From Academia to Industry: Lessons Learned in the Development of CAR-T Therapies

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10-July-2018

CASSS Cell and Gene Therapy Products 2018

Agenda

1. **Background**
2. Comparing the NCI/Kite Experience to the UPenn/Novartis Experience
3. Critical Quality Attributes: CD19 CAR-T Therapies
4. Final Thoughts

Relevant Disclosures and Forward Looking Statements

I am an employee of Mustang Bio.

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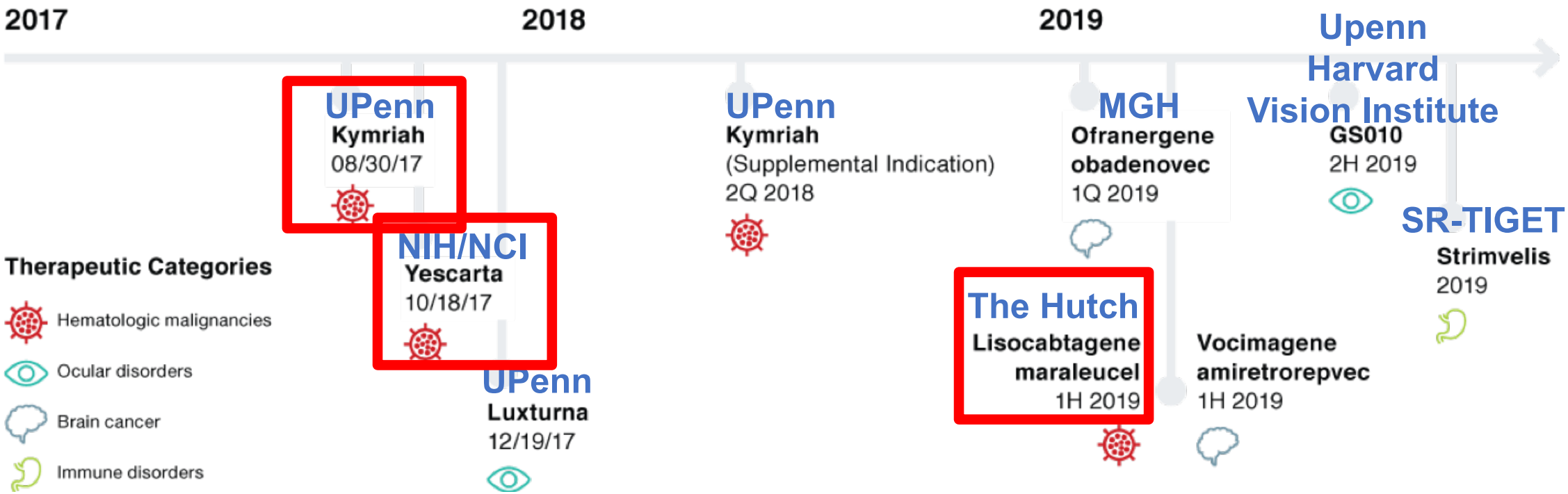
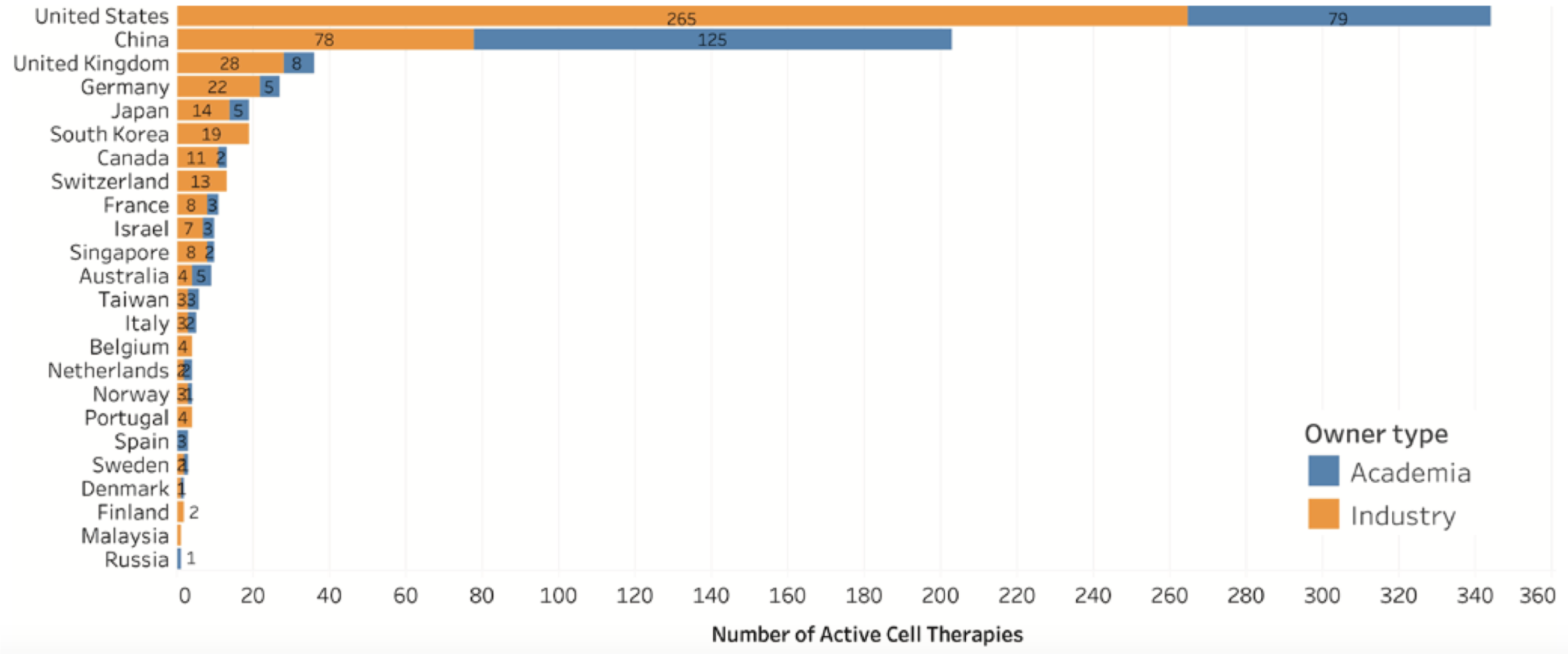
Cell and Gene Therapies are Highly Dependent on Academic Founders



CVS Health: January 23, 2018

Academic and Industry Sponsored Cellular Immunotherapy Trials



- "Unlike other areas of research and development, most innovation in cancer cell therapies is carried out in academic centres and then licensed by commercial entities."
- Academic centres own and are actively developing 251 cell therapies, of which 184 are already in clinical development.

