

DESIGNING THE FUTURE OF CELL THERAPIES

INTRODUCTION

Advancements in cancer immunology and recent clinical experience with emerging cellular therapeutics such as tumor infiltrating lymphocytes (TILs), engineered T-cell receptor (TCR), and Chimeric Antigen Receptor (CAR) T-cell therapies are generating huge interest and activity both academically and industrially. Additional technologies, including cellular therapies based on natural killer (NK) and other immune cells as well as novel gene editing approaches have or will enter the clinic soon. These emerging therapeutics have the potential to rapidly change cancer treatment and may represent a new treatment paradigm.

To date, CAR T-cell therapies have only been approved by the U.S. Food and Drug Administration (FDA) for two types of cancers (certain types of leukemia and lymphoma); other T-cell based therapies have shown remarkable activity in a limited number of solid tumors but have not yet progressed to FDA approval.^{1,2,3,4,5} There is great interest in exploring these new treatment modalities to encompass the treatment of solid tumors, which comprise 90% of all cancers and the majority of cancer deaths.⁶ Currently, multiple challenges exist for the successful use of T-cell-based therapies in solid tumors, including issues related to antigen selectivity and expression, the immunosuppressive nature of the tumor microenvironment, tumor T-cell infiltration, and the phenomenon of T-cell exhaustion. Academia and industry are working on multiple ideas to address these barriers, and numerous T-cell-based product candidates are being developed, involving various cell sub-types, autologous and allogeneic approaches, various molecular manipulation strategies, and many different targets. However, due to the diversity of potential targets and the specificity of the human immune system, *in vivo* animal models are limited in their ability to predict product safety and efficacy for T-cell-based therapeutics.

¹ Stevanović S et al. Science 356, 200–205. April 2017

² Zacharakis N, et al. Nature Medicine 24, 724–730. June 2018

³ Tran E et al. Science 344, 641–645. January 2014

⁴ D'Angelo et al. Cancer Discovery 8:944. August 2018

⁵ Brown et al. NEJM 375:2561–2569. December 2016

⁶ SEER Cancer Stat Facts 2019. <https://seer.cancer.gov/statfacts/html/all.html>

ABOUT FRIENDS OF CANCER RESEARCH

Friends of Cancer Research drives collaboration among partners from every healthcare sector to power advances in science, policy, and regulation that speed life-saving treatments to patients.

ABOUT PARKER INSTITUTE FOR CANCER IMMUNOTHERAPY

The Parker Institute for Cancer Immunotherapy brings together the best scientists, clinicians and industry partners to build a smarter and more coordinated cancer immunotherapy research effort.

The Parker Institute is an unprecedented collaboration between the country's leading immunologists and cancer centers. The program started by providing institutional support to six academic centers, including Memorial Sloan Kettering Cancer Center, Stanford Medicine, the University of California, Los Angeles, the University of California, San Francisco, the University of Pennsylvania and The University of Texas MD Anderson Cancer Center. The institute also provides programmatic support for top immunotherapy investigators, including a group of researchers at Dana-Farber Cancer Institute, Robert Schreiber, PhD, of Washington University School of Medicine in St. Louis, Nina Bhardwaj, MD, PhD, of the Icahn School of Medicine at Mount Sinai, Philip Greenberg, MD, of the Fred Hutchinson Cancer Research Center, and Stephen Forman, MD, of City of Hope.

The Parker Institute network also includes more than 40 industry and nonprofit partners, more than 60 labs and more than 170 of the nation's top researchers focused on treating the deadliest cancers. The goal is to accelerate the development of breakthrough immune therapies capable of turning most cancers into curable diseases. The institute was created through a \$250 million grant from The Parker Foundation.

To potentially help a much larger number of patients, in particular those patients with solid tumors and no remaining treatment options, it would be desirable to advance small, data-intensive clinical exploratory studies to differentiate which approaches warrant further focus. These studies would provide an opportunity to optimize the choice of candidates to advance into full product development by generating knowledge that cannot be gained using currently available nonclinical models. Small, early clinical studies also have the potential to facilitate better understanding of the biology of T-cell-based therapeutics and the product attributes driving efficacy and safety. However, clinical data can typically be obtained only after the compilation and submission of an investigational new drug application (IND) for each candidate to be evaluated. These IND procedural requirements can make it prohibitively slow and expensive to pursue this critical opportunity for more than a select few product candidates.

Furthermore, there can be varying interpretations of FDA guidance regarding phase appropriate current Good Manufacturing Practice (cGMP) requirements for manufacturing reagents, plasmids, vectors, and T-cell infusion products for use in the early investigational setting. In consequence, some institutions have imposed very strict cGMP requirements that are more applicable for later stage clinical development on all investigators, significantly increasing the cost and time to manufacture early investigational cell products. Likewise, while existing International Council for Harmonisation (ICH) guidance provide some direction, many of these documents were published at a time when cell therapy was in its infancy; while many of the concepts remain applicable, updated guidance specifically addressing the unique aspects of cellular therapies is needed. Due to the time required to manufacture most cellular therapies (encompassing plasmid and viral vector manufacturing and development of the cellular product manufacturing process and appropriate quality control testing), early clarity in their development is needed regarding the acceptability of a more phase appropriate cGMP approach to manufacturing for early clinical studies.

Ensuring that T-cell-based therapeutics are impactful for the greatest number of patients requires the adoption of new manufacturing technologies as more patients are treated and more clinical, translational, and product quality data is collected during a product lifecycle. This may require modifications to the manufacturing process throughout the different stages of a development program. As product and process knowledge increases, a regulatory strategy that enables adjustment of a process based on patient or patient-specific raw material information to maximize product quality for all patients will be necessary without conducting extensive costly and lengthy studies. This adds complexity to development as current regulatory requirements and processes may not readily allow for patient-level modifications, especially when the understanding of the linkage among product quality attributes, manufacturing processes, clinical efficacy, and safety continue to evolve late in development or after licensure. As product and process knowledge accumulate through the pivotal trial and post-market, an *adaptive* manufacturing process with the goal of generating a highly similar drug product from the patient-specific starting material should be enabled.

Part 1 of this paper outlines a number of regulatory opportunities to accelerate the development of these promising new therapeutics:

- **Opportunities to accelerate early discovery through IND flexibility**
 - o Expansion of the Exploratory IND paradigm to encompass early clinical studies of cell therapies
 - o Flexibility in the application of phase appropriate cGMPs to the manufacturing and testing of plasmids, viral vectors, ancillary materials and reagents, and T-cell-based infusion products for early exploratory clinical trials
 - o Opportunities for flexibility in cell processing and flexibility to permit the use of representative (e.g., high quality, pilot batch) viral vectors in cell product engineering runs
 - o Development of a “parent-child” IND framework to reduce the regulatory burden associated with entering the clinic to test multiple potential product candidates
- **Opportunities to accelerate the optimization of cell products during late stage development and post licensure**
 - o Establishment an adaptive manufacturing process for greatest patient benefit
 - o Develop additional guidance on classification of Chemistry, Manufacturing, and Controls (CMC) commercial process changes

Science- and risk-based approaches will be critical to mitigating and balancing any potential risk associated with either early clinical research or more flexible manufacturing paradigms versus the benefits of developing and optimizing these promising new therapeutics for patients with life-threatening cancers with limited or no therapeutic options. Many of the concepts outlined in this whitepaper may be broadly applicable to multiple types of immuno-oncology cell therapies. T-cell-based therapies, in particular CAR Ts, are used here to highlight specific examples.

Part 2 of the paper describes opportunities for research collaborations and data sharing to advance the cell and gene therapy field:

- **A scientific development consortium to share fundamental data and/or expedite investigational product development and testing processes**
 - o Establish a consortium to promote and facilitate prospective data collection
 - o Develop an exploratory adaptive platform study to evaluate the safety and efficacy of multiple clinical hypotheses and mechanistically defined cell and gene therapies
- **Establish agreed upon standard technologies to facilitate technology transfer between academic innovators and industry GMP producers**

The establishment of research collaborations and data sharing efforts can help facilitate harmonization of cell and gene therapy studies as well as allow for efficient implementation of manufacturing changes or modification of patient cohorts based on accruing clinical data.

