Forum on Regenerative Medicine

An Academic Manufacturing Center's Perspective on "Decentralized" Manufacturing

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Dana-Farber Cancer Institute

Disclosures

Ad Hoc Advisory Boards for A2 Bio, Glaxo Smith Kline, Iovance, Legend Biotech, Kite/Gilead, SmartImmune, and Sobi

Overview

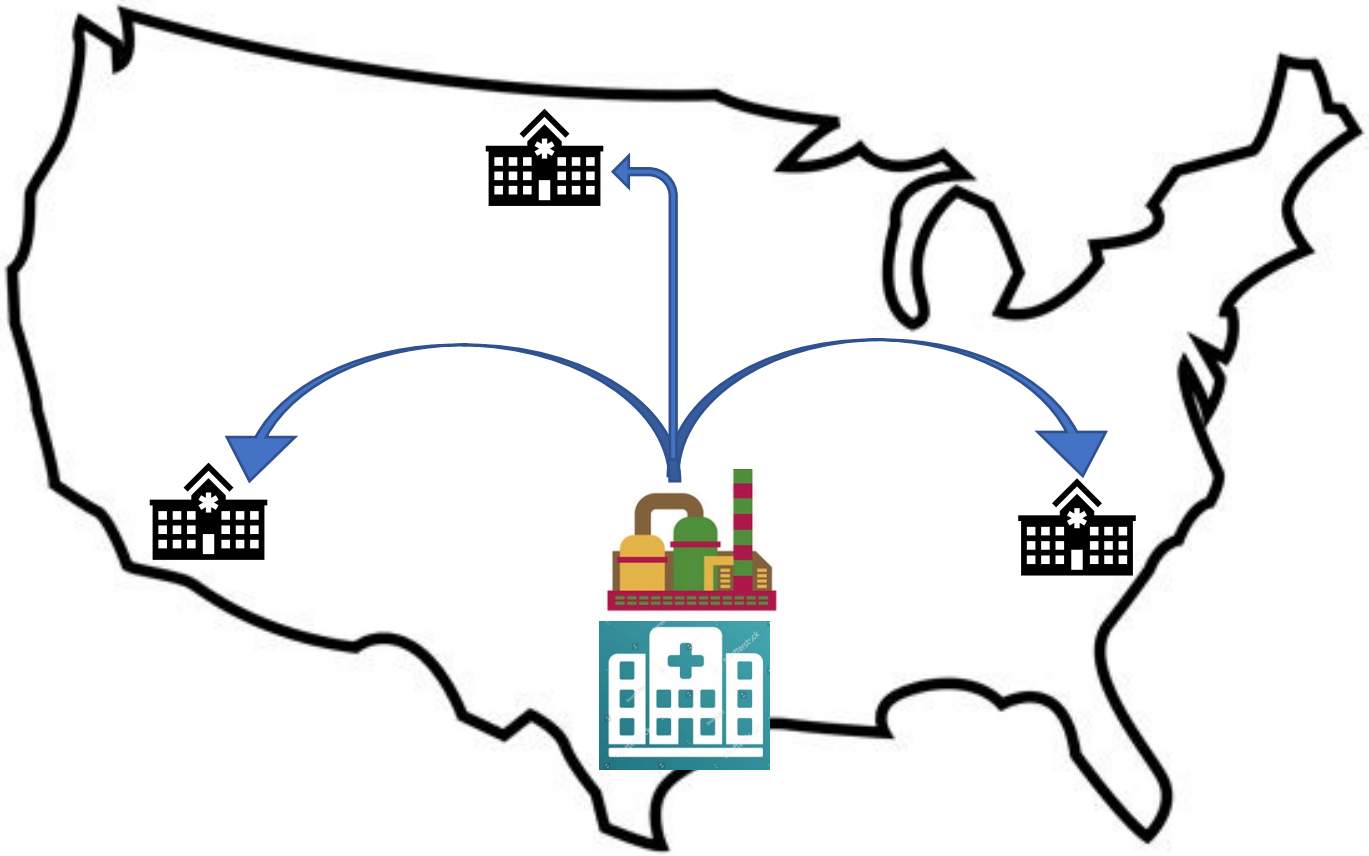
- Nomenclature and DFCI Cell Manufacturing Facility Perspective
- Status to date – US and globally
- Pros/Cons and Requirements
- What is our actual goal?

  Rapid access to cheap anti-CD19 CARs for all pt with NHL

  vs

  Create infrastructure for academic Phase 1 ideas/products to have a future outside of purchase by pharma

Centralized ***

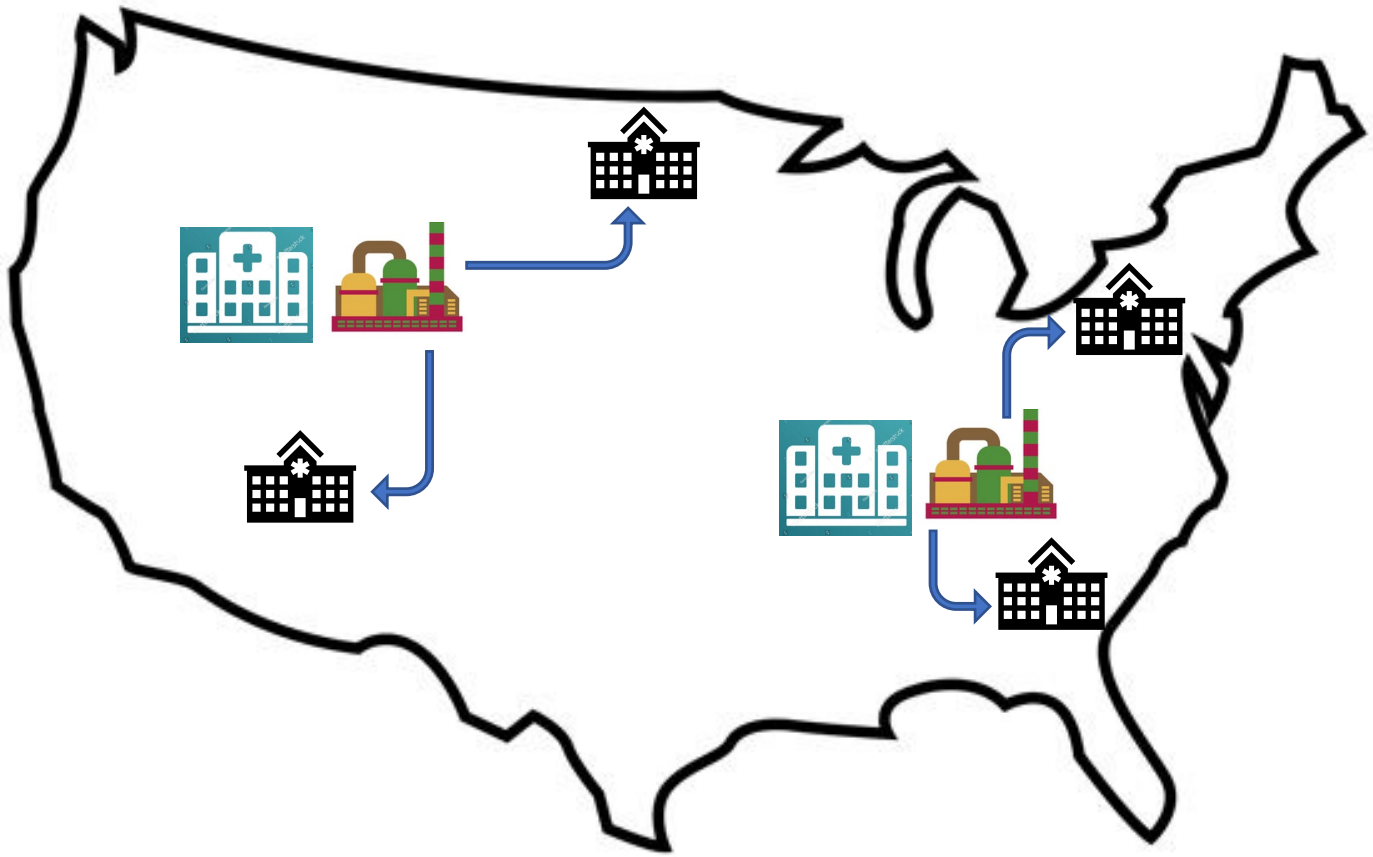


Examples of nomenclature

Adapted from Dr. Kimberly Schultz's Presentation at ISCT NAm Houston, Sept 2023
Office of Gene Therapy, CBER/FDA

! NOT official FDA-approved terminology !

