



CDDF WORKSHOP

29 - 30 November 2021

HYBRID WORKSHOP

*Gene-and Cell Therapies
in Oncology*



Laura Pearce, MS
Clinical Development Lead
Sr. Director
Cell and Gene Therapies
Oncology Clinical Development
GSK

Clinical Trials with Cell Therapies - Challenges and Opportunities The Industry Perspective

Disclosures

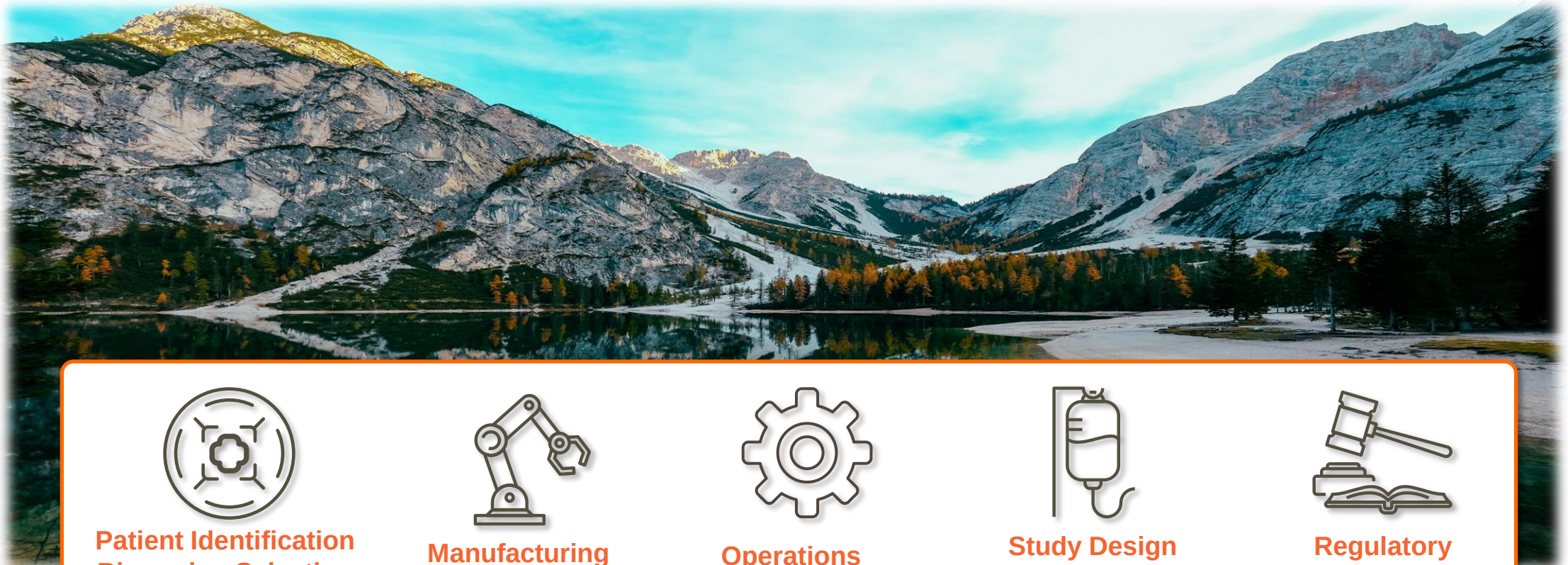


- ❑ Laura Pearce is an employee and shareholder of GSK
- ❑ All Cell Therapies mentioned in the presentation are investigational and are not approved for use anywhere in the world
- ❑ All human biological samples from shown experiments were sourced ethically and their research use was in accordance with the terms of the informed consents under an IRB/EC approved protocol
- ❑ Views expressed in this presentation are speaker's own and do not necessarily represent the position of GSK

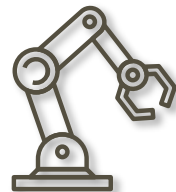
Forward-Looking Statements

This presentation may contain forward-looking statements. Forward-looking statements give the Group's current expectations or forecasts of future events. An investor can identify these statements by the fact that they do not relate strictly to historical or current facts. They use words such as 'anticipate', 'estimate', 'expect', 'intend', 'will', 'project', 'plan', 'believe', 'target' and other words and terms of similar meaning in connection with any discussion of future operating or financial performance. In particular, these include statements relating to future actions, prospective products or product approvals, future performance or results of current and anticipated products, sales efforts, expenses, the outcome of contingencies such as legal proceedings, dividend payments and financial results. Other than in accordance with its legal or regulatory obligations (including under the Market Abuse Regulations, UK Listing Rules and the Disclosure Guidance and Transparency Rules of the Financial Conduct Authority), the Group undertakes no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise. Investors should, however, consult any additional disclosures that the Group may make in any documents which it publishes and/or files with the US Securities and Exchange Commission (SEC). All investors, wherever located, should take note of these disclosures. Accordingly, no assurance can be given that any particular expectation will be met and investors are cautioned not to place undue reliance on the forward-looking statements. Forward-looking statements are subject to assumptions, inherent risks and uncertainties, many of which relate to factors that are beyond the Group's control or precise estimate. The Group cautions investors that a number of important factors, including those in this presentation, could cause actual results to differ materially from those expressed or implied in any forward-looking statement. Such factors include, but are not limited to, those discussed under Item 3.D 'Risk factors' in the Group's Annual Report on Form 20-F for FY 2019 and any impacts of the COVID-19 pandemic. Any forward-looking statements made by or on behalf of the Group speak only as of the date they are made and are based upon the knowledge and information available to the Directors on the date of this presentation. A number of adjusted measures are used to report the performance of our business, which are non-IFRS measures. These measures are defined and reconciliations to the nearest IFRS measure are available in our full year and fourth quarter 2020 earnings release and Annual Report on Form 20-F for FY 2019. All expectations and targets regarding future performance and the dividend should be read together with the section "Outlook, assumptions and cautionary statements" on pages 64 and 65 of our full year and fourth quarter 2020 earnings release.

