FROM BENCH TO BEDSIDE: THE CURRENT LANDSCAPE OF IMMUNE EFFECTOR CELL (IEC) THERAPIES IN NORTH DAKOTA

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SANFORD HEALTH

Disclosures

- Kayleigh Buescher, MLS – no financial disclosures
- Nicholas Gau, MD – no financial disclosures
- *Descriptions of FDA-approved products are illustrative only and do not indicate presenter endorsement*

OBJECTIVES

- Compare and contrast types of immune effector cell (IEC) therapies (e.g. chimeric antigen receptor T cells, tumor infiltrating lymphocytes, adoptive natural killer cells).
- List conditions currently being treated with FDA-approved IECs and clinical trial IECs.
- Discuss the laboratory workflow involved in manufacturing IEC therapies.
- Evaluate challenges laboratories face in working with multiple 3rd party IEC manufacturers.

USEFUL CONTEXT

KEY TERMS

- Cellular Therapy:
  - The use of HCT/Ps to treat, or support treatment of, medical conditions

  X ~~Blood and blood components, human organs~~

- Immune Effector Cell:
  - “A cell that has differentiated or manufactured into a form capable of modulating or effecting a specific immune response” (FACT)

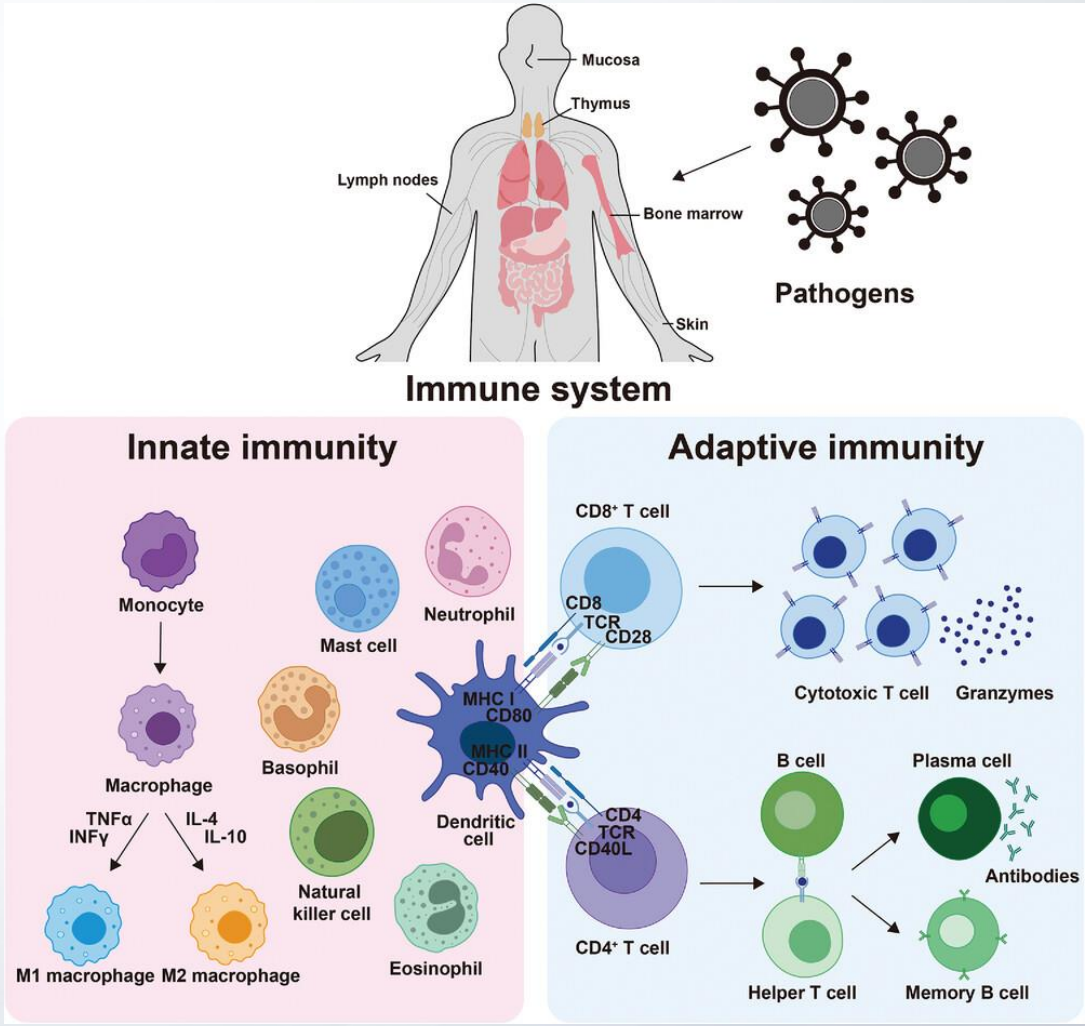
- Autologous:
  - Source of cells/tissue is self
- Allogeneic:
  - Source of cells/tissue is another

