ANC-80: LATEST UPDATES ON THE NOVEL ANC-AAV GENE THERAPY VECTOR

SPOTLIGHT

INTERVIEW

Meeting the Demand: Next-generation Viral Vectors for Gene Therapy

RYAN SCANLON has been the commercial leader for Lonza's viral gene therapy business since 2013, where he has been instrumental in shaping Lonza's gene therapy strategy by driving the business case for the recent relocation and expansion of the new Lonza Houston site. His current focus at Lonza includes commercial development and partnering activities for the next generation Ancestral AAV (Anc-AAV) technology which Lonza exclusively in-licensed from Mass. Eye & Ear and the lab of Dr Luk Vandenberghe, Harvard Medical School. Prior to his time in the gene therapy sector, Ryan served as the Head of Business Development for the Lonza Microbial Development Services business since 2009 where he performed strategic planning and led the launch of several new services and proprietary technologies. He joined Lonza in 2007 as Associate Director of Marketing & Intelligence for the Custom Manufacturing business where his analysis of the gene therapy market supported the case to acquire Vivante GMP Solutions (now Lonza Houston). Ryan has a BSc in Biochemistry from the College of Engineering and Applied Science at Lehigh University.

Q What is your perspective on the reported viral vector shortages, and what do you see as the key factors that have contributed to this bottleneck in the cell and gene therapy supply chain?

RS: The demand has been absolutely amazing and it's clearly driven by the coming of age of gene therapy. Look at the historic

events that have taken place in recent times, including several just last year – the approval of Novartis's Kymriah, Kite/Gilead's Yescarta and Spark's Luxturna, which of course was the first AAV-based therapy approved by the US FDA. This was followed by some outstanding clinical trial results – AveXis' spinal muscular atrophy (SMA) clinical data, for example, which showed that *in vivo* gene therapy was effectively curing babies with this terrible, fatal rare disease.

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These are some of the more notable transformative events showing that gene therapy has arrived which has, in turn, kept investment levels high for a reasonably sustained period of time. And the most effective way to deliver the DNA to make these gene therapies a reality is through the use of safe viral vectors. This has been driven mainly by the successful use of lentivirus with autologous *ex vivo* modified cells - such as CAR-T therapies and CD34+ stem cells and, on the *in vivo* side, predominantly utilizing AAV.

The reason we are seeing some bottlenecks is because on the demand side you have this substantial growth in pipeline of viral vector based gene therapies, but on the supply side, you have a series of process technologies that are not able to match the growth.

In his presentation at the recent ASGCT event in Chicago, Dr Kaspar of AveXis was open about the fact they achieved amazing data in early clinical trials, whilst fully realising that their manufacturing process needs improvement to match the modern bioprocessing techniques, such as you would see with monoclonal antibodies today, for instance. When you have a cure, you want to get to market as quickly as possible to help these patients – and with so much in the nature of your process potentially able to affect product quality, you don't want to take any risks by changing the process and affecting the product profile. You can therefore completely understand that fewer industrial process technologies are getting to market in this fashion. But we are now at the point where big pharma and biotechs are taking notice, and where the likes of Lonza

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are investing in novel process technologies to create platforms that are scalable, robust and reproducible. With this, we can look seriously at reducing operational risks, driving down cost of goods, and unlocking the ability to get into larger patient populations (many of which may only become commercially viable at lower cost of goods). In the future we hope to witness the migration of curative gene therapies beyond the monogenic rare diseases and towards some of the larger diseases, such as diabetes, Parkinson's, Alzheimer's and heart disease. Manufacturing capabilities will need to match this clinical progress for such products to ever make it to market in a sustainable way.

Q Can you tell us more about some of Lonza's specific approaches in this regard?

RS: Looking at the sort of technologies that are used in the industry today, we see a lot that are inefficient, highly manual, non-robust unit operations which means you can't rely on these manufacturing methods to perform consistently. And of course, the desired productivity levels are just not there either.

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Lonza's historical success in the biologics industry with monoclonal antibody and protein production means we have a great wealth of knowledge of how to industrialise and scale biologics. And a virus, despite the obvious differences to a monoclonal antibody or any other kind of recombinant protein, is still fundamentally a biologic – it is made up of proteins and DNA. It's more complex, but not fundamentally different from other types of biologics produced in stable clonal cell lines that can be relied upon to scale up with a high level of reproducibility.

Our internal R&D investment in process technology focuses on developing platforms that have a few principles:

- all the unit operations need to be scalable,
- they need to be able to be validated, and
- they need to offer reliability by producing robustly or reproducibly.

The upstream bioprocessing needs to be in suspension culture, because we believe that's the most efficient way to scale compared to adherent formats used in the industry today. And we also want to maximise adoption of single-use technologies to remain flexible and nimble in our facilities.

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That last point about flexibility is a core principle, on how we designed our new facility that we recently opened in Houston, Texas.