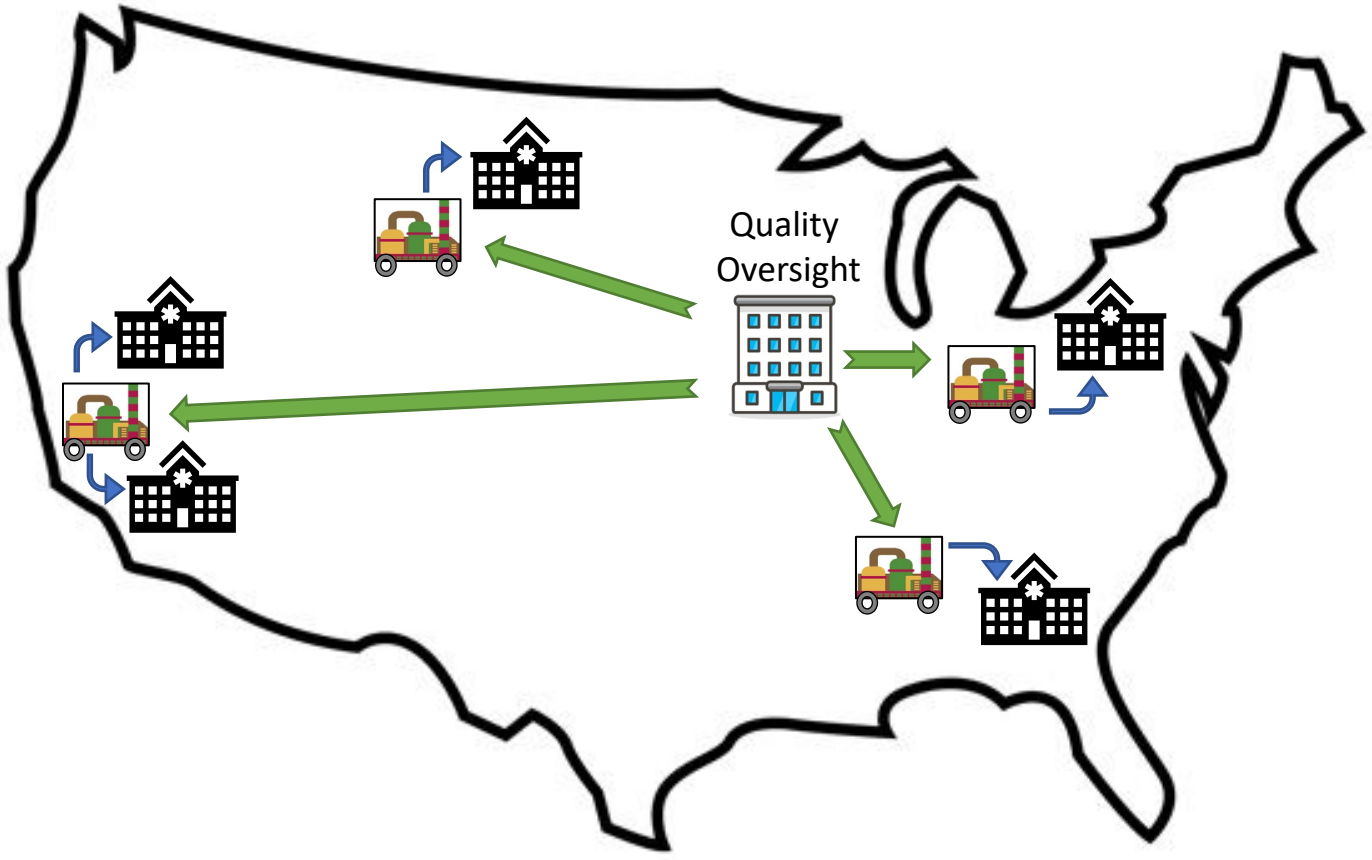
Decentralized *** – several regional facilities



e.g., Pediatric Consortia – Gene Therapy Trials or VST network

Similar Comparability Issues Encountered when tech transferring from academic facility Phase 1 to CMO Phase 2 registration study

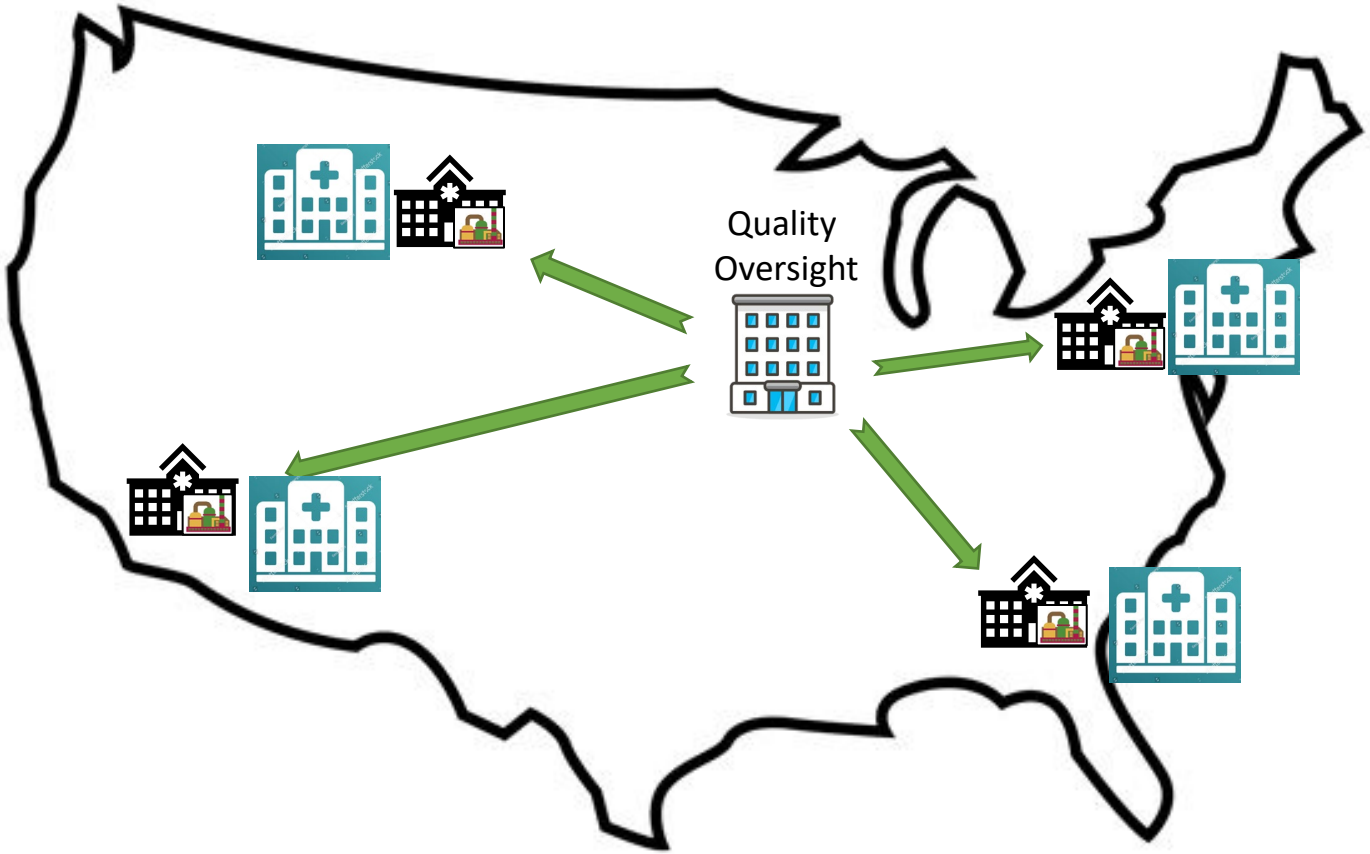
Distributed – deployed manufacturing units



- **Regulatory Framework**
- **Quality oversight plan**
- **Comparability of methodology**
- **Location/ comparability of QC testing**

e.g., Pediatric VST network

Point of Care – potentially nonGMP



U.S. FOOD & DRUG ADMINISTRATION

Stakeholder Feedback on Distributed and Point-of-Care Manufacturing Discussion Paper