PART 1: OPPORTUNITIES TO ACCELERATE EARLY DISCOVERY THROUGH IND FLEXIBILITY

1.1 Expansion of the Exploratory IND paradigm to encompass early clinical studies of cell therapies

FDA's 2006 Exploratory IND Guidance acknowledged the need "to reduce the time and resources expended on candidate products that are unlikely to succeed" and described "some early phase 1 exploratory approaches that are consistent with regulatory requirements while maintaining needed human subject protection, but that involve fewer resources than is customary, enabling sponsors to move ahead more efficiently with the development of promising candidates." This guidance also acknowledged that there is a great deal of flexibility in the amount of data that needs to be submitted with an IND application, depending on "the goals of the proposed investigation, the specific human testing proposed, and the expected risks." The stated purpose of exploratory INDs is to "assess feasibility for further development of a drug or biological product."⁷

Application of the exploratory IND concept to very early, small clinical studies for the purpose of candidate selection for T-cell-based therapeutics would facilitate the critical opportunities described above. However, certain modifications would be needed. The current Guidance explicitly states that an exploratory IND study is intended to involve "very limited human exposure" and to have "no therapeutic or diagnostic intent." Post-infusion expansion of cellular therapies, the durable nature of cellular products, and the ethical requirement to ensure clinical equipoise for patients with life-threatening cancers necessitate that they be dosed at therapeutic levels and with therapeutic intent. Nonetheless, a science-and risk-based approach to an expansion of the exploratory IND concept as it is applied to T-cell-based therapies, to facilitate the critical evaluation of the safety and activity of next generation T-cell-based therapeutics that could fundamentally improve their efficacy via small, data-intensive clinical studies, is possible and appropriate.

An expanded exploratory IND pathway would facilitate the efficient generation of clinical data on multiple T-cell-based product candidates or hypotheses in small (N generally less than 30 patients per cohort) studies, reducing the procedural regulatory burden for both the sponsor and the FDA reviewing division. To ensure patient protection, enrollment in exploratory cellular therapy INDs should be limited to patients with advanced cancers and limited or no treatment alternatives and the total numbers of patients to be treated under an exploratory IND should be limited to the number required to elucidate the hypotheses to be tested. The sponsor should thoroughly justify the number to be treated in the IND and/or protocol.

Exploratory phase protocols should be designed with a focus on patient safety and should incorporate opportunities to minimize risks. Evaluating the behavior of cellular products in humans is currently the most effective way to assess safety, since animal models have been unreliable and product quality attributes that predict safety have been difficult to identify.

⁷ Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies. <https://www.fda.gov/downloads/drugs/guidance-compliance/regulatoryinformation/guidances/ucmo78933.pdf>

Therefore, appropriate consideration should be given to protocol design features such as:

- Judicious dose escalation schemes, dose cohorts, and dose-limiting toxicity (DLT) windows
- Adequate dosing interval and safety assessments between patients enrolled at each dose level during the dose escalation phase
- Ongoing assessment of safety by a safety monitoring committee, including prior to dose escalations and expansion cohorts
- Consideration of incorporation of pre-specified safety, efficacy, and/or futility gates during the expansion phase, such as with a Simon 2-stage design, to ensure appropriate risk-benefit is maintained
- Pre-planned early reporting of safety results could be incorporated into the clinical plan, which could be agreed to during an INTERACT or pre-IND meeting or during IND review to avoid introducing unnecessary delay

Additional procedures to ensure patient protection could include explicit characterization of these INDs and the associated protocols as “exploratory,” intended to support studies involving “very early clinical research,” ensuring appropriate patient informed consent and IRB and FDA oversight with particular scrutiny applied to ensure that the appropriate patient population will be enrolled.

Such an approach is consistent with FDA’s many expedited development programs that, while focused on later stages of development, explicitly acknowledge the need to balance the risks associated with early exposure to unproven investigational therapies against the potential benefits of early access to those therapies.

The following sections outline how phase appropriate cGMP compliance focused on product quality and patient safety, and a streamlined “parent-child” IND alternative to the current single IND per drug product process would further facilitate the conduct of these studies under an expanded exploratory IND paradigm. T-cell-based therapies are used as specific examples. We note that some of the proposals may be relevant for other types of gene-editing technologies or immune cell therapies.

1.2 Flexibility in the application of phase appropriate cGMPs to the manufacture and testing of plasmids, viral vectors, ancillary materials and reagents, and T-cell-based infusion products for early exploratory clinical trials

FDA’s 2008 Guidance for Industry: cGMP for Phase 1 Investigational Drugs⁸ provides a framework whereby more phase appropriate manufacturing can occur for early studies. The recognition that smaller scale manufacturing processes may be excluded from some of the controls required for later stages of development where larger numbers of patients are exposed to treatment or for

⁸ Guidance for Industry CGMP for Phase 1 Investigational Drugs. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/20Guidances/UCMO70273.htm>

commercialization is critical to innovative research and establishing a better understanding of the human biological impacts of new therapeutics in small investigational human studies. However, consistent understanding and interpretation of this guidance, especially as it would apply to exploratory cellular therapy INDs, is needed. We provide several key examples below where explicit alignment between FDA, academic and government institutions, and industry with flexible approaches would facilitate the early exploratory clinical studies described above.

Implicit in any approach for manufacturing Phase 1 appropriate materials is a focus on patient safety, and the concepts below are proposed with an emphasis on risk assessments and analytical testing to determine and manage potential impact to patient safety. As such, T-cell-based cellular products would undergo release testing following manufacture for standard safety attributes, such as sterility, absence of mycoplasma and endotoxin, viral integration elements (vector copy number), identity, purity, and potency.

The principle of a more flexible approach, if chosen, would be to ensure patient safety and to take steps to ensure that if the decision is made to pursue full product development, results obtained during the exploratory study would be similar to those for the subsequent investigational product used in the full development IND. However, reductions or deferral of testing relating to process consistency and long-term stability in these early “screening” studies would result in time and resource savings. Process optimization aspects of product development would be fully addressed during subsequent development for any candidate for which a decision has been made to move forward with full development. We note that sponsors may wish to assure that an adequate number of retain samples are obtained during the early product manufacturing to facilitate subsequent manufacturing comparability.

We note that if remarkable efficacy were seen for a product development candidate tested in an “exploratory IND, the requirement for a full IND with more standard manufacturing process development would still apply with the potential for associated delays. Sponsors may determine this risk is acceptable given the potential to save time and resources by eliminating product candidates that are destined to fail, resources that could be dedicated to intensive efforts to accelerate the development of the promising candidate. Finally, sponsors may decide to mitigate this risk by pursuing limited process development activities in parallel with clinical studies under an exploratory IND.

A risk-based approach to requirements for the production of raw materials and drug substance (DS) (e.g., viral vectors, including lentiviral vectors) for T-cell-based therapeutics could more rapidly lead research teams to better combinations of therapeutics, scFv alterations, novel manufacturing interventions, etc., which would lead to more robust products that don't fail in later stage development studies. Flexibility to permit the use of representative viral vectors in cell product engineering runs would result in significant time savings at little or no risk to patients. These opportunities could reduce the total time to manufacture investigational T-cell-based

therapeutic candidates for use in an early clinical study under an exploratory IND by approximately 50%, as depicted in Appendix 1: Section A and described in greater detail below.

1.2.1 Reduction in the infrastructure requirements for the manufacture of plasmids

Currently, production of plasmid DNA for downstream production of viral vectors and/or for gene editing tools is often outsourced to a limited number of companies, resulting in high costs and long manufacturing queues. Generally, sponsors and academic researchers have the technical capabilities to produce these plasmid DNA's, but interpretations of FDA guidance have led to institutional policies requiring cGMP grade plasmids for clinical studies. Due to the high infrastructure requirements (ISO-7 clean rooms, fully developed quality systems and cGMP trained personnel and associated resources) needed to produce cGMP grade plasmid DNA, many institutions have not invested in the development of the manufacturing and quality infrastructure to produce these raw materials internally. In the industry setting, the impression that cGMP grade plasmids may be required increases the cost and time associated with manufacturing investigational cellular products. Manufacture of cGMP grade plasmids for small, exploratory clinical trials of multiple early cellular product candidates would unnecessarily increase the cost and time to conduct these studies since it is expected that many of the candidates would not progress into full product development.

As an alternative to a requirement for cGMP grade plasmids, *high-quality (HQ) fit-for-purpose* plasmids may be acceptable. Plasmid DNA can be tested and sufficiently characterized to confirm its fit-for-purpose suitability for downstream use in early, exploratory clinical trials with little risk to patient safety.