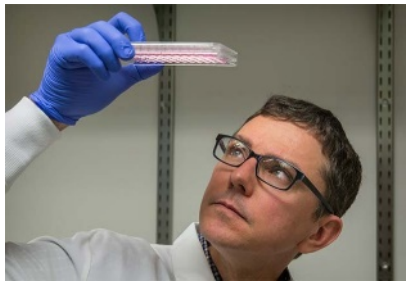
Tang et al. *Nature Reviews Drug Discovery* (2018)

Mustang Bio's Portfolio is Dependent on Academic Partnerships

- Founded by Fortress Biotech in 2015; publicly traded (NASDAQ: MBIO)
- Focus on Chimeric Antigen Receptor (CAR) T Cell technology in Oncology
- Technology licensed from City of Hope (COH), Fred Hutch Cancer Research Center (FHCRC), & Harvard; ongoing research collaborations
  - COH: Stephen Forman & Christine Brown
  - FHCRC: Brian Till & Oliver Press[1]
  - Harvard / Beth Israel Deaconess: Chad Cowan

City of Hope

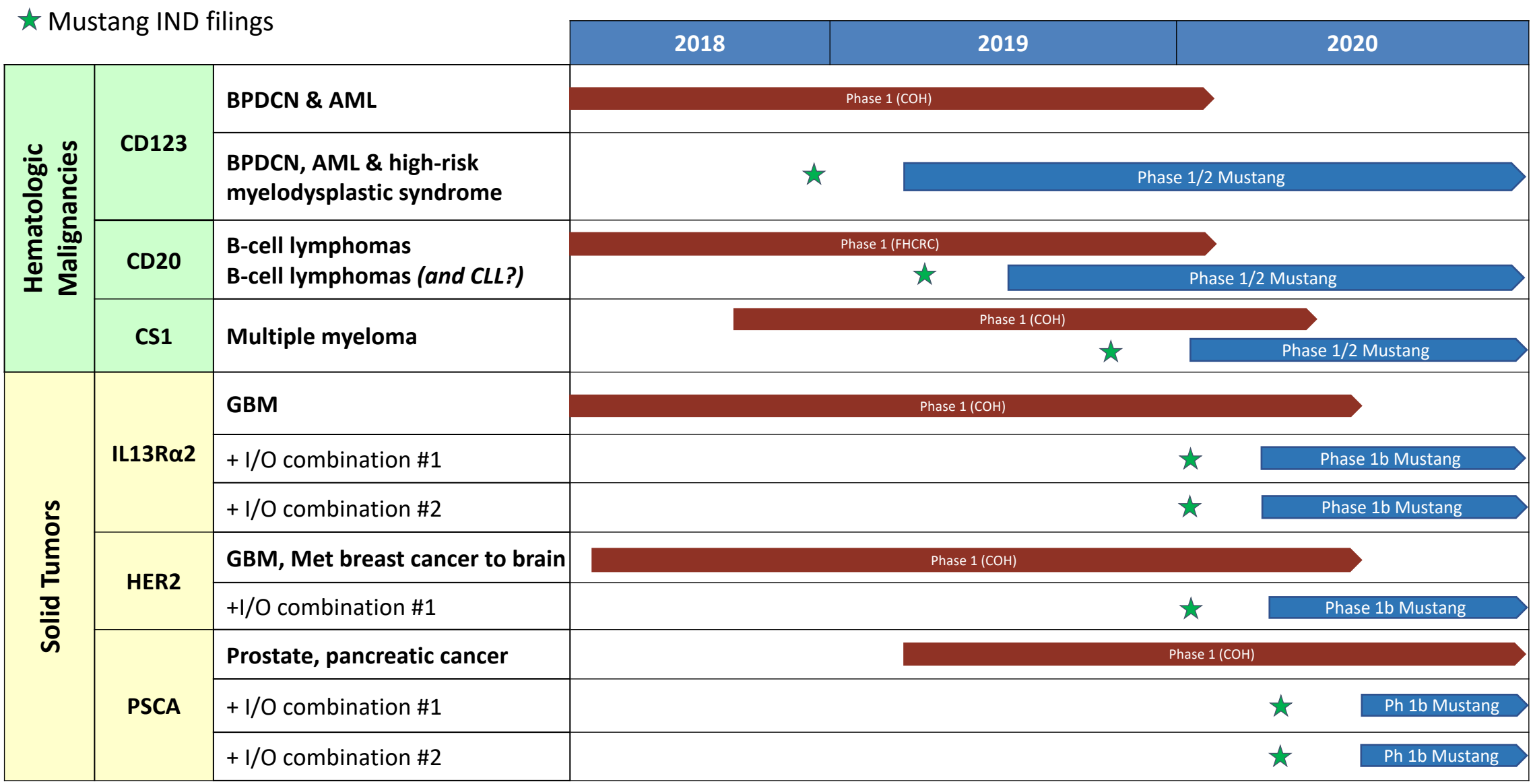
FRED HUTCH



HARVARD UNIVERSITY

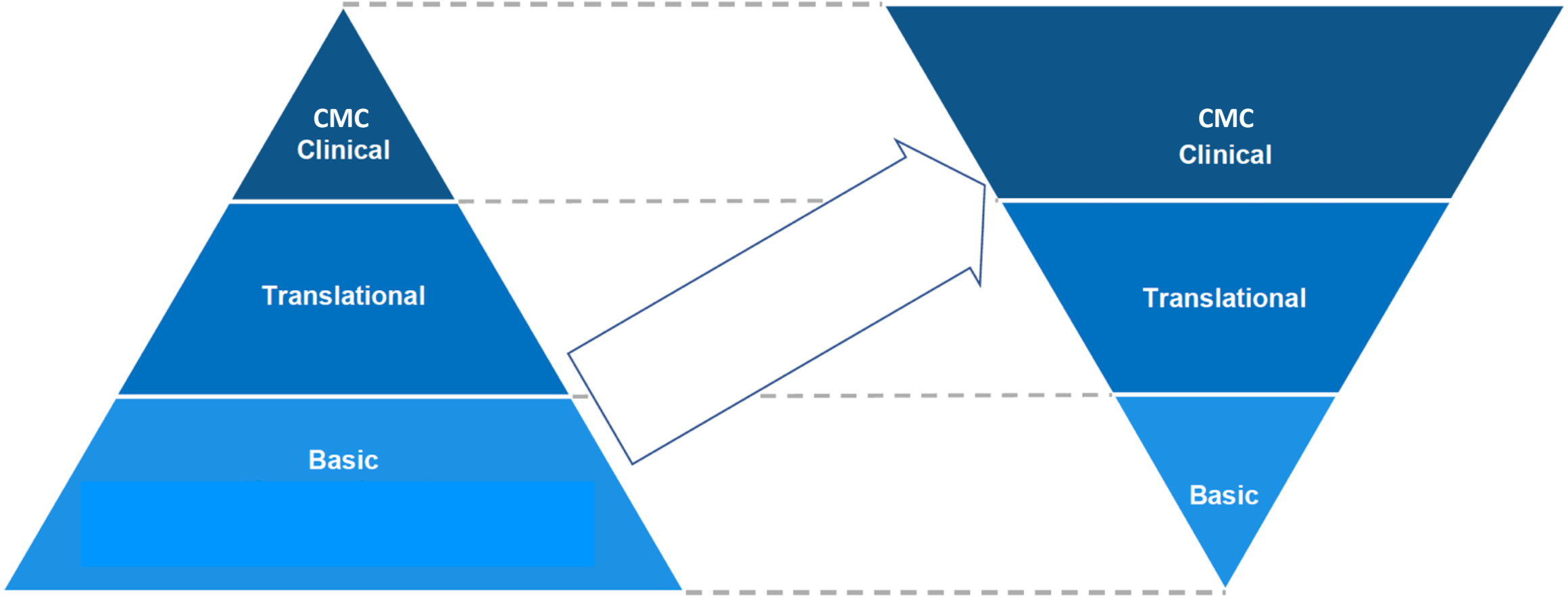
[1] *d. 2017*

Mustang Portfolio: First-in-Human Investigator IND Trials *(red)*, Followed by Mustang IND Trials *(blue)*



Relative Biotech Investment: Academic vs. Industry

-Public and private investments in biotech and life sciences are roughly equal, yet spent in markedly different ways.
-Typically, public funding drives the innovation which private industry then acquires.



Sources: GAO, Celdara, and E. Zerhouni.