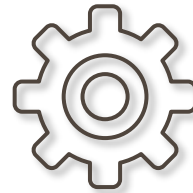
Cell Therapies – Challenges and Opportunities



**Patient Identification
Biomarker Selection**



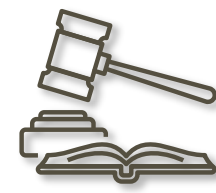
Manufacturing



Operations



**Study Design
Clinical Development**



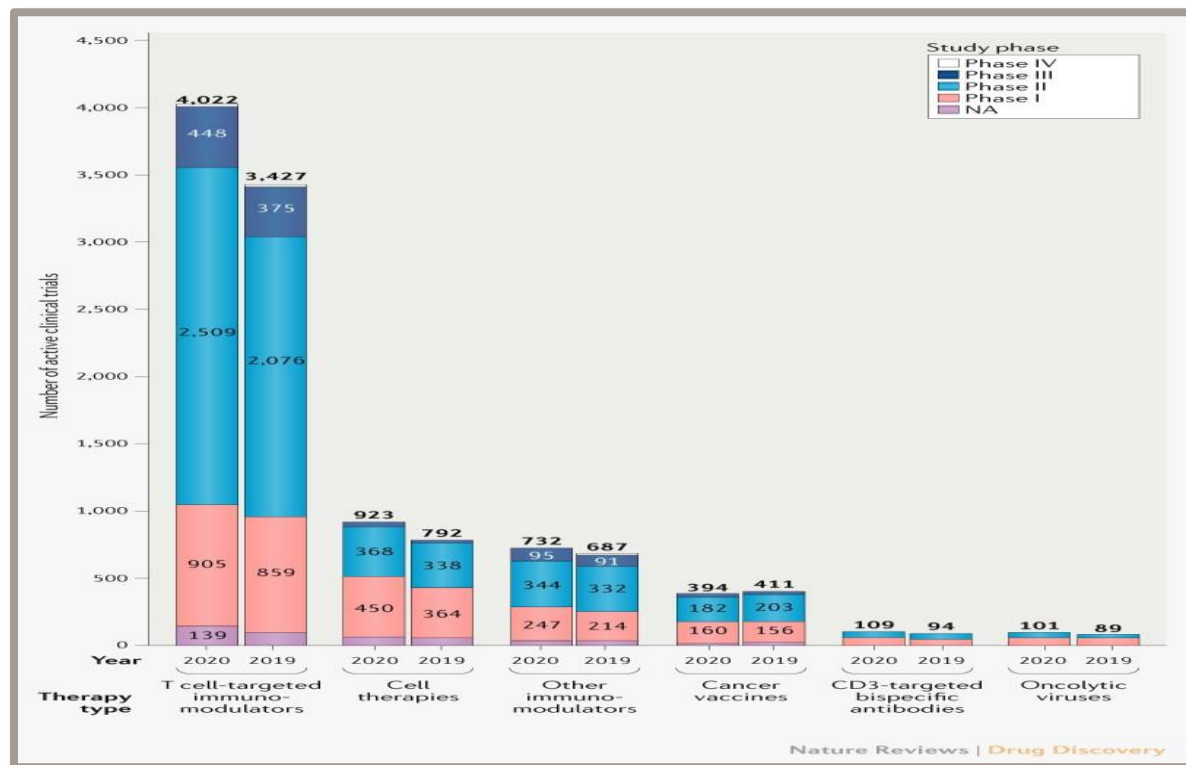
Regulatory

Patient Focus

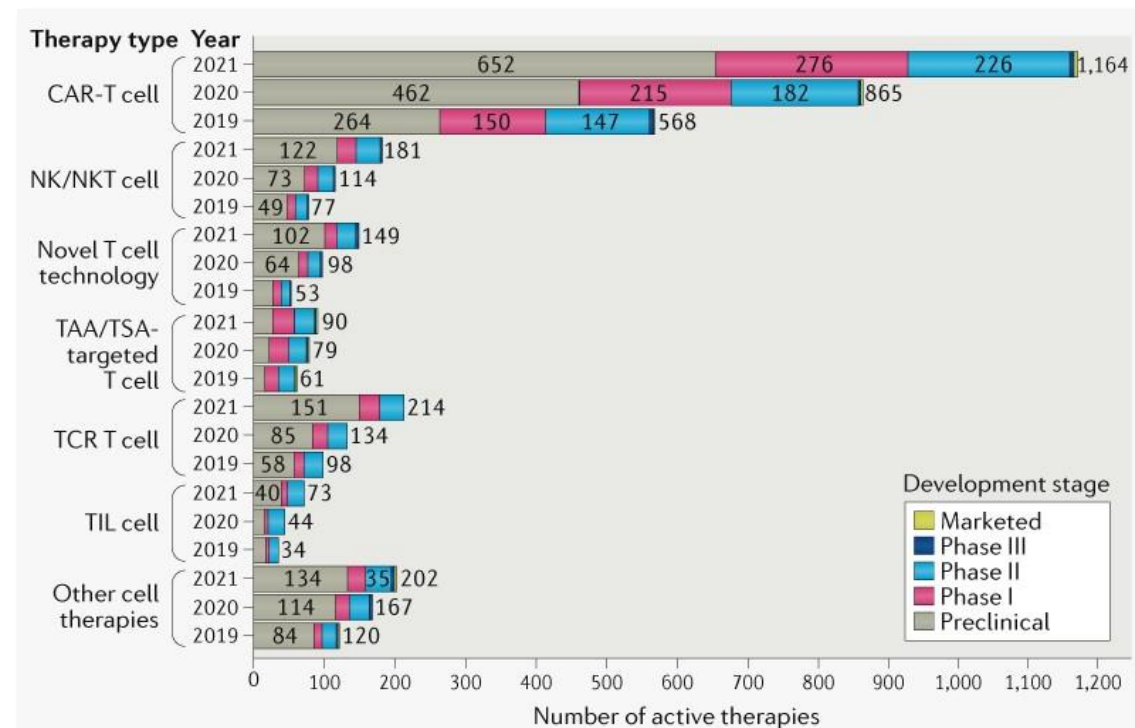
Dynamic Growth in Therapies for Cancer



Increase in agents, trials and competition for small patient populations



Upadhaya et al., *Nature Reviews Drug Discovery*, 18 SEP 2020



Upadhaya et al, *Nature Reviews Drug Discovery*, 04 JUNE 2021



4720 IO Agents in global pipeline



22% growth from 2019
223% from 2017