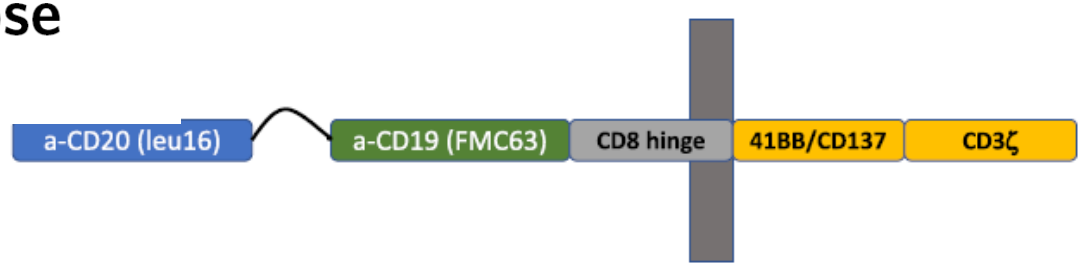
Highlights from Public Docket (FDA-2022-N-2316)

https://www.regulations.gov/document/FDA-2022-N-2316-0001

nature medicine
LETTERS
https://doi.org/10.1038/s41591-020-1081-3
Check for updates

Shah NN. Nature Medicine 2020

Bispecific anti-CD20, anti-CD19 CAR T cells for relapsed B cell malignancies: a phase 1 dose escalation and expansion trial



- Initial trial results led to development of multi-center Phase II
  - As LV20.19 was not an approved construct, FDA guidance was to perform a centralized manufacturing-based trial FIRST, and then re-visit a trial with individual site manufactured CAR T-cells
  - Ongoing Phase II, multicenter study with CENTRALIZED manufacturing ongoing with LV20.19 construct
  - Pending above results, possibility for a de-centralized program of LV20.19 with POC manufacturing

Global Accessibility/Scalability

- Spain: POC development of ARI-0001
  - Spain: Developed ARI-0001, a unique CD19 targeting CAR T-cell with 41BB/CD3zeta costimulatory domain
  - CAR-T cells produced via Miltenyi Prodigy CliniMACS
  - Price of this product is 1/3 the commercial product and is treated as a "publicly owned CAR-T"
  - Received approval for administration for adult ALL patients >25 years with Hospital Exemption pathway

- YESCARTA vs ARI-0001 CD19 CAR-T cells
  - Multicenter trial in the Netherlands: NCT05641428
  - 300 patients, non-inferiority trial
  - FRESH infusion, 12-day manufacturing process, all manufacturing of ARI-0001 at academic sites in a point of care fashion versus YESCARTA

Global Accessibility/Scalability

- Russia: POC, anti-CD19 CAR-T for pediatric ALL
  - 31 patients treated, MRD negative CR rate was 89%
  - Comparative analysis done with Cleveland Clinic who was utilizing identical vector for B-cell NHL
  - Manufacturing outcomes were similar across continents
  - Preclinical models demonstrated cryopreserved CAR-T cells were less efficient killers
- Israel: Point of Care anti-CD19 CAR-T for R/R aggressive B-cell Lymphoma
  - 73 patients treated, median age 49 years
  - FRESH leukapheresis/FRESH Infusion, manufactured using G-Rex
  - 12 month PFS was 52.1%

Maschan et al. Nature Communications 2021
Kedmi et al. TCT 2022

Miltenyi Biotec

Number of cell manufacturing sites in academic settings with CliniMACS Prodigy

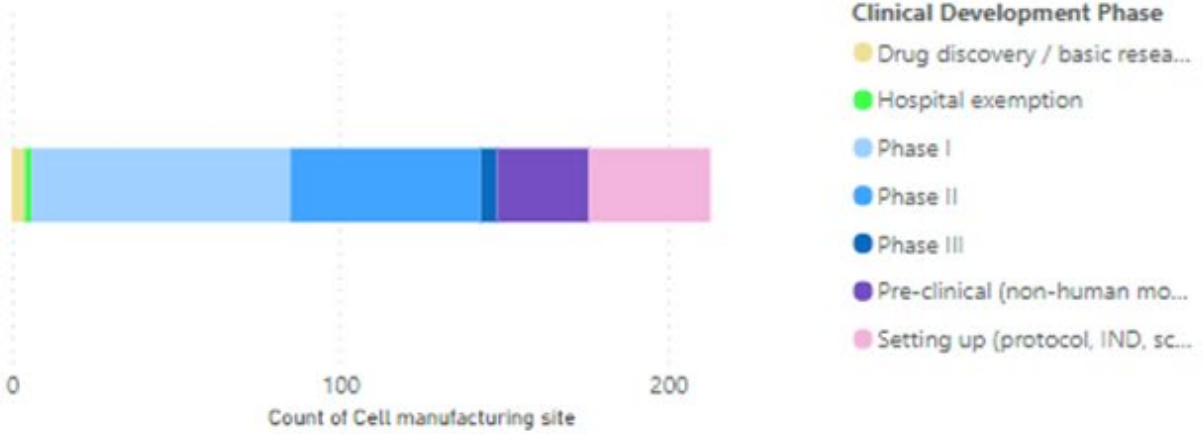
159

Number of cell manufacturing sites with CliniMACS Prodigy in Phase I or II

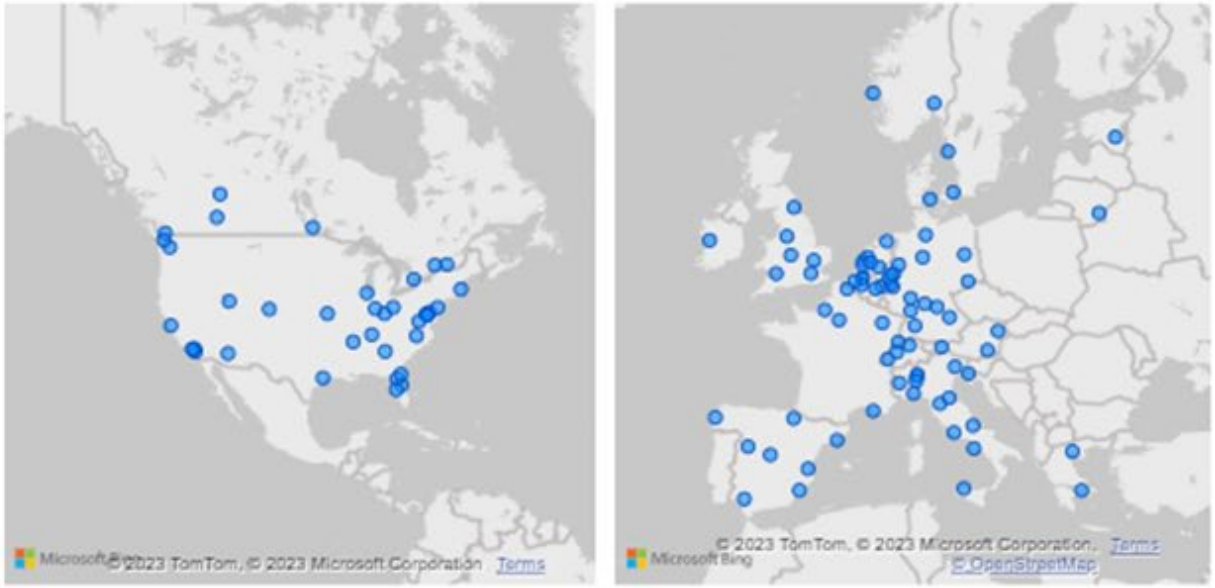
60

Courtesy of Yongping Wang, MD, PhD
Director, Cell and Gene Therapy Lab, Children's Hospital of Philadelphia

