Taking CAR T Cells From First-in-man Trials To Marketing Authorisation – The View From A Pharmaceutical Developer

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Disclaimer

- The views and opinions expressed in this presentation and discussion are not necessarily the views of Celgene Corporation, its corporate partners, or that of Columbia University.

Design Characteristics To Define A Pharmaceutical Product Profile

- Target
- Mechanism of Action
- Pharmaceutical properties
  - Specificity
  - Potency/Affinity
- Dose selection
  - Starting dose
  - Optimal/Maximal tolerable dose
- Schedule/Duration
- Risk benefit profile
  - Clinical activity in a defined population
  - Adverse events
- Regulatory comparators for unmet medical need
- Commercial competition and potential differentiation

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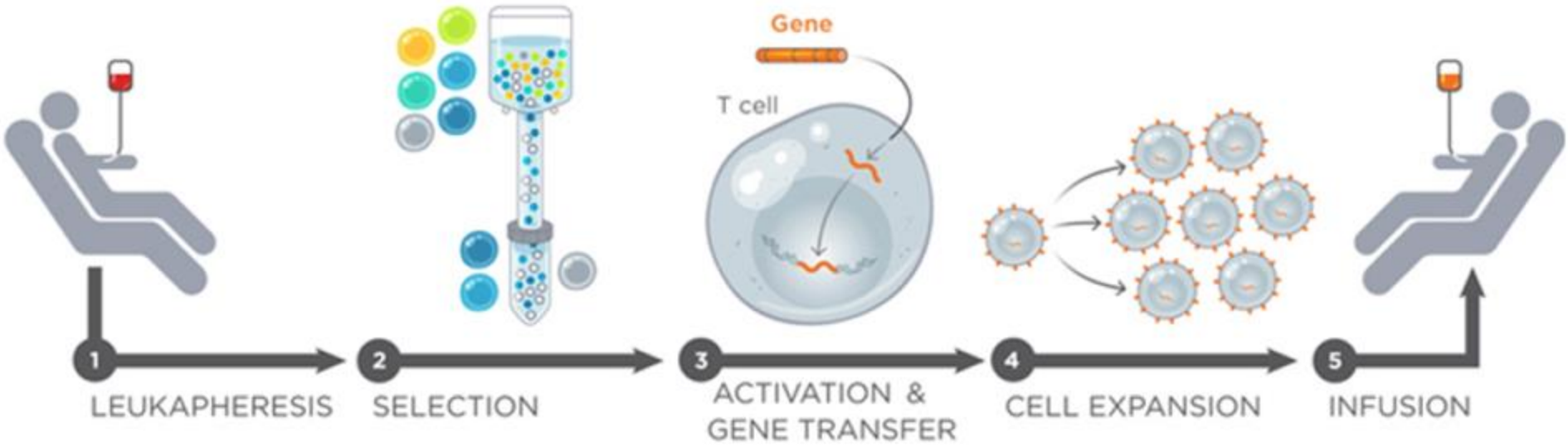
- Chimeric Antigen Receptor modified autologous T cells directed against CD19 have the potential to provide cure.
- The curative potential of CD19 directed CAR T cells is balanced by considerable safety risks that continue to be defined and addressed.
- The substantial clinical activity and considerable safety risks provided by CD19 directed CAR T cells and rapid advances in clinical development by multiple sponsors challenge the regulatory status quo.
- Despite some convergence in observed biology, each construct, manufacturing process, clinical protocol, disease state are different
- Rapid scientific advances in altering the design and composition of CAR T therapies pose substantial regulatory and development challenges
- Iterative improvements in CAR T design, manufacturing, and therapeutic management are anticipated but the regulatory path to allow for innovation may require legislative changes

CD19 CART Products JCAR015 and JCAR017 Manufacturing Process Flow

Multiple, complex variables for CMC complicate development



PBMCs obtained from patient via standard leukapheresis collection

T cells isolated,

JCAR015: CD4+/CD8+ together

JCAR017: CD4+ & CD8+ separately

T cells activated, and transduced with viral vector

JCAR015: CAR gene via gammaretrovirus

JCAR017: CAR/EGFRt genes via lentivirus

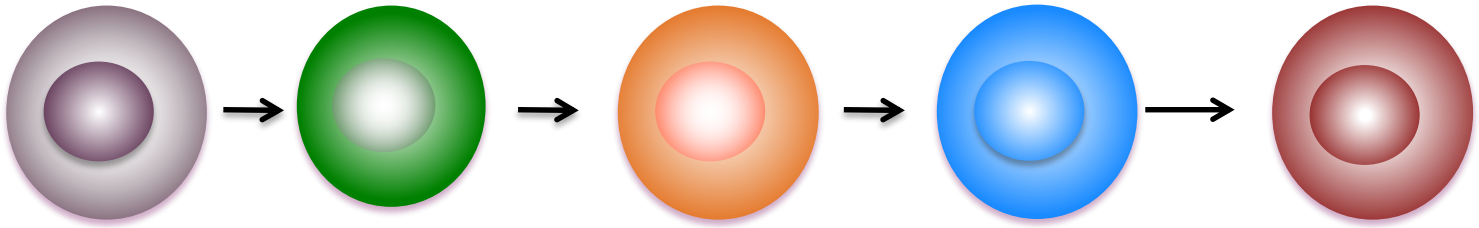
CAR T cells expanded and conditioned to therapeutic dose, formulated and cryopreserved

QC/QA release

CAR T cells infused into patient after lymphodepleting chemotherapy

Defined Composition for Improved Potency Activity of T cells in Mice with Human Lymphoma Xenografts

CD8 and CD4 T Cell Subsets



Naïve T cell
(CD45RA+CD62L+, CD28+CD95-)