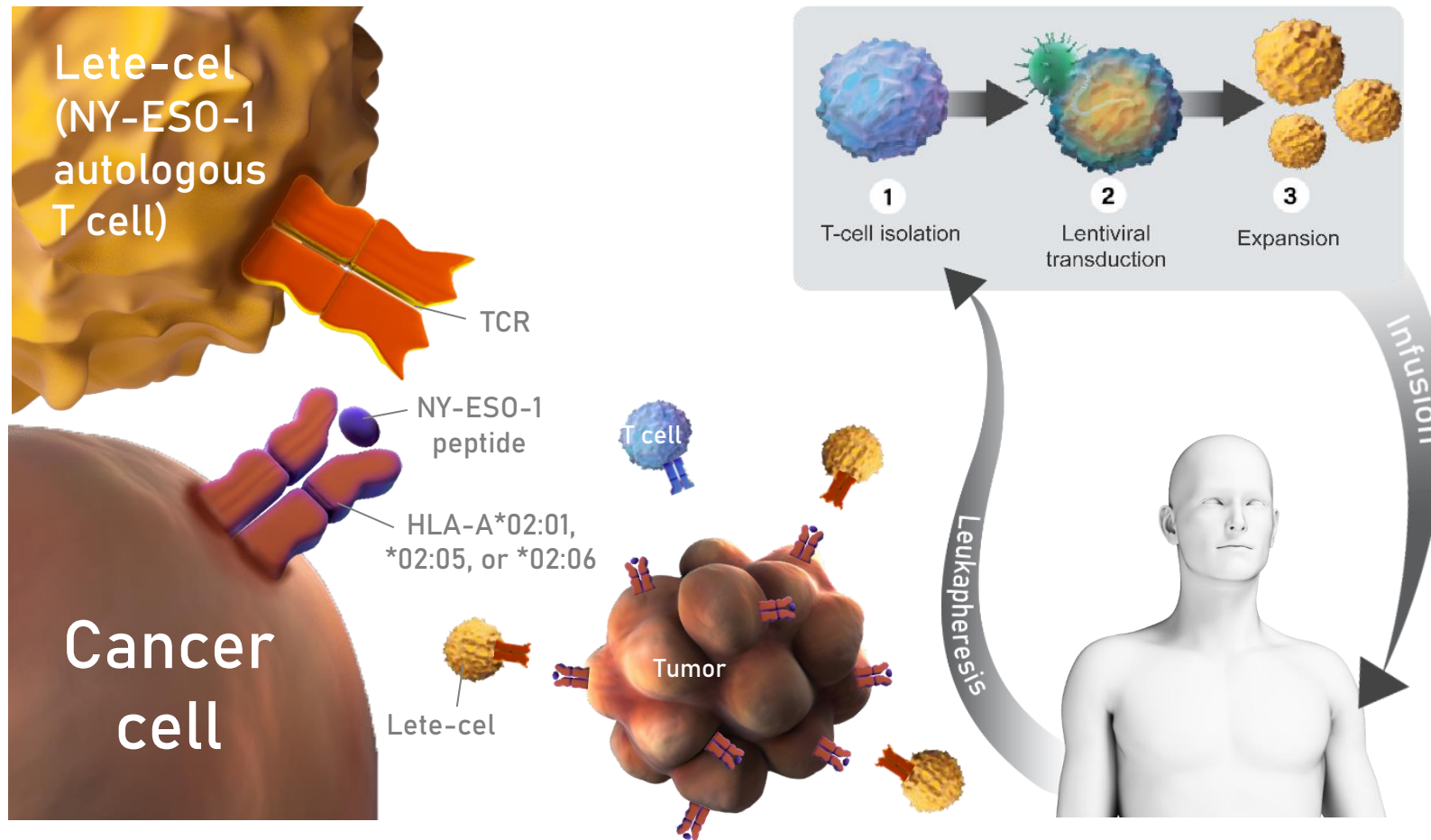


6281 trials



14% growth from 2019

Lete-cel: Personalized T-Cell Therapy With Improved Recognition of Cancer Cells



- Patient T cells are isolated and transduced with a lentivirus to express a genetically modified TCR with improved recognition of NY-ESO-1¹⁻³
- The cells are expanded in the laboratory then infused IV into the patient where they infiltrate the tumor^{1,3}
- Lete-cel has > 12-fold greater binding to an NY-ESO-1:HLA complex than naturally occurring TCRs⁴
- Lete-cel may result in immune cell persistence with a single administration^{1-2,5}

HLA, human leukocyte antigen; NY-ESO-1, New York esophageal squamous cell carcinoma 1; TCR, T-cell receptor.

