SITC Cellular Therapy Regulatory Summit Executive Summary

August 3, 2023 • 10:00a.m.-2:30p.m. PT • Napa, California

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Society for Immunotherapy of Cancer

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Society for Immunotherapy of Cancer

The Society for Immunotherapy of Cancer (SITC) is the world's leading member-driven organization specifically dedicated to professionals working in the field of cancer immunology and immunotherapy. Established in 1984, SITC is a 501(c)(3) not-for-profit medical professional society comprised of over 4,300 influential research scientists, physician scientists, clinicians, patients, patient advocates, government representatives and industry leaders dedicated to improving cancer patient outcomes by advancing the science and application of cancer immunotherapy.

Through emphasis on high-caliber scientific meetings; dedication to education and outreach activities; focus on initiatives of major importance in the field; and commitment to collaborations with like-minded domestic and international organizations, government and regulatory agencies, associations and patient advocacy groups, SITC brings together all aspects of the cancer immunology and immunotherapy community. SITC aims to make cancer immunotherapy a standard of care and the word "cure" a reality for cancer patients everywhere.

Mission Statement

It is the mission of the society to improve cancer patient outcomes by advancing the science, development and application of cancer immunology and immunotherapy through our core values of interaction/integration, innovation, translation and leadership in the field.

Core Values

- Interaction/Integration: Facilitate the exchange of information and education among basic and translational researchers, clinicians, young investigators, patients, societies and groups sharing the mission of SITC
- Innovation: Challenge the thinking and seek the best research in the development of cancer immunotherapy
- Translation: Facilitate the transfer of cancer immunology and immunotherapy research from the bench to the clinic and back
- Leadership: Define what is new and important and effectively communicate it to all relevant stakeholders

Summit Overview and Introduction

Organizers

Marco Ruella, MD – *University of Pennsylvania Perelman School of Medicine*
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Participants

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Shalina S. Gidwani, MS – *Allogene Therapeutics*
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Kristen Hege, MD – *Bristol Myers Squibb*
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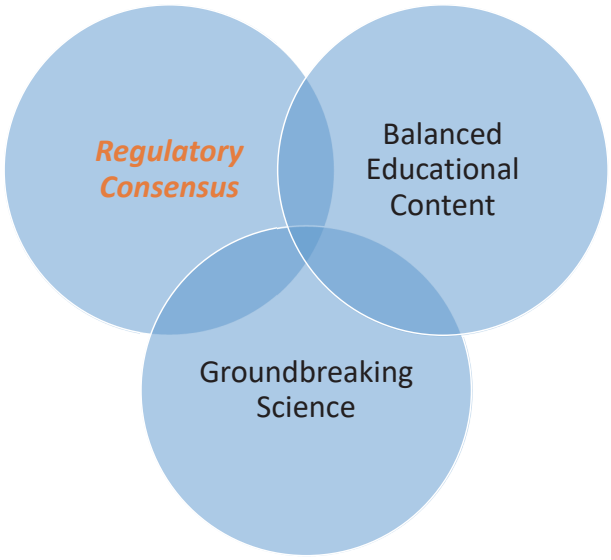
Summit Background

The number of cellular and gene therapy-based oncology treatments being developed by the field has grown exponentially over the past ten years. As a result of this rapid advancement, many hurdles exist in the field that are causing delays in development and regulatory review of these important products. To help address this, the Society for Immunotherapy of Cancer (SITC) convened a Cellular Therapy Strategic Taskforce in 2021. The purpose of this taskforce was to formulate a strategic plan for the society aimed at increasing SITC's overall impact in advancing the most promising cellular therapies to improve oncology patient care. The strategic plan consisted of three key pillars including groundbreaking science, balanced educational content, and regulatory consensus. As a first step in facilitating regulatory consensus, SITC hosted the Cellular Therapy Regulatory Summit. This summit consisted of cellular therapy experts from academia, industry, and government meeting hybridly to further the goals of the SITC cellular therapy strategic plan.



