CAR-TCR Strategic Dive Summaries

Boston, September 2019

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Engineering A Cancer-Free World

T Cell Fitness, a Major Product Attribute Influencing Clinical Performance of CAR-T Cells

John Rossi, Director, Translational Sciences, **Kite, A Gilead Company**
Katie Newhall, Director, Immuno-Oncology & Cellular Therapy Translational Sciences, **Celgene Corporation**

How do you measure T cell fitness in manufacturing?

- Phenotypic markers of early T cell differentiation
- Signs of stress -> ER and mitochondrial function
- Improve fitness by growth factors, small molecule inhibitors, selection for certain cell populations
- In the future allo and IPSC approaches could help improve fitness

Discussion around earlier lines of therapy

- Hypothesize that cells will be more fit -> does this translate into more toxicity?
- It is early days on both Kite and Celgene trials in 2nd and 1st lines of therapy for CAR T, but to date it seems unlikely that CAR T therapy in these populations translates to more CRS or NTx
- Toxicity can be due to other factors (e.g. CAR T design, myeloid cells, TME)

Discussion around differences in safety between bispecific antibodies vs. cellular therapy

- Stage dosing with bispecifics to mitigate safety and improve efficacy
- Discussion of how to date the field has not demonstrated that subjects can be re-dosed with CAR T. Is it something to do with the TME?

Facility Design Considerations for Autologous Cell Therapies

Loren Wagner, Head, CAR-T Manufacturing Operations, **Celgene Corporation**

- Design of all manufacturing aspects need to be contiguous all the way from the design of individual stations through the layout of the site and network as a whole
- Cell therapy business needs change so rapidly that your design needs to be adaptable to new products and highly variable demand requirements
- Each product brings its own challenges; no single design will encompass the needs of all cell therapy assets - so stay open minded for each new product's requirements

Develop & Execute a Successful Cross-Functional Strategy to Optimize Commercial Success: Key Takeaways from Autologous CAR-T for Prostate Cancer Case Study

Andrew Hobbs, Managing Director, **Huron,** Mark Perrott, Senior Director, **Huron,** Santanu Das, Managing Director, **Huron**

Treatment delivery model

- Starting with model B (one regional manufacturing and multiple treatment delivery centres) and gradually moving towards a more decentralised approach (multiple manufacturing and treatment delivery centres) was seen as the preferred approach

Challenges

- Quality control and care harmonisation across multiple manufacturing sites and treatment delivery sites is a big challenge
- Company risk increases due to distance of the manufacture away from the 'owner'
- Capacity bottlenecks at the delivery site due to a large patient population that is primarily treated in community hospitals

Integrated solutions

- Patient management systems including referral platforms and concierge service will be key to funnel patients from a community setting and ensure eligibility for therapy and therefore access
- Patient tracking using a data collection platform that collects information in real time from treatment qualification all the way to follow up will be key. This system needs to be interactive and respond to the dynamic requirements of multiple stakeholders in the process i.e. regulators, providers, and payers

Strategies & Considerations of IND Submission for CAR-T Cell Therapies

Dong Geng, Senior Director of Non-clinical Development, **Legend Biotech**
Raghu Tadagavadi, Associate Director, Non-clinical Safety, **Legend Biotech**

- It is a challenge to assess target or organ toxicities without relevant animal models, NHP model for oncology might not provide significant benefit due to lack of tumor bearing
- *In vitro* assay used to assess off target cross activities should be carefully selected, not one-side-fit all approach
- *In vivo* toxicity studies is worthy of considering for solid tumor indications when target is not exclusively expressed

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Labelling to Secure Tracking & Monitor Movement

Chris Baldwin, Director, Supply Chain, Cell & Gene Therapy,
GlaxoSmithKline

- Current commercial labels are a blend of traditional pharmaceutical labels including Names, NDC, Expiry, Batch/Lot numbers with elements of blood/tissue product identifiers and statements