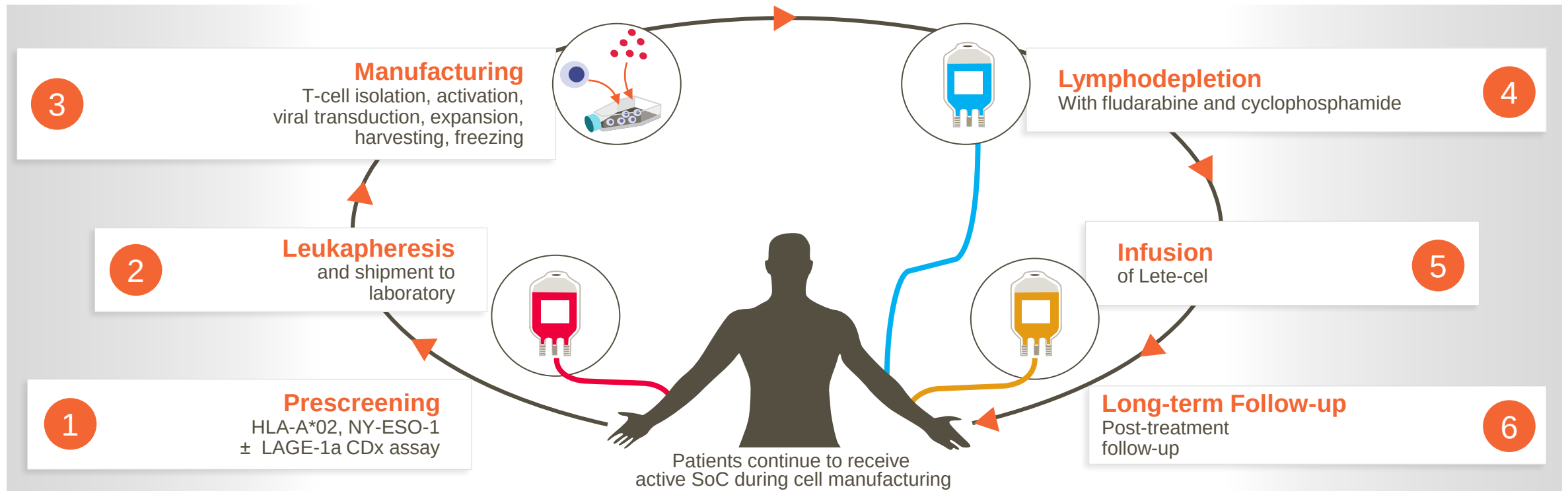
1. Rapoport AP, et al. *Nat Med*. 2015;21:914-921. 2. Rapoport AP, et al. ASH 2017 [abstract 845]. 3. D'Angelo SP, et al. CTOS 2017 [abstract 012]. 4. Robbins P, et al. *J Immunol*. 2008;180:6116-6131. 5. D'Angelo SP, et al. *Cancer Discov*. 2018;8:944-957.

Rapid Technology Advancements to Enhance Efficacy



	Target	Efficacy Enhancement	Description
First generation	 TCRT NY-ESO-1	NA	NY-ESO-1 TCR T cell (lete-cel; GSK3377794) > 12-fold greater binding to an NY-ESO-1:HLA complex than naturally occurring TCRs
	 TCRT NY-ESO-1	 TGF-β	dnTGF-βRII/NY-ESO-1 TCR T cell (GSK3845097) Co-expresses dnTGF-βRII to sequester immunosuppressive TGF-β in the tumor microenvironment
Multiple efficacy enhancements built onto TCR T platform	 TCRT NY-ESO-1	 CD8α	CD8α/NY-ESO-1 TCR T cell (GSK3901961) Co-expresses CD8α to stabilize the TCR-HLA:NY-ESO-1 interaction on both cytotoxic CD8+ and helper CD4+ T cells
	 TCRT NY-ESO-1	 Stemness	Stemness/NY-ESO-1 TCR T cell Improves T-cell function
	 TCRT NY-ESO-1	 Anti-exhaustion	Anti-exhaustion/NY-ESO-1 TCR T cell Counters T-cell exhaustion

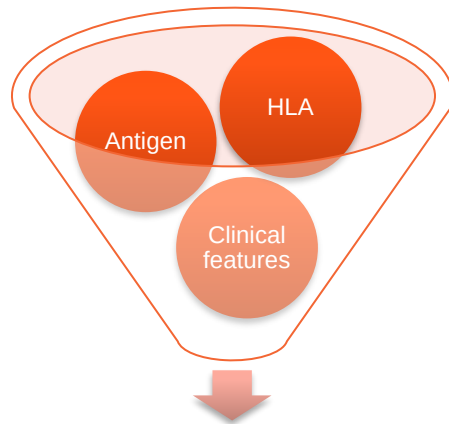
Patient Care Pathway



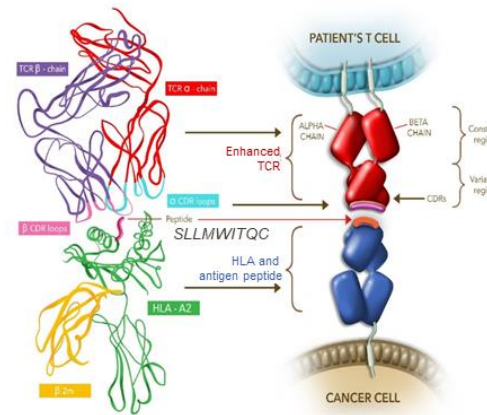
HLA, human leukocyte antigen; LAGE-1a, L antigen family member 1 isoform a; NY-ESO-1, New York esophageal squamous cell carcinoma 1; SoC, standard of care; TCR, T-cell receptor.