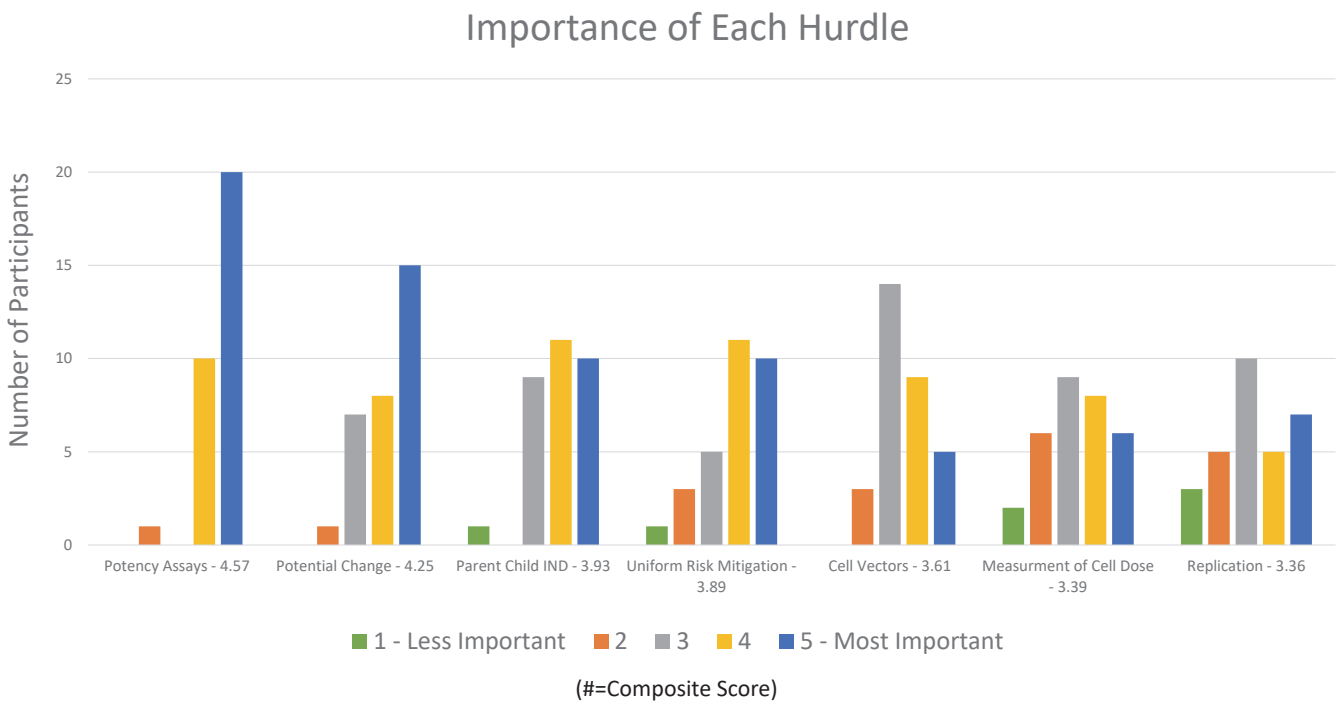
Summit Overview and Introduction

Summit Goals and Structure

The main goal of the SITC Cellular Therapy Regulatory Summit was to identity the most significant hurdles facing cellular therapy researchers throughout the Investigational New Drug (IND) Application process. In order to facilitate this process, the attendees participated in a pre-summit survey asking them to assign a ranking of 1-5 for each hurdle, 5 meaning the hurdle is most important to address and 1 being of least importance. The identified hurdles included:

1. Potency Assays
2. Which product attributes should be monitored and are indicative of potential changes in safety and efficacy?
3. What is a 'new product' versus an iterative manufacturing upgrade (parent-child IND)
4. Uniform Risk Evaluation and Mitigation Strategies (REMS) for future approvals
5. Recommended number of copies per cell of vector
6. Timing for measurement of a cell dose (eg, pre- or post-freeze)
7. Replication competent lentivirus therapy and applications

Through the survey process the four hurdles were identified as the largest barriers within the IND process. The prioritized hurdles included Potency Assays, Potential Change, Parent Child IND, and Uniform Risk Mitigation.



(#=Composite Score)

The hybrid summit was then dedicated to discussing, in detail, each of these four hurdles and identifying what makes them critical, and potential ideas for how to address them moving forward.

SITC's Next Steps in Addressing the Hurdles

As a direct output of the summit, SITC will be pursuing a number of initiatives meant to address the hurdles detailed below. These volunteer led initiatives will include field wide participation to ensure a diverse set of perspectives and the highest level of expertise.