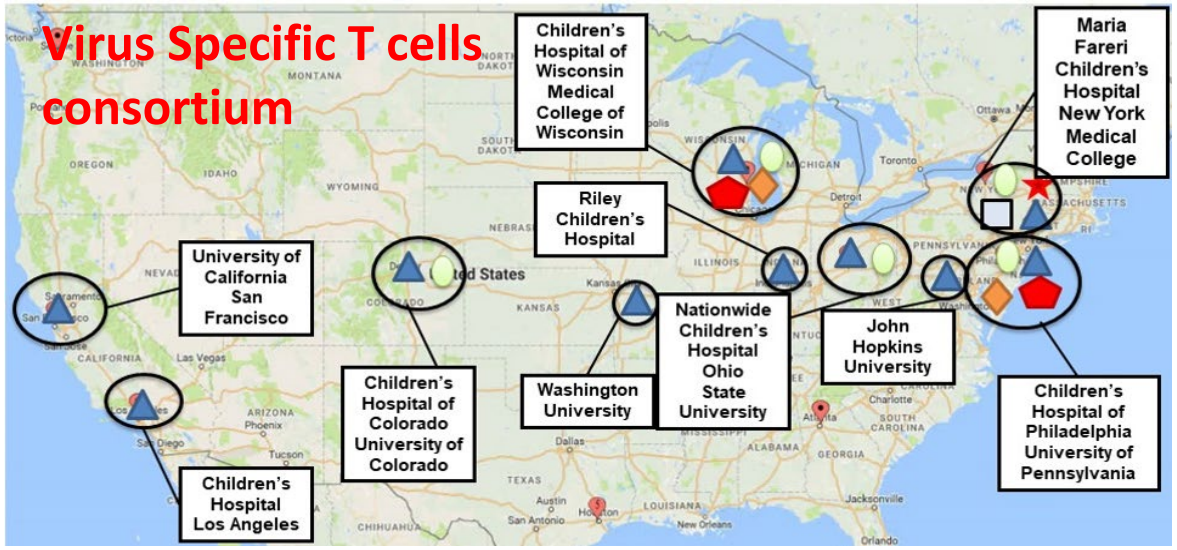
Cell manufacturing site by Clinical Development Phase



CliniMACS Prodigy in academic hospitals per region



(each dot refers to a city with one or more CliniMACS Prodigy)



“Novel Cell Therapy” Space - Smith 12th Floor

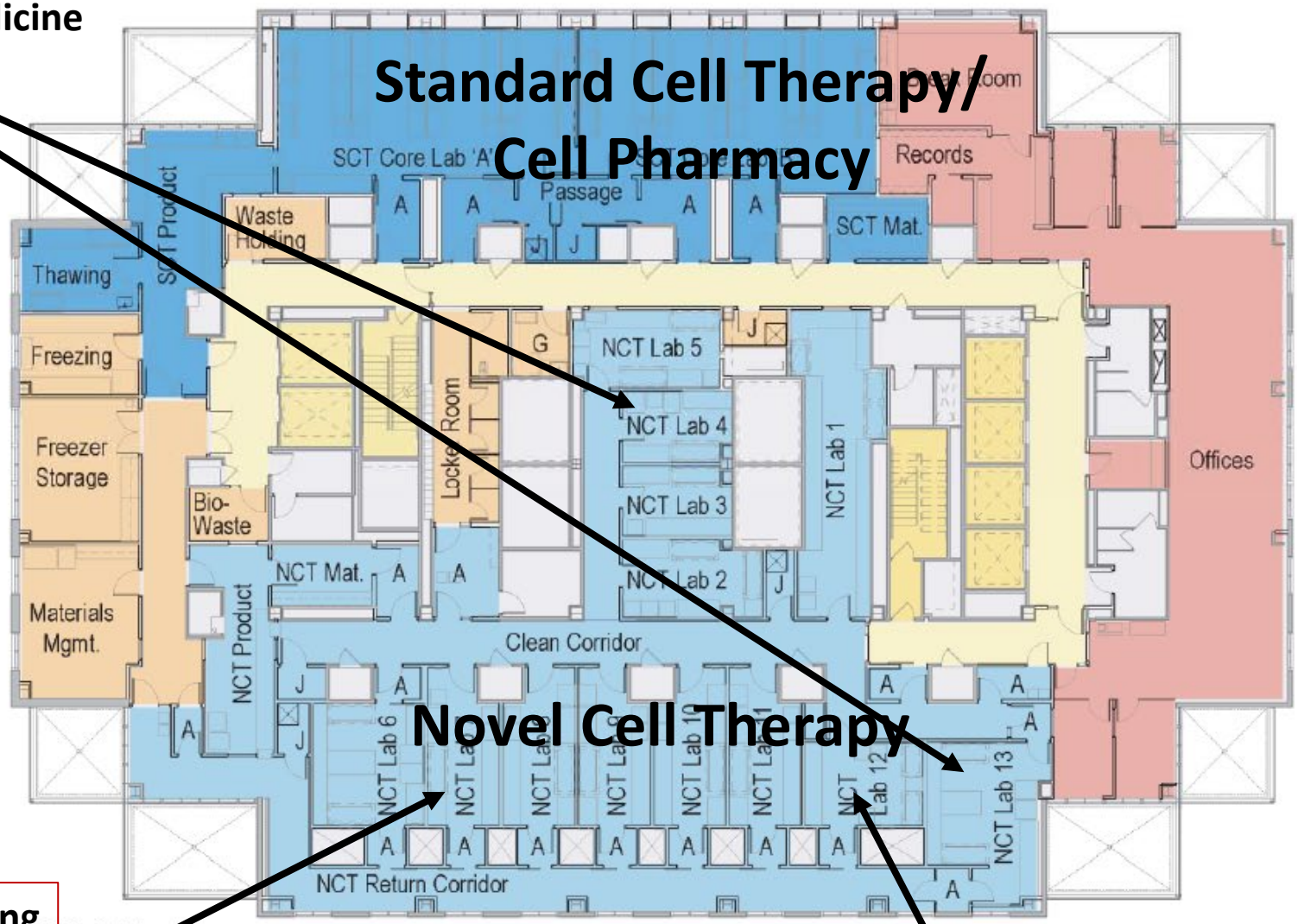
Regenerative Medicine

Manufacturing space

SCT – 12 workstations, 2 rooms

NCT - 13 workstations

Thaw space, CRFs, LN2 tanks, Materials



Genetic Engineering Negative Pressure

Vaccine Development

- **70 FTEs**
- **80 Clinical Trial Supported**
- **25 INDs with complex manufacturing**

- **Investigator-initiated trials**
- **Commercial Sponsor Trials**
- **Prior and Current Stem Cell Gene Therapy**
- **Wave, Grex, bags, Prodigy experience**

1.

Star
fres

Day 0
Initial
Processing

TCT - Cultivation - 8.4

Day	Time	Activity (Parameter)	Volu
1	14:30	Transduction (reagent vol.: 10)	100
3	11:00	Culture wash (cycles: 1)	200
3	11:50	Activate shaker (shaker type 2)	200
5	11:00	Feed (port: 3, vol (+): 50)	250
6	11:00	Media exchange (port: 3, vol (-/+): 125/125)	250
6	11:30	Activate shaker (shaker type 3)	250
7	09:00	Media exchange (port: 3, vol (-/+): 150/150)	250
7	11:00	End of culture	250

ation
nt programmed.

Activation
Transduction
and
Cultivation

Day 1 Transduction
- *Add Vector to culture*
- *Static Culture*

3.

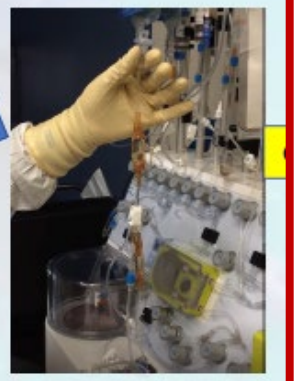
Day 0
T-cell
Selection

Final Selected Pro
- *Eluted into Re-appl*

2.