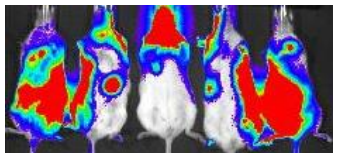
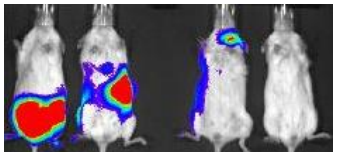
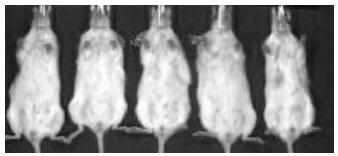
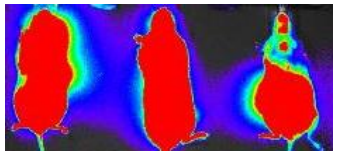
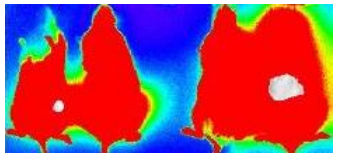
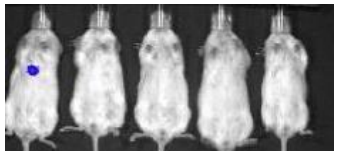
Memory Stem Cell
(CD45RA+CD62L+ CD28+,CD95+)

Central Memory (T_{CM})
(CD45RO+CD62L+ CD28+, CD95+)

Effector Memory (T_{EM})
(CD45RO+CD62L-,CD28+/- CD95+)

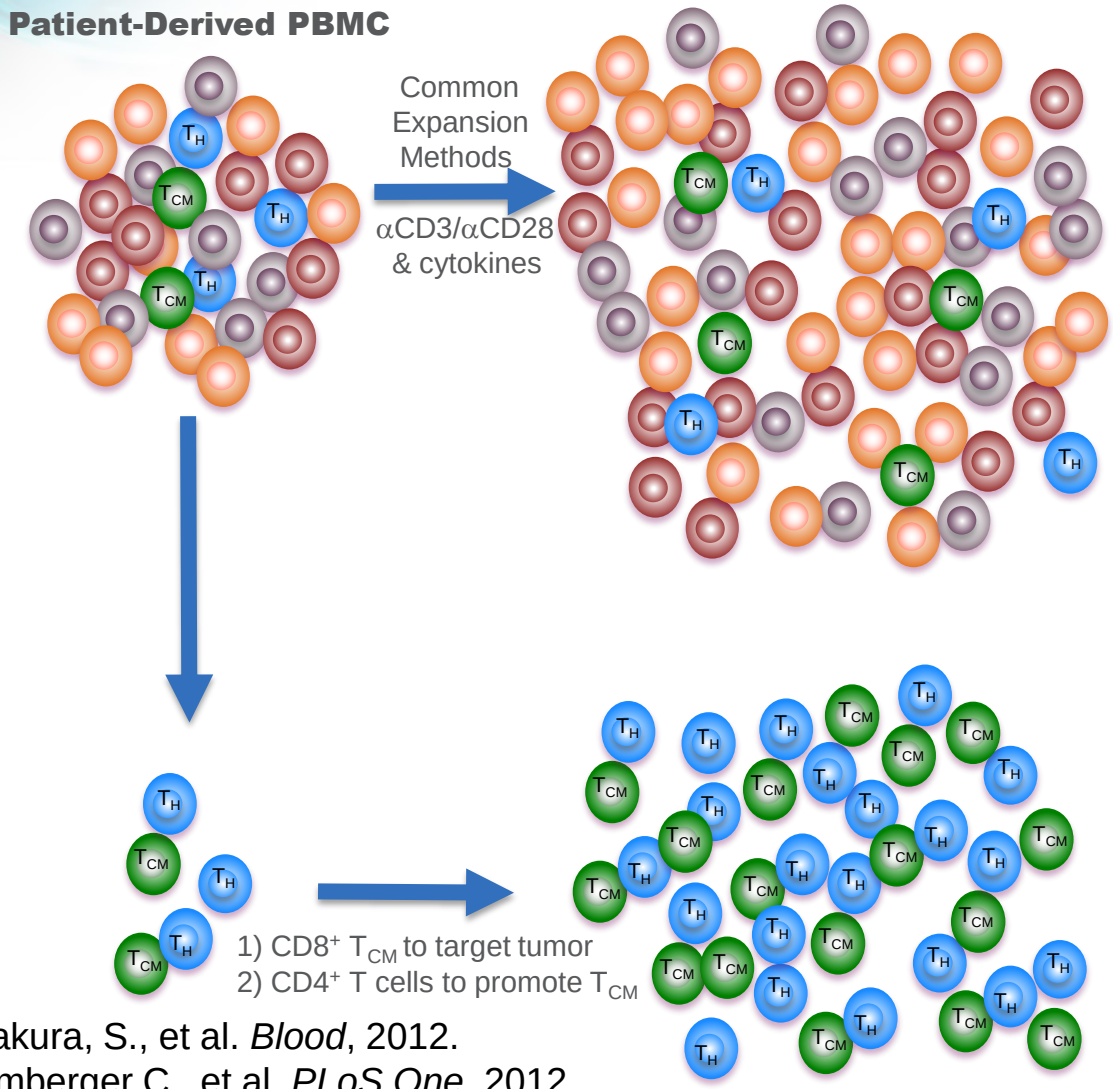
Effector T cells (T_E)
(CD45RO+, CD62L-, CD28-. Perforin^{hi,} Granzyme^{hi})

CAR-T cell dose $1x10^6$

Day	PBMC	$CD8_{CM}$	$CD8_{CM}$/CD4 (Defined Ratio)
26			
47			

Sommermeyer, D., et al. *Leukemia*, 2016.

