IMPLEMENTING AN EFFICIENT ALLOGENEIC MANUFACTURING STRATEGY

A conversation with Marty Giedlin, Senti Bio

ABOUT

Marty Giedlin, VP, head of tech ops at Senti Bio. Marty leads process development for the firm's allogeneic natural killer cell-based CAR-T cell therapies, which are due to enter clinical trials this year. Moderator Ben Locwin is a healthcare executive with quantitative and qualitative analytics expertise. He works with senior managers at biopharmaceutical, vaccine, and medical device companies to market at higher velocity and with higher quality.

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Ben Locwin: Marty, at Senti, you are working with natural killer cells to make therapies, but you've worked with a huge range of cells. Can you tell us about your background?

MG: For most of my career I have been a T-cell biologist from training at a transplant lab. I've had 10 years at Novartis where I helped develop the Kymriah (Tisagenlecleucel) process after we did the tech transfer for Penn. I've also worked at Poseida [Therapeutics] and PACT [Pharma} where we're looking at non-viral ways to make CAR-Ts.

So this is kind of a turnabout for me as I've treated NKs as a contaminant through most of my career. Now my main focus is trying to understand NKs and use them to make cell therapy products that are truly off the shelf.

BL: So the NK cells that you once thought of as a contaminant are now a therapeutic avenue?

MG: NK cells are interesting little guys. They have commonalities with T cells but a lot of interesting differences that present some unique challenges with respect to finding a manufacturing process, particularly because we want to make enough doses to treat a lot of patients.

Instead of multiple small batches for individual patients, we are really looking at scaling up into multiple litre scale to treat many patients from a single batch. But scaling up NK production is complex. [Continues...]

MG: In our sector, we use material from donors. We are trying to understand not only the nuances from donor to donor but also from leukophoresis to leukophoresis and build that in to process development.

Output capacity is a key consideration. For example, if you are looking at preparing materials for a Phase I study you know you will need 30 to 40 patients worth of product. So, you need to ask can your process produce enough material to support that.

BL: Are there any other challenges involved in manufacturing NK-based cell therapies for trials?

MG: Most CAR-T therapies are one shot. There's very little data on second and third shots of an autologous therapy to the same patient to either ignite a response or continue a response.

And there is even less clinical data for NK based therapies - particularly for products like ours which is probably going to be given as a multi infusion cycle or as a couple of different cycles. So potentially your process must be able to produce multiple doses per patient spread over weeks or months, so that also impacts on your manufacturing expectations.

If you're going from single shots to multiple shots or multiple doses per patient, you really need to figure out how much you have to make, vial and put on the shelf ahead of time.

BL: What about the materials you use to make cell therapies, are there any challenges? What are the challenges associated with using them as the basis for commercial-scale manufacturing?

MG: With autologous therapy you're sort of stuck with what you get in terms of starting material. With allogeneic, in contrast, you're starting from healthy material. Indeed there are ways of collecting - using cord blood or iPSCs [induced pluripotent stem cells] - that minimize variability.

One of our biggest jobs is screening potential donors for their ability to be activated, transduced and expand in a manner that we think is necessary to get multiple doses out of a run. So right off the bat we're working to pinpoint that fraction of the donor population that fits our needs.

And that's a lot of work for our vendor as well as within the company to come up a screening process that can more or less predict how material from a particular healthy donor may act in our clinical scale manufacturing.

BL: Our understanding of the science of natural killer cells, how they function and how we can harness for therapeutic use is rapidly evolving. Do you have any examples of how science is driving your manufacturing strategy or operations?

MG: So much has been done to really understand the biology of natural killer cells and what they can and cannot do. So you're trying to use the science to help you understand the best scenario in order to activate them.

Developers need to ask themselves "what kind of vector do you want?" and "what is the size of your package for NKs?" NKs are also fairly finicky about what they need to sustain expansion post activation, so you need to keep that in mind.

Really it depends what kind of cell you want at the end of the process. For NKs it's primarily about cytotoxic activity. So you need to ask are they good killers? But you also want durability and sometimes the cell with the best expansion profile and does not have the best cytotoxic toxic profile.

The key is how you control your process with either cytokine combinations, basal media serum, etc to really get the product with the attributes that you think is going to make a good clinical product. The biology of NKs really has a lot to teach us about how to do this better.

BL: Do you have any recommendations about using data in chemistry manufacturing and controls during process development and manufacturing?