Media
Exchange,
Expansion
and Final
Harvest

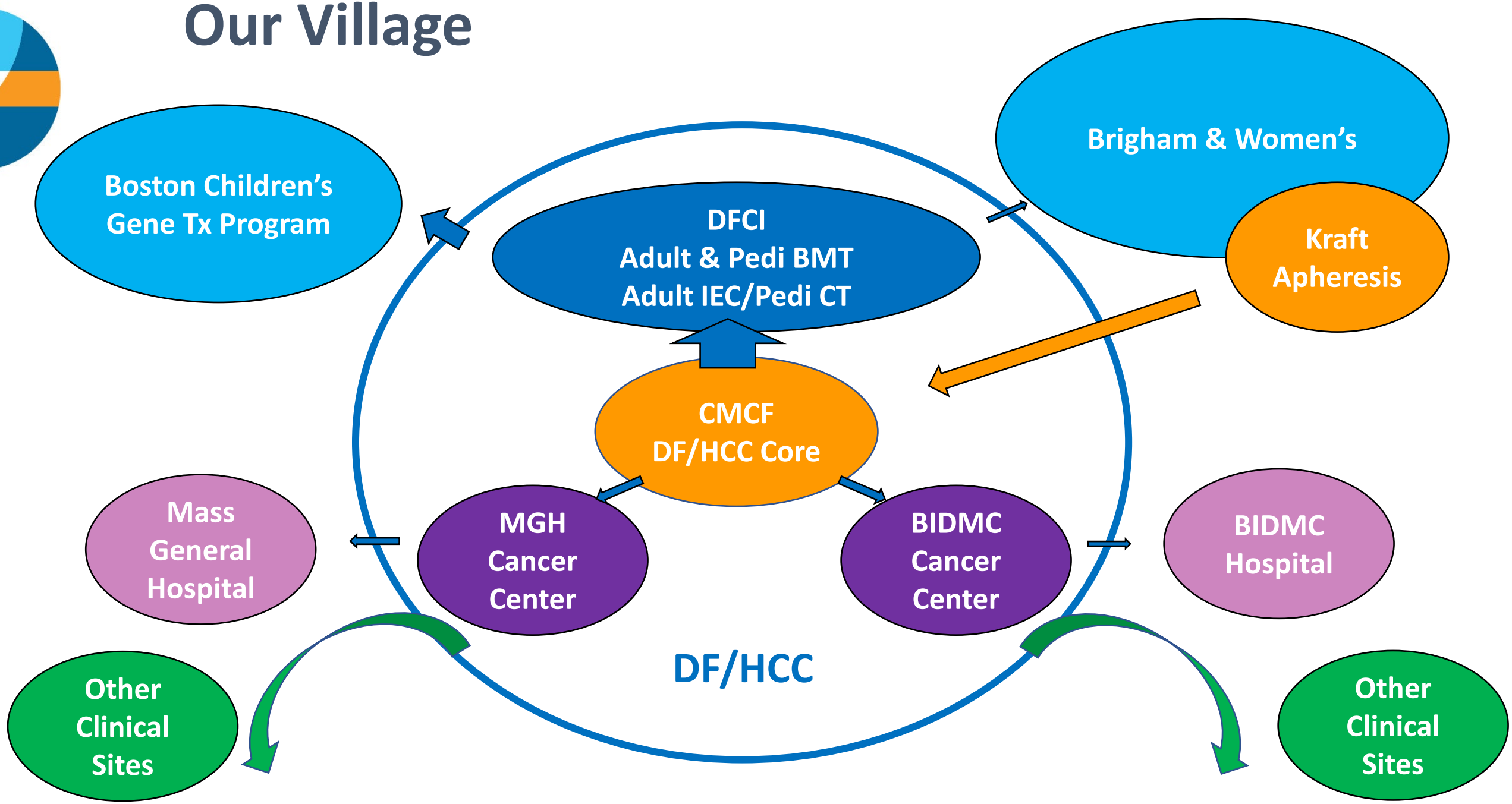
- *Can s*
aroun



4.

>180 runs on
Miltenyi Prodigy – still
learning!!

Our Village


Boston Children's
Gene Tx Program
Brigham & Women's
Kraft
Apheresis
DFCI
Adult & Pedi BMT
Adult IEC/Pedi CT
CMCF
DF/HCC Core
Mass
General
Hospital
MGH
Cancer
Center
BIDMC
Cancer
Center
BIDMC
Hospital
DF/HCC
Other
Clinical
Sites
Other
Clinical
Sites

Benefits to “Local” and Academic Manufacturing

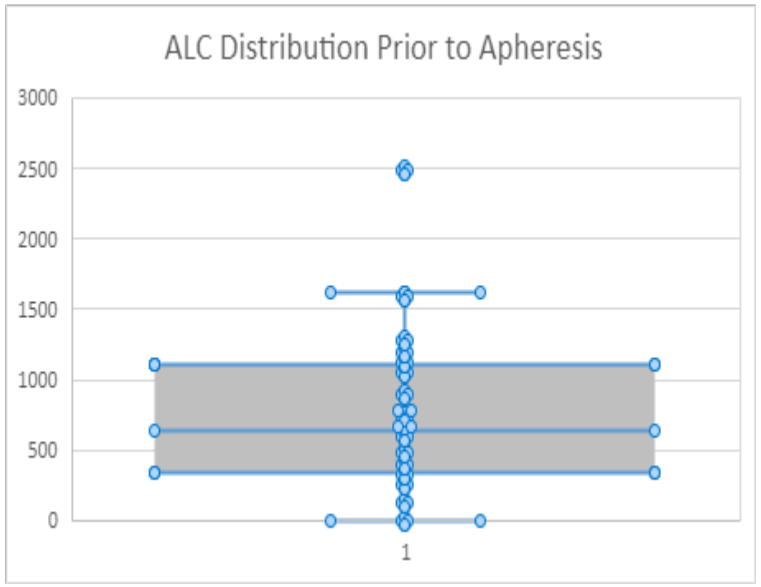
- Simpler Logistics and FASTER
- CHEAPER per run (our costs do NOT include vector manufacturing)
- Slot assignment with patient variables in mind
- Direct communication with clinicians and informed manufacturing adaptations
- No silos between manufacturing, QC testing and QA groups

Recognize prior investment in infrastructure and building expertise

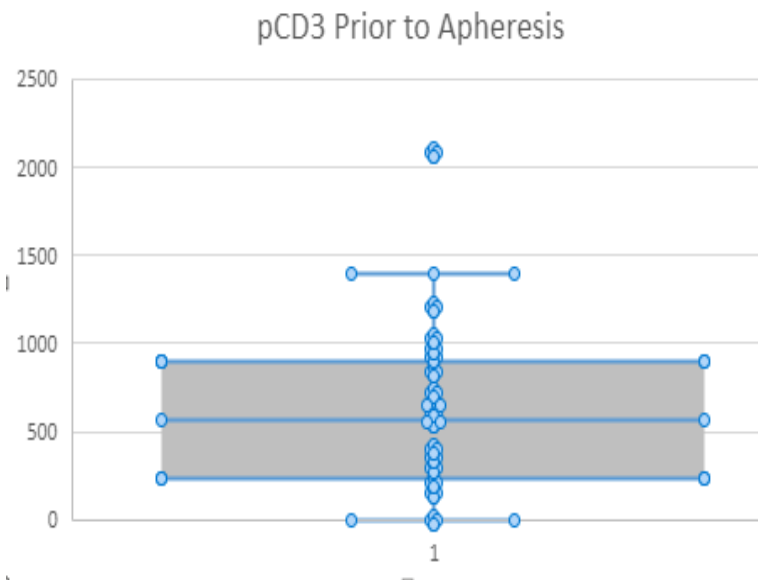
Do you really just need a “box” to start manufacturing?! Heterogeneity of Normal Donor and Patient Aphereses

Number of Lymphocytes (K/uL) pre apheresis – 35 Patients

Instructions 2-3 Blood Volumes



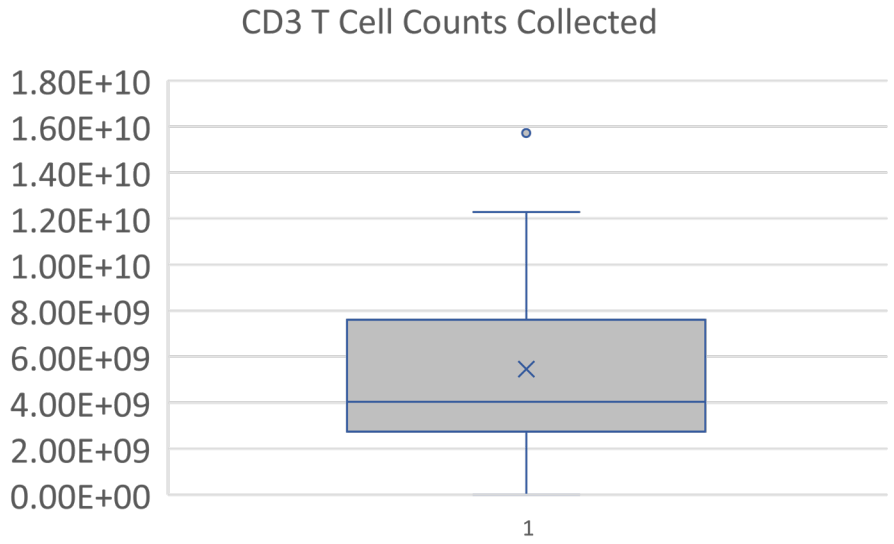
Median	700
Min	130
Max	2490



Median	577
Min	150
Max	2079

CD3% of Lymphs

Median 54% (range, 23-79%)



Median	4.1x10^9
Min	0.7x10^9
Max	15.8x10^9

Medians **Post Seln** Protocol 1

CD4 38% (14 – 82%)