Optimizing T cell composition
The right T cell populations matter



JCAR014/JCAR015/JCAR017

Provides:

- Defined cell products
- Higher % CAR T cells
- Permits lower cell doses
- May improve efficacy
- May have lower toxicity

Terakura, S., et al. *Blood*, 2012.
Stemberger C., et al. *PLoS One*, 2012.
Sommermeyer, D., et al. *Leukemia*, 2016

Efficacy and Safety Data
Available Academic Data in R/R ALL

Product Candidate	JCAR014	JCAR015	JCAR017
Trial	r/r Adult ALL N = 36 Evaluable = **34 (1)**	r/r Adult ALL N = 51 Response Evaluable = 50 Toxicity Evaluable = 51 (2)	r/r Pediatric ALL N = 37 Evaluable = 33 (3)
Complete Response / Remission	**100%**	**82%**	**91%**
Complete Molecular Remission	**94%**	**67%**	**91%**
Severe Cytokine Release Syndrome	**21%**	**28%**	**27%**
Severe Neurotoxicity	**26%**	**29%**	**18%**

(1) Turtle, Abstract 102, ASCO 2016; (2) Park, Abstract 7003, ASCO 2016; (3) Gardner, Abstract 3048, ASCO 2016

Median follow-up: 6 months (1-45 months)
Cumulative follow-up: 20/45 (44%) patients with ≥ 6 months of follow up
9/45 (20%) patients with ≥ 1 year of follow up

Cytokine Release Syndrome & Neurological Toxicities By Baseline Disease Burden: MSKCC R/R Adult ALL

	Morphologic Disease (N=31)	Minimal Disease (N=20)
Severe CRS	13 (42%)	1 (5%)
Grade 3/4 Neuro Toxicities	11 (35%)	4 (20%)
Severe CRS *&* Gr 3/4 Neuro Tox	7 (23%)	1 (5%)
Severe CRS *or* Gr 3/4 Neuro Tox	17 (55%)	4 (20%)
Grade 5 Toxicity	4 (13%)¶	
Management Treated with Tocilizumab Treated with Steroids Treated with Toci & Steroids	 12 (39%) 11 (35%) 10 (32%)	 0 (0%) 1 (5%) 0 (0%)

¶ All pts received a higher dose ($3x10^6$ CAR T cells/kg): 2 pts with sepsis/multi-organ failure; 1 pt had seizure, but unknown cause of death

- Use of Tocilizumab and/or Steroids had no impact on RFS or OS.

Park et al, ASCO 2016: 7003

MSKCC Adult R/R B-lineage ALL Study Outcome: Complete Remission (CR) rates

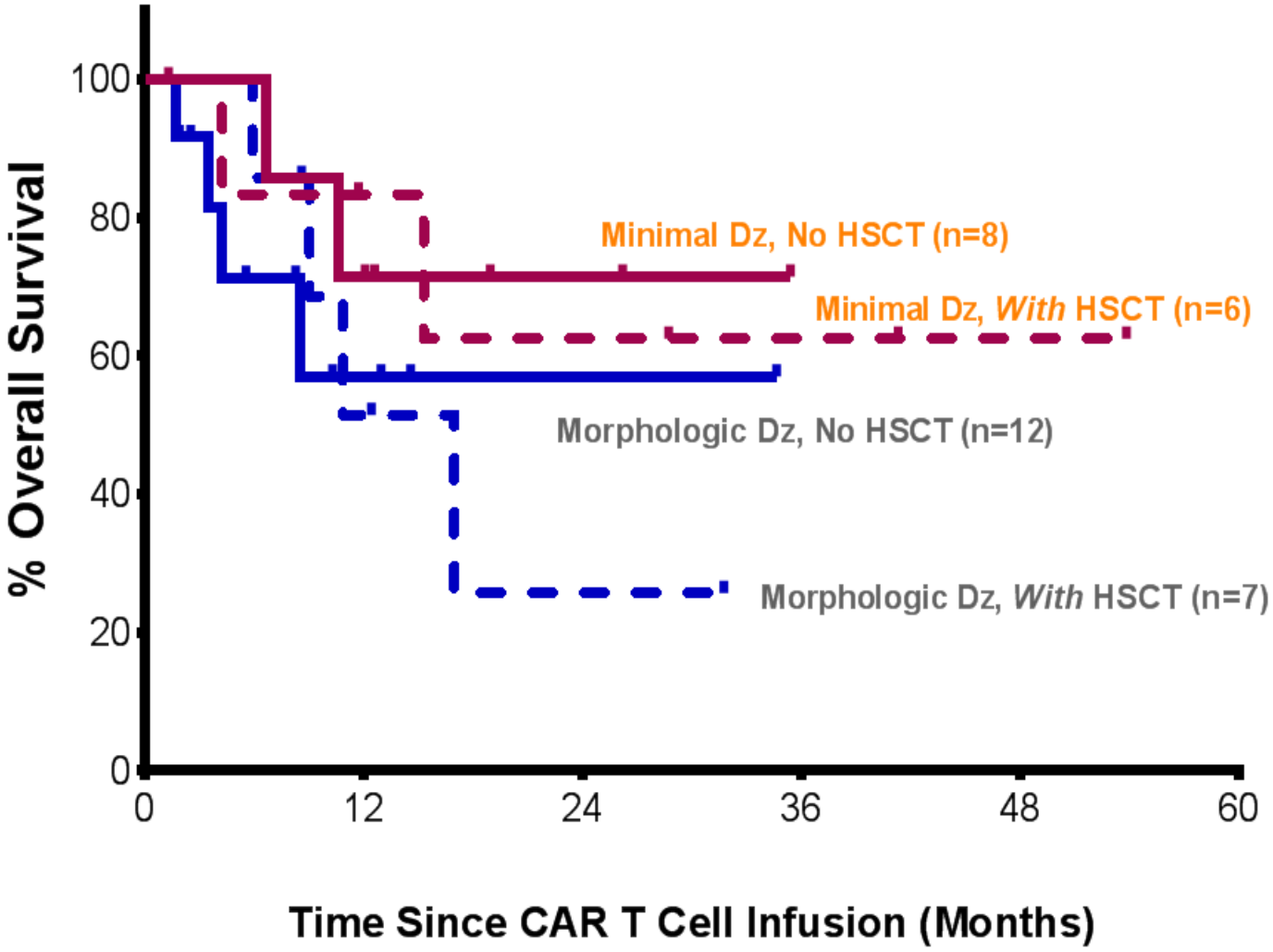
	Morphologic Disease N=30 (%)	**Minimal Disease N=20 (%)**
CR Rate	23 (77%) [58 – 90]	18 (90%) [68 – 99]
MRD negative CR Rate*	19/21 (90%) [70 – 99]	14/18 (78%) [52 – 94]
Time to CR, Mean (SD)	20 days (9)	25 days (9)

*MRD assessment was not available in 2 patients.