1. D'Angelo SP, et al. Poster presented at SITC 2019; Poster P453 (Image adapted). 2. D'Angelo SP, et al. *Cancer Discov.* 2018;8:944-957. (Adapted)

Cellular Therapy as “Personalized Medicine”



**Patient Screening
Eligibility**



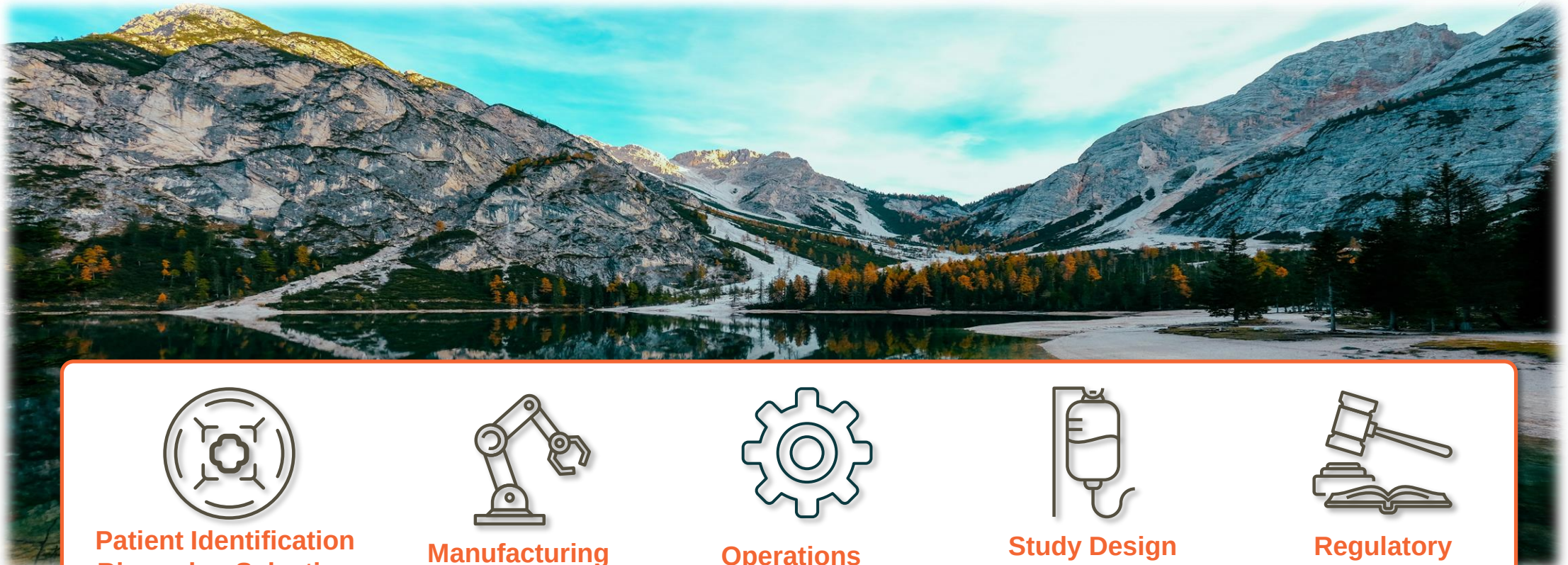
**Made for each patient
Not “off the shelf”**

Enhancements

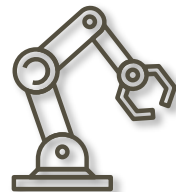


**Time
Treatment windows,
Assessments**

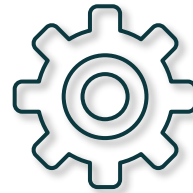
Cell Therapies – Challenges and Opportunities



**Patient Identification
Biomarker Selection**



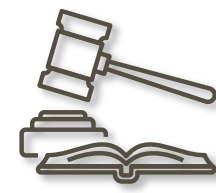
Manufacturing



Operations



**Study Design
Clinical Development**



Regulatory

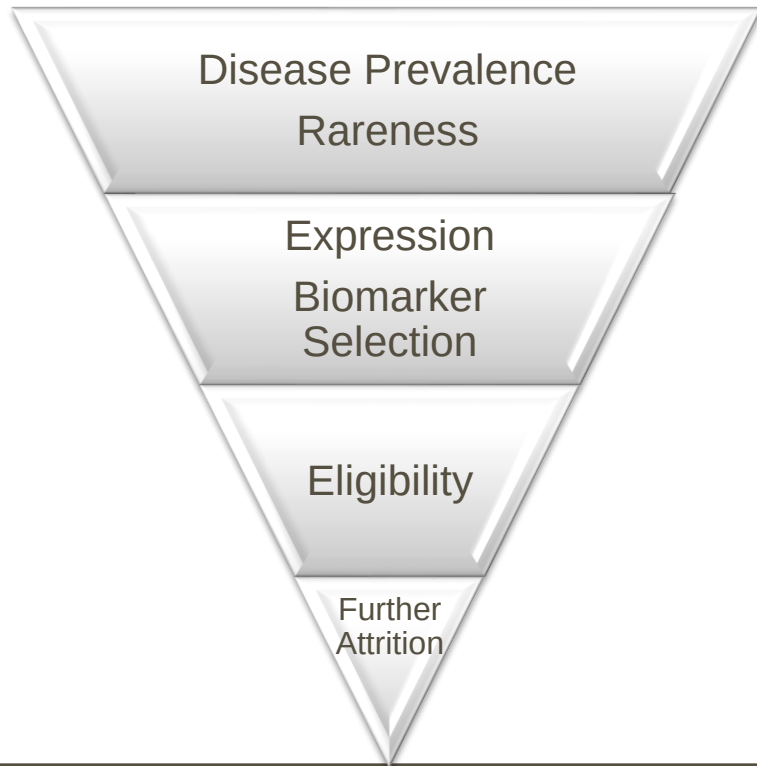
Patient Focus



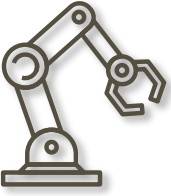
Patient Identification, Biomarker Selection