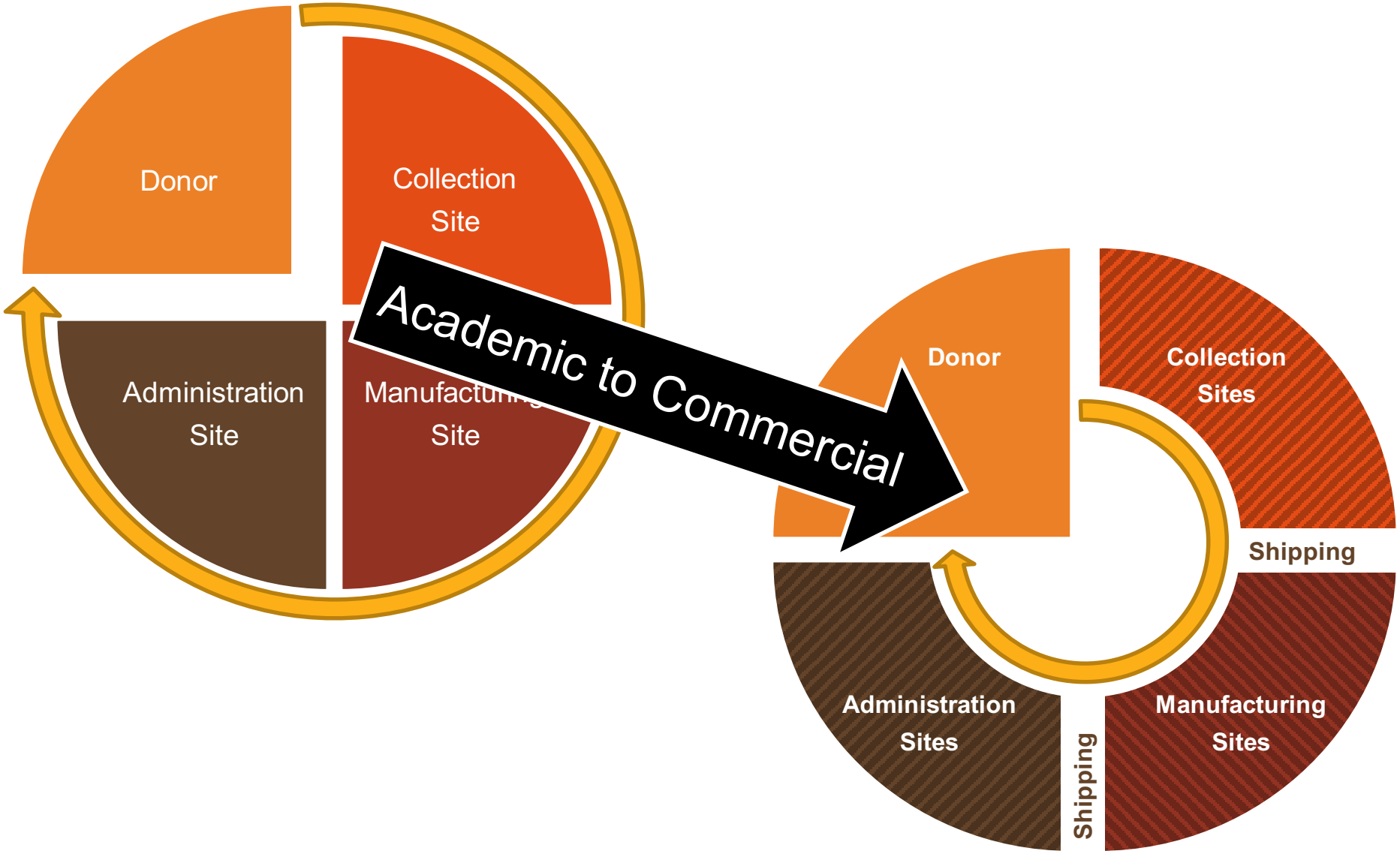
CMC Is the Primary Challenge for Cell and Gene Therapies

"**A lot of the complexity with gene therapy is in product-related issues**, not the clinical issues. Whereas with normal drug review, I'd say 80% is the clinical portion and 20% is the CMC and product portion of the review. I think with gene therapy and cell-based regenerative medicine it's completely inverted. We're having to think very differently about the regulatory issues with these."

Scott Gottlieb_2018 Bio International Convention

Moving From Academic to Commercial Manufacturing

Moving from one academic facility to many collection sites, multiple manufacturing sites, and many patient treatment sites



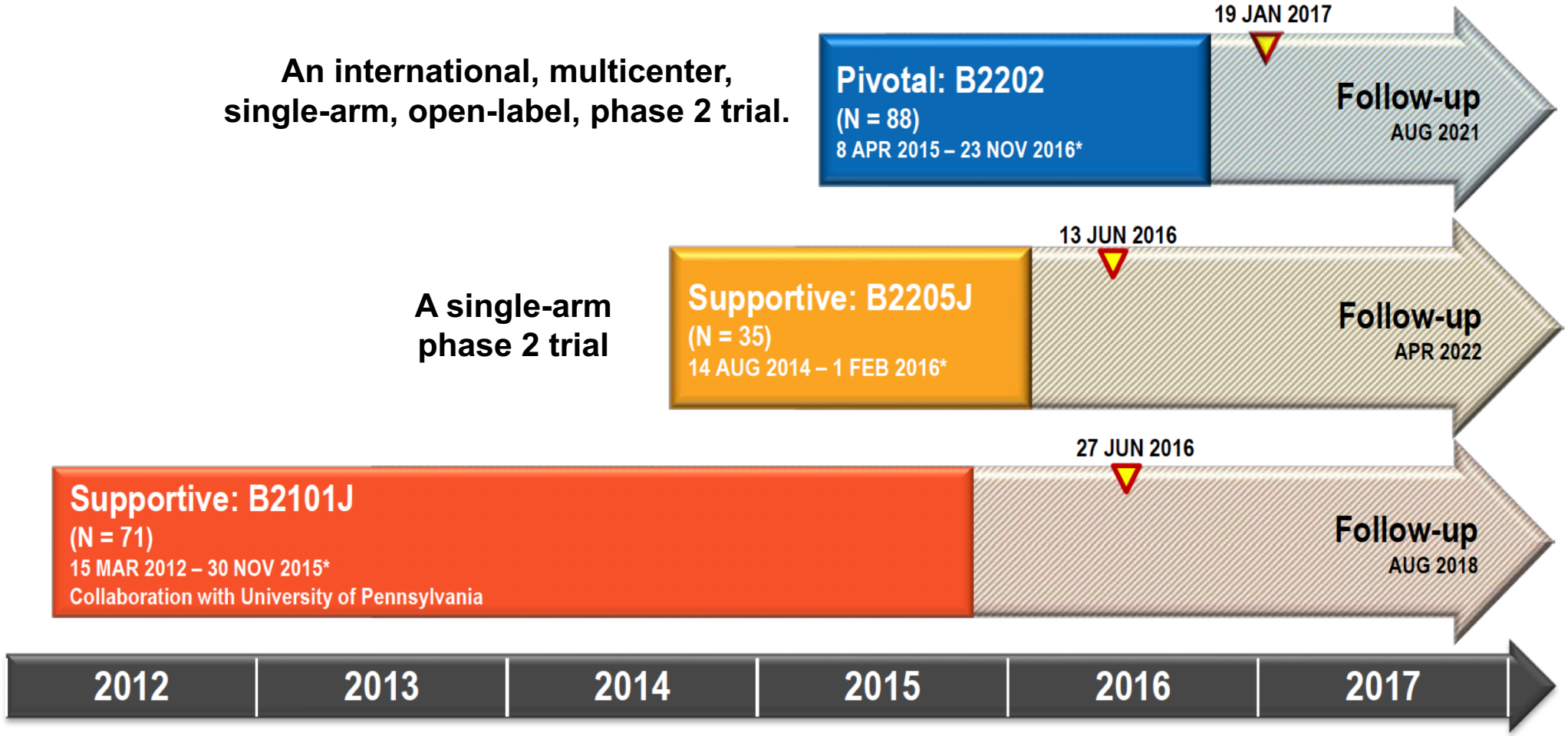
Agenda

1. **Background**
2. **Comparing the NCI/Kite Experience to the UPenn/Novartis Experience**
3. **Critical Quality Attributes: CD19 CAR-T Therapies**
4. **Final Thoughts**

The UPenn/Novartis Experience

An international, multicenter, single-arm, open-label, phase 2 trial.