CD8 53% (11-79%)

NK 2% (<1-**25**%)

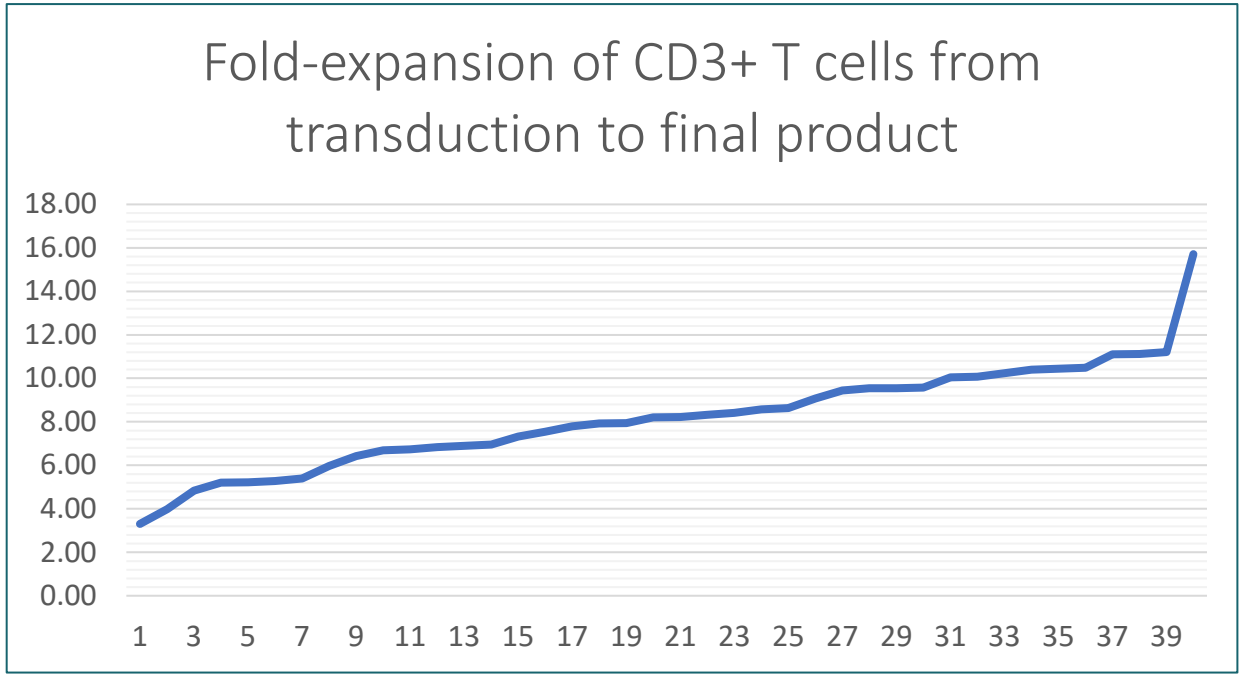
NKT 6% (<1 – **34**%)