For example, the regulatory burden associated with the manufacture of HQ DNA plasmids for exploratory clinical studies could be reduced by eliminating the need for an *E. coli* master cell bank (MCB). Note that a sponsor could also make a business decision to create the MCB and then freeze it, deferring the need for time consuming and expensive testing until a decision was made to go forward with full development with that product candidate. Manufacturing could occur with review of production protocols, analytical results, manufacturing batch records, and release tests could be performed by a second technical rather than quality assurance personnel. A certificate of testing (CoT) could be produced summarizing the test results and could include tests similar to those in Table 1 below. In essence, a CoT is similar to a certificate of analysis (CoA) but differs in a few key elements: 1) tests are mostly compendial and may not be fully qualified/validated; 2) tests may be peer reviewed by a technical expert (in lieu of a quality assurance resource); and 3) test results have a "Target Value" in lieu of "Acceptance Criterion." In addition, because the plasmid DNA materials are stable when frozen and anticipated to be used quickly in downstream manufacturing of viral vectors, at this stage the need to generate stability data could be weighed against the timing of use and available research data and in some cases, waived.

Table 1: Proposed “fit for purpose” testing of plasmid DNA for early phase clinical studies.

Attribute	Test Method	Target Value
Appearance	Visual	Clear, colorless, no visible particulates
Concentration	Absorbance (A280)	Target +/- 10%
Purity	Absorbance (A260:280)	1.7 – 2.0
Safety	Endotoxin by LAL	< 25 EU/mg
Safety	Bioburden Testing	< 10 CFU/10mL
DNA Homogeneity	Gel Electrophoresis	>75% Supercoiled
Residual Host Protein	BCA Assay	Report result
Residual Host DNA	qPCR	Report result
Residual Host RNA	SYBR/Gel electrophoresis	Report result
Identity	Restriction digest and AGE	Conforms to reference
Identity	DNA sequencing	Confirm expected sequence at appropriate method sensitivity

The above proposals supported by appropriate documentation would facilitate the creation of greater manufacturing capacity by reducing the barriers to entry, permitting manufacturing of plasmid DNAs (for use in downstream manufacturing of viral vectors) at the academic or sponsor level, and further decompressing full-scale GMP manufacturing capacity for full product development manufacturing needs.

1.2.2 Use of phase appropriate vector testing strategies, including reductions in the replication competency testing requirements

In the context of early, exploratory clinical studies in patients with limited or no remaining treatment options and very poor long-term survival, the risk-benefit of earlier access to potentially beneficial T-cell-based therapeutic treatment is reasonable. Despite theoretical concerns, the risk of replication competency-related recombination events using 3rd generation viral vectors is extremely low as the elements required for virus replication are separated across 3 or 4 different plasmid DNAs and the 3' UTR portion of the transfer plasmids have been modified resulting in transcriptional inactivation of the LTR in the proviruses after integration. With respect to viral vectors currently used in cell therapy products, researchers have documented that, to date, no viral vector recombination events have been observed across hundreds of patient product tests.^{9,10}

⁹ Cornetta K et al. *Molecular Therapy* 26:1. January 2018

¹⁰ Cornetta K et al. *Molecular Therapy: Methods & Clinical Development* 10:371-378. September 2018

The current replication competency virus assay is based on testing vector supernatant or end of production cells on susceptible human cells over an 8-10-week period; this requirement adds significant expense and time to the overall product manufacture and release timelines. In order to address lengthy timelines required for viral vectors to be manufactured and released, elimination of the replication competency test for release of viral vector drug substance (DS) is proposed. In lieu of testing for the replication competency test in the viral vector DS material, it is proposed that a surrogate qualified/validated qualitative polymerase chain reaction (qPCR) test be done for the GAG and vesicular stomatitis virus G glycoprotein (VSV-G) or similar envelope gene sequences depending on the viral vector pseudotype, as has been recently suggested by Skrdlant et al.¹¹

Vector and cellular drug product release decisions for such exploratory studies could be made on the basis of surrogate testing; if required, full, culture-based replication competency-based testing could be conducted in parallel in the background. The results of the full-culture testing would be available within the period of post-infusion patient follow up during which time patients would be followed for the development of treatment-related malignancy.

1.2.3 Use of risk-based approach for determining safety of reagents used in early clinical trials

Many reagents are employed in the production of viral vectors and therapeutic T-cells. Extensive manufacturing requirements for reagents (e.g., activation beads, selection reagents, cytokines, recombinant growth factors, etc.) create a time and cost burden in early development. Typically, these reagents are produced and stored frozen at higher concentrations to ensure greater stability. During manufacturing, a reagent would be thawed and diluted to the working concentration and then added to a much larger culture volume. Unless the reagent is used constantly throughout the entire manufacturing process, several rounds of washing, media changes, and formulation of the final cell product will significantly dilute the reagent. Similar to the manufacturing requirements for plasmid DNA, fit for purpose requirements (relying on science- and risk-based approaches to ensure patient safety and quality of the reagent) for HQ reagents used within the manufacturing process for early phase clinical studies would significantly reduce the cost and time burden associated with using innovative reagents. An emphasis on risk assessments to identify potential impact to patients (e.g., sterility/bioburden, products of animal origin, etc.) could provide guidance to academic researchers and industry partners. For non-pharmacopoeial reagents of non-biological origin, a review of a certificate of testing may provide assurance that a reagent is fit-for-purpose for use in the manufacturing of cellular products for small, early clinical studies. For reagents of biological origin (e.g., human serum), purchase from an accredited supplier, along with a certificate of analysis (source, sterility, endotoxin, infectious agents, mycoplasma) can confer suitability of use.

¹¹ Skrdlant LM et al. *Molecular Therapy: Methods & Clinical Development* Vol. 8 March 2018

Table 2 below provides an illustrative example of the approach to characterization of a novel recombinant cytokine, such as one that may be used as a media supplement in a representative T-cell-based therapeutic manufacturing process, which could form the basis of a “Certificate of Testing.” These testing elements are based on the concepts provided in ICH Q6B and other regulatory guidance and represent an assessment of the reagent’s identity, purity/impurity, potency and safety. Historical knowledge of production of the intended reagent should be utilized to set appropriate quantitative or qualitative science- and risk-based acceptance limits.

Table 2. Representative characterization testing of a recombinant protein cytokine reagent.

Attribute	Test Method	Target Value
Appearance	Visual	Clear, colorless, no visible particulates
Concentration	Appropriate methodology (protein-based BCA or other)	Target concentration +/- 20%
Purity	HPLC – SEC	≥ 90% product peak
Safety	Endotoxin by LAL	≤ 25 EU/mg
Safety	Sterility	USP <71>
Safety*	As needed	Report results
Residual Host Cell Protein	ELISA (if available)	Report result
Residual Host DNA	qPCR or PicoGreen Assay (for dsDNA)	Report result
Potency	Appropriate methodology (ELISA or activity assay)	Report result
Identity	Identity by MS	Confirmation of identity

*Additional test(s) may be required based on the source of the reagent (e.g., mammalian production may require additional mycoplasma testing)

1.3 Opportunities for flexibility in cell processing

Given the resources required and complexity of manufacturing T-cell based therapeutic products, identifying similar flexibilities in the cell processing space would provide significant opportunities for innovation. While a robust discussion of the kinds of flexibility desired is out of scope for this document, a few examples and the anticipated impacts are offered below. Typically, a T-cell-based therapeutic is engineered using a relatively similar set of manufacturing unit operations: acquisition of patient starting material through apheresis/leukapheresis, isolation/purification of the T-cells through gradient, magnetic or alternative selection means, activation, and retroviral transduction to introduce the CAR or TCR, expansion of the engineered T-cells, and final harvest and cryopreservation. While there are variations on the above approach and a number of different pieces of equipment employed in various manufacturing processes, the general process lends itself to some potential flexibilities in the early development space.

1.3.1 Flexibility to permit the use of representative viral vectors in cell product engineering runs

For T-cell-based therapeutic products, current process development is often interpreted as requiring the use of GMP grade viral vector in the three engineering runs conducted to confirm the adequacy of the cellular product manufacturing process. Clarity that the use of “representative pilot” (i.e., development grade viral vectors manufactured in accordance with the final manufacturing process) would be acceptable, could result in significant time savings because the cellular product engineering runs could be run in parallel with the final GMP production runs for the viral vector. Additionally, because much of the development work for autologous cell therapies is done at scale, fewer engineering runs (e.g., 2) would be reasonable. As such, data from both development runs (e.g., in the process development lab) and engineering runs (e.g., in the GMP manufacturing facility) could be combined to demonstrate adequate control of the process.

1.3.2 Utilization of scale-models

Leveraging scale-down models is critical in examining variations in the manufacturing process and impact to T-cell phenotype and functionality. Currently, many of these experiments are often repeated numerous times at scale to demonstrate control of the process. This often requires significant investment in time, personnel, and reagent resources to accomplish. Given the significant patient-to-patient variability introduced by the various conditions of starting apheresis materials in many of these early clinical studies (e.g., age of patient, extent of prior lines of therapy, T-cell health and baseline population distribution, viability, etc.), it is difficult to precisely identify sources of variability. This exercise is challenging even in more mature areas, such as current approved CAR T therapies for hematological malignancies. Flexibility in the use

of scale-down models (as mentioned above in conjunction with a limited number of “at scale” development and engineering runs) would provide much needed ability to move promising pre-clinical programs into these early exploratory studies.

