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Cell Therapy Analytics: Overcoming CMC Challenges

A Conversation with Bruce Thompson
Chief Executive Officer, Kincell

ABOUT

Bruce Thompson is chief executive officer at Kincell and formerly vice president and technical lead for the cell therapy franchise at Resilience. In this session moderated by Dominic Clarke, chief technical officer, Cell and Gene Therapy, Discovery Life Sciences, Thompson shares his experiences and provides his advice on how cell therapy companies can address key analytical challenges, including: (1) Identifying proper analytical development timelines; (2) Understanding product biology to develop proper potency assays; (3) Staying current on the rapid safety testing landscape; (4) The latest iterations and most exciting new analytical techniques.

Bruce Thompson,
Chief Executive Officer
Kincell

Dominic Clarke,
Chief Technical Officer, Cell and Gene Therapy,
Discovery Life Sciences

Dominic Clarke: Welcome Bruce, please introduce yourself and tell us your background and expertise.

Bruce Thompson: I'm a T cell immunologist by training and I like to tell everybody that I grew up in large pharma. I spent about 10 years at Pfizer learning drug development, start to finish, as an analytical leader, where I got to build all the CMC aspects for programs and was lucky enough to build some of the early allogeneic CAR T assets that were partnered with Cellexus and Servier. From there, I moved from the allogeneic T cell space to the autologous CAR T space and spent the last seven or eight years in academic medicine at Fred Hutch in Seattle, and a couple of startups, one being an innovator Lyell Immunopharma, where I led their process and analytical developments and then moved to Resilience, where I led the cell therapy franchise build in the process and analytical development space. I'm in the midst of a transition to build a new cell and gene therapy company and excited to say more in the coming weeks as we mature.

Clarke: Let's jump right in with two questions in one: How do you identify the proper analytical methods and targets? And then how do they factor into your development timelines?

Thompson: I often distill this into a pretty simplistic approach, which is there are two types of problems in the field: biology and engineering. I think analytics are meant to bridge the two. So the more we understand about biology of the product and the intended utilization, the better we can design comparability, think about process changes, and understand the impact to the product. Analytics are crucial to our understanding of not only process performance,

but also the product and understanding the characterization of that product, which enables us to perhaps decrease the risk of future changes, because analytically we know what the changes are doing to the product. To me, analytics almost come first. But that's a chicken and egg scenario. When we think about tech transfer to our CMC and manufacturing colleagues, we often think we'll transfer the process, then we'll transfer the methods, and then we'll qualify the methods. But in reality, you don't know what good looks like if you don't have the methods already in place. So, being thoughtful about when and where to have your analytical package prepared is important, which means the analytics should come either equivalent to, or along with, the process unit operations. As we think about tech transfer, often the process tech transfer is six to nine months, the analytical tech transfer is six to nine months, plus the qualification on the back end. So you have to be really thoughtful about winding those two up as you think about your entrée into Phase One clinical studies.

Clarke: So how do you find the balance between the two?

Thompson: There are a couple ways to look at it. If you take the assumption that you're using a relatively standardized cell therapy modality like a CAR T, we have now a couple of approved products, we have a framework in which we can build the analytical control strategy, we sorted out what we need for purity, identity, potency, safety, etc. We know the main tenets of what we need to build. Often, if you have a pipeline, you can utilize your backbone assays and safety, you're adding maybe a CAR T detection reagent to your flow panel. So you can quickly amend those methods for product specificity. If you're starting from scratch, obviously, it's a different story and you have to think through what you are trying to do with your control strategy. You want to understand the product population, you want to understand the safety impacts for microbial contaminants and residuals, you want to understand the phenotype impacts. If it's a CAR T, you need to show that you have the targeting mechanism. If you're knocking something in or out, you'll have to have the safety assays around on target, all target, and those are all built on a particular timeline. If you can leverage earlier programs, great. If you can't, then ensuring you have an early FDA interaction to say this is the control strategy we're building, it was just appropriate for the type of product that we want to take into the clinic. That will help get ahead of any last-minute requirements for new assays that take a long time to be built and qualified.