WHAT RULES MUST BE FOLLOWED?

- 21 CFR 1271 – defines "Human Cells, Tissues, and Cell-and-Tissue-Based Products" (HCT/Ps)
  - Regulations nicknamed "Good Tissue Practice"
  - Enforced by US FDA
  - Focused on preventing harm from transmissible disease, mix-ups, and contamination
- Genetically modified HCT/Ps also regulated as drugs
- Bodies that accredit cell processing labs:
  - Foundation for Accreditation of Cellular Therapy (FACT)
  - Association for the Advancement of Blood and Biotherapies (AABB)
  - College of American Pathologists (CAP)

EXAMPLE CELLULAR IMMUNOTHERAPIES

- Cancer "Vaccines"
  - Autologous dendritic cells activated and uploaded with cancer antigen
- Tumor Infiltrating Lymphocytes (TILs)
  - Autologous lymphocytes isolated from tumor, activated with cytokines, and reinfused
- Chimeric Antigen Receptors (CARs)
  - Autologous NK cells or T cells given engineered cell membrane receptor targeting cancer



CANCER "VACCINES"

- Macrophages & dendritic cells engulf and process antigens
- May migrate to regional lymph nodes
- Present antigens on cell surface in MHC II protein
- Lymphocyte recognizes antigen in MHC and activates