1.3.3 Phase appropriate release testing

For early phase exploratory trials, a focus on testing cell product components related to safety can provide flexibility. Safety would be assessed via testing for sterility, mycoplasma (via a rapid testing paradigm), endotoxin, etc., that are each important to demonstrating a lack of contamination of the cell product. Testing the cell product for elements of the viral engineering activity through assessment of integration of the vector into the T-cell genome can be done by determining the average vector copy number (VCN) via qPCR. Additionally, surrogate measures of viral replication competency can be done using qPCR with primers against various elements of the viral genome (discussed above as part of the relaxation of RCR/RCL testing above). Identity, purity, and potency are important release assays used to demonstrate that a particular manufacturing process was able to successfully yield the expected product. Identity is confirmed by flow cytometric staining for key cell surface markers, such as CD3, CD4, CD8, specific introduced CAR or TCR, etc., are typically used to provide assurance that the appropriate cell product was produced. This is of considerable importance if a manufacturing facility is involved in producing multiple products targeting different antigens. Many sponsors conduct additional characterization with numerous other cell surface markers to further understand their product, but these analyses should be focused on gathering additional data. Potency of CAR and TCR-based cell products is often demonstrated using either a cytokine release (e.g., IFN-gamma or TNF-alpha production) or cytolytic killing assay whereby the cell product is incubated with cells expressing the target and shown to bind and kill these “target” cells. Complexity and variability in both of these testing approaches in the early phase of development results in challenges in establishing numerical acceptance criteria. Additionally, limitations in the amounts of samples available, condition of the cell products (e.g., fresh testing vs. cryopreserved product testing) also contribute to variability and challenges with numerical acceptance criteria. Flexibility on the acceptance criteria would be advantageous and utilizing the report result verbiage for reporting could help move programs into the clinic faster.

1.4 Regulatory procedural flexibility – Development of a “parent-child” IND framework to reduce the regulatory burden associated with the clinical testing of multiple potential product candidates

Currently, outside of the area of non-engineered T-cells, sponsors must submit a new IND for each potential T-cell product candidate for which they wish to conduct clinical testing, and each IND requires significant time, resources, and expense both for the sponsor and the FDA reviewing division. In the setting of small, early data-intensive clinical studies intended to investigate the safety, feasibility, and mechanism of action of several closely-related T-cell-based can-

didates or related manufacturing process alterations (for example process alterations to maintain “stemness”) a more efficient “parent-child” IND structure and process may be appropriate.

An exploratory “parent-child” IND is a feasible approach to reducing the regulatory procedural burden associated with evaluating multiple highly-related T-cell-based therapeutic constructs or manufacturing alterations in small clinical studies. The “parent” IND would contain common sections providing all of the common information relevant for the to-be-tested initial candidates or manufacturing alterations. For each candidate or manufacturing alteration, a “child” IND would also be submitted. This “child” IND would depend on heavy cross-referencing to the common sections in the “parent” IND while providing only the candidate or process specific information (e.g., CMC or nonclinical data) in separate sections (see Appendix 1: Section B). We note that cross-referencing to previously submitted information, with appropriate authorization, is an accepted practice.

At the time of initial IND submission, the “parent” and “child” IND could be assigned separate IND numbers, to facilitate safety reporting, etc., but reviewed in parallel within the standard 30-day IND review window. Each subsequent “child” IND would be subject to the normal 30-day review window. Consistency in approach to each “child” IND may be facilitated by assignment of the “parent” and all related “child” INDs to the same FDA review team.

The exploratory IND would include an explicit agreement by the sponsor that once the early testing of a particular construct or process is completed or discontinued, the associated exploratory “child” IND would be withdrawn. If the sponsor intends to proceed with full development of a candidate or manufacturing process, a new, traditional IND would be submitted for that candidate. Subsequent candidates or processes consistent with the common information in the original “parent” IND could subsequently be added as additional “children” to the original “parent”, again relying heavily on cross-references. FDA would have an opportunity during the 30-day review to reject any proposed “child” as insufficiently related to the “parent” to justify acceptance. Ultimately, once the sponsor determines that no additional early candidates closely related to the original exploratory IND will be tested, the exploratory IND would be withdrawn.

The use of the parent-child IND approach would result in significant time and resource savings for sponsors and the FDA reviewing division and could facilitate the generation of critical knowledge regarding the safety, feasibility, and mechanism of action of many more T-cell-based therapeutic constructs and manufacturing alternations than is possible under the current regulatory paradigm and that cannot be generated in nonclinical studies. This reduced burden has the potential to be particularly significant for the most innovative academic and small biotech sponsors with limited resources.

Because the time and resource savings associated with the use of “parent-child” INDs would only be realized in situations where most of the information contained in the “parent” IND

would be relevant to all of the investigational candidates, the use of “parent-child” INDs would be limited to situations where the commonalities between the early cellular therapy candidates or manufacturing interventions are great enough to produce real gains in efficiency for both sponsor and the FDA reviewing division. For example, an exploratory IND might be limited to candidates directed at the same target. Whether a parent-child IND is appropriate for a particular set of candidates could be discussed in an INTERACT or pre-IND meeting or the justification could be provided in the IND itself (with an associated risk of delay if FDA disagrees).

1.5 Flexible Regulatory pathways to enable manufacturing and testing evolution during late stage development and post licensure

1.5.1 Regulatory opportunities to enable adaptive manufacturing processes for greatest patient benefit

In the case of T-cell-based therapeutics and other cell-based therapies, making these products impactful for the greatest number of patients may require adjusting manufacturing parameters for specific patient subsets. The first generation of engineered T-cell products treating patients with hematological malignancies (e.g., ALL, DLBCL, CLL, Multiple Myeloma) use the same manufacturing process for all patients. These products have made a meaningful impact over the standard of care in these diseases. The single manufacturing process framework was chosen for regulatory expediency and a lack of product knowledge to discriminate between patients. At the same time, patient-to-patient variability in the quality of T-cells from these patients leads to suboptimal drug product quality for a subset of patients, when a single manufacturing process is used for all patients. In order to increase the number of patients responding to these treatments, it may be necessary to adapt the manufacturing process for a subset of patients to increase the efficacy for the specific patient cohort, without impacting safety and efficacy for patients already responding using the original manufacturing process.

These new process parameter combinations for patient subsets are discovered during clinical development as more patients are treated and more clinical, translational, and product quality data are collected. As product and process knowledge increases, a regulatory strategy that adjusts a process based on patient or patient-specific raw material information to maximize product quality for all patients will be necessary without conducting extensive costly and lengthy clinical studies. This adds complexity to development as current regulatory requirements and processes may not readily allow for patient-level modifications, especially when the understanding of the linkage among product quality attributes, manufacturing processes, clinical efficacy, and safety continue to evolve late in development or after licensure.

Traditionally, manufacturing process lock is completed in advance of late-stage clinical trials to be able to repeatedly measure effect across many patients. Product and process knowledge is currently being generated to enable the development of an adaptive manufacturing process

with the goal of generating a highly similar drug product from the patient-specific starting material. The product and process knowledge to enable adaptive manufacturing in most cases will not emerge until a large number of patients are treated since the correlative analysis to discover the relationship is not available until enrollment of the pivotal trial. An example of this type of relationship includes the frequency of specific T-cell subtypes.¹² An example of emerging product knowledge and the rationale for an “adaptive” approach are discussed below.

Box 1. Example of Emerging Product Knowledge

A licensed product using a fixed manufacturing process leads to a durable response in 40% of patients. During clinical development, it is observed in a small subset (~10%) of non-responders that adapting the manufacturing process can convert these non-responders to responders. If a cohort can be identified with a control point and a separate set of process parameters that will meaningfully change product attributes to improve the biological activity of the product for a subset of patients, a regulatory mechanism permitting these adaptive changes would benefit patients in later trials and commercially. Running a prospective trial to support a supplemental approval for a very small subset of patients would not be viable. Existing guidance, such as ICH Q11 and ICH Q5, provide a framework for prospective process flexibility in the presence of strong product attribute understanding, including the application of Quality by Design (QbD) principles.

However, the challenge is that in the cellular therapy field, because of the small numbers and variability in patient-derived starting materials, product and process knowledge emerges only as clinical experience grows, which makes it difficult to plan into the prospective pivotal trial. In the case of cell therapies, an “adaptive” approach incorporating evolving product and process understanding is needed. Having to restart regulatory processes for each potential manufacturing adaptation is not feasible and has the unintended consequence of discouraging process improvements that could benefit patients.