Patient Focus



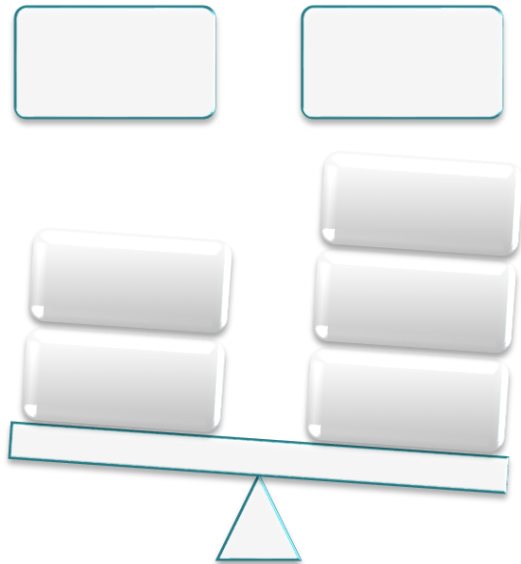
- Biomarker testing (robustness, readiness)
- Feasibility and accessibility of trials
- Attrition factors (eligibility, COVID)
- Screening Exhaustion



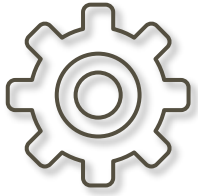
Manufacturing



Patient Focus



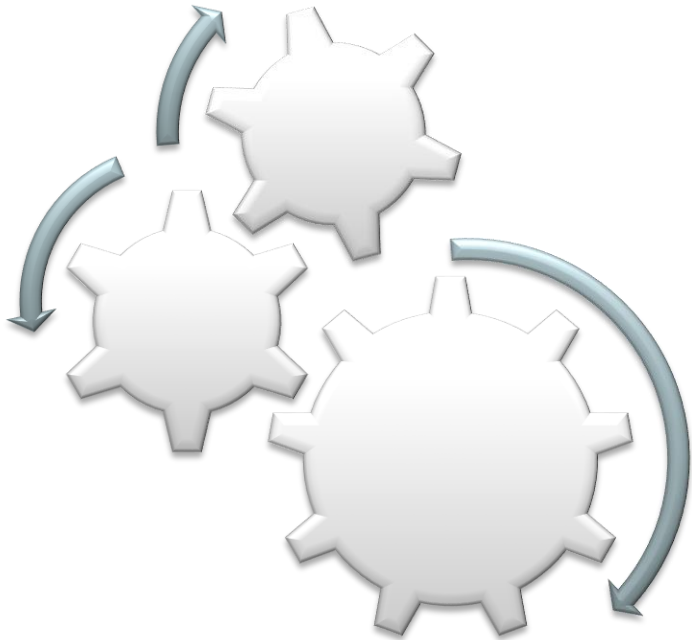
- Manufacturing / GMP Readiness & Vector Supply
 - Cell Logistics (time, apheresis/cryopreservation)
 - Transportation & Maintaining Supply Chain
 - Import/Export
- Footprint (FACT/JACIE / accreditation)
- Capacity Management
- Coordination and communication



Operations



Patient Focus



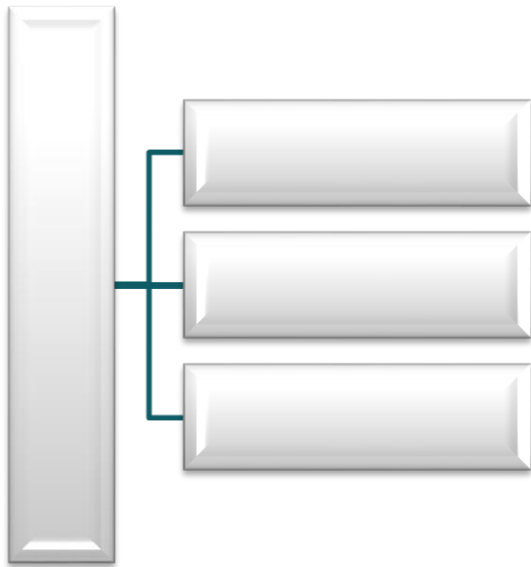
- Resource demand
- Long-Term Follow Up Requirements
- GCP and GMP intersection
- Study Setup & Site Footprint
- Systems and Ways of Working
- Patient Journey Management



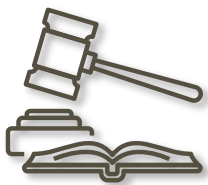
Study Design, Clinical Development



Patient Focus



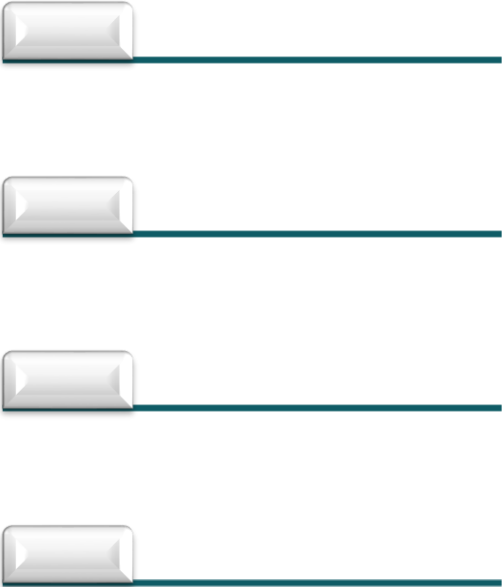
- Early vs Late
- Objectives and Endpoints
- Single arm vs RCT
- Patient population – rare, small sample size
- Study duration
- Assessments and Evaluations (Safety & Efficacy)
- Biomarkers and Correlatives
- Apheresis and Manufacturing Strategy
- Retreatment Strategy
- Adaptive Designs