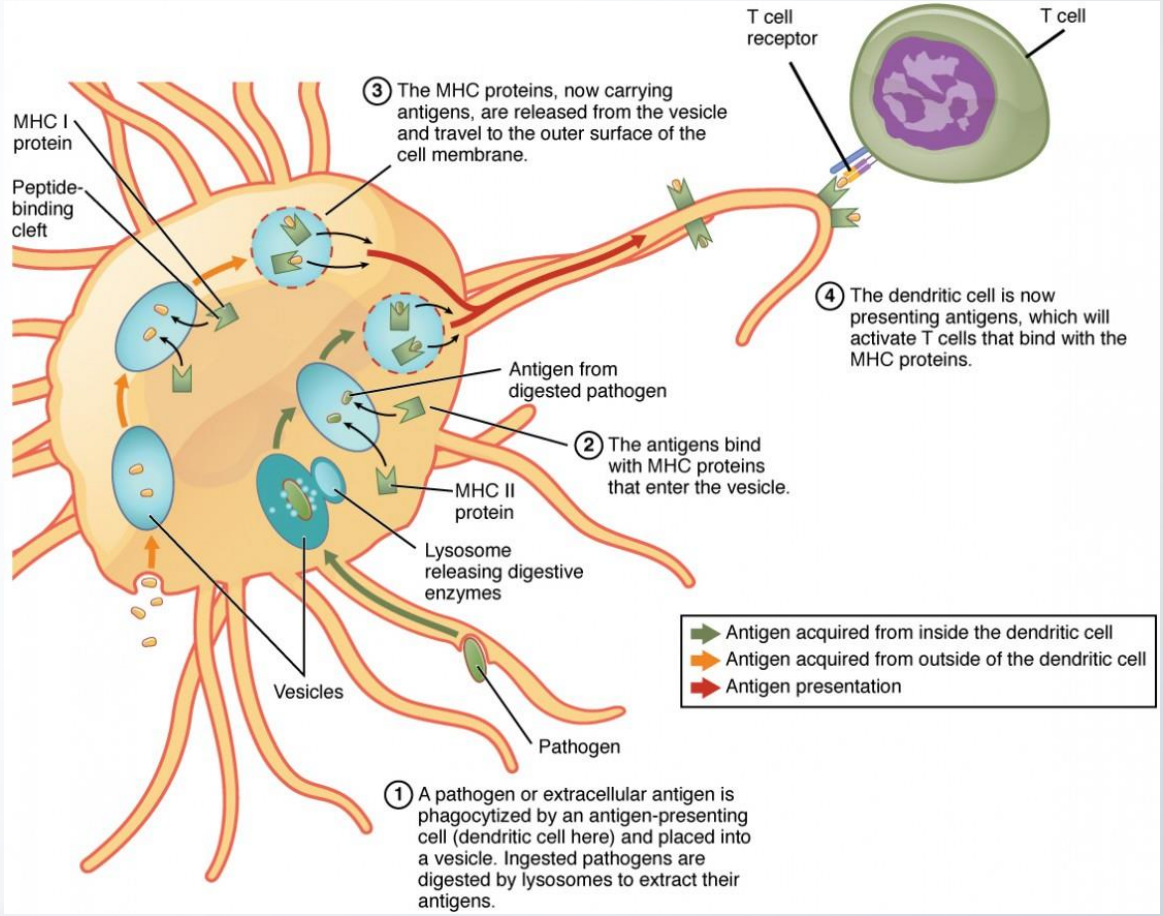


Image Credit: Figure 3. Antigen Processing and Presentation. https://courses.lumenlearning.com/pgcc-ap2/chapter/the-adaptive-immune-response-t-lymphocytes-and-their-functional-types/

IEC THERAPY: SIPLEUCEL-T (PROVENGE®)

- Autologous “cancer vaccine” targeting prostate cancer
- Manufacturing[2]:
  - Ex-vivo exposure to prostatic acid phosphatase (PAP) and activating cytokines
- Efficacy of 3 infusions for metastatic prostate cancer[3]:
  - 22% reduction in risk of death vs. placebo
  - Median survival increased by 4 months; longer for those with lower PSA