After toxicity observed at 3 x 10^6 CAR T cells/kg; patients with morphologic disease dosed at 1 x 10^6 CAR T cells/kg; Minimal Disease patients remain dosed at 3 x 10^6 CAR T cells/kg
Dose:toxicity relationship with disease burden as a variable demonstrated

Park et al, ASCO 2016: 7003

Overall Survival by baseline disease burden: MRD-CR patients by post CAR-T HSCT



Park et al, ASCO 2016: 7003

No Dose: Toxicity Relationship Observed CTL019 in CLL

Response	*High Dose*	*Low Dose*	Total
CRS*	6 (55%)	7 (54%)	13 (54%)
No CRS	5 (45%)	6 (46%)	11 (46%)
Total	11	13	24 (p=1.0)

Presented By David Porter at 2016 ASCO Annual Meeting; Abstract 3009

No Dose:Response Relationship Observed? CTL019 in CLL

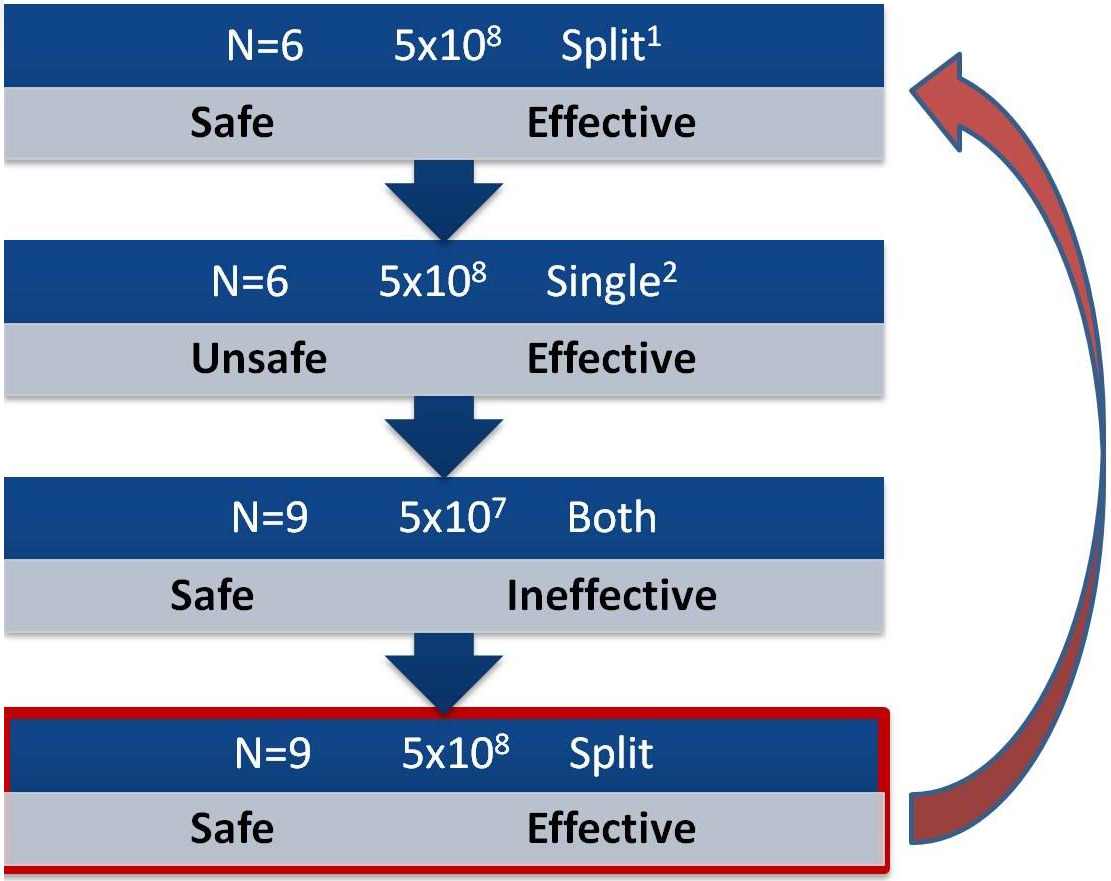
Response*	*High Dose*	*Low Dose*	Total
CR/PR	6 (54%)	4 (31%)	10 (42%)
No response	5 (46%)	9 (69%)	14 (58%)
Total	11	13	24 (p=0.41)

ASCO 2016

UNIVERSITY OF PENNSYLVANIA Abramson Cancer Center

Presented By David Porter at 2016 ASCO Annual Meeting

Dose:Response and Dose:Toxicity in Adult ALL CTL019



Split Dosing[1]
Day1: 10%
Day2*: 30%
Day3*: 60%
*Doses held for early signs of CRS
Single Dosing[2]
Day1: 100% Dose

Perelman School of Medicine University of Pennsylvania

Presented By Noelle Frey at 2016 ASCO Annual Meeting; Abstract 7002

4192 Transcend NHL 001: Immunotherapy with the CD19-Directed CAR T-Cell Product JCAR017 Results in High Complete Response Rates in Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma

Jeremy S. Abramson, MD[1], Lia Palomba, MD[2], Leo I Gordon, MD[3], Matthew Lunning, DO[4], Jon Arnason, MD[5], Andres Forero-Torres, MD[6], Tina M. Albertson, MD, PhD[7], Victoria Shaw Exton[7], Claire Sutherland, PhD[7*], Benhuai Xie, PhD[7*], Susan Snodgrass, MD[7] and Tanya Siddiqi,*

- No minimum absolute lymphocyte count (ALC) requirement for apheresis and no test expansion required.
- Lymphodepletion (fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 daily for 3 days) and JCAR017 given 2-7 days post-lymphodepletion at a starting dose of 5 x 10^7 CAR$^+$ T cells (DL1).
- Single-dose and two-dose schedules are being evaluated.
- 13 patients treated with JCAR017 with relapsed/refractory diffuse large B-cell lymphoma,
- 2 or 14% experienced severe neurotoxicity both of which resolved
- No patients experienced severe cytokine release syndrome.
- In 11 patients available for efficacy, the overall response rate was 82% with a complete response rate of 73%.

