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Hot Topic Industry Roundtable Session III – Panel Abstract

Preparing for the Future of CAR T Manufacturing

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Moderator: **Bruce Levine**, Barbara and Edward Netter Professor in Cancer Gene Therapy, Perelman School of Medicine, University of Pennsylvania, USA

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On May 28th, industry experts gathered online at **ISCT 2021 New Orleans Virtual** to discuss how the cell and gene therapy industry can best prepare for the future of CAR T manufacturing. The Roundtable Session, moderated by ISCT President, Bruce Levine (Penn Medicine) had experts: David DiGiusto (Resilience) and Michael Maguire (Avectas) discuss strategies to optimize the process development and manufacturing of CAR T therapies in addition to current pipeline pain-points.

The Session's conversation produced three key themes:

1. Collaborative Relationships
2. "Destination" Clarity
3. Mistake Tolerance and Shared Risk

Consensus was achieved from panelists as they all agreed the above points are critical to the success of CAR T manufacturing in both the short and long term.

Below, Michael Maguire and David DiGiusto share their answers to questions facing the manufacturing industry.

1) **What are critical early-stage questions developers should be asking to set up for future manufacturing success? What are the key questions that you ask developers? What discussion do we have to have early?**

Michael Maguire - *Typical early questions that developers should ask solution providers include; data in a relevant cell type, technology readiness for clinical use, regulatory pathway and business model.*

Solution providers need to listen to tx developers and, firstly, learn the essentials of their lead product or pipeline, including (cell source and type, scale at which engineering occurs, transfection/transduction step(s), post-modification steps) then progress the discussion to timelines and risk management, in a collaborative and tolerant spirit.

David DiGiusto - *When considering the development of a drug candidate (cell therapy) the sponsor should be able to describe the target product profile (TPP) and ask the manufacturing group how they can ensure that the drug will meet the requirements. What prior experience and technologies can they bring forward? Are there any obvious barriers in production like supply chain, scalability or development of potency assays. Can the developer solve these issues or does the sponsor need to provide support.*

2) **What are the analytics assays you need to have in place as you move into manufacturing?**

David DiGiusto - *Basic assay would include identity, purity, potency and safety. Potency is probably one of the biggest challenges. FDA requires the development of biologically relevant potency assays for products. Need to demonstrate that the drug can correct the biological deficiency of the disease.*

3) **Who are key partners to engage in the CAR T manufacturing journey? How can these relationships be optimized? (academia, small biotech, Pharma)**

Michael Maguire - *All of the partners mentioned, academia, small biotech and pharma play an important and distinct role in the CAR-T manufacturing journey. For Avectas, we engage with;*

- *Research Institutes; where we endeavour to seed our Solupore technology into early studies*
- *Small biotech and Pharma; where we engage in technology feasibility studies to validate our technology and build to development and license agreements.*
- *We also interact extensively with the CDMO sector, where we procure process development and other services. We also seek to partner with CDMOs on technology and process development for the CDMO's customers.*

Our experience on how best to optimize these relationships is to seek clarity in objectives from the start and to be diligent about the agreements that govern these interactions.

David DiGiusto: *Key partners in the CAR-T (or any) drug development space include supply chain partners (vendors, hospitals, transportation), manufacturing personnel, analytical personnel, clinical trial partners (MDs, Internal Review*

Board,Data Safety Monitoring Board), regulatory professional and financial oversight teams. Partnerships with biotech and or pharmaceutical companies should be established early on to gain clear understanding of expectation of roles and responsibilities early in the drug development lifecycle.