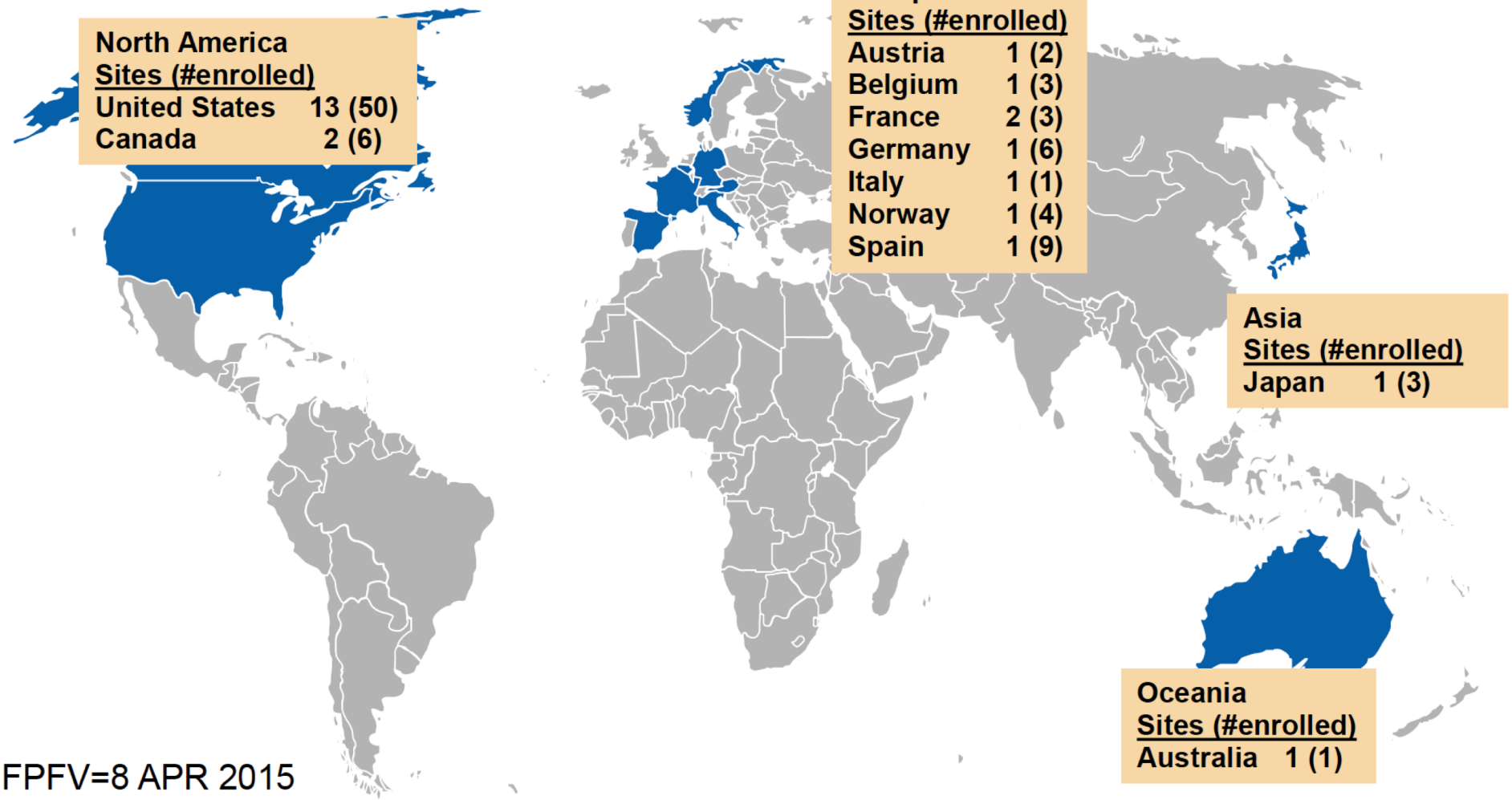
A single-arm phase 2 trial



- August 2012-Upenn/Novartis sign deal.
- December 2012-Novartis buys 173k sqft Dendreon manufacturing facility.
- August 2013-Novartis signs exclusive deal for Dynabeads with Life Technologies.
- October 2014-Novartis signs lentivirus vector deal with Oxford Biomedica.
- The primary objective of Novartis was rapid global scale out of the UPenn CD19 CAR-T manufacturing process and pivotal/registration trial.