¹² Fraietta JA, Lacey SF, Orlando EJ, et al. Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia. *Nature Medicine* 24, 563-571 (2018).

1.5.2 Using Post Approval Lifecycle Management (PALM)-like plan for making manufacturing and testing changes

As we gain stronger product knowledge and process understanding and are able to correlate their impacts to clinical safety, efficacy, and durability results, the insights gained are likely to lead to improvements that can be made to the manufacturing process and/or quality control tests. For example, based on data gained during clinical development, a process adaptation (e.g., culture medium optimization, culture condition optimization) is identified, which modestly increases the efficacy or reduces adverse events (i.e., does not impact labeled dose). The magnitude of change in clinical profile may not be large enough to justify a full clinical development but is still beneficial to patients. For these changes, modifications could be managed via a pre-negotiated plan with health authorities (e.g., Post-Approval Lifecycle Management or Comparability Protocol). The filing requirements for the change may include a combination of an analytical comparability assessment, and/or a small clinical study, analogous to a bioequivalence study for a new process. A post-market commitment could be considered to demonstrate/confirm the efficacy of the new process.

1.5.3 Create CMC commercial process change reporting categories for cell-based therapies

FDA issued a draft guidance in December 2017 for CMC changes to an approved application intended to assist manufacturers of biological products in assessing the reporting category for CMC changes. This guidance provides a starting framework that can be further extended to T-cell-based therapies. As the cell-based therapeutic industry accumulates commercial manufacturing experience, sponsors can identify the most frequent manufacturing changes and propose recommended reporting categories based on risk assessment: Annual Reportable (AR), Changes Being Effected (CBE)-0, CBE-30, or Post Approval Supplement (PAS). Consistent with the fundamental guiding principle from the biologics guideline, the reporting category selected should be commensurate with the risk of an unintended outcome resulting from changes involving these elements. When assessing the impact of change on product quality, the historical product and process knowledge including experience gained during commercial manufacturing should be fully leveraged. Developing a best practice guide for cell therapy with specific examples of process and testing changes for the range of categorization would be a beneficial activity to be created by an industrial consortium.

However, it should be noted that the overall variability in cell-based therapy processes is predominantly influenced by the incoming patient-to-patient variability. Therefore, the traditional process performance qualification (PPQ) approach utilizing three healthy donor batches to qualify each change has limited applicability and instead a rigorous, continuous process verification (CPV) plays a larger role in demonstrating process control. Use of healthy donors to characterize process and analytical variability in theory is a good approach, but a significant number of healthy donors are potentially needed to quantify the variability contribution of the process and analytics. This consumes resources and manufacturing capacity that otherwise would be used to produce clinical or

commercial products. Hence, a concurrent qualification approach, where a change is introduced in manufacturing based on small scale data and is subject to verification through a CPV program during clinical/commercial use, is not only more efficient but would also allow the confirmation of change in the setting of real patients instead of healthy donors. In addition, standalone qualification of the specific process or manufacturing change without the need for end-to-end full PPQ may be sufficient in some cases (e.g., a change in a supplier of raw materials, reagents, and solvents that have a minimal potential to affect product quality) provided that the materials' specific use, physicochemical properties, impurity content, and acceptance criteria remain comparable could be validated offline and reported as an AR. Additionally, a change from a manual operation to an automated operation that does not change the process parameter set points could be addressed through automation qualification and reported as AR.

Lastly, in some cases demonstrating analytical comparability at the appropriate in-process intermediate level may be sufficient. For example, demonstration of comparability for the vector bulk material due to a process change in the vector manufacturing process should not require demonstration of final product comparability post-transduction. Analytical comparability of the bulk viral vector and, if needed, use of small-scale model to confirm transducibility of the cellular in-process product should be considered sufficient. The life cycle plan for process and method changes needs to be carefully sequenced so that potential impact of the changes is seen throughout the CPV program. Changes to process parameters outside of previously validated ranges should be assessed with respect to criticality to process performance and product quality.

Several other examples of post-approval changes are likely. The reporting categories and extent of requalification for these changes will be assessed keeping the above considerations in mind. A risk based approach to determine the extent and approach of qualification should be used which would determine if 1) qualification can be performed using small scale or whether full scale confirmation is needed; 2) qualification exercise can be limited to evaluating product attributes of the impacted intermediate or the final drug product; and 3) separate qualification is needed or if heightened CPV program for a period of time can be used. Given that many cell therapy companies are focused on early access to the promising therapies, several process improvements are deferred and become part of the post-approval life cycle plan. Examples of such deferred changes include: new primary packaging components for the final product to simplify ease of administration and enable more clinical sites; new activation reagents; introduction of a new media processing system to improve manufacturing robustness; a higher-grade of fetal bovine serum (FBS) to improve reliability; change of buffer manufacturer from in-house to an external manufacturer; automation of manual processing steps; automation of flow cytometry data analysis; increase in vector production scale to meet increasing demand; change to a rapid sterility method, rapid microbiologic testing, and change of vector manufacturing process to a suspension cell culture process; the addition of an identical manufacturing suite to double capacity for both vector and drug product; change in the antibiotic resistance in the vector cell bank/plasmid; improved potency method; and change to stability data for expiry extension.

1.5.4 Quality standards for ancillary materials used in the manufacturing of cell-based therapy products intended to be developed as commercial products

Currently, sponsor companies are restrained by the limited numbers of GMP producers of these ancillary materials (e.g., recombinant proteins, growth factors, cytokines, and small molecules) because of the regulatory requirements associated with choosing novel reagents. For the foreseeable future, the supply chain will be a critical path for product commercialization. The root cause for this supply chain is multi-factorial, but some modifications of applicable regulatory guidance could accelerate innovation.

In addition, stakeholders desire more uniform feedback from individual reviewers around quality and testing standards for non-GMP ancillary materials. Stronger guidance on how to stratify quality and/or characterization requirements based on whether they are excipients, product contacting (primary) or secondary ancillary material (e.g., plasmids used in viral vector manufacturing) or tertiary ancillary materials would be beneficial to the field. Moreover, greater health authority alignment with the principles published in USP <1043> or other guidance documents could result in greater consistency in CMC development across multiple phases.

1.5.5 Other regulatory opportunities to support cell-based therapies

The use of medical devices in the manufacturing of cell-based therapies: In the current generation of engineered T-cell products, approved medical devices are used in the manufacturing of cell-based therapy products. These medical devices are sometimes used outside of their approved “intended use,” and equipment validation is done by the biotechnology manufacturing sponsor. This usage outside of the approved “intended use” causes tension with the device manufacturer as they don’t want to put their medical device license at risk due to a biotechnology application.

Regulatory guidance for new cell therapy digital platform: The digital platform is a unique and critical aspect of cell therapy manufacturing, and various components such as Chain of Identity (COI) must be described in the BLA. It will behoove the field to develop regulatory guidance akin to regulating the manufacturing facility where it would be inspectable at any time but operational changes under controlled procedures are allowed.

Additional unique cell therapy regulations – setting lot specific specifications: Adapting a mid- or late- stage trial to incorporate multiple products to patient subsets would improve the pace of development for patient-specific therapies. In the case of cell-based therapies, the ability to engineer change into the cell provides for innumerable therapeutic opportunities and the ability to overcome challenges. If a change to product attributes is identified as an important factor while in P2 or P3 development, that change could be made and reset to a “child” IND to quickly gain groundwork experience to advance to later development.

PART 2: DRIVING INNOVATION IN CELL AND GENE THERAPY FOR THE TREATMENT OF CANCER THROUGH RESEARCH COLLABORATIONS & DATA SHARING

2.1 A scientific development consortium comprised of academic, government, nonprofit, and industry could share fundamental data and/or expedite investigational product development and testing processes, in early stage development and characterization, to advance the cell and gene therapy field for cancer patients.