4) **What are the risks of point of care manufacturing as opposed to centralized manufacturing?**

Michael Maguire - *Point of care manufacturing holds great promise, but appropriate regulatory challenges are likely to be as significant as some of the technical challenges involved. The main patient risks for point of care are product release testing and thus losing the current centralized process standardization that an FDA approved product affords. The advantages of point of care include the potential not to freeze the the CAR-T blood products and to eliminate specialised transporatation logistics.*

David DiGiusto - *In addition to those points made above, point of care can provide rapid and low cost solutions to product manufacturing but may introduce variability in product quality depending on the robustness of the the manufacturing process. I agree that Quality review and testing cold be problematic in a distributed model of manufacturing. This requires expertise at every manufacturing site.*

5) **Are next-generation (viral, non-viral etc.) delivery technologies ready for early phase, multi-center, late-phase clinical trial timing? Effect of process development, instrument/software improvements?**

Michael Maguire - *Yes; As an emerging industry sector, next-gen technologies are maturing in terms of technology readiness for manufacturing and regulatory pathways. Some platforms are undoubtedly ready for early phase trials now, and some are nearing readiness. This advancing maturity is in response to the fast-paced developing market need for non-viral (and viral + non-viral) manufacturing processes addressing T cells, NK Cells, CD34+ and IPS cells. Typical next-gen applications include sequential gene editing, entirely non-viral process and hybrid viral and non-viral manufacturing processes. Leading platforms for non-viral delivery platforms include Maxcyte, SQZ Bio and Solupore.*

David DiGiusto - *Non viral delivery methods are already in clinical trials but not yet fully integrated into routine cell therapy product development. Non-viral delivery methods will likely reduce the cost of goods for products and eliminate some of the safety concerns. Non-viral methods also lend themselves to automation and scaling to accommodate very small or very large batches of drug as required.*

6) **How does one find economies of scale and reduce COGS in autologous manufacturing?**

Michael Maguire - *Advancing wholly non-viral solutions to the clinic using technology to site-specifically and permanently introduce a transgene would deliver many benefits in autologous manufacturing and reduce COGS. Specifically, shortening expansion time and infusing the CAR-T product earlier would be an advantage. Preceding this, integrating and rationalizing manufacturing unit processes would also be an advantage, lastly, optimizing starting material from apheresis and any selection processes to maximize yield will be economically beneficial.*

David DiGiusto - *The major drivers of cost are labor, high complexity reagents (endonucleases, viral vectors, specialty reagents), GMP manufacturing facilities (Cleanrooms) and lack of scalability. Automation, simplification of process, closed manufacturing systems and bulk manufacturing of many doses at once will all lead to reduction on COGs.*

7) **If, how and when will allogeneic therapies replace autologous therapies and what is the implication for technology development? Will each serve a purpose running in parallel?**

Michael Maguire - *I do not believe that allogeneic therapies will replace autologous therapies but that each will serve a purpose in the future. I think autologous therapies will lead the industry for several years to come, and these products will become smarter and address more diseases. I believe cell engineering technologies will become smarter, have more integrated unit processes, and ultimately move closer to the patient, notwithstanding some very legitimate regulatory challenges.*

Allogeneic therapies could be either built-up or edited down depending on the starting material. The target product profile will determine the best approach, but IPS cells form a promising foundation for allogeneic products.

David DiGiusto - *Allogeneic therapies will likely augment but not replace autologous therapies. Immune barriers will be one of the first challenges for this field. Genetic engineering of allogeneic cells (iPSC) will likely address some of these challenges. Scalable technologies for the generation of large batches of cell therapy products will be required to realize the value of allogeneic therapies.*

8) **What will be the next high impact product? Addressing large market size, rapid low-cost manufacturing, robust distribution system.**

Michael Maguire - *I think the next high-impact product will be a better version of an existing CAR rather than something entirely new. The momentum for CAR-T therapy will continue to grow and the 'better' may be in terms of accessability, novel low-cost manufacturing process, non-viral, point-of-care delivered. I think the product will be autologous and the indication may be solid mass and so more complex cell engineering required to tolerate the tumor microenviroment.*

David DiGiusto - *Impact will be realized when we are able to treat major diseases like solid tumors, diabetes, cardiovascular disease, major trauma injuries etc. This may involve new modalities that are either not under development or are early in the development lifecycle. The likelihood of such treatments becoming common will be impacted by cost, distribution channels, delivery without highly specialized skill sets and a reassessment of what private healthcare markets can bare.*