more of them in the years ahead. By 2025, the FDA expects to approve up to 20 CGT products annually,[1] and biotechs are racing to realize that prediction.

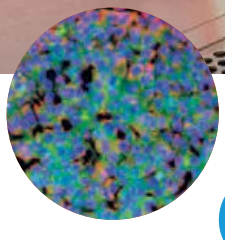
The challenge is how to generate the number of cells required (which can amount to tens to hundreds of billions) with limited resources and time. The move toward allogeneic, "one-to-many" programs has required scale-out and scale-up from the bench at a breakneck clip. One adult patient, for example, might require hundreds of millions of cells in a single therapeutic dose.[2] Multiply that by hundreds of patients enrolled in a clinical trial, and the demand can become bewilderingly large for a seed train that originates from just one cryogenic vial.

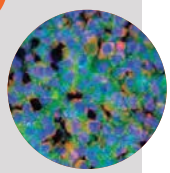
As life scientists and process engineers know, there are nuances to biomanufacturing that make achieving this kind of scale difficult in the lab. Cell type is one factor. If the cells of interest are attachment-dependent, such as induced pluripotent stem cells (iPSCs), there are specific advantages to using an attachment-friendly adherent cell culture platform for cell expansion. These choices can have operational impacts on manufacturability, from footprint, labor and cost of goods sold, to process control and GMP compliance.

Underlying all of this is the fact that cells are living things that are prone to unpredictability, stress, damage, and death. Scale requires getting to a level of cell production that's compatible with a clinical application *without* sacrificing the phenotype or quality of the cells or losing their potency over time. For example, some types of stem cells may only divide a handful of times before they lose the stemness properties that make therapies effective.

"Sometimes the cells come from a really specialized biological niche with a multitude of factors that support their function *in vivo*," says Cat Siler, Ph.D., Field Application Scientist at Corning Life Sciences. "You can replicate that niche in culture just fine at the bench, but when you want to scale, it can require an alteration in order to get it to work as intended."

Maintaining culture in adherent conditions at scale is possible with forethought into workflow integrations, automation, and platform choices in developing a manufacture-ready seed train for these powerful cultures. This guide explores what researchers should consider when they are creating a risk-mitigating adherent culture process for cell and gene therapy scale-up.





Think Long-term at the Start

The most important component of a scale-up strategy is the long-term plan. If researchers hope to achieve commercial scale someday for their gene or cell therapy, it would be wise to start thinking today about how they'll get there, suggests Tom Bongiorno, Ph.D., Field Application Scientist at Corning Life Sciences.

"I'm seeing a recent trend where even early-stage groups are starting to think much further down the manufacturing pipeline," he said. "So instead of just considering what they need solely for research or process development, they're putting a lot of preliminary thought into manufacturing."

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The core reason for this goes back to the biology, which doesn't always translate immediately from the lab to production scale, and validation is critical along the pathway to production. It's important to think backward from your goals, assessing the desired yield against limiting factors such as budget, labor, space, and time.

"At some point, you will need to do all that optimization anyway," Bongiorno said. "The sooner you work that into your pipeline, the better your chances of success when you go into the clinic."

One opportunity to be more proactive about the pipeline is in platform selection. Changing platforms as infrequently as possible during a transition from small to commercial scale can enable labs to maintain more stability in their seed train without having to adapt and train on new instrumentation as the protocol advances.

Additionally, if you invest earlier in automated technology that accommodates multiple applications, you'll also stand to save on labor and capital costs in a time when shortages and inflation have been felt worldwide. For some industry stakeholders, such as CDMOs, getting that degree of multipurpose utility for multiple cell or gene therapy programs through a single equipment acquisition can make all the difference.

Modular systems can also help investigators balance short-term resources and long-term demand. With the option to use tubing manifolds and other connectors to advance the seed train as needed, investing in small-to-large equipment compatibility can enable the technology to evolve with the real-time needs of the program.

Select the Right Platform for Cell Scale-up

Naturally, researchers have choices in selecting scale-up platforms, but until recently, those choices were always limited with regard to the adherent cells required for many cell and gene therapy applications. In a way, the science had outpaced the infrastructure supporting it.

"These therapies were evolving so quickly, with so much innovation going on in the space," according to Tara St. Amand, Ph.D., Director of Business Technology, Bioprocess at Corning Life Sciences. "But there hadn't really been a standard platform designed specifically to solve the very real manufacturing problems companies have been facing."

Those problems include the significant challenge of reaching scale without compromising cell quality, introducing contamination risk, or filling a space-constrained lab with piles of vessels. After all, the only supplies designed to culture adherent cells, at least historically, were flasks and plates, which can't feasibly be scaled up without suppliers rethinking their designs — which they have. The market has by now produced a range of closed system technologies that address these concerns, from multilayer and stacked vessels that pack more surface area into smaller footprints to fixed bed bioreactors (FBRs) that bring automation and control to a high-density adherent cell culture platform.
For example:

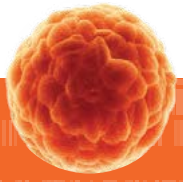
Corning® HYPERFlask® Vessel:
1,720 cm^2 surface area

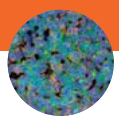
Corning CellSTACK® Vessel:
6,360 cm^2 surface area

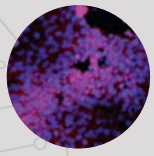
Corning HYPERStack® Vessel:
18,000 cm^2 surface area

