SCALING UPDATES

FORGE BIOLOGICS
A member of Ajinomoto Bio-Pharma Services

July 8, 2026
This month's newsletter is 1,393 words—a 6-minute read.

David Shinsuke
Chief Technical Officer

Welcome to the July issue of Scaling Updates! It was a pleasure collaborating with my colleague, Dr. Frank Agbodjo, on a recent review examining the evolution and future of AAV manufacturing. Putting it to paper reinforced just how much the field has accelerated. We've moved from proving gene therapy could work to applying real science to manufacturing and quality control, driving impressive improvements in yields, process consistency, and analytical capabilities. The work ahead isn't just about better vectors. The next decade will be defined by continued advances in the manufacturing science and systems that bring more gene therapies to more patients. I hope you'll give it a read and let me know what you think!

- **From the Lab**: Curious how we got where we are in AAV manufacturing? We've got the full review!
- **"Viral" News**: Announcing our partnership with Skylark Bio.
- **Ember Events**: Meet with our team at JSGCT this month.
- **Dr. Barrett's Bench to Batch Advice**: rcAAV: So Yesterday.
- **Genes of Interest**: Jeremy Hynick ensures the manufacturing environment is just right.
- **Factoid of the Month:** Staying cool with TCUs.
- **Gene-ius Jobs**: Computer Systems Validation (CSV) Engineer

From the Lab

Forge experts publish new review: "Status and Future of Recombinant Adeno-Associated Virus Vector Manufacturing"

The industrialization of AAV gene therapy manufacturing is no longer a future state, it's the present one. A review paper by Forge's Frank Agbodjo, Ph.D., and David Okunuki, Ph.D., just published in Bioprocess Technology draws a clear line from where the field has been to where it's going, and the conclusion is clear: standardization, platform processes, and commercial-scale thinking will define the next decade.

At Forge, this is exactly the lens through which we've built our capabilities, from our molecular development work supporting plasmid and construct design assessment for manufacturability from the start to our FUEL™ platform focused on manufacturing efficiency so developers can get more doses from every run. As gene therapy expands beyond rare diseases into indications like Alzheimer's, Parkinson's, and diabetes, the manufacturing infrastructure has to be ready. We've been building for that moment.

The full review paper can be accessed here.

"Viral" News

The latest and greatest news about Forge

- **PRESS RELEASE: June 16,** Skylark Bio and Forge Biologics Announce Strategic AAV Development and cGMP Manufacturing Partnership Supporting Skylark's Clinical Development
- **June 17,** Skylark Bio, Forge Biologics Partner on AAV Development and Manufacturing (Boston Life Sciences Times)

Read more coverage of our Skylark announcement and always find the latest Forge news here.

Ember Events

Opportunities to connect with our team live at these events

- **July 23-25**: JSGCT / Tokyo
- **Aug 10-13**: Bioprocessing Summit / Boston

Can't make it to an upcoming event? Connect with us virtually.

Every AAV program comes with critical manufacturing decisions and a labyrinth of options. In this advice column, our **Head of Technical Sales and Scientific Advisory,** Dr. Brianna Barrett, Ph.D., answers real developer questions about program manufacturing strategy with practical guidance shaped by supporting over 65 gene therapy programs. Consider it direct access to the manufacturing strategist from early planning through delivery.

Dear Dr. Barrett,

We see replication competent AAV (rcAAV) on the standard clinical release panel at many CDMOs. Is there anything we can do early on to ensure this assay passes as well as scale and transition to cGMP?

— rcAAV: So Yesterday

Dear rcAAV: So Yesterday,

Way to think ahead! You are correct, for safety, every clinical AAV release panel has a line for rcAAV, even though you almost never see it at the bench. That's exactly what makes it challenging. **It is vanishingly rare per molecule, but it becomes real once you are transfecting grams of plasmid into hundreds of liters of cells.** Let's quickly cover how rcAAV forms, and why the fix lives in the molecular design of the input plasmids.