MG: For allogeneic products it's extremely important to control your process and really understand the key attributes. You've got to look at things other than just viability, you've got to understand the basic parameters and metabolites, dissolved oxygen, lactate, glucose metabolic activity or cell cycle. So process testing is really important.

Also if you're going to be manufacturing really large batches then you are going to be using some element of automation. And with automation you need to know how to derive your set points, your upper and lower limits for each process and that relies on generating and using data.
To be blunt, with this type of manufacturing the data stream is huge and managing it is always going to be a challenge.

BL: We had a question come in here on the topic of technology. What kind of technologies are you looking at for improving expansion and operations in the bioreactor?

MG: Our focus is in the bioreactor. Right now, just for the expansion, if you can get higher cell concentrations per ml in a smaller volume that's something that we're really interested in doing. You have to understand how to control that process at that end.[Continues...]

MG: People are using various wave bioreactors or stirred tank reactors to get up to larger volumes. I think 25 to 50 litres is where the industry is going so we will need to be a lot more control of the expansion process as opposed to throwing cells in the bag and letting them rock with minimal inspection other than doing a cell count every now and then.

Systems are becoming much more sophisticated in providing data but you also want reactive analytics. You want the system eventually to perform the fix independently of an operator pushing a button. So I think that's where, at least in the allogeneic field, we really need to go.

We are getting better at it. There's companies out there like Ori biotech, Cytiva that are trying to come up with those kind of integrated systems to provide not only the data but also the automatic reaction. The ideal solution is to attack the problem before the operator has to do anything, so that's all going to be driven by data during process development and early clinical trial manufacturing.

BL: Cryopreservation and thawing are major topics for your sector. How do you approach these steps?

MG: For our process we have several separate work streams: one for generating our NK cell banks from healthy donor feeder cells which are frozen; and then production of our final product which is also frozen. We have three cryo streams within our current process that we are looking to optimize to make sure we get good recovery.

As an aside, recovery might be a better CQA attribute than cell viability because you know how many cells you're actually dealing with and you can account for any loss.

But anyway, to refocus on cryo-preservation and processing, people are getting more sophisticated about cryo-formulations with respect to how to better maintain cells going into cryo, during cryo and post-cryo.

A lot of work is also being done on thaw methods. The basic idea is that you minimize the water transfer back into the cell during thawing so you tone down whatever membrane swelling occurs as that can lead to further damage of the cells.

Another issue is that thawing protocols need to be translated to the clinical site, it can't just be a lab thing. This is something we are doing through our process development team. We can present a kit or a process to the clinical pharmacy telling them “you need to thaw the cells, in this fashion, under these conditions to optimize recovery so that the patient gets the majority of the cells that are ready to go once they hit the vein.”

That is really something that we're paying a lot of attention to. The last couple of meetings I've been at there have been almost day-long conversations about this.

BL: A question came in from our audience asking if there is anything that can be done to better maintain NKs killing functions coming out of cryo?

MG: The obvious answer is yes. For the most part you just want NKs to be metabolically active coming out of the thaw and able to react to an antigen, or a ligand stimulus.

So there certain ex-vivo things we can do to try and achieve that. There's animal experiments that give you trafficking information. With those you can ask "can the thawed NK cells find the tumor and kill it?" which gives you a bit of an idea of how its going to work.

BL: How much innovation in cryopreservation and thawing do you expect to see in the next five years?

MG: Our industry as a whole is still very new and people are constantly looking at ways to improve every aspect of the overall process.

I think we're just at the beginning of really understanding how best to make and preserve cells to make the best product so I see this as a continuum.

Again you know non-DMSO [dimethyl sulfoxide] containing cryo formulations are just coming out and being adapted which have certain advantages over those that contain DMSO, so I think that's just going to take more time.

I don't think anybody is totally happy with their cryo preservation and how they thaw and Infuse, so I think there's just going to be continuous Improvement over the next several years

BL: Looking at wider aspects of process development, how import is it that developers be willing to revise methods in response to clinical data or emerging science?

MG: I had my first experience with that when I was at Novartis where we had to change our process. As we learn more about the role of NKs and the more biology we may have to be able to tweak the process to either make more of the same or to better control differentiation. I think that's just going to take clinical experience and clinical feedback.

I think you just have to be prepared to tweak your process to adapt to those different situations. And when I say tweak, I mean NK cells can have different subtypes and different cytokine combinations that impact expansion time.

Basically, the more we learn about how we can modulate the processes, the more we can understand the feedback we're going to get from the clinic about what works best.

This case study was originally presented at Evaluating Biopharma's Cell therapy strategies online and interactive event

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