(ClinicalTrials.gov Identifier: NCT02631044) ASH Presentation December 5, 2016

Development Parameters To Be Defined
Unique Challenges of Individual Living Cellular Products

Manufacturing Steps Are Complex

- Cell Yield
- Viability
- Cell Selection
- Activation
- Transduction
- Expansion
- Process qualification
- Formulation/fill/cryopreservation
- Control of Materials:
  - Raw materials
  - Consumables
  - Biologic raw materials
  - Media/buffers/Virus

How Are Autologous CAR T Cells Different From Other Pharmaceutical Products?

- This is an individual product
- Manufacturing takes time; Release of product takes time
- This is a living drug; dose infused is a starting point
  - Expansion and durability may not be fully proportional to infused dose
  - Limited dosing expected (1-2 doses for potential cure)
  - In vivo rate, peak, and persistent expansion likely more important that infused dose
- Variability rather than consistency in biological behavior following infused dose is anticipated
- Management of adverse events by corticosteroids may alter PK of CAR T cells
- Rapidity and extent of CAR T cell expansion may be related to accessible target and tumor burden
- Long term follow up and monitoring are required due to safety concerns related to viral transduction
- Manufacturing costs are high; potential impact of manufacturing errors/failure is extremely high

Potential Explanations For Therapeutic Failure

- Infused cell dose too low
- Viability of cells too low
- Insufficient in vivo expansion
  - Physiologic milieu at time of infusion not sufficiently hospitable for expansion or durability (lymphodepletion)
  - Target is not accessible
  - Target is absent (antigen escape)
  - Anti CAR T immune response (B or T cell mediated)
  - Blunting of T-cell activity by tumor microenvironment, e.g. immune checkpoint activation

Points of Control or Divergence

- Apheresis material
  - Challenges of a smaller blood volume for pediatric patients
- Processing of material: PBMC or T cell Selection
  - Undefined or defined cell ratio CD4:CD8
- Transduction method
  - Gamma retrovirus
  - Lentivirus
  - Transposons
  - Variable frequency and insertion sites
- Murine or human binders
- Costimulation
  - CD28
  - 4-1BB
  - Dual
  - Side CARs
- Single or multiple antigen recognition

Root Cause Analysis of Variable Toxicity and Efficacy

- Costimulatory domain
- Starting Material
- Viability
- Quality

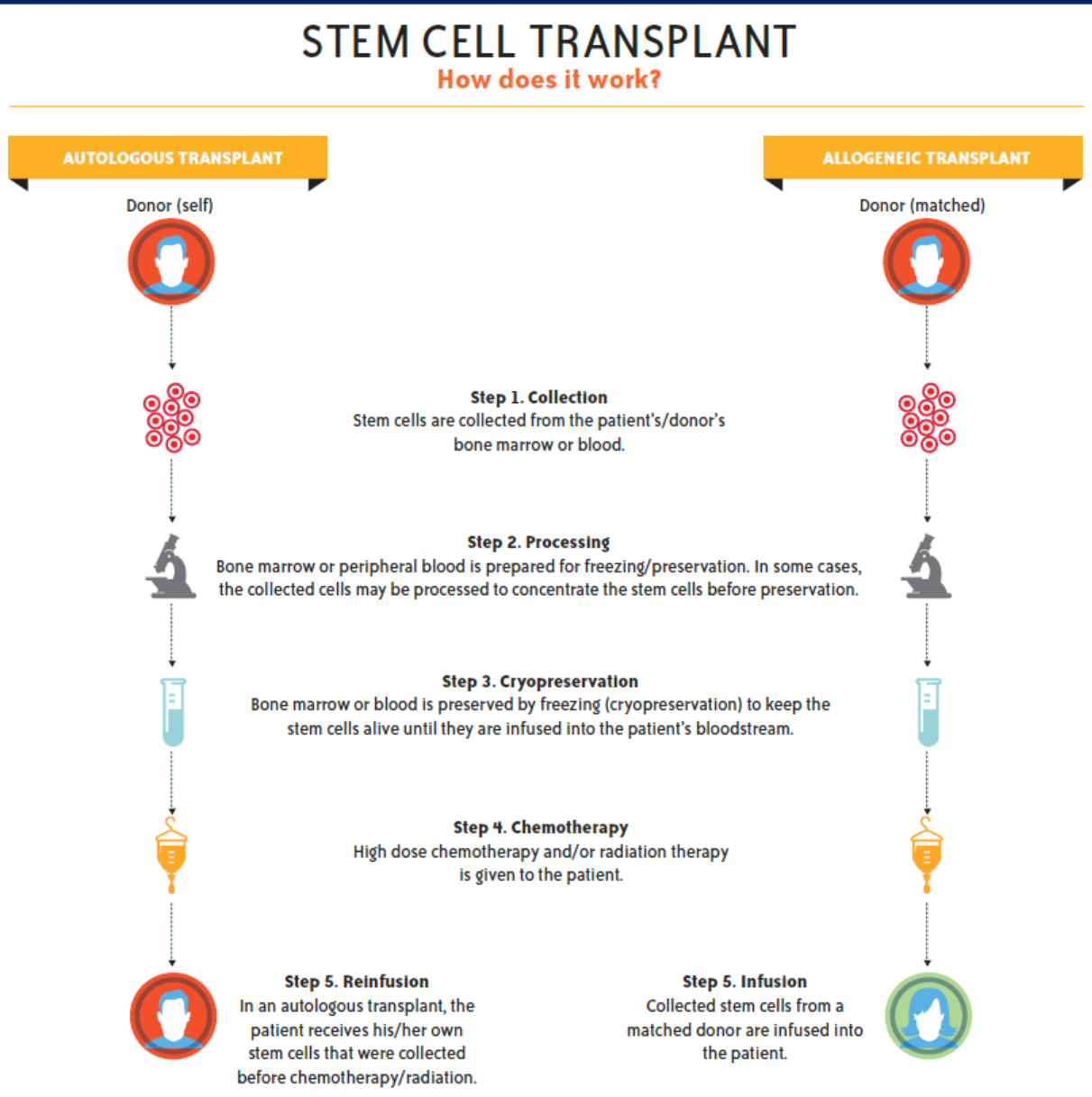
- Cell Dose
- Dose Fraction
- Lymphodepletion

