EVALUATING BIOPHARMA

www.evaluatingbiopharma.com

Gene Therapy Analytics: Implementing Better CMC Strategies

Jim Richardson, Senior Director Analytical Development, Interius Biotherapeutics

ABOUT

Jim Richardson is the senior director of analytical development at Interius Biotherapeutics. In this presentation, Sinclair shares his knowledge of the learning curve for scientists and enabling technologies in the gene therapy sector.

Jim Richardson,
Senior Director Analytical Development,
Interius Biotherapeutics

Ben Locwin,
Vice President of Project Solutions,
Black Diamond Networks

Ben Locwin, Black Diamond Networks: Hello everyone, I'll be your host and moderator. For our first presentation, I'd like to introduce Jim Richardson. Jim, can your give a little background on yourself?

Jim Richardson: Sure. I'm a trained virologist, a PhD biologist. I started working in gene therapy earlier than most folks— about 25 or 26 years ago. Over my career, I have bounced between cell and gene therapy and nonprofits and biotech, and actually worked for a good portion of that time for a contract development and manufacturing organization.

BL: You mentioned two-and-a-half decades of experience, and it's interesting because when we think about the gene therapy space, it reminds me of the situation we had with biotech about two-and-a-half decades ago. It's such a bright future, and has as many questions and new avenues as we have answers. Let's start with the analytical learning curve. What have we learned in this industry about analytical strategies that work?

JR: I'll just chart my recent experience with Interius. As a startup, you don't always have all the resources you need. The first challenge I faced here is the lack of resources and a lack of staff. What's been critical is hiring the right people. We're early stage, we're preclinical and we need to develop novel analytics for novel products. We need people who can think and not just follow protocols and run assays. There's a place for that in our company, but the people I've hired have been able to think beyond their remit and help us develop some novel analytical tools that have helped us characterize our product. The more precise essays you apply

as early as possible, the better you'll be set for transitioning through preclinical into clinical development.

BL: Taking the talent angle, is there a particular phenotype of person you are looking for?

JR: What I look for is somebody who's curious, and when I talk to people who apply to the company, there is no ceiling, I don't require a PhD for any one position. I have a director working for me who doesn't have a PhD; the lead scientist is not a PhD. That's not the bar. The bar is being able to critically analyze problems, to troubleshoot and come up with solutions with little oversight from me. Because I don't have the bandwidth to do it. So we're looking for problem solvers, deep thinkers, people who will look in the literature and come up with solutions for what we're doing. There's a lot out there to learn from and everybody has to take advantage of that . You can't just come to work, do your job, and go home if you want to move forward.

BL: So how can people curve jump then, leapfrog the learning curve, if they're new to this technology and looking to advance their approach?

JR: Someone mentioned this to me earlier who had a long career in large molecules and is transitioning to gene therapy. That's not an uncommon path, but it is a different world. One way to do that is to attend events like this and speak to other people who have solved problems and are implementing strategies to characterize their products. There are other resources and organizations that have formed. ASGCT (American Society of Gene & Cell Therapy) is a pretty dynamic community and it's grown into a huge meeting. They have developed a lot of resources. You also have the Alliance for Regenerative Medicine and PDA. All these groups have formed cell and gene therapy committees to help developers network and learn from each other. There's always new stuff to learn. FDA is putting out new guidances, EMA is putting out new guidances, new tools are becoming available, new equipment is coming online. Another thing to mention is to take advantage of the instrument manufacturers. They're interested in working with people developing novel products, to show that their technology can solve a problem for everybody. They will put out a white paper and do things for you. You can demo their equipment and see what it will do for your characterization needs.

BL: You mentioned the FDA and other regulatory agencies. So to switch gears, with all the changes in cell and gene therapy, do you have any recommendations for the best ways to manage expectations of comparability?

JR: Comparability is something that we talk about a lot. The challenges are different for everybody. But everybody starts at early stage with limited process understanding, limited analytical understanding and then changes the assays, changes the products, and changes the process—all of those change as you as you proceed through development. What you really need to do is have your eyes open about the coming challenge to demonstrate comparability down the line. One of the big challenges is with small lot sizes, not many lots available, securing enough material, and socking it away so that you can do some side-by-side comparability down the line when your assays are better developed, or you have a better understanding. A lot of what we've done in the past year is generate material with a process that is not a Phase I process, but is fit for purpose to generate material to do preclinical studies. We now have to tie that material that generated that data into material that is made with a more GMP friendly process.

BL: We've heard a lot about potency issues. Why do you think it might be one of the most significant issues? And what do you recommend?