Proposed Future Initiatives

Comment

- Commentary papers and meetings on future/ past FDA guidance documents related to cellular therapies

Convene

- Future consensus meetings to address the hurdles specifically stated within this report

Publish

- Development of future manuscripts addressing:
  - Defining the relevance/necessity of potency assays
  - Guidance on new product comparability
  - Commentary/review on existing FDA parent-child guidance
  - Revisions to REMS guidance and requirements

Amplify

- Leverage the SITC annual meeting and other national scientific meetings to amplify these efforts for field wide adoption

Collaborate

- Collaborate with other like-minded societies including:
  - Friends of Cancer Research
  - Foundation for the Accreditation of Cellular Therapy
  - American Society for Transplantation and Cellular Therapies
  - International Society for Cell and Gene Therapy

Hurdle 1: Potency Assays

Hurdle Definition

The identification of accurate potency assays for novel therapies has been difficult throughout IO development and questions remain as to the effectiveness of using potency as a tool for measuring efficacy. These complications have led to number of novel agent approval delays and/or rejections.

Key Takeaways

- No consensus exists for specific potency measurements that are correlated to efficacy
- Potency has become more difficult to assess in novel therapies compared to past treatments
- More data is needed to validate novel potency assays and asses their role in determining efficacy and safety

General Discussion Notes:

- Attendees described experience with the FDA concerning potency
  - Attendees noted that the agency is primarily looking for biological effects that are consistent with activity. It was detailed that this may be difficult in TIL therapies where neoantigen engagement is variable and can result in inconsistent biology
  - It was also suggested that groups develop potency measurements early in the drug development process as it may lead to fewer complications later in the regulatory pathway
  - Attendees stated that thus far the agency has been lenient with potency during the IND stage
  - The FDA is also assessing potency for safety parameters in addition to efficacy
- Attendees discussed aspects as to why the FDA is requesting potency assessment. It was agreed that many of the current issues are based on predicate from previous drugs where potency is much easier to assess, such as chemical-based tablets. The example of bone marrow transplant was also provided, where potency was in place to ensure product purity rather than efficacy
- Attendees questioned what the true definition and purpose of a "potency assay" is. It was agreed that these aspects are vague and that further clarity from the FDA is warranted
  - To further this discussion, attendees discussed how manufacturing standards exist to ensure viable products. They questioned whether potency assays would become more accurate than current manufacturing standards already in place that assess product stability
- It was stated that potency seems to be more of a binary signal and while there is value in testing this aspect, it may not tell a complete story for a product. Attendees pointed out that many patients have disease that responds to treatment with products that would have failed potency assessment using current standards. This subsequently presents an ethical argument in what to do with products that could positively impact a patient but are deemed sub-potent
- There was discussion concerning differences between potency assays and potency specifications, which are required prior to filing a BLA. Attendees questioned whether potency specifications should be necessary for regulatory approval

Hurdle 1: Potency Assays

General Discussion Notes Continued:

- Attendees emphasized that potency assays require standardization across stakeholders and products if possible.
  - To accomplish this, attendees noted that better understanding product attributes is critical
  - Attendees agreed that there may be inherent variability on measuring potency between gene-based products and TIL products
  - It was noted that it may be difficult to control product variables and subsequent potency. Manufacturing, patient, and center variables will present issues in standardization
- Attendees discussed the difficulty of assessing potency for TIL therapies vs CAR T therapies
  - Concerning TIL therapies, the goal of assay is to show that the product contains functional T cells that operate in a non-HLA restricted manner. This results in difficulty identifying correlatives. An example of IFNgamma release was provided, but it does not correlate with response
  - Concerning CAR T products, vector copy number, cell viability, and transduction percentage seem to accurately measure potency
- Attendees stated that in certain cases, meeting manufacturing markers may reduce the need for assessing potency, as manufacturing markers are in place to ensure a viable product
- Attendees agreed that potency assays should not be conducted as a "release type" assay during manufacturing as data is limited at that point in time
- Suggestions on refining potency assays included using a matrix-based approach to assessing potency by relying on multiple assays and measurements, as well as identifying factors predicting low potency rather than factors predicting high potency
- Attendees agreed that once enough data were available to offer an effective potency assay that they would be happy to adhere to regulatory requirements
- One proposal was to collect potency-like data and "critical quality attributes" during Phase 1 clinical trials for research purposes only. This may be difficult, however, as potency data correlated with response would only become available after approval and clinical experience

Hurdle 2: Potential Changes

Hurdle Definition

Questions exist concerning which product attributes may be *indicative of potential changes in safety and efficacy* and require monitoring. In addition, product attributes may vary on a case-by-case basis for autologous cell therapy products.