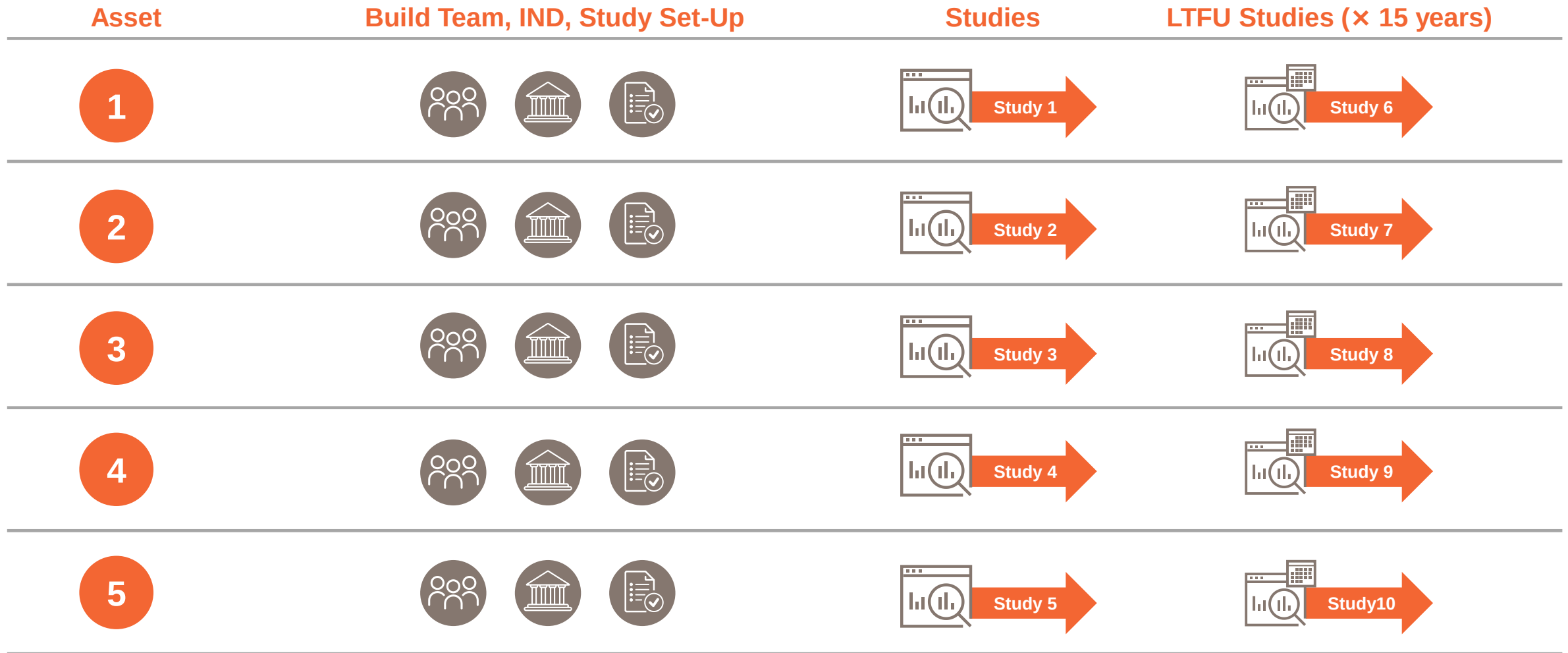
Regulatory



Patient Focus

- 
- 
- Acceptability of design and endpoints
 - Acceptability of single arm studies vs need for RCT
 - Companion Diagnostic Development
 - 'Sameness' and Indication extrapolation
 - Safety Reporting ('related' constructs)
 - Master Protocols
 - Parent-Child IND

Traditional Approach: 5 Teams, 5 INDs, Executing 10 studies



Parent-Child IND Concept From Friends of Cancer Research



Peter Marks (FDA)



Ellen Sigal (FOCR)



Parent-Child Development Strategy

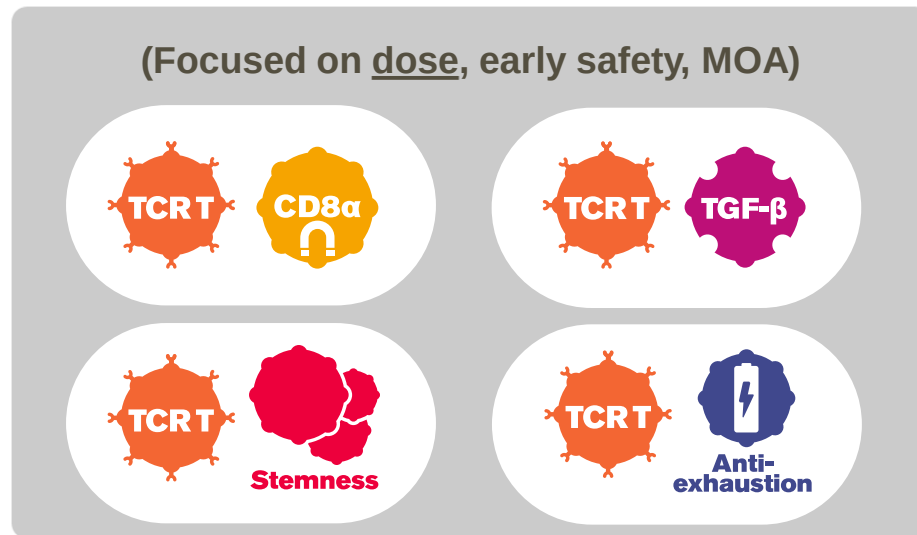
Two Master Protocols + One LTFU Study



Enabling faster, parallel development of multiple technologies in a cost- and resource-efficient way