- Disease Burden
- Target accessibility
- Age
- Biologic variables

Complexity of Multiple Parallel National and Local Review Processes Raises Costs

- Individual country GMO rules, sometimes at the local level as well as the state or national level, pose a barrier to rapid start of clinical trials in Europe
- Voluntary Harmonisation Procedure has not been successfully adapted to handle the different local and national standards

Hematopoietic Stem Cell Transplant Is the Comparable Clinically Relevant Technology for CAR T Cell Therapy



HSCT Has Not Been Regulated as a Drug

- Academically driven development without centralized manufacturing
- Evolved to “best curative option” for many hematologic cancers including relapsed/refractory adult acute lymphoblastic leukemia
- Standard of care in physiologically and economically capable patients for relapsed aggressive large B cell Non-Hodgkin’s lymphoma
- Lack of standardization across centers or across treatment protocols over decades
- Multiple variables in clinical protocols/clinical treatment

Is Allogeneic Stem Cell Transplant an Approvable Drug Product?

- Donor variability and type
  - Identical twin
  - HLA matched sibling
  - Haploidentical family donor
  - Matched unrelated donor; variable degrees of HLA mismatch
  - Umbilical cord blood
  - Bone marrow or peripheral blood stem cells
- Cell number from starting material with wide variability in dose
- Processing of product non-standardized
  - Unmanipulated
  - T cell depleted
- Variable patient diagnosis and prior treatments
- Variable cytoreductive and lymphodepletion conditioning regimens
- Variable graft vs host disease prophylaxis
- Variable supportive care and infection prophylaxis

Would allogeneic HSCT have advanced to its current status if subjected to drug regulations?

Are CD19 directed CAR T cells Superior to Allogeneic Stem Cell Transplant in in Acute Lymphoblastic Leukemia ?

- How optimized should the CD19 CART product be before such a study is conducted?
- How will the “transplant” be standardized as the control arm?
- How many products could be tested in such a design?

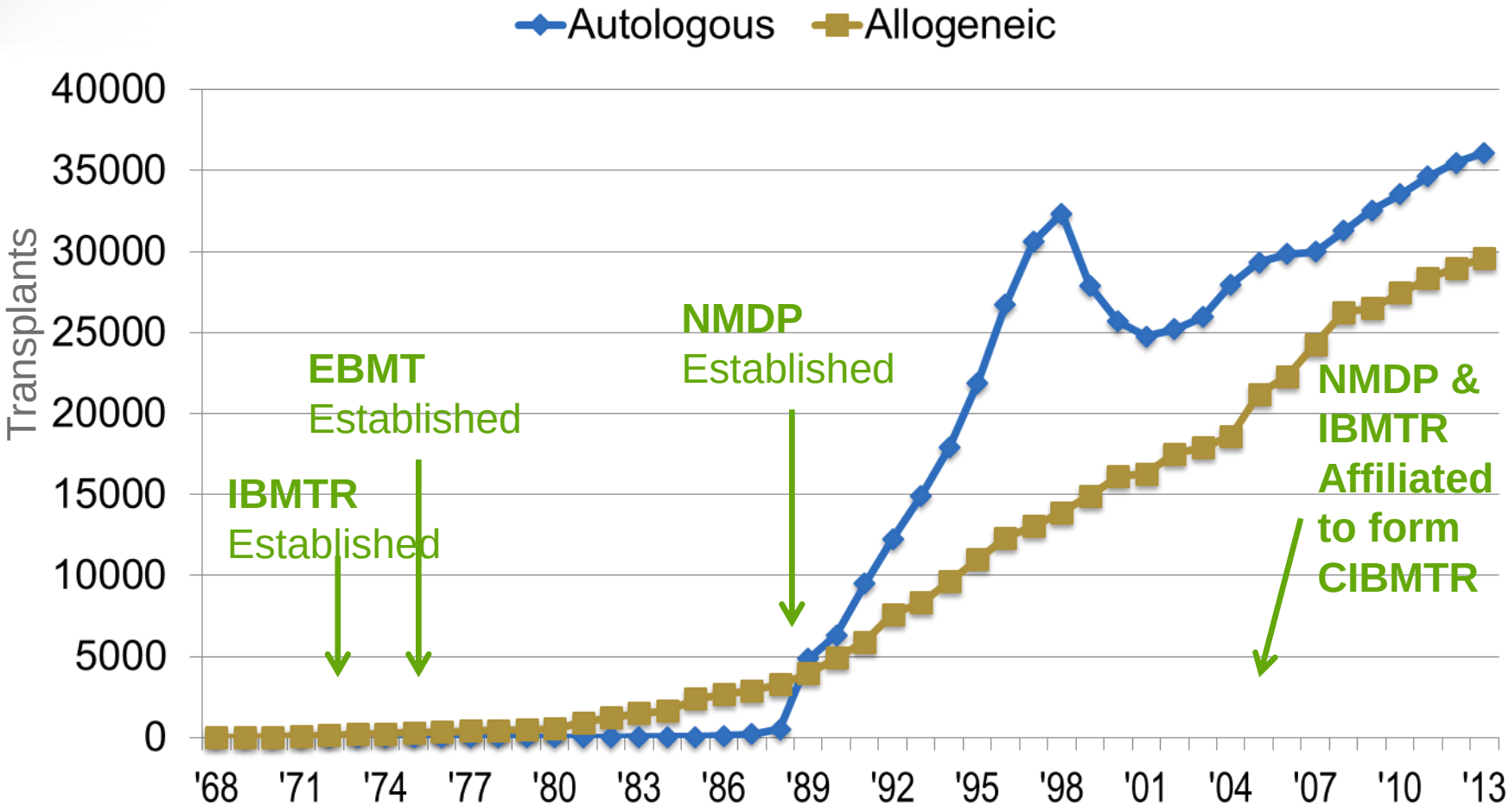
How Should Registry Data Be Captured And Analyzed By Regulatory Authorities?