FDA ODAC Meeting, July 12, 2017

B220: Novartis' Multi-Center Global Trial

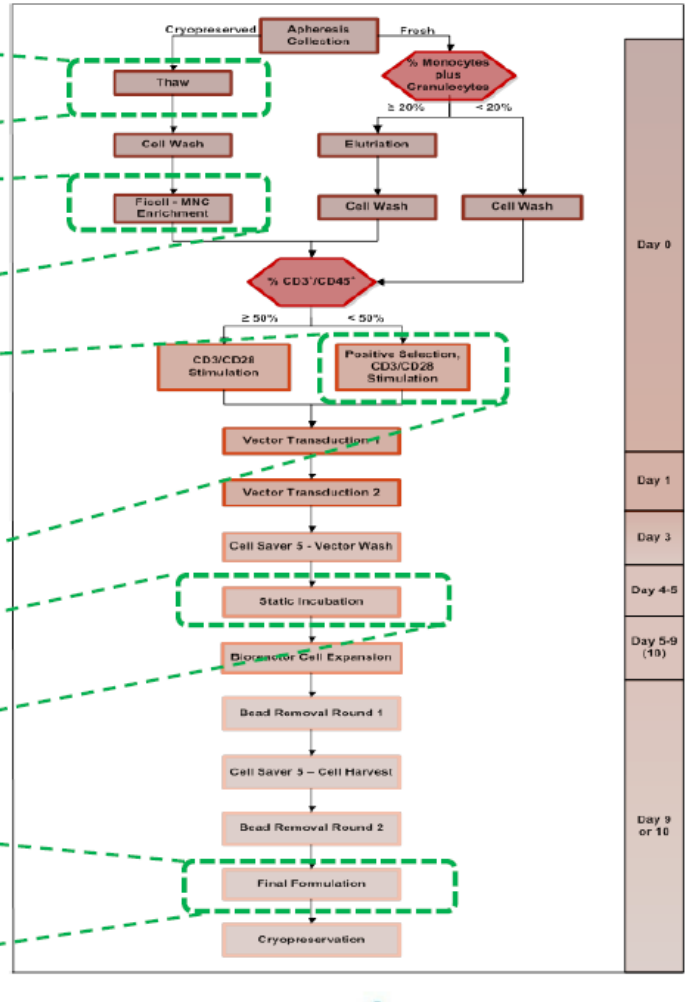


FPFV=8 APR 2015
Data cutoff: 23 NOV 2016

Novartis' Modifications of UPenn's Manufacturing Process

*Equipment Comparison to UPenn Process A**

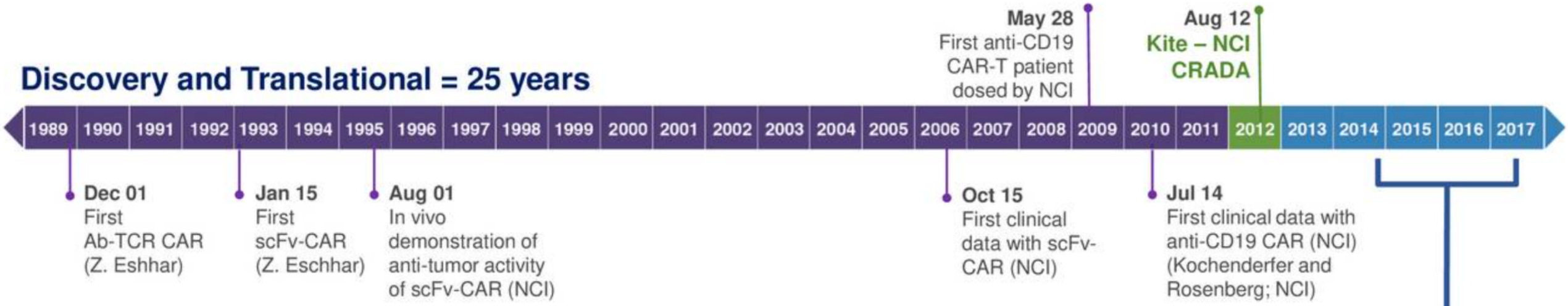
Process A	Process B	Rational
Water bath	Plasma therm	Reduce potential contamination
Manual ficoll	Sepax ficoll	Closed and automatic system.
MaxSep; Labnet spinning rotator; DynaMag CTS; Customized rotator for bags		MaxSep discontinued; CTS meets bead manufacturer recommendation Customized rotator for bags
Humidified incubator	Non-humidified incubator	Elimination of a water source in an ISO 7 area
Regular conical tubes	SaniSure Cap2v8	Closed system



The primary aim of Novartis was to maintain product comparability and reduce the amount of manual unit operations.

The NCI/Kite Experience

Discovery and Translational = 25 years



2014	2015		2016			2017			
Dec	Apr	Nov	Jul	Sep	Dec	Feb 28	Mar 31	Apr	Q4
IND Submitted	ZUMA-1 Ph1 Study: First Patient Enrolled	ZUMA-1 Ph2 Pivotal Study Opens	ZUMA-1 Pivotal Study Completes Enrollment	ZUMA-1 Pivotal Study Topline Interim Analysis	ZUMA-1 Pivotal Study Interim Analysis ASH Late Breaker	ZUMA-1 Pivotal Study Topline Primary Analysis	Complete BLA submission	ZUMA-1 Pivotal Study Primary Analysis at AACR	Expected PDUFA Date

Kite opens commercial manufacturing facility

How Can We Industrialize the NCI CD19 CAR-T Manufacturing Process?

Original NCI Process

- Manual Ficoll Separation of PMBC

Can we automate Ficoll separation?
Yes

- Stim in T175 Flask (open)
- AIM V+ 5% Hu serum supplemented with anti-CD3 Ab and rIL2
- Wash cells after Stim (open)

Days 0-2

Can we remove serum from the process?
Yes

- Transduction in 6-well plates by Spinoculation (open process)

Days 2-3

Can we remove retronectin?
No

Can we eliminate "spinoculation"?
Yes

- Expansion in T-175 flasks (open process)
- **7 day** expansion

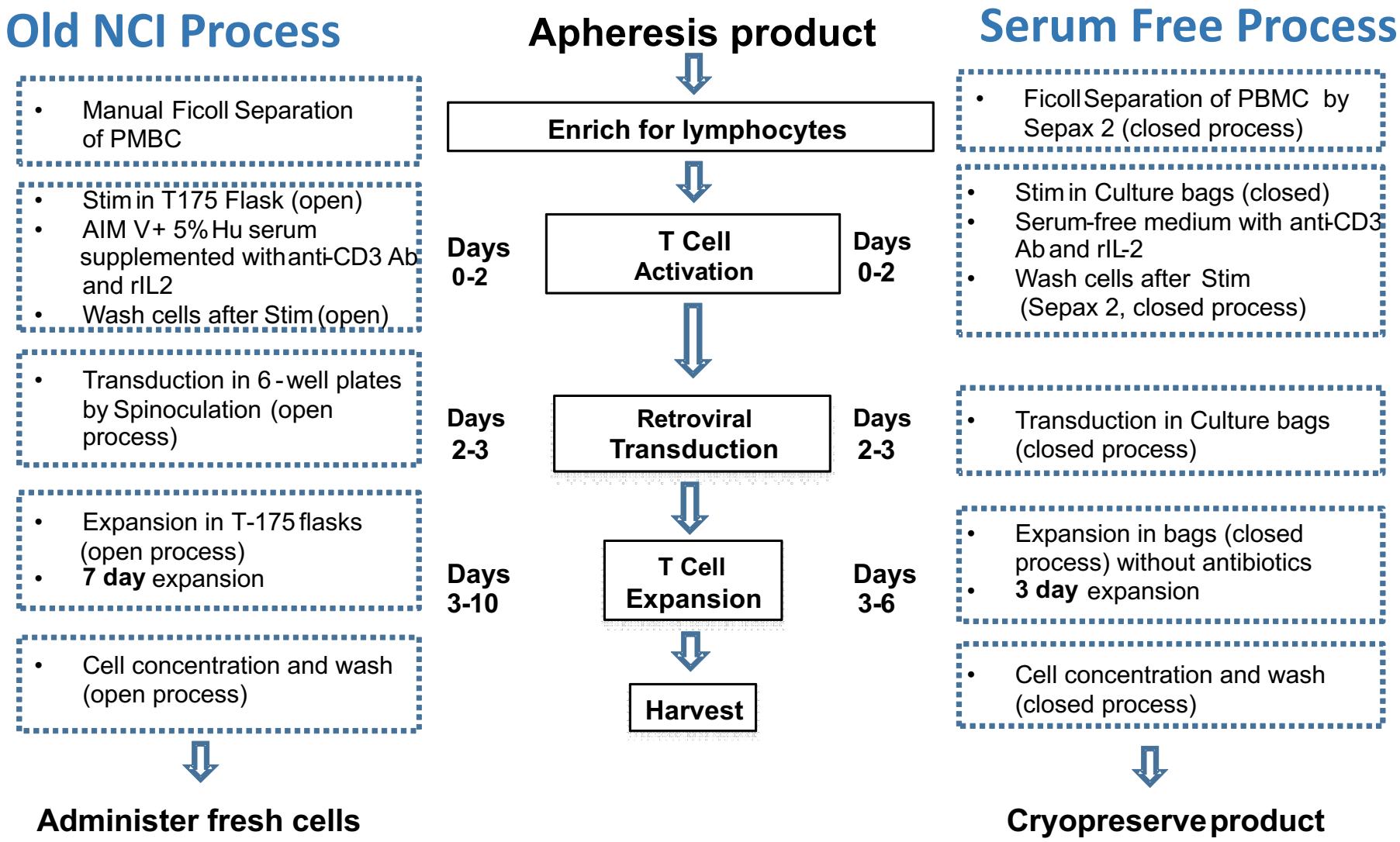
Days 3-10

- Cell concentration and wash (open process)

⇩

Administer fresh cells

The NCI's Legacy Process vs. Kite's Commercial Process



Better et al,
ASCO Annual Meeting, May 2014

Learning from the Pioneers

Change | No Change | Change in Pivotal Portion of Trial

Change (Ordered by Significance, High to Low)	NIH to Kite Pharma (CD19)	UPenn to Novartis (CD19)
Viral vector source		
T Cell Activation Reagent		
Cell Culture Media		
Cell Culture Duration		
Cell Culture Vessel		
Closed Process		
Cryopreserved Final Product		
Pre-clinical mouse studies required to justify change?	No	No

- Moving forward, are pre-clinical mouse studies required to justify process changes when transitioning from academic to industrial manufacturing?
- Hundreds of patients have now been treated with CAR-T therapies, worldwide.
- What have we learned about these patient products?