Key Takeaways

- When the starting material of a drug is variable on a patient-to-patient basis, there is significant difficulty in identifying what constitutes a change throughout the manufacturing process
- "Non-clinical comparability" is important to consider for these types of products, and the field should focus on data collection given limited clinical experience
- FDA guidance on new product comparability would help in providing clarity

General Discussion Notes:

- Attendees noted that there are many product characteristics to consider when trying to discern whether a change constitutes a new product
- Attendees stressed the importance of product starting material. Starting material is variable, that means that products are likely to also be different and assessment of whether a change constitutes a new product may need to be made on a case-by-case basis. This was especially true for products that are heterogeneous in nature such as TIL therapies
  - Examples of variabilities that can occur in starting materials include dosage, cell viability post-thaw, cell clumping
- Attendees discussed how the disease setting for similar products should also be considered. The example of axicabtagene ciloleucel and brexucabtagene autoleucel was provided as they are similar products in different disease settings
- Attendees discussed how the phase of a clinical trial may impact the rigor of whether a change should constitute a new product. For example, a Phase 1 product likely should have increased flexibility for manufacturing changes towards optimizing product and developing proof of principle. Tests in phase 1 would be considered "characterization assays." Phase 3 products, however, should be more rigid and have reduced flexibility for manufacturing changes. These would function more as "release assays."
- Attendees agreed that clinical experience can help characterize product identity that can be utilized when considering if a change constitutes a new product
- Attendees mentioned "non-clinical comparability" as being important to consider for these types of products, and they agreed that this should be the focus for the field as of now given limited clinical data
- Attendees stated that manufacturing changes occur post-approval as new efficiencies are implemented. This can include:
  - Vector supplier
  - Manufacturing facility
  - New automation
  - Reagent availability
  - New technologies
- This creates a problem as a sponsor will not repeat registrational trials for small manufacturing changes if a regulator deems such a change as yielding a new product

Hurdle 2: Potential Changes

General Discussion Notes Continued:

- Attendees listed product characteristics that they felt may be necessary to assess, including:
  - Cytotoxity
  - Cytokine release
  - Proliferation rate
- Attendees felt that if the field measured these characteristics on all products moving forward, then the supplied data could help refine the definition of what constitutes a new product Guidance on monitoring characteristics to field alignment may be helpful, then standardize and harmonize
- The concept of using patient-specific samples for all product characterization was discussed for potentially limiting inconsistencies
- Attendees questioned whether the discussion was honing in on requiring proficiency testing, such as existing CAP/CLIA standards. It was stressed, however, that some previous efforts on this front had already occurred and that they were unsuccessful due to center-to-center variability
- One suggestion included asking the FDA to consider publishing guidance for product comparability, especially regarding manufacturing changes. It was noted that EMA has guidance at this time, and that the FDA may also be developing a document

Hurdle 3: Parent Child IND

Hurdle Definition

The point at which a product should be defined as a 'New Product' versus an iterative manufacturing upgrade that can utilize a parent-child IND is unclear. Clear definitions of what constitutes a new product is needed for the field.

Key Takeaways

- Improvements in the areas of the previous two hurdles on potency assays and potential changes will help in providing clarity for assessing whether a change resulted in a new product
- Past FDA guidance on this have been helpful

General Discussion Notes:

- It was agreed that the purpose of a Parent-Child IND was to reduce the administrative burden and the need for redundant data collection. Attendees noted successful examples of Parent-Child IND processes in non-cellular therapy products and stressed that they should be analyzed for extrapolation to these novel treatments as well
- Attendees detailed previous efforts by the Parker Institute for Cancer Immunotherapy (PICI) and Friends of Cancer Research (FOCR) on further developing a parent-child IND process. Attendees also noted that the FDA has published guidance on this concept
- Discussions referred back to the previous topics of manufacturing changes and potency. Attendees agreed that if definitions were made in these two areas it would help in the development of a standardized parent-child IND process
- The possibility of a "child" product succeeding and a "parent" product failing was discussed, and attendees stressed how such a process should allow for child INDs to take up the parent status in such events
- Attendees stated that identical regulatory bodies should review all important aspects related to a specific Parent-Child IND to reduce confusion and inconsistencies