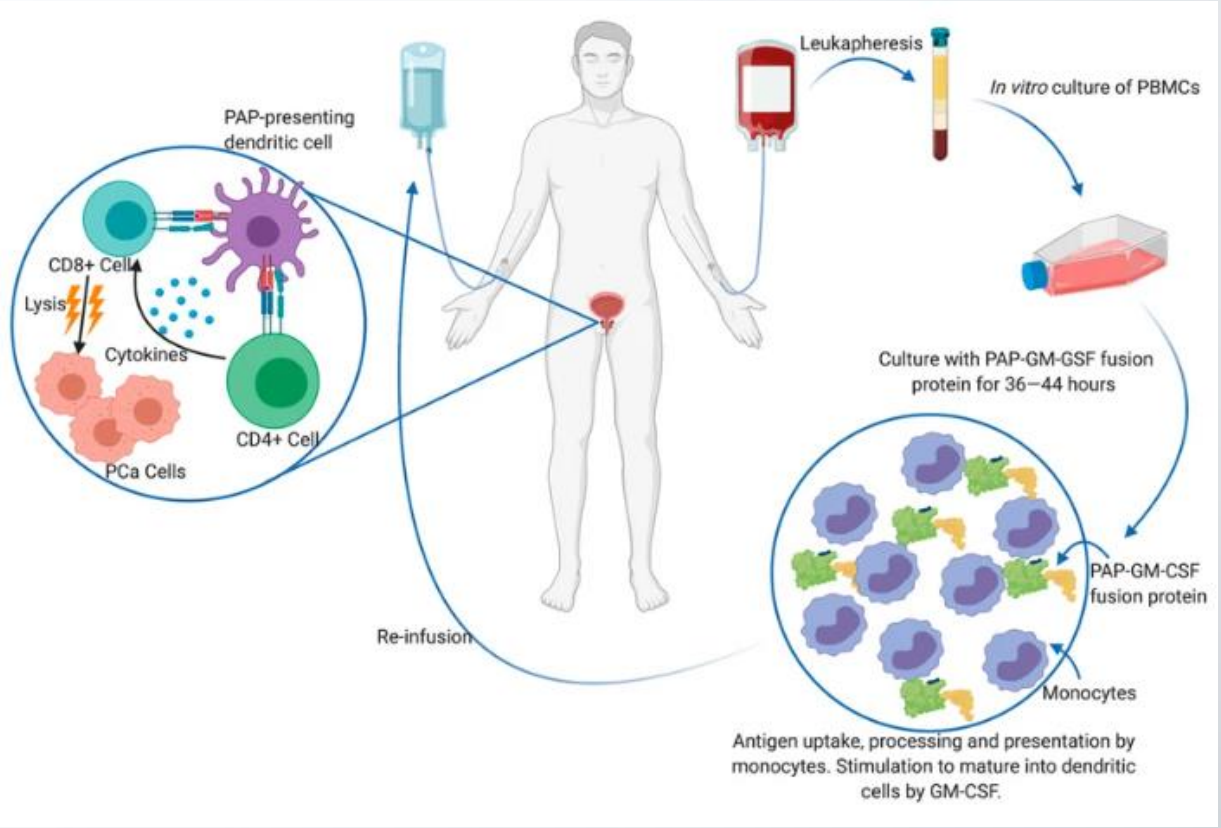
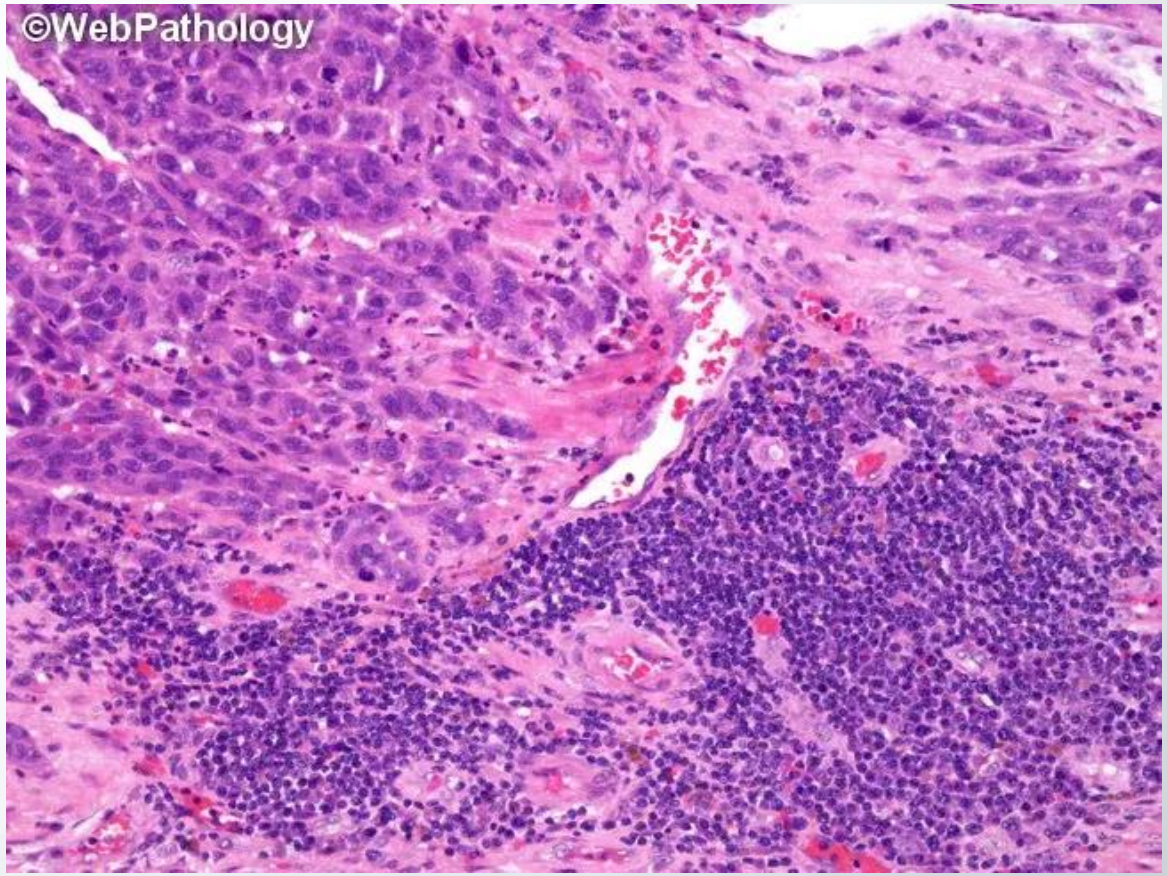