Corning CellCube® System:
up to 85,000 cm^2 surface area

Corning Ascent™ Fixed Bed Bioreactor System:
1 to 5 m^2 surface area (up to 1,000 m^2 in development)







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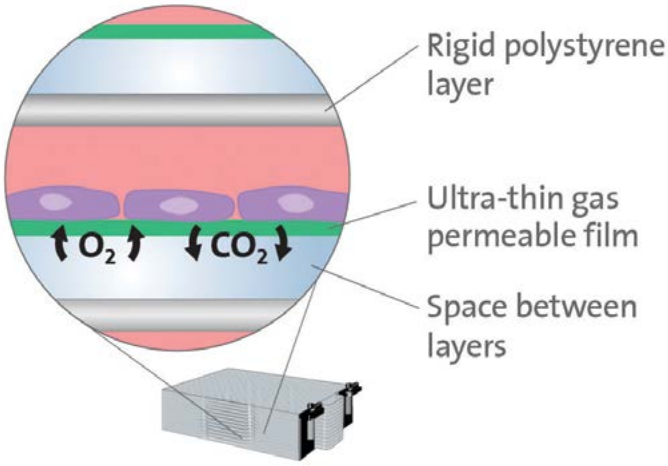
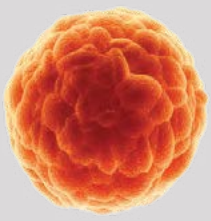
Corning High Yield PERformance (HYPER) Technology



Picking the right platform from these advanced options depends on several factors, especially desired yield and time. If you need significantly more cells, you might gravitate toward more complex and high-output platforms, such as the Corning® Ascent™ FBR system, which offers greater automation to reduce operator variability and improved reproducibility through more robust process control.

If every minute counts, and you need cells fast, scaling out through compatible multilayer and stacked vessels such as Corning CellSTACK® and HYPERStack® vessels could be the answer for faster cell expansion. These systems also provide the benefit of modular configuration, which can be especially useful when researchers encounter midstream issues that require optimization earlier in the seed chain. For example, if a finding requires the protocol to be reworked, it's much easier to troubleshoot in a single vessel and then bring that change to a series of CellSTACK or HYPERStack vessels connected by a manifold.



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Consider Operational Impacts of Platform Choice

Alongside time, cost and labor also matter in scaling up cell production for therapy. While an automated handling option such as the Corning Automated Manipulator Platform facilitates processing for stacked vessels, an FBR may be considered part of a more efficient workflow. For example, Corning's Ascent FBR platform facilitates automation of liquid transfer into and out of the instrument, saving time and avoiding operator variability. That efficiency carries through when technologies can be right-sized to the program needs, which is exactly why the Ascent FBR platform is designed to offer multiple bioreactor capacities within each of three instrument sizes, with fluid dynamics that scale from one to the next.

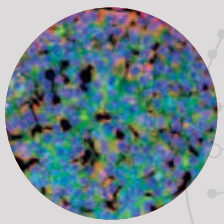
"You have process development scale, and then you have manufacturing scale," notes Angel Garcia Martin, Business Development Manager at Corning Life Sciences. "But if you can't translate from one to the other, it can create inefficiencies in having to reassess and reoptimize. Having an option that sits in the middle, such as the upcoming Ascent FBR Pilot scale system, can save time and costs from that additional effort."

Those efficiencies also extend to the ability to harvest cells, with some technologies offering better harvest management than others. For example, when an automated manipulator is used with the Corning® HYPERStack® vessel, it can execute the optimal angles and movements needed to coat surfaces with dissociation reagents evenly, driving more standardization and less labor in harvesting from batch to batch. But for the most hands-free handling, an FBR supports harvest workflows with minimal effort. Corning's Ascent FBR system stands out against other FBRs in that it enables high viability cell harvest within the platform after automating reagent distribution.

CORNING ASCENT™ IN ACTION: Addressing Type 1 Diabetes With a Fixed Bed Bioreactor

Researchers at the Gittes Lab for Diabetes and Pancreatitis Research at the University of Pittsburgh Medical Center and Children's Hospital of Pittsburgh may be closer than ever to a curative gene therapy for type 1 diabetes. Through a viral vector platform, scientists are modifying pancreatic cells to be insulin-producing and protected from immune destruction long-term. They're using Corning's Ascent FBR platform to reach the scale of viral vectors they need to achieve this potential breakthrough. Corning's fixed bed bioreactor has helped the team achieve significantly higher viral productivity than a 2D cell culture platform, at a scale that has been necessary for the team's primate studies.

LEARN MORE



From Bench to Billions: Solving Scale Together

As cell and gene therapies become more prominent in the clinic, the need for manufacturing scale platforms will only become more critical. In order to get there, investigators should start planning for their long-term needs now. Investing in a more efficient, effective process that works with, not against, the biology is critical in the so-called "race to billions," particularly as competition intensifies among startups and biopharma alike.

The best solutions will be customized, modular, and adapted to both the science and the market. They'll also be born of extensive collaboration with suppliers and other industry stakeholders, as no one group can solve these challenges alone. If you're on this path, Corning is available to help.

Ready to start your scale-up strategy? Work with a Corning Field Application Scientist to learn how you can multiply your cells, not costs, for a faster speed to market. **CONTACT US**

References

1. Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies. U.S. Food and Drug Administration. 2020. https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics.

2. Kabat M, Bobkov I, Kumar S, Grumet M. Trends in mesenchymal stem cell clinical trials 2004-2018: Is efficacy optimal in a narrow dose range? Stem Cells Transl. Med. 2019;9(1):17-27. doi:10.1002/sctm.19-0202.

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