The lack of available patient and product data necessary for effective data mining to inform manufacturing and clinical trial design is a major impediment to the advancement of cell and gene therapy for treatment of cancer. Pooling of data is currently limited because data sets and product characteristics need to be standardized in order to enable cross-study comparisons and data analysis. The competitive nature of development and the need to protect commercial, confidential, and proprietary information further complicate entities' ability to pool data and hinder opportunities for prospective data harmonization efforts. To move the cell and gene therapy field forward in immune-oncology, efforts are needed to define taxonomy and standardize data collection and measurement processes for analysis while exploring the potential for data sharing through pre-competitive collaborative groups. The establishment of a multi-stakeholder group of experts to serve as an ad hoc consult group to consortia participants (academic, government, nonprofit, and commercial) would potentially facilitate the development, review, and implementation of standard processes within individual development programs (e.g., review interim manufacturing and clinical data and approve/advise on subsequent modifications) based upon existing datasets and findings. The consult group could refer to previous efforts as potential models, such as the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline on Genomic Sampling and Management of Genomic Data (ICH E18)¹³, for the development of guidelines that facilitate harmonization of cell and gene therapy studies. Also, consortia participants could benefit from and be incentivized by having access to more real-time advice from technical experts, including FDA, in early stage development in exchange for implementing agreed upon processes for documentation and information sharing with other consortia members as appropriate. Additional topics that will need consideration include the merits of a single consortium vs multiple consortia linked by a common data structure that would enable cross-study analyses and what broad functions the consortium would be optimally positioned to perform on behalf of consortia members.

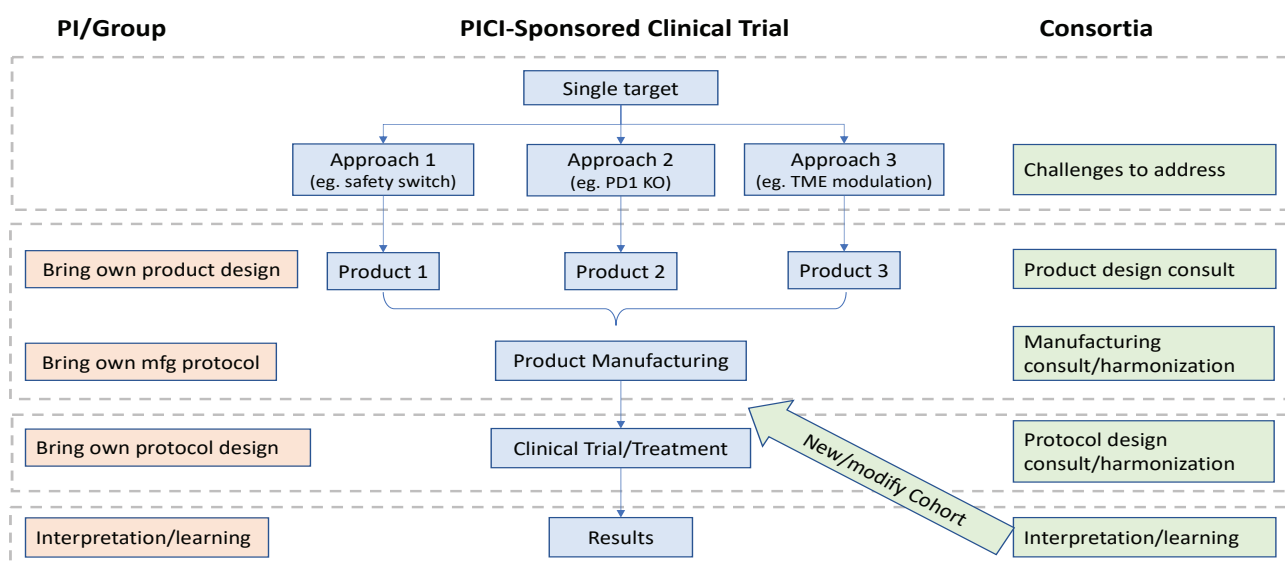
Collaborations that promote and facilitate prospective data collection using common data elements and controlled vocabularies to enable cross-study analyses are essential to significantly advance development of cell and gene therapies in oncology. Occurring well before commercialization, such collaborations would provide a proof-of-concept for generating standardized data to inform the early stages of investigational product development. The establishment of a common study platform would foster collaboration across multiple approaches with consistent design, standardized data collection, and analysis. For example, the Parker Institute for Cancer Immunotherapy (PICI) has pro-

¹³ International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. (2015). Guideline on Genomic Sampling and Management of Genomic Data (E18). Retrieved from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E18_Step2.pdf

posed a pioneering exploratory adaptive platform study to evaluate the safety and efficacy of multiple clinical hypotheses and mechanistically-defined cell and gene therapies/combinations. The platform study would be designed to investigate one cancer indication (**Figure 1**) and/or one set of targets (**Figure 2**) with the collective input from study primary investigators, consortia members (academic centers and industry), PICI, and the FDA. It would consist of a core protocol where the shared study design is described, with several appendices (cohorts) elaborating on cohort-specific designs included, and would feature:

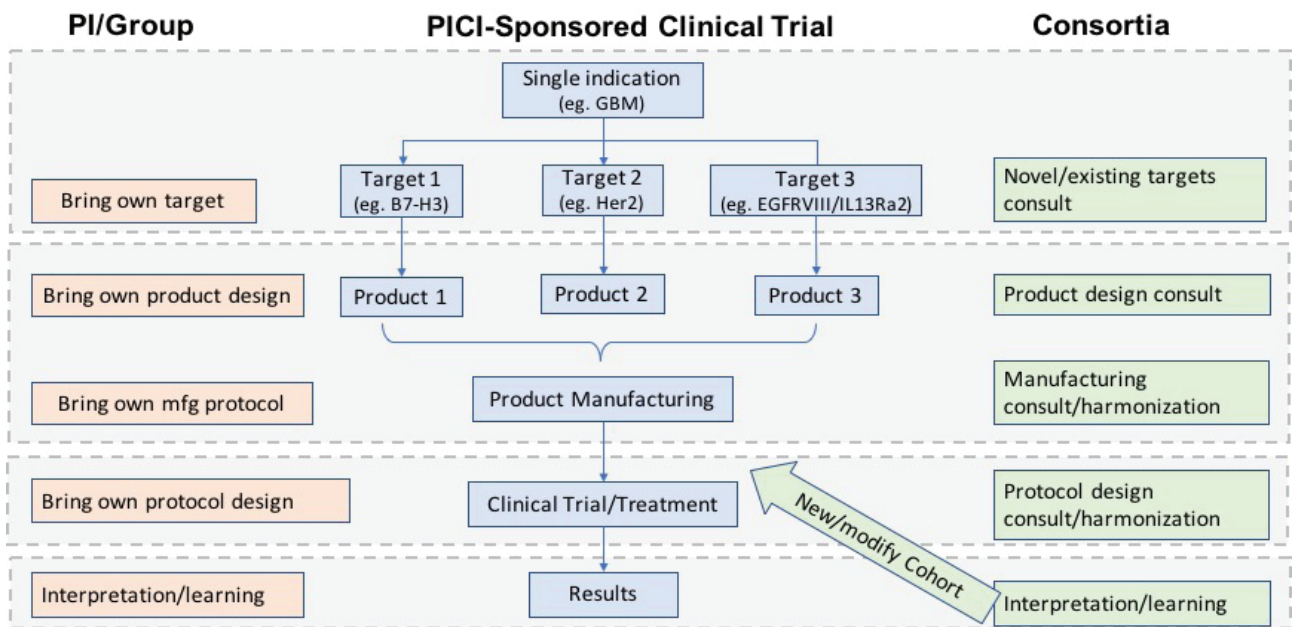
- 1) sharing of data analyses that could address common clinical, manufacturing, data, and regulatory issues;
- 2) prospectively planned modifications to one or more aspects of the investigational product based on accumulating data from participants in the trial;
- and 3) efficient implementation of changes based on clinical data after assessing the data by independent consortia and discussing with FDA.

Figure 1: Schema of a platform trial with a single target



Schema of a platform study that is investigating one specific target but histology or modality agnostic. Each cohort will be independent, and products can come from different organizations. This design offers some standardization across different cohorts such as eligibility criteria, dose limiting criteria definition, and go/no go decisions. Emerging data will only be accessible to the organization that owns the product and to the sponsor of the study. With the permission of the sponsor, data that could inform future cell and gene therapy development will be shared with a group of experts who can make either general recommendations to inform the field, a communication to the FDA, or specific product recommendations. Recommendations could also be utilized for further optimization of the product and its development process.

Figure 2: Schema of a platform study with a single indication



Schema of a platform study that is investigating one indication but allowing different products and modalities. The design and objectives are similar to the single target platform study described in Figure 1.

A key question in the field is: what are the features that characterize a safe, efficacious, and durable product? Therefore, as part of this platform, it will be important to establish harmonized strategies for collections and molecular profiling of the cells both before and after infusion. The variety of therapeutic approaches and indications that will be tested in a platform study provides tremendous opportunities to identify features of both the product and the manufacturing process, which lead to efficacious and safe therapies across a variety of contexts. These foundational learnings could be shared in a pre-competitive manner across consortium participants in order to accelerate the development of future therapies.