Image Credit: Shackleton EG, et al. *Cancers*, 2021;13:1145. https://doi.org/10.3390/cancers13051145

TUMOR INFILTRATING LYMPHOCYTES (TILS)

- Dense collar or infiltrate of lymphocytes portends more favorable prognosis in cutaneous melanoma
- Lymphocytes are mixed types (B cells, CD4+ T cells, CD8+ T cells)
- TILs decrease overall risk of death by 35%[4]



IEC THERAPY: LIFILEUCEL (AMTAGVI®)

- Autologous T lymphocyte product targeting melanoma
- Manufacturing[4]:
  - Harvest of living tumor tissue
  - Ex-vivo isolation, expansion, and activation of T cells with IL-2
- Efficacy for metastatic melanoma[5]:
  - 31.5% response rate
  - ~6 weeks to response; over 50% of responses maintained at 12 mo.

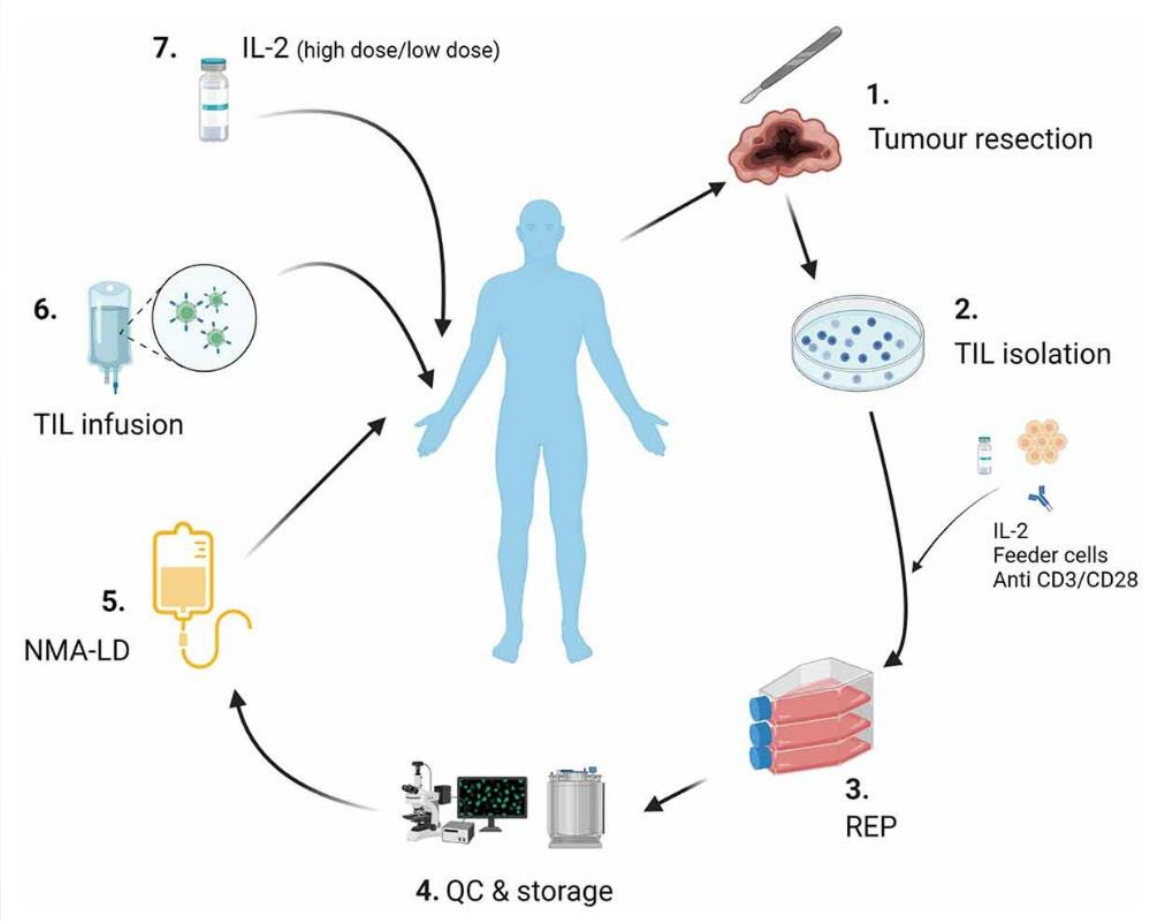


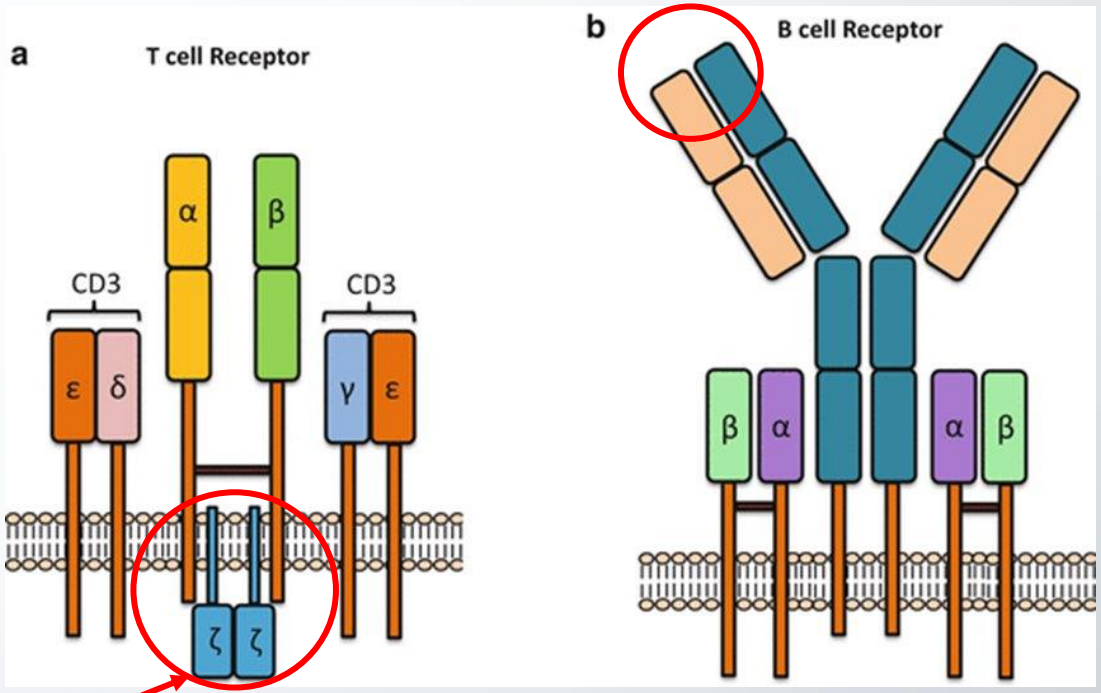
Image Credit: Julve M & Furness AJS. *Ex Opin Biol Ther*, 2023;23:319-23. https://doi.org/10.1080/14712598.2023.2193290

CHIMERIC ANTIGEN RECEPTOR T CELLS (CAR-T)

WHAT'S A CHIMERA?