- Due to the use of viral vectors, long term safety monitoring required for clinical trial administered product as well as commercial product
- Can ongoing registry data be used to support “full approval” without a prospective randomized trial?
- Can EMA work with Sponsors, EBMT, CIBMTR, FDA to define a uniform data set and format to optimize this process?
- Can Registry and real world data provide another route to assess relative risk/benefit and value of CAR T therapies compared to each other and to other available therapies?

CIBMTR Has Established HSCT Data Collection and Sharing

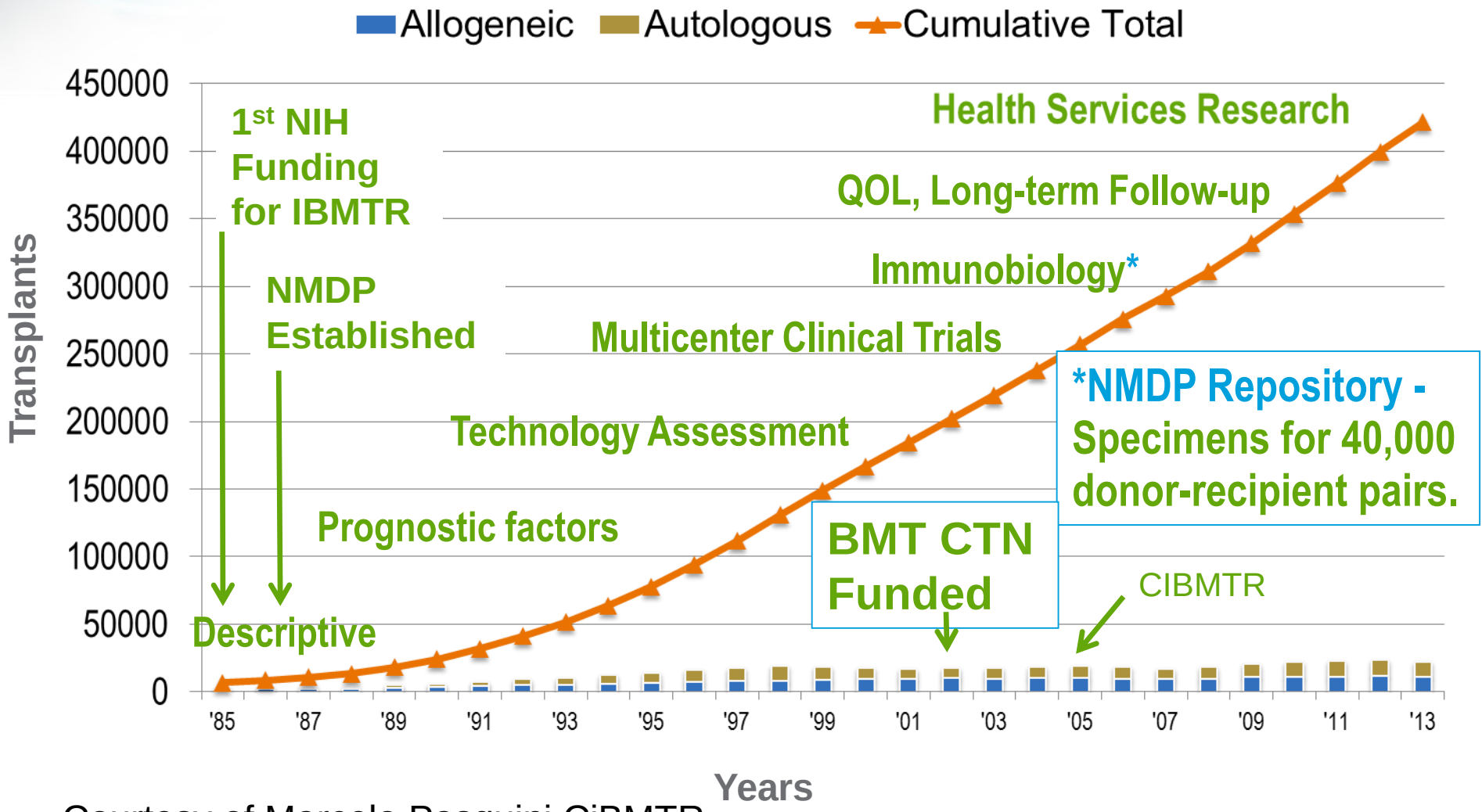
National: US, Japan, Germany, France, etc – 1980s-90s

International: 1990s-2000s



Courtesy of Marcelo Pasquini CiBMTR

CIBMTR 420,000 Cases Registered, up to ~10,000 variables per person (most with repeated observations, some extending over >30 years), >1000 publications



Courtesy of Marcelo Pasquini CiBMTR

Cellular Therapy Registry Issues

- Ability to capture all patients of interest
- Ability to capture all data of interest - no matter where it is generated
- Ensuring data quality
- Maintaining long-term follow-up
- Ensuring confidentiality, security and regulatory compliance
- Making data rapidly available for multiple uses/users
- Cost-effectiveness
- International regulatory agreement on needed standards and ability to use data to satisfy pharmacovigilance requirements and to form “comparator” for further regulatory filings

Courtesy of Marcelo Pasquini CiBMTR

Innovation, Academic Freedom, and Commercial Interest

- Is the HSCT academic model a preferred route to develop and provide CAR T therapy?
- What consistency standards are needed?
- What regulatory standards apply to device use for production and subsequent treatment at the hospital level?
  - Lower volume of product generation
  - Less scalable QC/QA
- Will regulatory burden and commercial cost result in medical tourism to less regulated, lower cost options?