The industry is evolving rapidly and we do expect to standardise on platforms, but we also expect to improve our platforms over time and to continue to optimise them. We don't want to limit ourselves through the fundamental nature of our facility – for example, by building it with a lot of hard piped stainless steel. So the nature of our facility is modular, employing designs that are flexible and that can be reconfigured over time if necessary with relatively minimal capital expenditure.

Q In terms of the exciting launch of the new Houston facility, I wondered if you wanted to talk a bit more about that and what it's capabilities and capacity would be, and how that's supporting commercialisation of these products?

RS: Lonza lived through the intense growth curve of monoclonal antibodies through the late 90s and early 2000s, and through that experience, we learned a lot about how to add capacity in line with demand. So when we looked at cell & gene therapy – a hot growth market – with the new facility in mind, we decided on a very, very large footprint – we believe the total footprint of what we've built is the largest in the world for a dedicated gene and cell therapy facility. And we wanted to be able to grow into it over time, so we have segregated the facility into different areas that are appropriate for manufacturing different types of products. You therefore have different areas split by clinical or commercial, and also by cell therapy or viral vectors.

We have multiple independent, modular cleanrooms set up in each respective production area where we can perform any process and produce the wide variety of different product types on the market today.

And as demand grows, we can add capacity in the form of additional modular clean rooms within the various areas. Our existing facility in Houston, from which we are relocating, has proven this expansion concept at a smaller scale – it's really the inspiration for this new facility.

On a few occasions over the past several years, we had customers come to us and ask for capacity and we just didn't have any available. But we were

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able to be creative in adding modular clean rooms in additional footprint areas as we expanded locally in other locations. So we've shown we can add new GMP capacity – from design to complete GMP readiness – in approximately 12 months. Given the excess footprint in each production area. We're at a point now where we don't believe the physical clean room capacity constraint should ever really impact a critical path for most projects. And to be clear, with the number of cleanrooms we've already constructed as we've just opened our new facility, we currently have new additional capacity available now and to supply most types of projects with relatively short term demands.

Q Which vectors will you manufacture at this new facility? Is that determined by client/market demand?

RS: Overall, we look at the marketplace and our history and experience in manufacturing viral vectors, which spans over 20 years – the resulting mix is a reflection of what customers need in the marketplace.

We have a great deal of experience in manufacturing lentivirus, which is obviously the most popular virus used for modifying autologous *ex vivo* gene therapies like CAR-T or CD34+ based gene therapies. While we hope to see gene modified T cell-based immunotherapies succeed in solid tumors, at the moment most of the applications for *ex vivo* gene therapies are limited to blood cancers and – in the case of modified CD34+ stem cells – a few other rare diseases.

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We also have a long track record of successful delivery on AAV projects. In the AAV segment, we're seeing the potential to treat a vast array of disorders across essentially every tissue and cell type throughout the whole body. With different route-of-administration approaches there's the potential for AAV-based therapies to effectively be delivered to any organ. This creates nearly endless possibilities for the types of disease that can be addressed and has the potential to have a historic positive impact to human health.

So we're obviously really excited about the future of AAV in particular. This excitement is what led us to try to create even more value for customers by expanding our offering into novel AAV capsid types. Through

the partnership we've established with the lab of Dr Luk Vandenberghe at Mass Eye & Ear (a Harvard Medical School affiliate) we're working to bring their next generation ancestral AAV capsids to market alongside our manufacturing platforms.

Q Beyond increasing capacity, how are you working to drive efficiency into viral vector manufacturing processes?

RS: A key aspect of our approach to process technology innovation is to look at the whole platform in its entirety – while we are focusing energy on developing novel cell line technologies, we also look to continually improve every step in the process.

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We hope and suspect that there will be many different ways to solve the problem of making things like lentivirus and AAV vectors in a stable packaging or producer cell line. But it's so much more than a cell line: you have to have all the parameters to scale this up in a productive way, you need to have your optimal scalable downstream unit operations, and the whole area of analytics related to viral vectors is essential, too. We're also investing in the development of new and improved platform analytical methods.

Again, it's in line with the principles on which Lonza has been successful in the biologics world to date. If you look at our industry-leading position in mammalian expression systems, with our GS Xceed technology, you can see the reason why GS has been such a long-standing market leader – sure, it's a great cell line, but it is also complemented by a complete platform for all protocols to be able to scale reliably, predictably and very quickly from a tiny lab scale into 20,000 liters. These are the same principles we are applying to the viral vector space.

Q You mentioned briefly the exciting collaboration with Dr Luk Vandenberghe. Through this, Lonza is working on the production of the next generation viral vector, Anc80. What was the rationale for this collaboration and how does it potentially improve on existing viral vectors?

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RS: If you're a company exploring AAV gene therapy as a new modality, and you're analysing what the technology can do today, you quickly realise there are two broad areas that stand out as possible limitations. One is the state of AAV manufacturing technology, which I just spoke about, and the other area is the limiting nature of existing AAV serotypes.