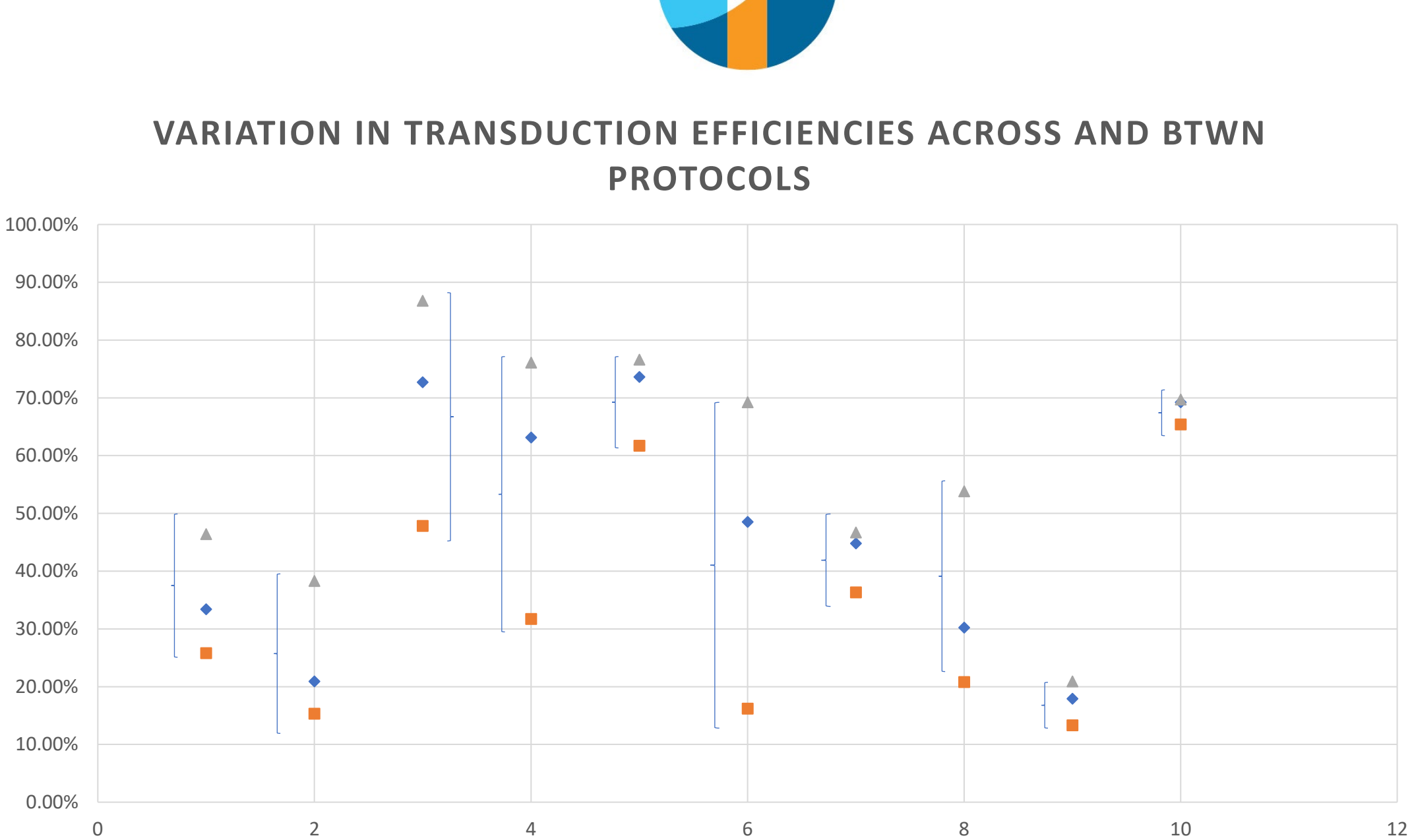
Ratio 0.66 (0.2-3.7%) **Post-Seln**

Medians **Final Product**

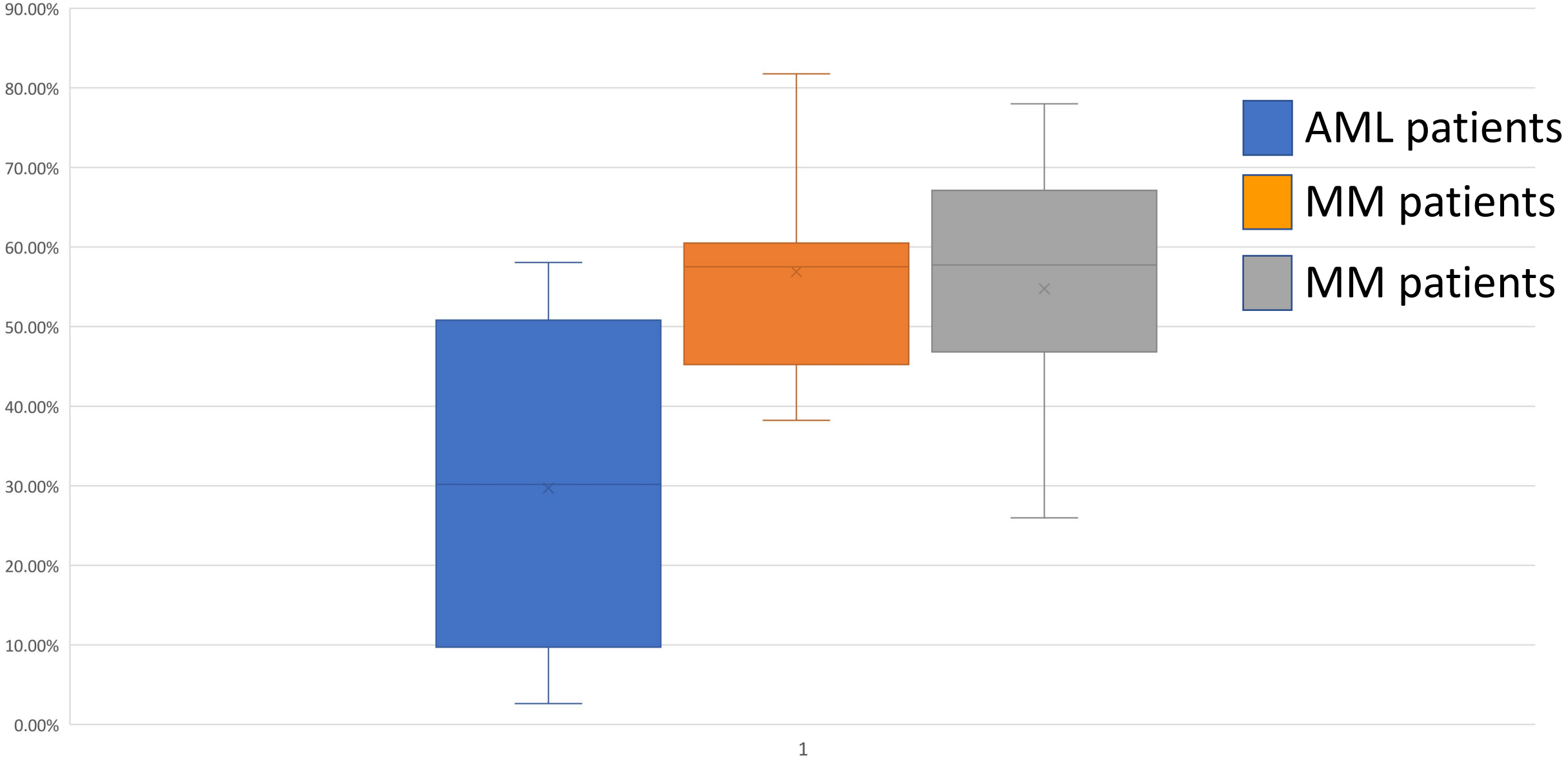
Ratio 2.85 (0.46-26) Protocol 1

- Patient samples are different than normal donor material
- What impurities are carried into final product and careful definition of release criteria
  - CD3+ cells, CD3+ T cells, CD3+CD56- T cells
- Be prepared to pivot/adjust manufacturing in a proof-of-concept Phase 1 study

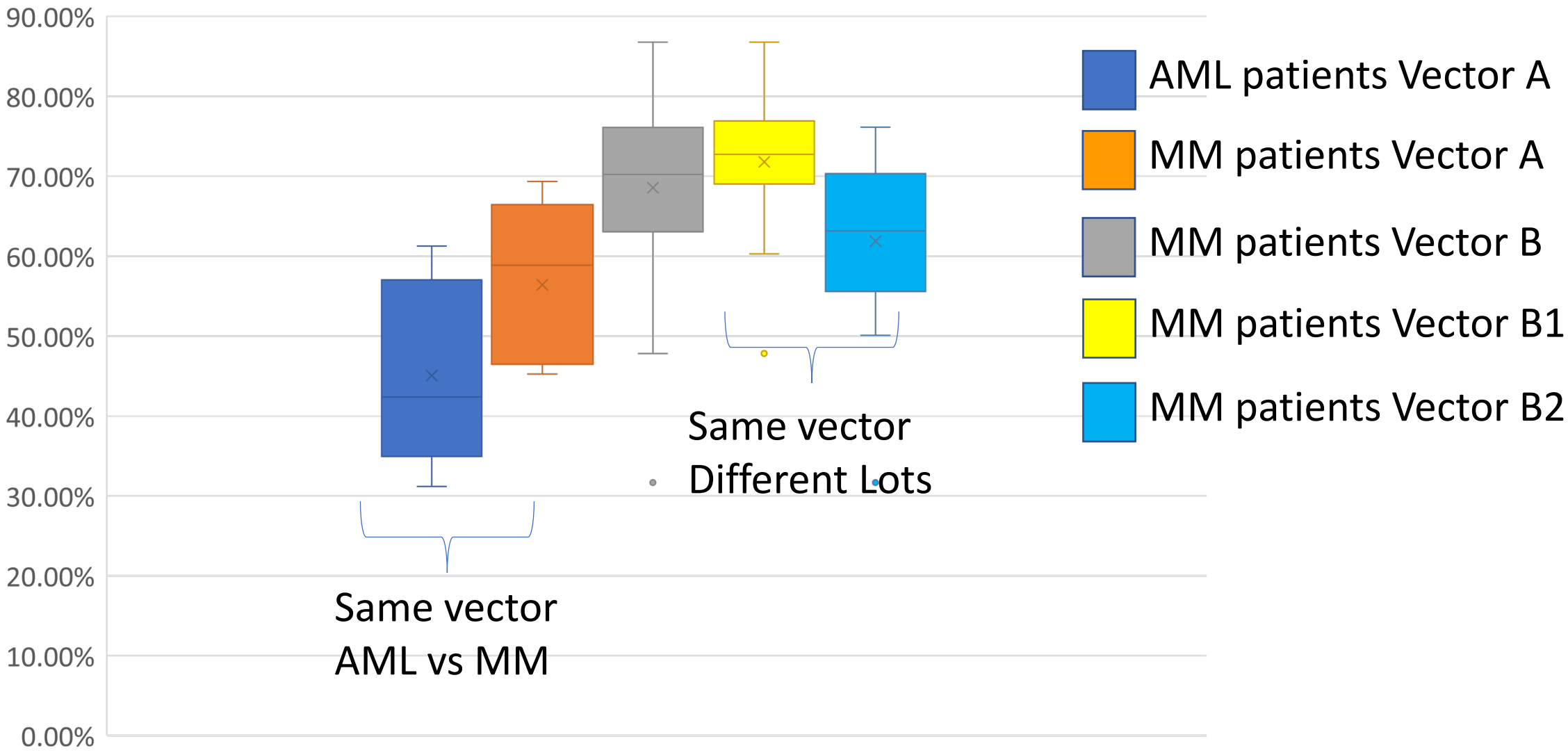



VARIATION IN TRANSDUCTION EFFICIENCIES ACROSS AND BTWN PROTOCOLS
100.00%
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
0
2
4
6
8
10
12