Local Designed CAR T Products Will Be Available

Cytotherapy, 2016; 18: 1002–1011

International Society for Cellular Therapy
ISCT®

CrossMark

Automated manufacturing of chimeric antigen receptor T cells for adoptive immunotherapy using CliniMACS Prodigy

ULRIKE MOCK[1,*], LAUREN NICKOLAY[1,*], BRIAN PHILIP[2], GORDON WENG-KIT CHEUNG[2], HONG ZHAN[1], IAN C.D. JOHNSTON[3], ANDREW D. KAISER[3], KARL PEGGS[2], MARTIN PULE[2], ADRIAN J. THRASHER[1] & WASEEM QASIM[1]

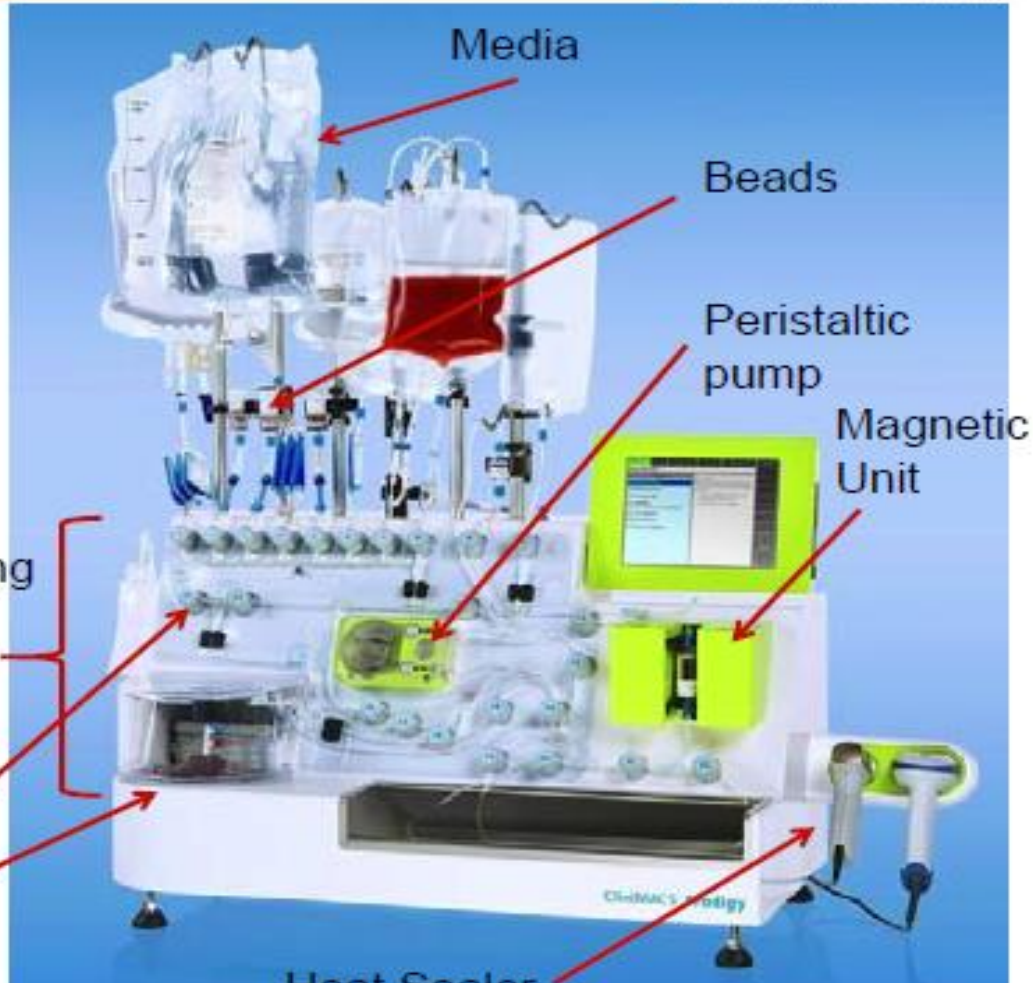
[1]Institute of Child Health, Molecular and Cellular Immunology Unit, University College London, London, UK, [2]University College London Cancer Institute, London, UK, and [3]Research & Development, Miltenyi Biotec GmbH, Bergisch Gladbach, Germany

Hospital Level GMP Cell Manufacturing Systems and Reagents Are Being Marketed

CliniMACS® Prodigy – Automated Cell Processing System for GMP Cell Manufacturing

Lentigen
a Miltenyi Biotec Company

- Integrated cell processing from starting material to final cellular product:
  - -Sample preparation
  - -Cell washing & density gradient separation
  - -MACS cell separation (CD4+8, CD62L)
  - -Cell activation (TransAct reagent)
  - -Genetic modification(LTI, LV)
  - -Cell culture
  - -Final product formulation
- Enabling complex processes
  - -Automated & controlled system
  - -Closed single-use tubing set



Potential Improvements to CAR T Products

- Fully human binders
- Multiple antigen specificity
- Tunable control modules
- Increased cytotoxic/metabolic activity and persistence
- Immune enhancements
- Allogeneic products

If each modification in design and manufacturing defines a new product, how will we improve, innovate and approve these new products?

What Is The Regulatory Path For "Improved" CAR T Products In The Near Future?

- Initial product approvals will occur within 2-3 years
- For a given manufacturer, how can process changes be implemented?
  - What is the "bridging" standard?
- Once "full approval" granted, will randomized trials be required for each successive product against the "approved" drug?
- How will commercial developers purchase/afford "the comparator product"?
- How will the concept of "similar active substance" in the context of the EU orphan legislation will be assessed for CAR T cell products?
- What are the clinical differentiators between CAR T cell products to demonstrate "clinical superiority"?