Another important initiative that is underway is a federally mandated and funded Regenerative Medicine Innovation Project (RMIP) established by the 21st Century Cures Act (Act).¹⁴ The Act authorizes the appropriation of specific funds to NIH “for clinical research to further the field of regenerative medicine using adult stem cells, including autologous cells.” Importantly, the Act requires that award recipients match, using non-federal contributions, in an amount at least equal to the federal award, which amplifies the federal investment and promotes collaboration across the public and private sectors. Moreover, the provision in the Act for the RMIP serves as a timely stimulus for NIH to work with NIST, FDA, DoD, and other partners in order to galvanize the field of cellular therapy in regenerative medicine (RM), foster major clinical advances, address key regulatory and technical issues in product development and clinical investigation, and ensure that RM clinical studies utilizing cell-based therapies are standardized, reproducible,

¹⁴ 21st Century Cures Act, Pub. .L. No. 114-255, § 1001, 130 Stat. 1041 (2016).

and generalizable. To support the RMIP, NIH is establishing a Regenerative Medicine Innovation Catalyst (RMIC), as outlined in **Figure 3**, that will provide critical services to support RMIP clinical research, including development of common data elements for stem cell products and clinical outcomes, clinical data standards to facilitate preparation and commercialization of clinical grade stem cell products, and regulatory support. RMIC partners will be expected to make pre-competitive RM data and analyses publicly accessible to the broad biomedical community. Furthermore, the RMIC will perform prospective in-depth and

Figure 3: Framework for the NIH Regenerative Medicine Innovation Catalyst to facilitate clinical research and further the field of regenerative medicine

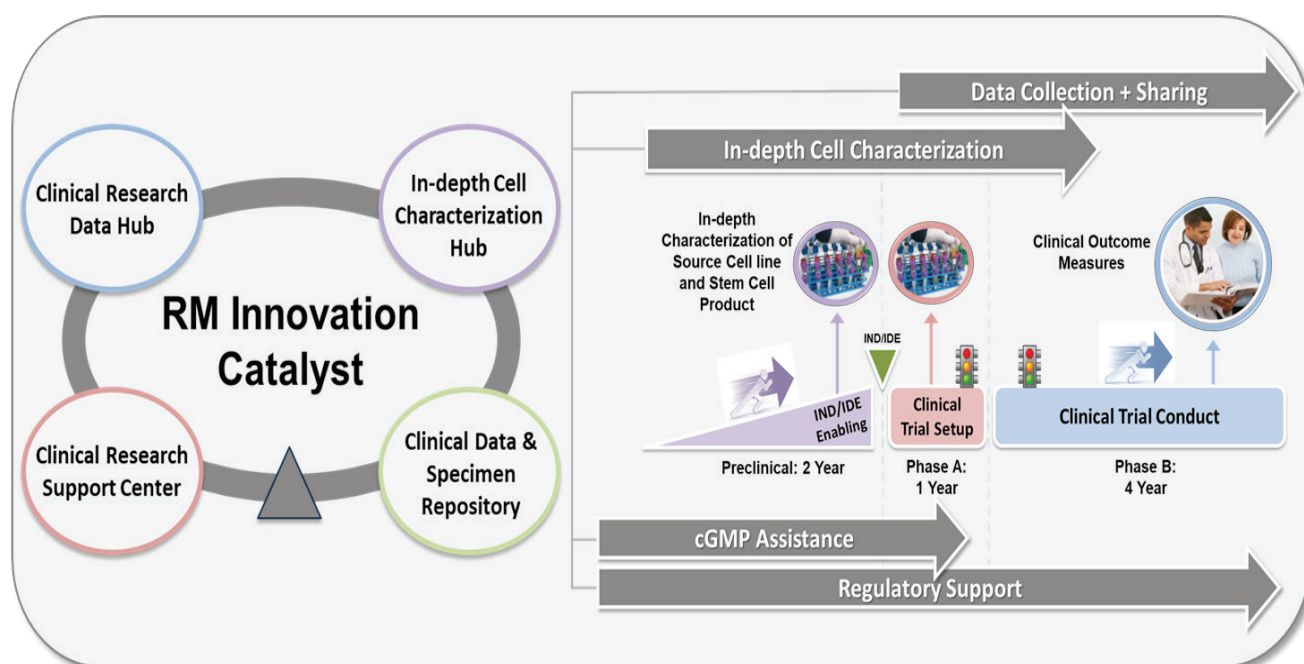


Figure 3 depicts the four major components of the Regenerative Medicine Innovation Catalyst (RMIC) and outlines the services and functions of the Catalyst throughout the RM pre-clinical development and clinical trial lifecycle. The RMIC consists of: (1) the Clinical Research Support Center, which will provide assistance in cGMP or phase-appropriate cell product manufacturing and regulatory support; (2) the In-depth Cell Characterization Hub which will coordinate the state-of-the art characterization of source stem cells as well as final clinical grade product and participate in development of common data elements describing cell products; (3) the Clinical Research and Data Standards Hub will develop, test, and implement common data elements for RM clinical research to enable cross-study analyses; and (4) the Clinical Data and Specimen Repository will provide both a controlled access database as well as a biorepository. The database will provide harmonized cell product data and clinical safety and efficacy data to facilitate correlation of cell characteristics with clinical outcomes. The biorepository will provide samples of source stem cell and cell products as well as a clinical biospecimens for subsequent analyses.

independent characterization of representative samples of source stem cells as well as final clinical-grade product and coordinate the storage and sharing of cell product characterization data linked to individual participant level outcomes data using cloud-based systems to help facilitate downstream correlation of key cell attributes to clinical safety and efficacy data. The RMIC is a pilot approach to providing critical support and data to the field of Regenerative Medicine, which, if successful, may be extended to all future NIH-sponsored RM clinical research. This new approach has the potential to address the major challenges for developing personalized cell-based therapies for cancer and many other diseases.

2.2 Establish agreed upon standard technologies (e.g., analytics for vectors, cell culture processes, potency assays for cells, simple manufacturing controls, and basic quality attributes) to facilitate technology transfer between academic innovators and industry GMP producers of these investigational therapies.

Difficulties with technology transfer from small academic institutional studies to larger, pharmaceutical company-sponsored trials are associated with an inability to expand trials beyond initial Phase 1 studies. Standard technologies are needed to understand the difficulty of the technology transfer process and guide design of smaller scale processes to enable replication and expansion to larger scale processes for further development by a commercial partner. The agreement upon a set of parameters for use by academic investigators that could enable rapid technology transfer would be mutually beneficial by adding value to the field for this

Box 2. Proposal to Facilitate Technology Transfer from Academic to Clinical Scale Industrial Process

STEP 1: Define and transfer the as-is process.

STEP 2: If starting with a lab scale academic process, the first step should be to mimic the scale production of the lab that developed the product and/or conducted the phase I study.

STEP 3: Develop the full-scale, clinical/commercial process – in a step-wise, operation by operation fashion if necessary.

SUCCESS FACTORS IN THE THREE STEP TECH TRANSFER MODEL

1. Establish Quality Attributes early in the tech transfer and use common analytical platforms to assess suitability across all stages.
2. Introduce and qualify GMP grade materials as early in the process as possible.
3. Careful consideration of plasmid and vector sourcing and manufacturing is needed at each stage. Final engineering runs should include clinical grade vector, if possible.
4. Conduct post-transfer proficiency testing to validate process and product controls.

therapeutic approach. Academics would have an asset with a more robust data package to help determine developability and risk/probability of success and companies would have an investigational product with a standardized data package and would be able to leverage a broader data set for evaluation of a specific program for developability. Further, it would enable leveraging of prior knowledge especially when using platform processes (e.g., same plasmid or vector with a different transgene). One way this could work would be for different industry producers of these therapies to agree upon non-proprietary common features that could subsequently be transitioned into their proprietary systems. These common features could then be provided to the academic innovators in the form of a toolkit or could even inform guidance around early stage clinical programs and a list of the Key Quality attributes that can/cannot be changed at a predetermined point during the Process Development Steps.

Several recommendations were identified to address key opportunities and help guide initial priorities for consortium-led efforts:

- Efforts should be undertaken to define taxonomy and standardize data collection and measurement processes for analysis.
- Pre-competitive collaborative groups should be formed to facilitate data sharing and include a multi-stakeholder group of experts to serve as an ad hoc consult group to consortia participants to facilitate the development, review, and implementation of standard processes within individual development programs.
- Non-profit clinical research organizations, as neutral and unbiased organizations, can play an integral role in harmonizing clinical trials and translational research. A platform study can offer commonality and opportunity for information sharing. This can lead to less redundancy and subjecting less patients to unnecessary risks.
- Collaborations that promote and facilitate prospective data collection using common data elements and controlled vocabularies should be formed to enable cross-study analyses.
- Deep molecular characterization of the cellular product will be key to identifying features of safe, efficacious, and durable therapies. Standardization of assays and collection strategies will provide opportunities to integrate data across a broad variety of indications and therapeutic strategies.
- Standard technologies should be developed to guide design of smaller scale processes to enable replication and expansion to larger scale processes for further development by a commercial partner.