Lonza's ability to create value through process technology innovation for the industry is central to what customers come to expect from Lonza, but quickly after meeting Dr Vandenberghe and learning about his novel ancestral AAV technology (Anc-AAVs, of which the lead capsid is named Anc80) we realized that partnering with him and his lab would give us the opportunity to extend our offering in AAV to also provide improved next generation capsids.

For some applications, like those that have reached the market to date, the existing naturally occurring serotypes work well – for example, in Spark's application of local injection for a rare genetic blindness disorder. But for other potential applications and diseases, existing naturally occurring AAVs may lack the transduction efficiency needed to be effective or to be commercially viable, or some other desirable phenotypes (tissue specificity, manufacturability etc).

For certain rare diseases, you can potentially get to market with high cost of goods – if you're getting reimbursed at somewhere between half a million and a million dollars per patient, then you can afford these high cost of goods.

But if we want to take the exciting potential of AAV and apply it to larger patient populations – in heart disease, for example – it's unlikely you'll be able to get reimbursed for upwards of a million dollars per patient. You definitely need to find ways to develop vectors that are more efficient, so you can drive dosages lower. Some of the Anc-AAV that Luk Vandenberghe and team have generated in the research sponsored by Lonza offer the potential for more efficient transduction across various target tissues, and in some instances possibly in a tissue-specific way.

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The other major limitation related to capsids has to do with this problem of pre-existing immunity. Patients today are typically screened to see if they have neutralising antibodies to existing natural serotypes – if they do, they unfortunately may be excluded from a clinical trial.

Obviously, that's tragic for the patients excluded from a potentially life-changing therapy. Dr Vandenberghe's concept of ancestral AAV takes us back in time using a statistical bioinformatics technique to predict the ancestral family tree for some types of viruses that may have existed in the past, and that therefore do not occur naturally today – meaning patients wouldn't necessarily have the same sort of pre-existing immunity issues they might with today's naturally occurring serotypes. So a patient excluded from a trial today using a naturally occurring serotype has the potential to be treated with an Anc-AAV in the future.

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Dr Vandenberghe's lab seeks to address both the limitations around gene expression of naturally occurring vectors and the limitations caused by pre-existing immunity. Then there are the parallel manufacturing limitations. We are working together in partnership with him to basically address all three of them.

Finally, I do want to add that AAV gene therapy development is technically complex and the biology is complicated. There are several nuanced aspects related to AAV development beyond manufacturing and the capsid itself that are technically challenging but these two areas are the ones that stand out as major hurdles the industry is facing today.

Q How is Lonza working to further develop Anc-AAVs, and potentially other innovative viral vectors? And how far along are you in addressing any unique challenges of commercial scale manufacture of the Anc80 that would be different to AAV?

RS: So the first vector that was studied out of Dr Vandenberghe's lab was this vector called Anc80L65, or simply Anc80 for short. It has some seemingly amazing properties relating to tissue tropism and gene expression across the many tissue types and routes of administrations in which it's been studied. It also has this potential benefit of an improved pre-existing immunity profile.

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The one area where it was a little weaker compared to other naturally occurring serotypes, like AAV9, was that it wasn't as good a producer when manufactured using traditional methods. And it's not to say Anc80 is a bad producer – it's in line with AAV2, which is a well-studied and known naturally occurring serotype. However, we have studied Anc80 and managed to manufacture it at commercially viable levels using our existing manufacturing platforms.

Part of our partnership with Dr Vandenberghe's lab includes multi-year sponsored research to develop newer ancestral AAVs and through this relationship, we're excited to see vectors that are potentially higher producers – maybe even higher than naturally occurring serotypes like AAV9 – coming through. Based on some of his newer methods for screening large volumes of different Anc-AAV variants simultaneously, we're excited and very hopeful there will be vectors that have the same sort of tissue tropism properties and pre-existing immunity properties, combined with higher producing properties.

We're excited that better, easier-to-produce vectors and our improvements in novel process technologies will combine to be able to create the most productive and commercially attractive viral vectors. The combination of the promise of substantially higher manufacturing productivities along with the possible improved transduction efficiency that Anc-AAVs may offer leads us to believe there's nearly an inevitable future where the cost-per-patient is driven low enough to be viable to address major large diseases.

Q Obviously, this is an incredibly exciting time for the sector as a whole - what are the strategic goals for Lonza over the next five years to really support the growth and success of the cell and gene therapy industry?

RS: Lonza understands there are major challenges related to commercial viability and scalability of these newer types of biologics in the gene and cell therapy space. Over the next 5 years, I expect Lonza will continue to aggressively pursue the development of novel technologies that will enable our customers to best meet their goals

of transforming the lives of their patients for the better. I expect Lonza will innovate and focus on higher producing technologies, more robust and reliable unit operations, scalable technologies, and technologies that can be more easily tech transferred and automated (less reliant on manual operations).

We're in an exciting phase where the market reality of these therapies has arrived. Now the industry needs to industrialise these products through more efficient, reliable manufacturing technologies and techniques.

AFFILIATION

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