JR: The difficulty with potency is that it is product-specific by its very nature. Early stage, you can rely on some platform type assays to measure the strength of your product, the infectivity for viral vector, things like that. But as you proceed, the expectation is that it will tie better to the mechanism of action and the clinical efficacy of the product. You can imagine for a viral vector cell therapy, the stages in between the product, and the actual biological effect are many and varied and you can test every step along the way. But as you get closer to the clinical effect, your ability to have an assay that measures that with any degree of precision goes down. So it's very challenging, especially if you don't well understand your mechanism of action, or it requires an animal or a human being in order to show it. Basically, the approach is a matrix approach—FDA and others recommend this.

The idea is that you develop multiple assays to measure strength and potency, then develop more of a mechanism of action-based potency assay as you go along and possibly discard some of those early measures. It's an orthogonal approach, using a variety of different measures for a viral vector. We measure genome copies, particle copies, particle titer, infectious titer expression of the protein, target cell killing *in vitro* and *in vivo*. That's a large number of assays. We don't apply it to every batch we make, but we get a lot of looks at potency, even at an early stage. The earlier you do it, and the better you develop those assays, the more precise and accurate you can make them.

BL: Have you run into any challenges in reviewing what the FDA has to say with regard to some orthogonal approaches and whether or not they stand up in the long run?

JR: For potency, it's always going to be case by case. So you've put up a proposal and especially in a first-in-human in Phase I, the FDA says, "Good enough, but think about this down the line." You can lay out your potency assay strategy and they can review it. The challenge for them is learning all these new products, novel assays. They are very difficult and it is lengthy to develop a good one, and even filing for has been held up because of potency assay issues. The regulators have a difficult challenge, understanding all these different platforms and products and diseases and everything else that encompasses what is now cell and gene therapy, regenerative medicine. The better we can lay out a logical strategy, the easier it is for our partners, the FDA, to review them.

BL: You rightly focus on functionality of analytical assays, can you say more about promising new technologies?

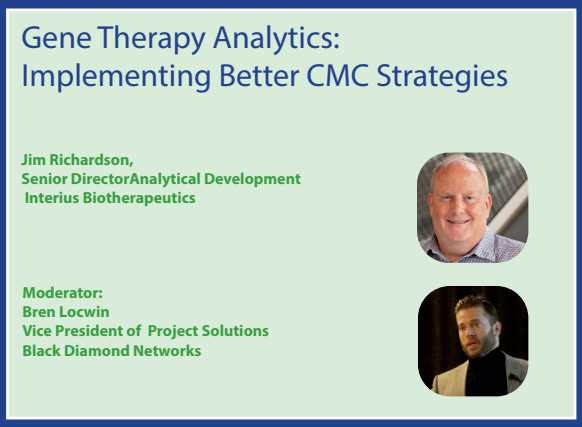
JR: There are a lot of new technologies out there and I haven't evaluated them all. But there are things like the LUMICKS, which can test the affinity of your cell or another cell, a target cell; the Incucyte and other instruments that can do live cell imaging. Those are tools that we dreamed of years ago, to be able to capture the kinetics of cell killing over time. I'm sure there are a ton of things I'm missing. But I look at particle size instrumentation. We had DLS 20 years ago, and we looked at AAV and it was difficult, because the AAVs we were looking at were not very highly purified. Now, we can purify things a lot better and it enable us to get a better look at particle size and distribution. Also, the attributes that are present on those particles with things like NanoView, an instrument for lentiviruses and other particles that you can use to characterize not only size, but the surface properties of the virus in terms of its protein component. Mass spec has come a long way, an old tool, but being applied to cell and gene therapy for both quantitation of the virus itself and characterization of the virus, but also the residual proteins that come along with it.

EVALUATING BIOPHARMA www.evaluatingbiopharma.com

This case study was presented at Evaluating Biopharma's virtual networking and educational event *Gene Therapy Analytics: Implementing Better CMC Strategies*, which included two additional presentations and two interactive networking sessions.

Details of future events can be found here.

You can watch Jim's presentation in full and on-demand here.



ABOUT EVALUATING BIOPHARMA

Evaluating Biopharma is a convener of knowledge, data, and industry leaders within the biopharma and bioprocessing industries. Built upon the foundation of BioPlan Associates decades of data collection and analysis, Evaluating Biopharma brings together top industry experts, innovators, decision-makers, and leading providers so that together they can share, evaluate and discuss critical topics that will help biopharma and bioprocessing leaders advance life sciences.

Evaluating Biopharma is made possible with the generous support from our industry sponsors.

SPONSORS

PENDOTECH Adding Value To Your Process

Black Diamond networks

Center for Breakthrough Medicines

MEDIA PARTNERS

Cambridge HEALTHTECH Institute

BioPlan associates, inc.