How Does rcAAV Form?
For the therapeutic rAAV the genome we package is the GOI flanked by the two ITRs, which carry the packaging signal and origin of replication but none of the machinery to replicate the genome itself. We supply the rep and cap genes in trans, on a plasmid that deliberately has no ITRs. So, a finished particle can transduce a cell, but it cannot make more of itself.

rcAAV breaks that guarantee. It is a particle whose ITR-flanked genome also contains functional rep and cap, essentially a pseudo-wild-type AAV that can replicate and re-package itself wherever helper functions are present. It forms when that separation fails at the DNA level. The dominant route is homologous recombination between the cis (ITR) plasmid and the trans (rep/cap) plasmid wherever they share sequence: residual wild-type AAV flanking the ITRs, homology around the p5 promoter, or shared backbone. Any common stretch becomes a landing pad that splices rep and cap into an ITR-bearing molecule.

Why Manufacturing Scale Changes Everything
At process development benchtop scale, the odds of any single event round to zero. But scale up the plasmid mass and the number of transfection events, and a rate you never saw on the bench becomes a countable population in the batch. That is why the durable control lives upstream of the bioreactor, in the sequence. Here are some common design strategies to reduce rcAAV risk.

- Start by eliminating homology overlap between the cis and trans plasmids, because no common sequence means no efficient recombination
- Relocate the p5 promoter out from upstream of rep to remove a hotspot and cripple any crossover product
- Split rep and cap so no single event can reconstitute a self-sufficient genome.
- Diverge the coding sequences and trim the backbones to shrink the attack surface

Testing Should Confirm Design, Not Replace It
We still test, of course. Serial passage with adenoviral helper, then qPCR for rep and cap. But there is a real difference between depending on that assay to catch rcAAV and using it to confirm what the design already made improbable. The safest route is preventing your process from encountering the impurity in the first place.

— Dr. Barrett

Got a question? Email Dr. Barrett!

Genes of Interest

Our employee spotlight showcasing the individuals behind Forge that make our team unique

Behind every client program and manufacturing run at Forge is a team making sure the environment is exactly right.

Jeremy Hynick is one of the leaders behind that work.

As Senior Manager of QC Microbiology and Environmental Monitoring, he helps keep Forge's spaces controlled, qualified, and ready for life-changing gene therapies.

Outside of work, Jeremy is a multi-instrument musician, former member of THE Ohio State University Marching Band (TBDBITL IYKYK) and proud dad of three.

Get to know Jeremy in our latest Genes of Interest spotlight!

Factoid of the Month

Temperature Control Units keep cGMP suites cool during heat waves and year round

As much of the country experiences intense summer heat, staying cool has been on everyone's mind, including our Facilities and Engineering team at the Hewitt. Maintaining precise temperature control inside cGMP manufacturing suites isn't just a comfort issue; it's a regulatory and scientific imperative.

That's where **Temperature Control Units (TCUs)** come in, quietly doing the unglamorous but essential work of keeping bioreactors running at exact conditions batch after batch. As Forge has scaled operations, the team recently made a smart facilities move, relocating the TCUs out of the manufacturing suites and up onto an external walkable platform ceiling adjacent to the cleanroom suites. It packed an efficiency one-two punch, freeing up valuable floor space inside the suites themselves, creating a more efficient manufacturing environment which makes the maintenance easier.

Not every innovation happens at the bench; sometimes it happens on the ceiling!

Gene-ius Jobs

Featuring the latest career opportunities at Forge

We're hiring a **Computer Systems Validation (CSV) Engineer**!

Join our team and lead validation efforts for GxP computerized systems that support our gene therapy manufacturing operations. In this role, you will work with critical platforms, laboratory instruments, and facility systems to ensure compliance, data integrity, and inspection readiness. You will apply industry-standard CSV practices while driving risk assessments, change management, and validation activities that help maintain systems in a state of control.

From supporting key regulatory requirements to safeguarding product quality and advancing patient safety, this role plays an important part in helping deliver life-changing therapies to patients.

Take a look at the job description and browse the latest career opportunities at Forge. Apply now!

Did someone you know (perhaps a **genius**) forward this email to you, and you want to get it, too? Subscribe here to receive the Scaling Updates newsletter straight to your inbox.

Stay inspired, stay curious, and keep the fires of innovation burning!

Warm regards,
The Forge Team

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