Hurdle 4: Uniform REMS

Hurdle Definition

Many approved cell therapy products require risk evaluation and mitigation strategies (REMS). As the number of new and approved products increases, complexity of differing REMS protocols and site requirements/qualifications threatens treatment efficiency and limits patient access.

Key Takeaways

- The massive increase of new products has created an influx of REMS that are creating an undue administrative burden on centers
- The field needs to find a way to standardize REMS across products without compromising safety
- Reevaluation of REMS after specified time periods and clinical experience are warranted

General Discussion Notes:

- Attendees agreed that ensuring safety of cellular therapy products during labeling and post-approval is important for the success of the field
- It was detailed that a company develops a REMS for their individual product based on the risk-profile identified during development. As this isn't standardized by regulators, divergences exist across REMS for various products
- Differences across REMS for products cause increased burden for sites as accreditation is often required for each individual process. In turn, attendees noted that some sites are declining to offer specific products due to the burden of introducing a new REMS if they have already committed to other products and REMS
- Attendees agreed that REMS also affect the discussion concerning whether cellular therapy products should be considered as inpatient or outpatient procedures. Certain REMS structures, as well as individualized center structures, may drive a product towards one direction or the other
- Attendees agreed that harmonization of REMS across products is necessary for the field. Multiple ideas were proposed, including the development of "core modules" that would be standardized and adopted by industry partners if applicable to their product
- The importance of toxicity guidelines was stressed. Guidelines on toxicity management provided by groups such as SITC could help with development of standardized, core modules
- The risk profile for each product should be identified prior to REMS
- Central repositories for data reporting, as well as standardized reporting architecture, were also identified by attendees as being critical to reduce the burden of REMS
- Re-evaluating REMS after approval and when clinical data become available was discussed. Attendees detailed how CAR T products currently require 15 years of data collection, and that given what the field now knows about the toxicity profile that may be extraneous
- Attendees stated that as data mature, it's possible that TCR and TIL based therapies may require individualized REMS and guidance. It's possible that individualized REMS may also need to be considered based on specific antigens being targeted by the product
- Attendees discussed the concept of parent-child REMS as well, suggesting that it may be warranted as various products stem from a parent IND

Hurdle 4: Uniform REMS

General Discussion Notes Continued:

- Attendees noted that the requirement for long-term follow up for cellular therapies creates an opportunity for "chance" events to influence safety profiles. The example of secondary malignancies related to events unrelated to cellular therapy was proposed as a real scenario that is observed in the clinic can occur

Conflicts of Interest

The Society for Immunotherapy of Cancer requires instructors, planners, managers and other individuals who are in a position to control the content of this activity to disclose any real or apparent conflicts of interest (COI) they may have as related to the content of this activity. All identified conflicts of interest are thoroughly vetted and resolved according to SITC policy.

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Royalty: Patents to Novartis and Tmunity managed by UPenn
IP Rights: IP on CART immunotherapy that is managed by the University of Pennsylvania
Consulting Fees: nanoString; Bayer; GLG; AbClon; Sana Therapeutics; BMS; GSK; viTToria Biotherapeutics
Fees for Non-CE Services : NanoString
Contracted Research: Abclon; Beckman-Coulter; viTToria Biotherapeutics
Other: Scientific Founder viTToria Biotherapeutics

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IP Rights: The H. Lee Moffitt Cancer Center and Research Institute has licensed intellectual property related to the proliferation and expansion of tumor-infiltrating lymphocytes (TILs) to Iovance Biotherapeutics. S.P.-T is an inventor on such intellectual property. The H. Lee Moffitt Cancer Center and Research Institute has licensed intellectual property related to receptor targeting on tumors to Tuhura Biopharma. S.P.-T is an inventor on such intellectual property.
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IP Rights: RAS (G12D), RAS (Q61R), and RAS (Q61K) TCRs
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