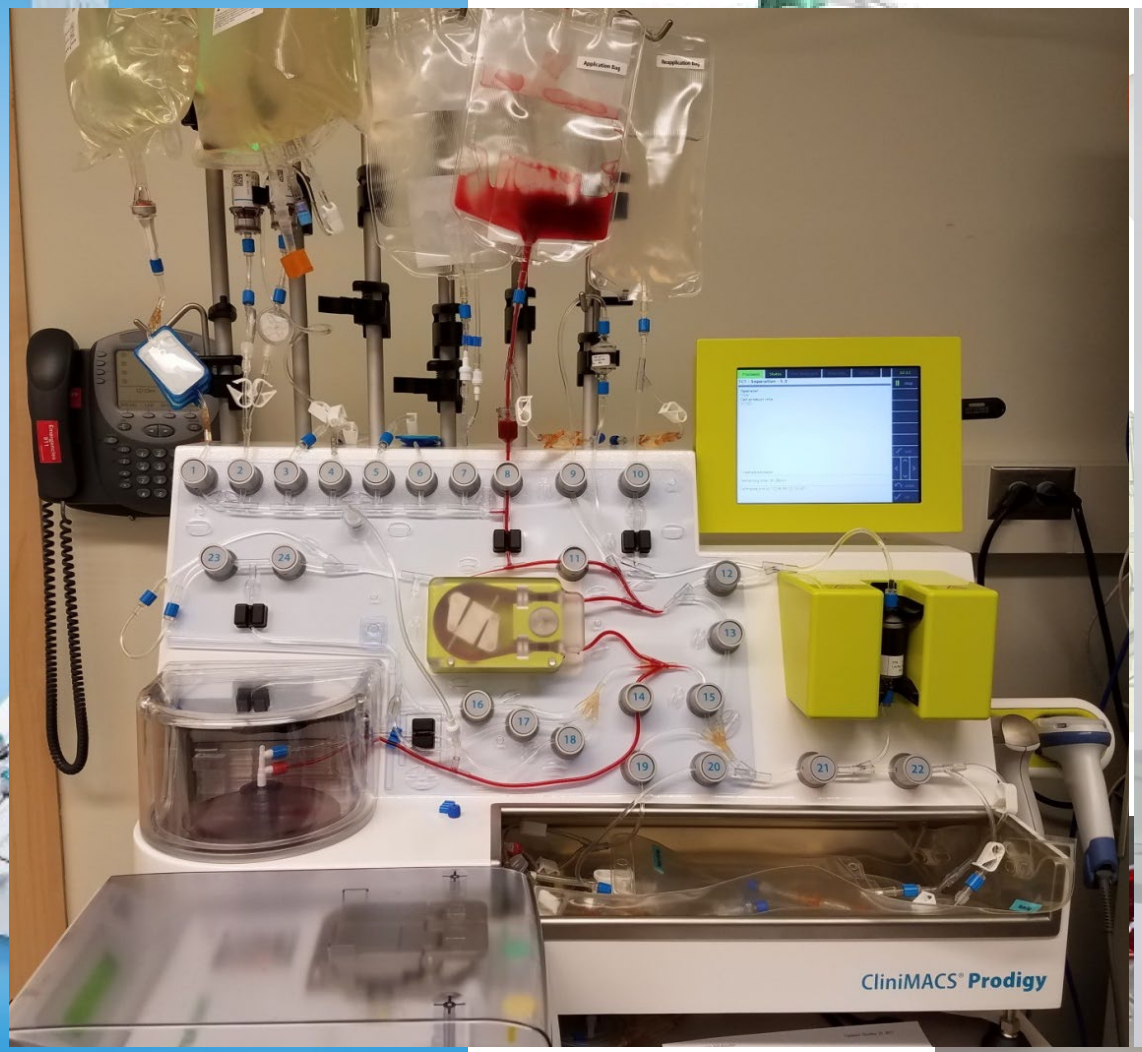
% CD3 of Leukocytes Initial Apheresis Products



Transduction Efficiency of T Cells Across Trials – Same manufacturing platform



Spectrum of Processing Complexity and Manufacturing Approaches



Manufacturing Culture Conditions Matter!!

- NCI/NIH Center for Cellular Engineering at CAR-TCR Summit
- Comparison between Prodigy, Grex (5L), Wave/Xuri Bioreactor (1L) and bags
- Massive impacts on cells #s AND state of T-cell differentiation of final product
- Also on cytokine expression, gene expression signatures re activation
- Cell density, feeding media and oxygenation level had massive impacts

- Hannah Song presented
- Cited were Steve Highfill, Ping Jin, Naomi Taylor and Javed Khan

Analytics are Key

- In-Process and Release Testing
  Cell counts, viability
  Sterility (BacT, Endotoxin, Mycoplasma)
  Transduction efficiency and purity
  VCN and RCL/RCR

- **All must be clearly stated in IND, worked out in validations**
  (Reproducibility, accuracy, linearity, LLOQ, LLOD
  Lack of inhibitory substances)

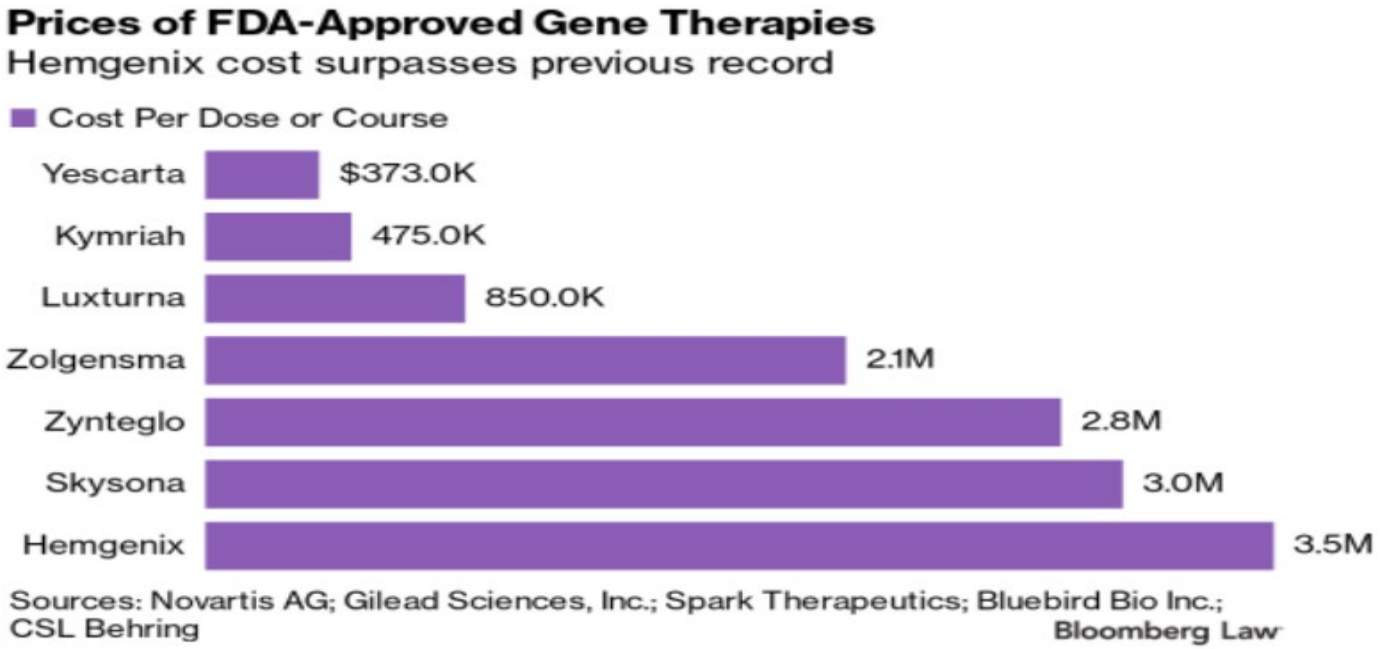
- If individual sites do not have capability to do these internally, sending samples for central analysis adds time and cost to the process

Additional considerations

- How handle **out-of-specification** products**?**
- Rigorous **Stability** testing
- **Potency**/functional testing
- The juggle of **staffing and scheduling**

Big difference between manufacturing one well-characterized product in rigorously defined patient population and having full platform to support local manufacturing

$$ (Less)



CART on Prodigy: ~$30K

β-Hgb HPC gene Rx: ~$150K

- **Included**:
  - -- Manufacturing
  - -- In process, release testing
  - -- Virus
  - -- Labor
- **Not included**:
  - -- Apheresis
  - -- Institution overhead
  - -- Instrument depreciation

Cost Recovery (21CFR § 312.8)

Courtesy of Yongping Wang, MD, PhD
Director, Cell and Gene Therapy Lab, Children's Hospital of Philadelphia

ecfr.gov

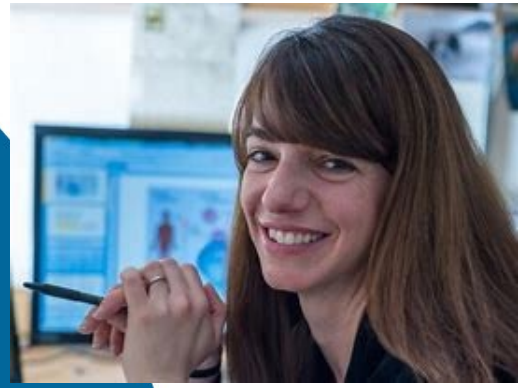
Take Aways – What is Our Goal??

- **Decentralized manufacturing is certainly possible** but rigorous demonstration of **comparability** of manufacturing and analytical testing is a major upfront investment.

- Particularly in the **Phase 1 setting, extensive expertise** is needed to troubleshoot manufacturing rendering extensive application of **distributive or point-of-care manufacturing (as term sometimes utilized) problematic.**

- Differences between **models of manufacturing** are additive to differences between **commercially sponsored and academic/clinically "owned" manufacturing**.

- **Academic/clinical facilities** manufacturing cell therapies for **local patient use** challenges manufacturing and regulatory frameworks but ALSO current financial **reimbursement/coverage models**.



Cell Therapy

A team effort!!

Cell Manipulation Core Facility

Dana-Farber Cancer Institute

Questions ?