- ISBT-128 Label tracking barcodes are more prominent than commercial products

- Until all apheresis sites have a global standard “Chain of Identity” identifier assigned by apheresis site, manufactures will require to define a unique identifier for control of product identity cross the supply chain

Capturing Product Strategy in a Target Product Profile

Clark Eid, Director of Project Management, Therapeutics Production,
St. Jude Children's Research Hospital

- Utilizing a TPP will help bring life-saving therapies to patient's faster
- A TPP is a well-established best practice to provide stakeholders a common vision and focus, and will facilitate dialogue with regulatory authorities
- Business goals are de-risked by using a TPP

Density Selective Target Binding to Improve Specificity & CAR T Cell Function

Eric von Hofe, President, **AffyImmune Therapeutics**

- Given the lower *in vitro* activity of affinity-tuned CAR T cells *in vitro,* it is important to simply have more data to give confidence. This includes both from cell lines having varying densities of the target as well as (ideally) a series of CAR T cells having different affinity variants

- As the *in vivo* activity does not correlate with *in vitro* activity, it is important to more rapidly consider animal studies

- Identify ways of increasing the affinity of CAR T cells specifically within the tumor environment

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En-route to the Off-the-Shelf Future of Cellular Therapy

Yannick Bulliard, Director Translational Development, **Immatics**

- Finding right balance between GvHD, persistence and clinical efficacy is key to the success of allogeneic cell therapy
- Most promising next-generation enhancements to improve on these parameters were discussed during the workshop
- The importance of finding smaller efficacious doses for solid cancers was reviewed as an alternative to increasing the yield of the manufacturing process

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Scaling Gene Therapy Using Sleeping Beauty System to Express CARs & TCRs to Target Hematologic Malignancies & Solid Tumors

Laurence Cooper, Chief Executive Officer, **Ziopharm Oncology**

- Targeting mutations that are specific to tumours attacks the very foundations (building blocks) that cause cancer and avoids targeting normal cells
- A subset of these mutations are “immunogenic” and referred to as neoantigens
- The majority of mutations are unique, not shared between types of tumour or between patients
- However, some of these mutations can be predicted and are shared between patients in “hotspots”
- Targeting tumour-specific mutations is:
    - A broad approach applicable to many cancers
    - Increases the chance of achieving anti-tumour effects as the tumours are “addicted” to these mutations
    - Limited toxicity due to cross-reactivity with normal/healthy cells

Bridge the Gap between Patient Support & Marketing

Claire White, Nurse Navigator for the Cancer Immunotherapy Program,
The Children's Hospital of Philadelphia

- There are 5 major barriers that providers and/or patients might experience when trying to access CAR T cell therapy. The group outlined the opportunity with this uniquely complicated therapy type to partner as industry and clinical teams to invest in creating meaningful education tools for both providers and patients

- Since this therapy is ever evolving and involves both primary teams and specialty CAR T teams, materials must move to a digital space so that all audiences that need it, can have access to it rather than the resources being siloed with the CAR T provider only

- There is a need for a single point of contact within the industry and clinical space that oversee access and can understand each other's needs/processes to best utilize each other as a resource. This same approach would be beneficial when insurance and payer issues arise

Explore Payment Systems for Next Generation CAR & TCR Therapies

Doug Danison, Vice President - Market Access, Value & Evidence Strategy, **bluebird bio**
Aura Mackenzie, Senior Director, AVES, **bluebird bio**
Jim Blanchette, Senior Director, Access, Value & Evidence Strategy, Oncology, **bluebird bio**

- Oncology VBP schemes will require coordination across a wide variety of stakeholders (providers/payers/manufacturers/payers/legal/regulatory), including policy changes to gain traction

- Oncology care delivery transformation and payment reform continues to drive the shift from volume to value based care. As a result, value-based pricing schemes for novel cell and gene based oncology therapies will become increasingly important

- VBP strategy in oncology will look different by indication and outcomes, and should inform and be informed by lifecycle management strategy