Clarke: It's obviously an evolution and then carefully balancing that with the timelines and it gets harder and harder to make changes as you advance that product further into the clinical pipeline. You touched on understanding a bit about the biology and constantly learning about that. How important is that and then how important is that work into the potency assay?

Thompson: That's a bit of Pandora's box in the field right now, but I think what's interesting is, if you think about process optimization, many times in the field what we see is, at least in the CAR T space, an interest in shortening the process. You're now impacting your cost of goods, you're getting the product to patients faster, but you're also changing the biology. The better your analytical control strategy is around understanding that, the better you can risk mitigate those process changes. One of the examples that is often not clearly thought about is years ago, we had a 14-day process. Now, we see processes of seven days, five days, three days, one day. The impact to the T cell population is significant. Where interferon gamma as a measurement of T cell activation works well for the longer processes, it actually doesn't quite correlate for the shorter duration processes, where IL-2 might be a better measurement. Being very thoughtful about what cytokine you're measuring based on your process understanding and your biological understanding of the product can lead you to a different potency assay, potentially, or measuring, again, a similar potency assay, but measuring a different outcome.

Often, we see killing assays done where you're looking at the ability of a T cell to kill the target cell. If you have a very short duration process, you may not have effector-differentiated cells to do that killing. So, you have to be very thoughtful about linking the biology to the assay, which again, I think underlies your analytical control strategy, and it may trip you up in comparability. If you're to shorten the process, you may have a slightly different product and that is where you have to be thoughtful about your FDA interactions or your health authority interactions, because you may have an improved process. You may have a more efficacious product, which is better for patients, but perhaps different

from what you had been developing and so you need to be very thoughtful about how you engage those discussions.

Clarke: That's a challenging one, right? Because if you're improving, and you come up with something that shows that benefit as you've just described, you're almost plagued with what do you do with that? Because how does that impact the current process and where you are within your clinical progression, your dose escalation? I'm sure it's collecting information and then figuring out what to do with that. In the same breath, are there ways to reduce those and how do you streamline that to your process?

Thompson: It's a really interesting question, because if you assume that cell and gene therapy will follow the trails that were blazed by monoclonal antibodies and large molecules, there is a push for multi-attribute methodologies. So, thinking about how can my flow method or my molecular method read a number of different elements. I do think there's a lot of room for that as technologies are being introduced into this space to reduce the overall number of individual assays, especially in autologous T cell manufacturing, where every product for every patient requires all the assets to be run to demonstrate the lot consistency, safety, etc. Having a reliable way to say this one assay gives me three answers and now I have six or seven assays instead of a dozen or 15, would be tremendously helpful, both in the cost of goods, the turnaround time, etc. Again, the more we understand the biology, the more we understand the correlates, the better we can build those multi-attribute methods to be reflective of the product itself.

Clarke: Let's transition here a little bit. We focus a lot on the process analytics. There's also this question mark on the release assays that sometimes get not necessarily forgotten, but separated. We know how much importance that is lot-to-lot, and then release and we know the timeframes and the challenges that come with that. What are your thoughts on how that factors into our analytics and our analytical challenges today?

Thompson: I think the traditional approach of in-process tests and process controls were important when we had a longer process, and we didn't see as highly successful manufacturing processes. I think as technology matures, and these process durations get shorter and shorter, in-process testing may become more characterization based to learn about the product, but less control based such that you're not varying different components of the process. The other way to look at it is you may find correlates that allow you to introduce elements of dynamic manufacturing, so that you're in- process controls now can point you in a particular direction to save a batch, or to add a particular growth factor or cytokine, that will allow for a successful manufacturing, versus a failed batch. I think as our understanding of the biology gets better, and our control over the processing gets better, we may see more of these dynamic personalized medicine products where it's batch to batch. Maybe with its established set of parameters, you can dial up or dial down different components of the manufacture and in that case, those in-process tests become critical. The release tests are always going to be there to remind you, did you make the same product batch-to-batch, lot-to-lot within the confines of patient-to -patient variability?

Clarke: Can you talk a little bit more about how you build the assays and change the process at the same time?