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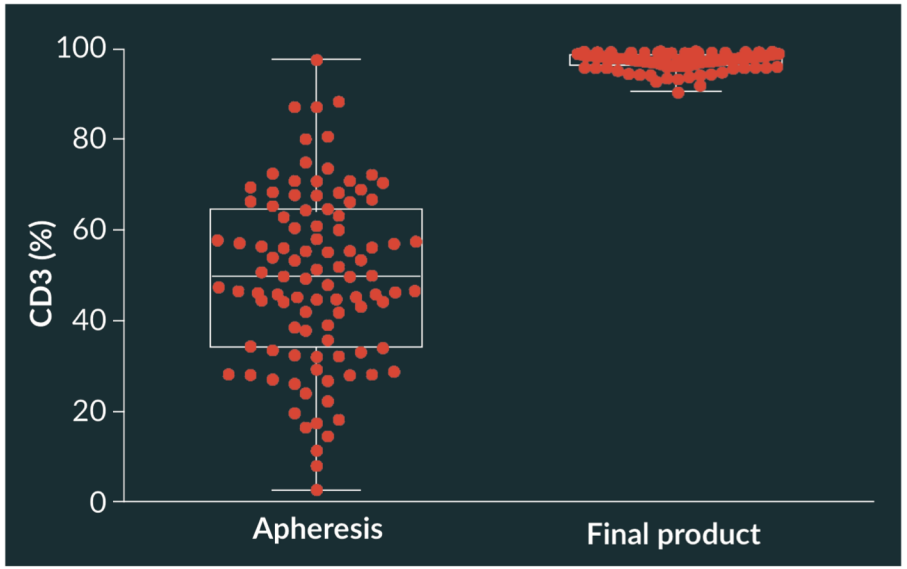
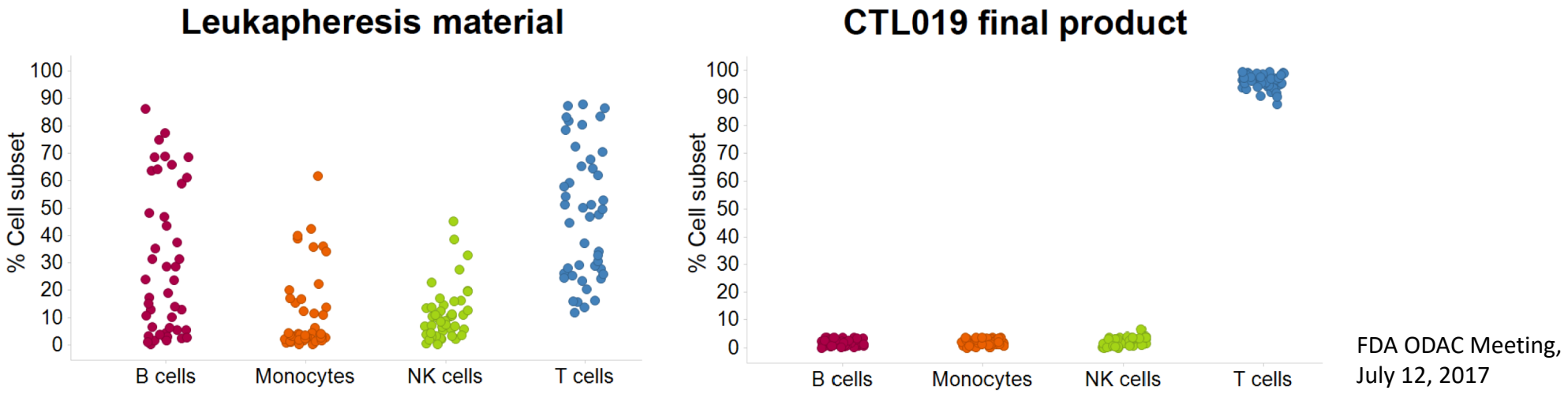
CD19 CAR-T Drug Products Were Routinely Manufactured Despite Heterogeneity in the Apheresis Material