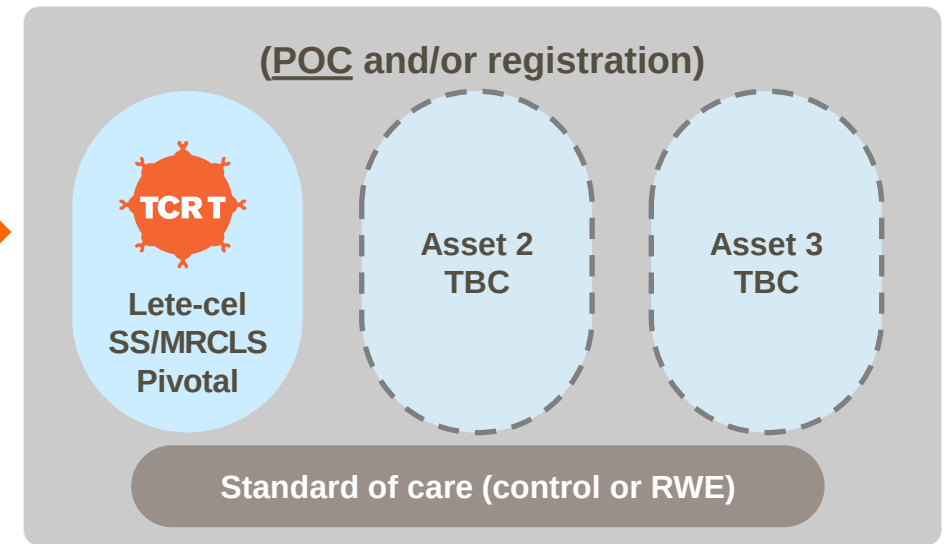


FTIH Master Protocol



Significant efficacy

Definitive Data Master Protocol

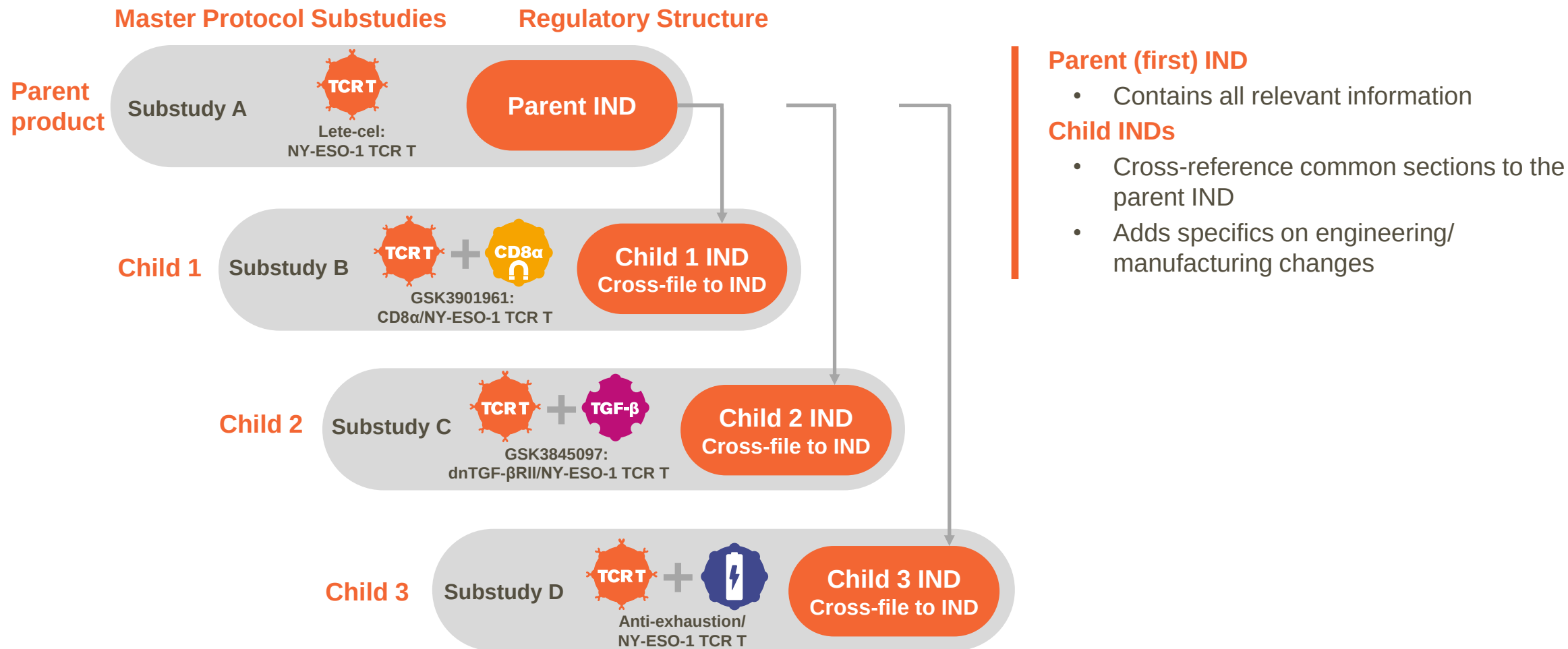


Long-Term Follow-Up Study
Amended to include all NY-ESO-1 agents
15-year safety monitoring for CGT

Parent-Child IND: An Efficient Development Paradigm for CGT



Parallel Examination of Multiple Assets in a Single Master Protocol With Cross-Referenced INDs



Clinical Trials with Cell Therapies....Requires New Ways of Working



Close Integration and Collaboration, Efficient Study Design & Operations, Adaptability