CONCLUSIONS AND NEXT STEPS

This whitepaper outlines several opportunities and strategies to expedite T-cell based therapies into first in human studies, and to ensure that T-cell-based therapeutics are impactful for the greatest number of patients by creating a more “adaptive” manufacturing process that would allow the adoption of new manufacturing technologies as more patients are treated and more clinical, translational, and product quality data is collected during a product lifecycle. Moreover, efforts to encourage transparency, collaboration, and data sharing are needed so changes can be appropriately monitored and would allow the field to adapt to improvements efficiently. The proposals outlined in this whitepaper could be particularly useful in bringing cutting edge biological and genetic approaches forward to enhance the current generation of cell therapies in the highly complicated tumor microenvironment. This whitepaper is intended to provide high-level ideas to accelerate early cell therapies into clinical trials.

To fully consider and implement the proposals and strategies outlined in this whitepaper, key stakeholders will need to be called upon to continue the dialogue that has been initiated with this whitepaper. Formation of pre-competitive consortiums to standardize technologies, and the implementation of integrated platform studies would also help enable efficient development and collection of common data elements across trials. Additional areas, such as pre-clinical and clinical testing and the development of clinically relevant biomarkers to guide selection of the right patient population and detection of proof-of-concept in the clinical study, will require additional discussions and proposals to be considered.

APPENDIX 1: TABULAR SUMMARY OF EFFICIENCIES GAINED THROUGH EARLY STAGE MANUFACTURING AND IND FLEXIBILITY FOR T-CELL THERAPY EXPLORATORY CLINICAL TRIALS

a) Alternative manufacturing paradigm for early stage, exploratory trials

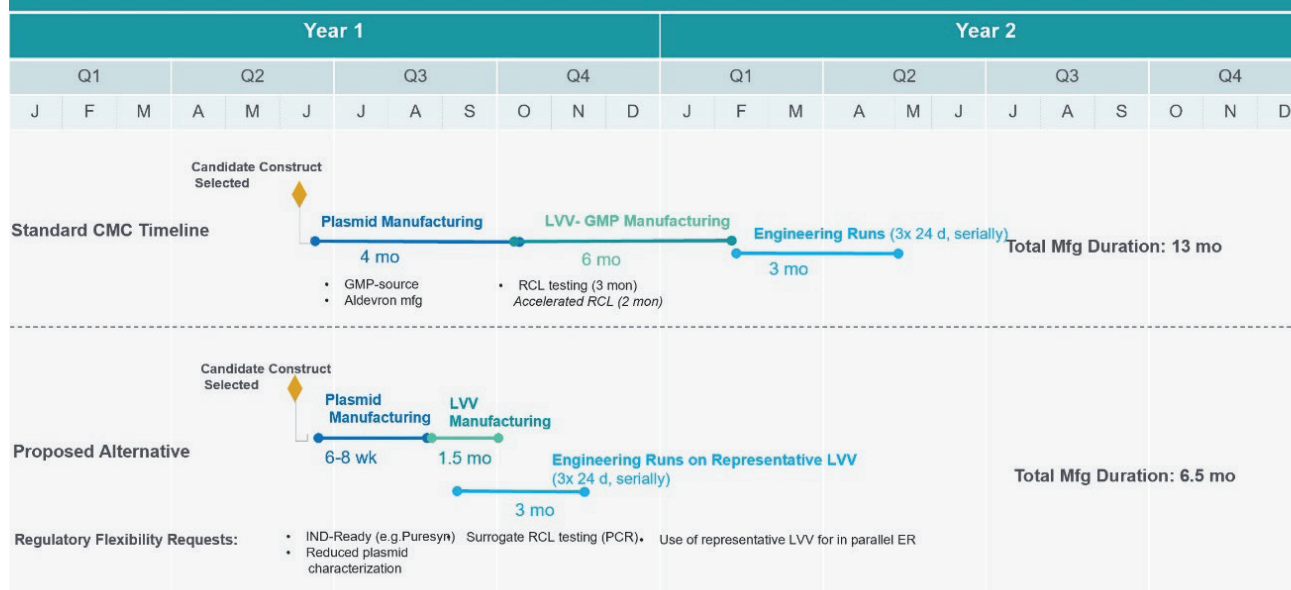
The potential time and cost savings for alternative approaches to use of R&D reagents, plasmid DNA, LVV manufacturing, and engineer run activities are outlined below.

CMC Activity	Typical Time ⁺ Investment	Areas of Proposed Flexibility	Potential Time ⁺ Savings	Potential Cost Savings
Use of R&D Reagents	3-6 months	Increasing options for use of R&D reagents and reducing cost and time to either enable or negotiate GMP manufacture of reagents	1-3 months	\$ to \$\$\$
Plasmid Manufacturing	4 months (+ 3 to 6 months in queue)	Reduced plasmid characterization & infrastructure requirements	5-7 months	\$\$
Viral Manufacturing	6 months (+ 9 to 12 months in queue)	Waive RCL testing in lieu of surrogate testing; reduced cGMP requirements for ancillary reagents	4 months	\$
Cell Product Engineering Runs (3 runs)	3 months	Use representative pilot virus for parallel cell product engineering runs	2 months*	N/A

+ All time estimates are approximate

* There is some overlap in the time savings between the shortened LVV manufacturing timelines, and the engineering runs utilizing pilot materials. Overall, the ability to demonstrate process control using representative materials means that activities are not reliant upon manufacturing and release of LVV

Figure 1: Alternative Manufacturing Paradigm for Early Iterative Clinical Studies



Expedited manufacturing of plasmid DNA and viral vectors coupled with cell product engineering run activities using representative viral vector could save time in getting into early phase clinical studies

b) "Parent-Child" IND paradigm for early stage, exploratory trials

Traditional development requires the submission of an IND for every product development candidate prior to the conduct of clinical trials. While the costs and time required to produce an IND vary significantly between sponsor types and experience, a reasonable estimate of the time and cost per IND is approximately 3-6 months of cross-functional document drafting and preparation and approximately \$100,000 in medical writing and regulatory operational costs for the initial IND and approximately \$25,000 per year in maintenance costs for the life of the IND. These time and cost estimates become prohibitive when a sponsor wishes to test several constructs or manufacturing process alterations.

A "parent-child" IND paradigm could result in significant savings in time and cost; the savings would increase with time and the number of constructs tested. An example table of contents of a "parent-child" IND is provided on the following page.

IND Module	Parent IND Contents	Required Section in Child IND	Child IND #2	Child IND #3
Module 1	1.1 Forms 1571 and 3674 1.2 Cover letter 1.3 Transfer of obligations 1.4 References Letters of authorization Right of reference (to DMFs etc.) 1.6 Meeting package 1.12 Environmental exclusion 1.14 Investigational brochure*	Forms 1571 and 3674 - Letter of cross reference to parent IND	Forms 1571 and 3674 Letter of cross reference to parent IND	Forms 1571 and 3674 Letter of cross reference to parent IND
Module 2	2.2 CTD Introduction 2.3 Intro to Quality overall summary – all candidates 2.4 Nonclinical overview – all candidates 2.5 Clinical overview – target disease, population and common aspects of all candidates	1.14 Investigational drug label for candidate #1	1.14 Investigational drug label for candidate #2	1.14 Investigational drug label for candidate #3
Module 3	2.6 Nonclinical summary – written and tabulated summary of nonclinical investigation of candidate #1 2.7 Aspects of clinical pharmacology – all candidates	2.6 Nonclinical summary – written and tabulated summary of nonclinical investigation of candidate #1 2.7 Aspects of clinical pharmacology specific to candidate #1	2.6 Nonclinical summary – written and tabulated summary of nonclinical investigation of candidate #2 2.7 Aspects of clinical pharmacology specific to candidate #2	2.6 Nonclinical summary – written and tabulated summary of nonclinical investigation of candidate #3 2.7 Aspects of clinical pharmacology specific to candidate #3
Module 4		3.2 Quality – specific to candidate / process #1 4.2 Nonclinical study reports – specific to candidate #1	3.2 Quality – specific to candidate / process #2 4.2 Nonclinical study reports – specific to candidate #2	3.2 Quality – specific to candidate / process #3 4.2 Nonclinical study reports – specific to candidate #3
Module 5	5.0. Clinical study reports – Not applicable			