Kite's Yescarta for Lymphoma



Better et al.
Cell and Gene Therapy Insights, 2018

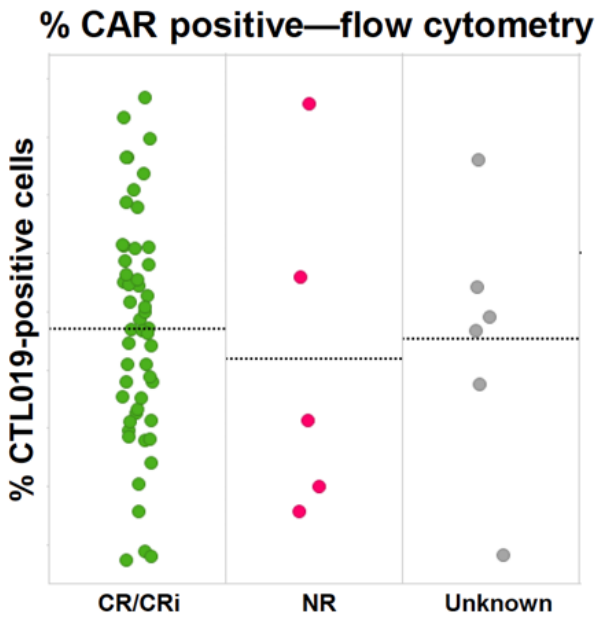
Novartis' Kymriah for PedALL

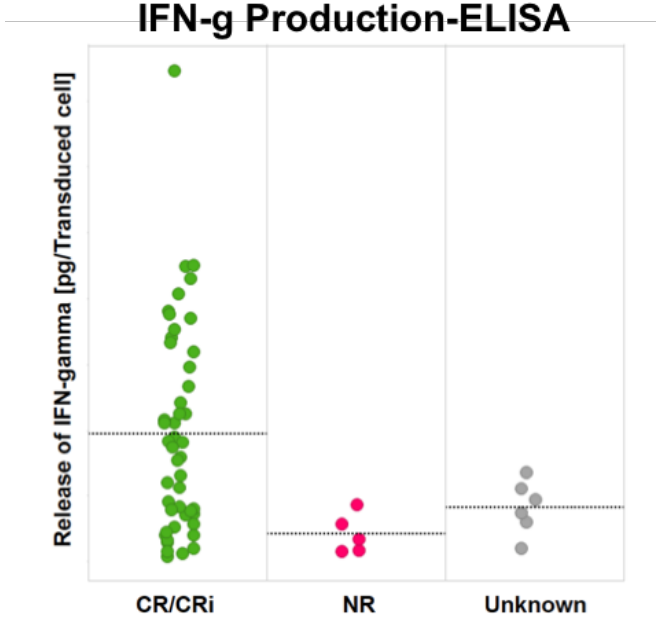


FDA ODAC Meeting,
July 12, 2017

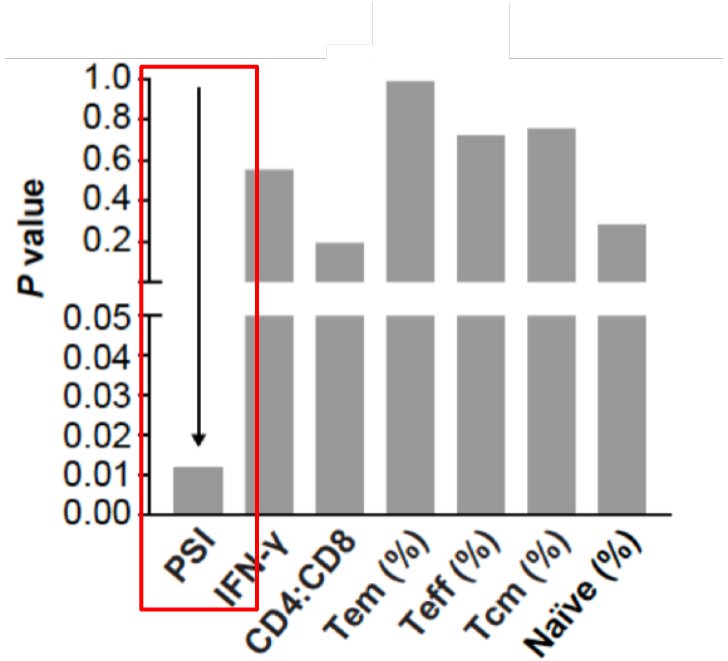
Neither the %CD19 CAR+ T Cells Nor IFN-g Production by Final Drug Product Predict Clinical Response

Novartis' Kymriah for PedALL





Kite's Yescarta for Lymphoma



"Preinfusion polyfunctional anti-CD19 chimeric antigen receptor T cells associate with clnical outcomes in Non-Hodgkin Lymphoma (NHL)"

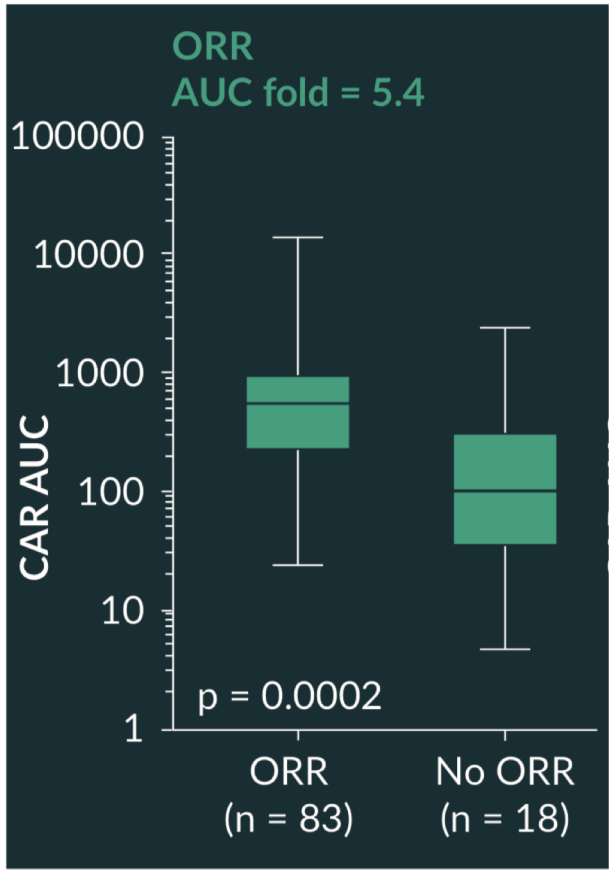
Rossi et al.

blood®

prepublished online June 12, 2018

CD19 CAR-T Products from Responders Display Greater *In Vivo* Cell Expansion Compared to Nonresponders

Kite: Yescarta



Novartis: Kymriah

	Responder N=42	Nonresponder N=3
Geometric mean (CV%)		
$AUC_{0\text{-}28d}$, copies/µg·day	349,000 (159)	210,000 (152)
C_{max}, copies/µg	41,000 (136)	23,500 (110)
Median (range)		
T_{max}, days	10 (0-27)	27 (19-63)
T_{last}, days	93 (27-366)	68 (29-84)

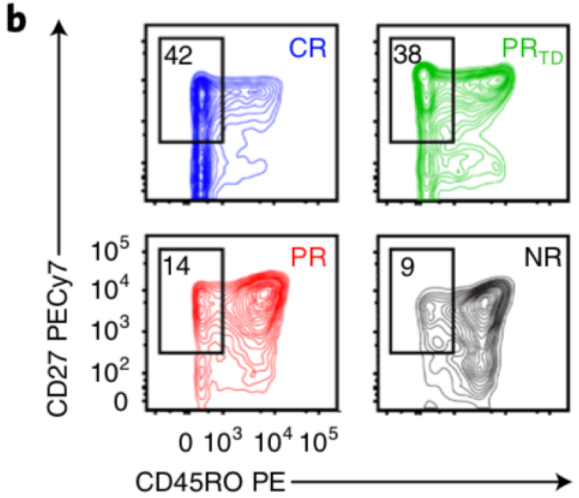
FDA ODAC Meeting, July 12, 2017

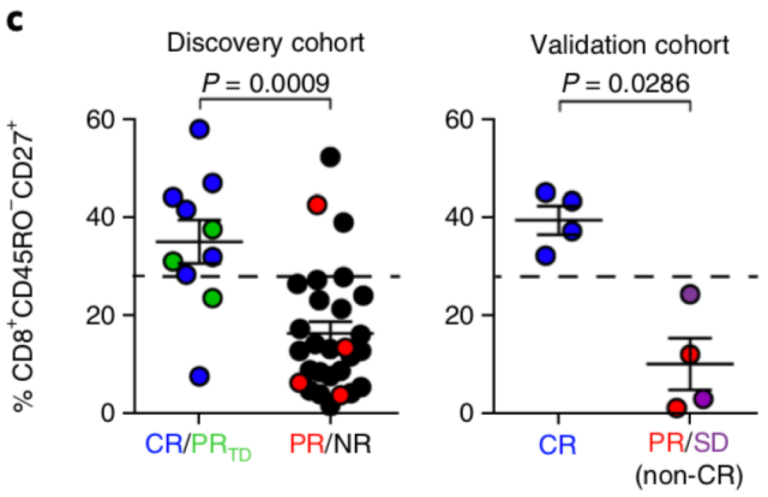
Better et al.
Cell and Gene Therapy Insights, 2018

- **Novartis:** "2-fold higher expansion in responders vs nonresponders and delayed Tmax in nonresponders (Study B2202)."
- **Kite:** "CAR T cell engraftment/expansion correlates with clinical outcome."

- Can we identify any attributes, earlier in the manufacturing process, that associate with response?