Thompson: Again, I think it comes down to your understanding of the biology. One of the things I always harken back to is what are known knowns. If your assays can accurately detect those known knowns, you can feel more confident. If you're making analytical updates, and you're not necessarily seeing the difference as you would expect, that may call the assay into question and may call the biology into question. But if you know the biology and the assay is not performing as you might predict, I think that's a guiding post. The other question as we mature the landscape is, some of our analytical tests are very complicated. They require a highly skilled analyst, high precision. We're detecting pretty small differences, so thinking about the overall assay precision, the ability to execute on a scale, thousands of times, is going to be probably as important as the overall accuracy of that method. The reason I say that is if you employ them early in your dose escalating, the accuracy piece sort of gets washed out in the dose escalation. It's really that intermediate precision that becomes important to measure on a batch-to-batch or patient-to-patient basis.

Clarke: There's a lot of data, a lot of assays, you are building a platform of assays. How do you manage the amount of data that you're collecting and what do you do with that? How do you work with that, as you're working with the regulatory bodies—what to share and what not to share? Because we know the guidance is a guidance, but everybody's learning together. So, how do you factor in the data package and then all the analytics we're looking at?

Thompson: That's a huge question and a huge challenge, because we do have a wealth of data, and we're probably not looking at it appropriately. Sequencing data comes to mind. There's so much available information on an NGS assay, but being able to do the bioinformatics, being able to interpret it in a correlative manner to efficacy, safety outcomes, etc., is not well established.

One of the things we have to be thoughtful about is the digitalization of our analytics, as well as our process. We have MESes that are becoming more widely used in the cell therapy space, but we don't have really good data analytic repositories. We have LIMs systems, we have various ways to capture and archive the data, but I'm going to throw the ML/AI buzzwords out there. There's a lot of opportunity for us to learn from the datasets we have. I think the challenge becomes decoupling all of the front end—all the patient preconditioning, all the chemotherapeutic regimens, all the impacts that have an outcome difference across the whole process, testing, etc. It's hard to decouple all of that. Unless and until we understand the biology, and then we can apply the data retrospectively. We're still going to struggle to have a wealth of data without a strong way to interpret that data.

Clarke: Thinking about digital—we need to continue to move towards that. Is there a solution that's on the horizon that you can think of to really bring the ability to see the data and use the data earlier in the process?

Thompson: It comes down to what you're trying to solve for with digitalization. When you're trying to solve for vein-to-vein time, or getting the product back to the patient very quickly, reducing the amount of time it takes to test that product and releasing that product is critical. That's where I think digitalization is really helpful. It used to be your compendial mycoplasma assay was 28 days, so you could never have a release cycle shorter than probably 40 days by the time we got data analyzed and QA released. Now, we could do a qPCR assay in two hours, so now that window has closed, or at least it's moved.

I think the need to look at the paper data and change hands and have on site QA staff, and time, effort cost, etc., Digitalizing that means you can have a centralized resource reviewing that data, or you can queue by exception now. Did it meet target? Did it meet spec? Then it becomes a very quick review versus something that you would have to go paper and then sort it all out. To me, if you're trying to solve for the vein-to-vein time or release timing, the digitalization of all of that data becomes really helpful because it allows for, again, review by exception activities and it decreases the amount of time required to get the product to the patient.

Clarke: Thinking about digital—we need to continue to move towards that. Is there a solution that's on the horizon that you can think of to really bring the ability to see the data and use the data earlier in the process?

Thompson: I'll go back to what are we trying to solve for. If we're trying to solve for vein-to-vein time, if we're trying to solve for cost of goods, there are a lot of multi-attribute methods that are going to be exciting. I've seen some combination elements where instruments now can do impedance, they can do visualization, they can do metabolomics. So now you're getting an entire wealth of data that needs to be interpreted correctly. You're now generating a lot of information that you can correlate to successful manufacturing, to patient outcomes. The better we're able to collect the data, look across different types of technologies, and then correlate back to successes, either in the manufacturing space, or certainly in the patient outcomes space, the more we can refine those. I think things like transcriptomics and thinking about the correlation of cell surface phenotype measurement by flow and other methods to the activity in the cell will be really interesting. It'll help us understand where we're going with respect to the current T field.

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

Details of future events can be found here.

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

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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.

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