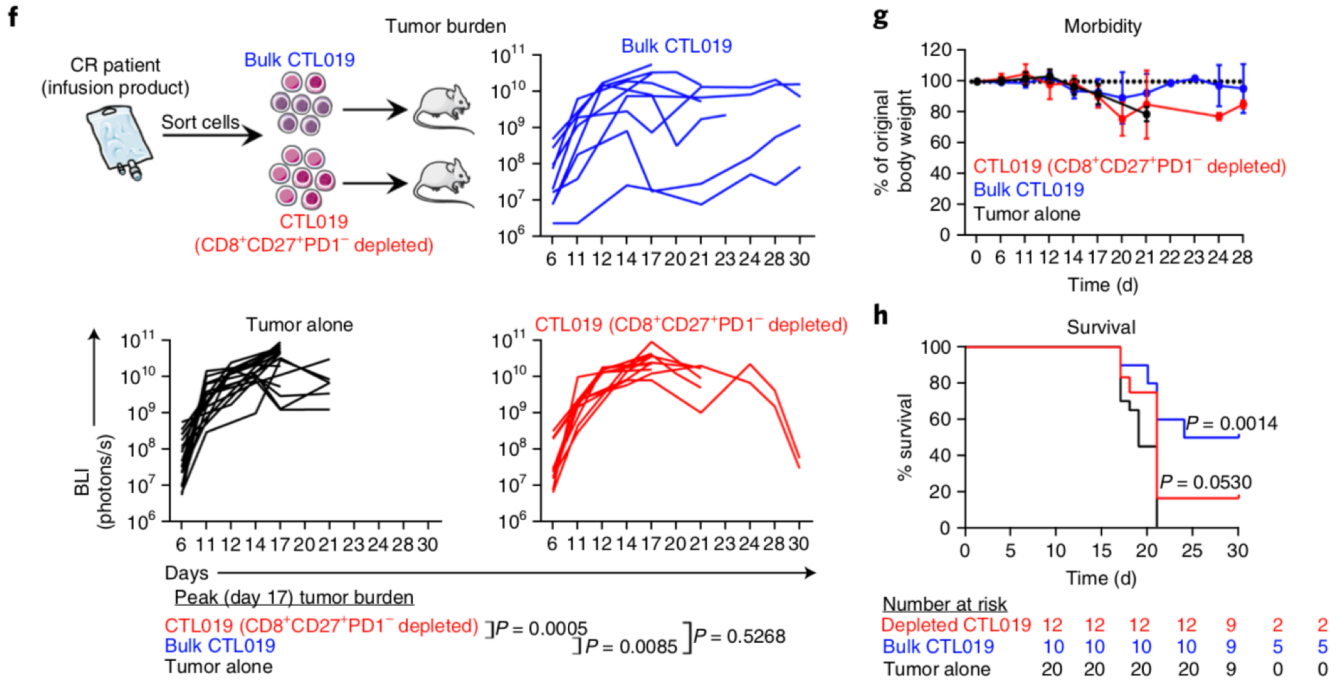
Frequency of CD27+ T Cell Subset within Starting Apheresis and Final CD19 CAR-T Drug Product Associates with Clinical Outcome in CLL Patients





Leukapheresis biomarker (CD8$^+$CD45RO$^-$CD27$^+$)

	Specificity	Sensitivity
Discovery	89%	80%
Validation	100%	100%



Fraietta et al.
Nature Medicine, 2018

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Summary

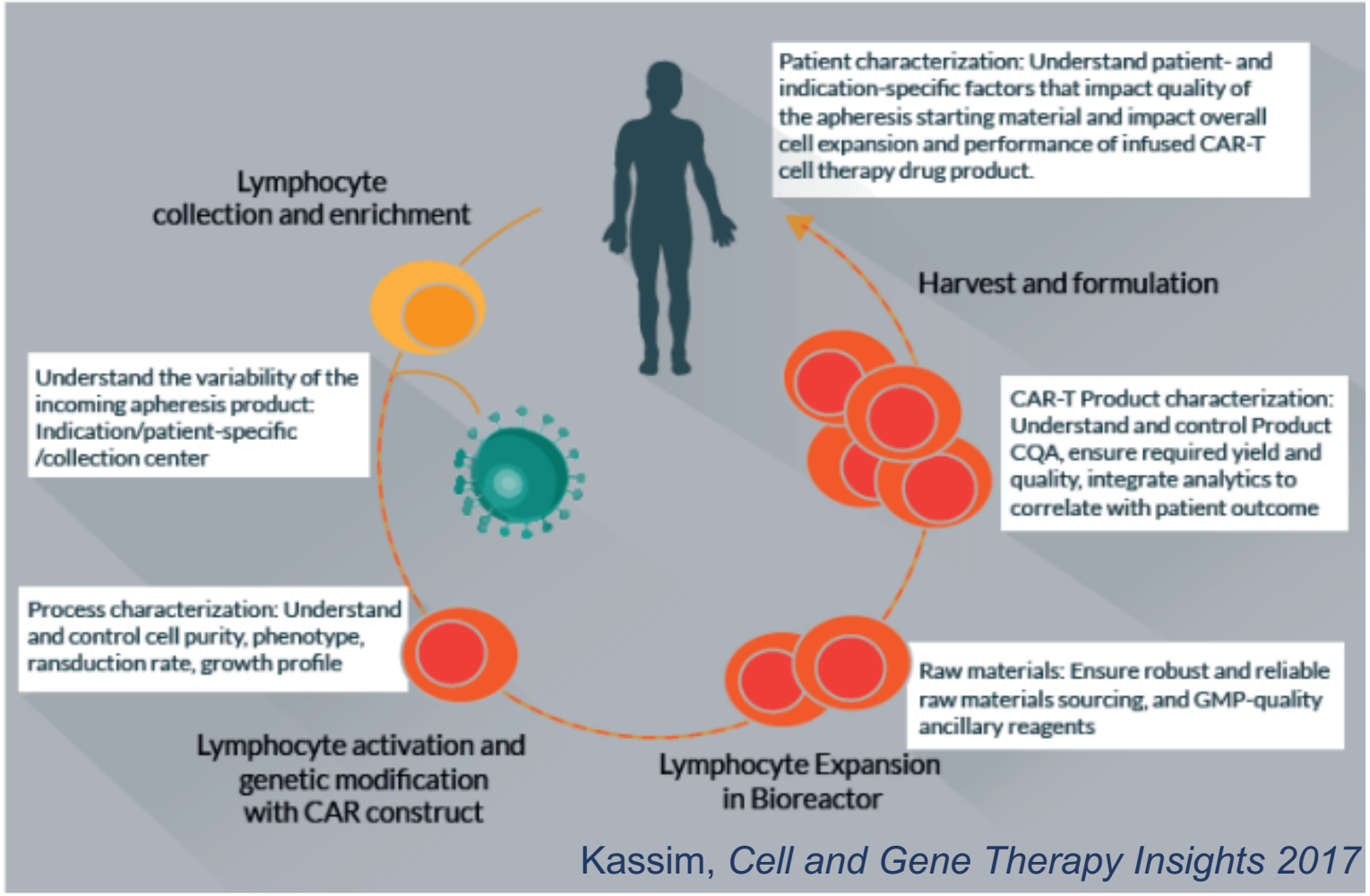
-Current academic CAR T cell manufacturing processes contain common operations that can be simplified and automated to enable scale up and scale out.

-Kite's primary objective was to develop a serum-free, bead-free, closed manufacturing process to enable a multi-center CAR-T trial.

-Novartis' primary objective was to increase automation and minimize raw material/ancillary material changes to enable rapid global scale out of CAR-T trials.

-Integrated analytical characterization throughout the drug development process will enable a more seamless transition of CAR-T therapies from academia to industry.

The Role of Integrated Analytics in CAR-T Drug Product Development



Kassim, *Cell and Gene Therapy Insights 2017*

<u>An Integrated Analytical Strategy Can Enable:</u>

1) A more seamless transition from academic institutions to industry.
2) Reproducible manufacturing.
3) Patient selection and improved clinical outcome.