- Combines parts from different animals

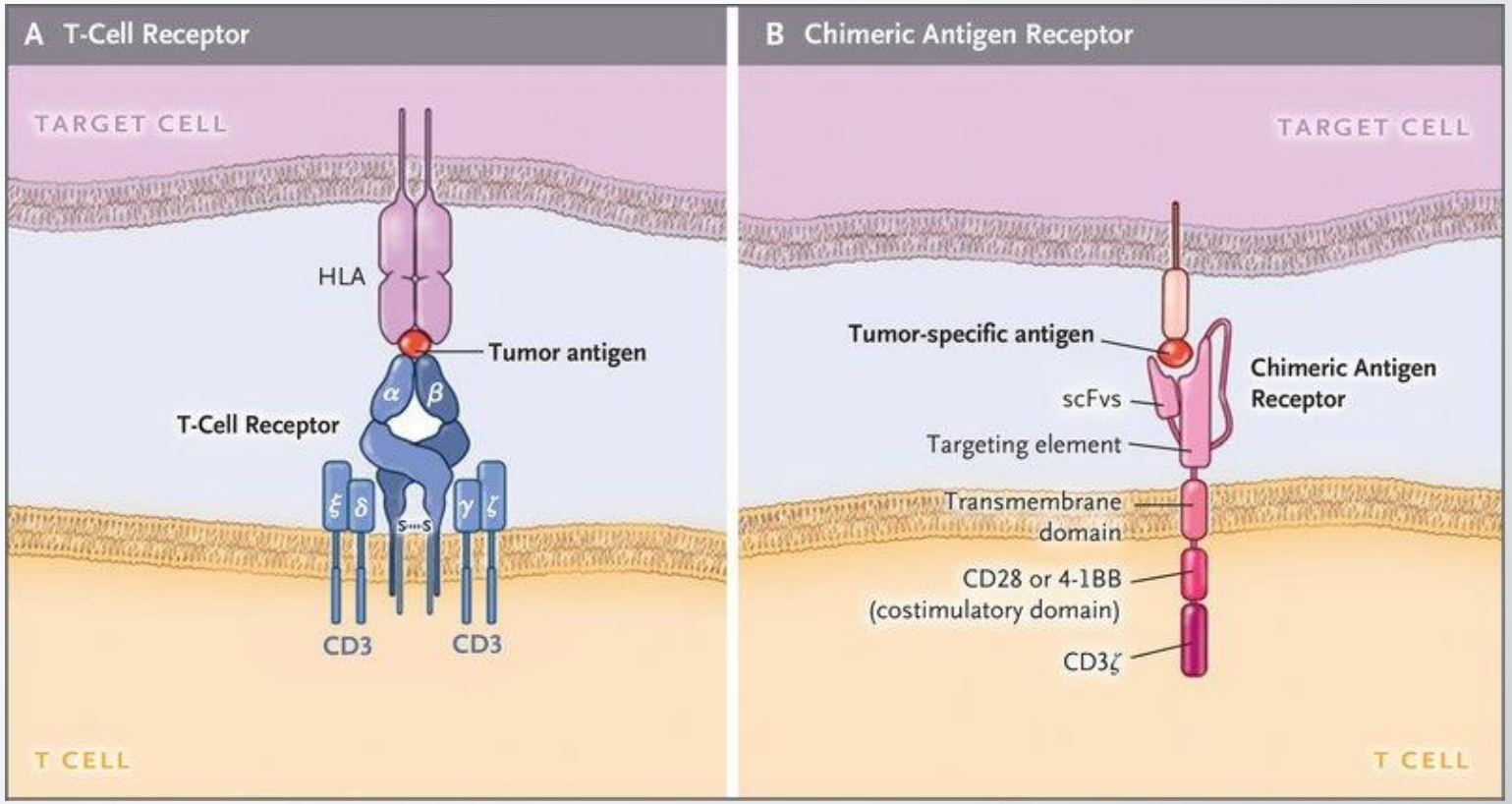
B cells receptors are similar to membrane-bound antibody; recognize "free" antigens



Internal T cell receptor domains result in activation and effector functions

CHIMERIC ANTIGEN RECEPTORS (CARS)

- Engages with target antigen without MHC
- Internal activation domains cause cell signaling and activation
- Removes some natural brakes on immune response



June CH & Sadelain M. *N Engl J Med*, 2018;379:64-73. Doi: 10.1056/NEJMra1706169.

CAR-T CELL MANUFACTURING

- Marketed products use a lentiviral vector to introduce CAR to activated T cells
- Dose varies, but ~ 1.0 x 10^8 living CAR-T cells desired for infusion
- Collection to infusion ~3 weeks

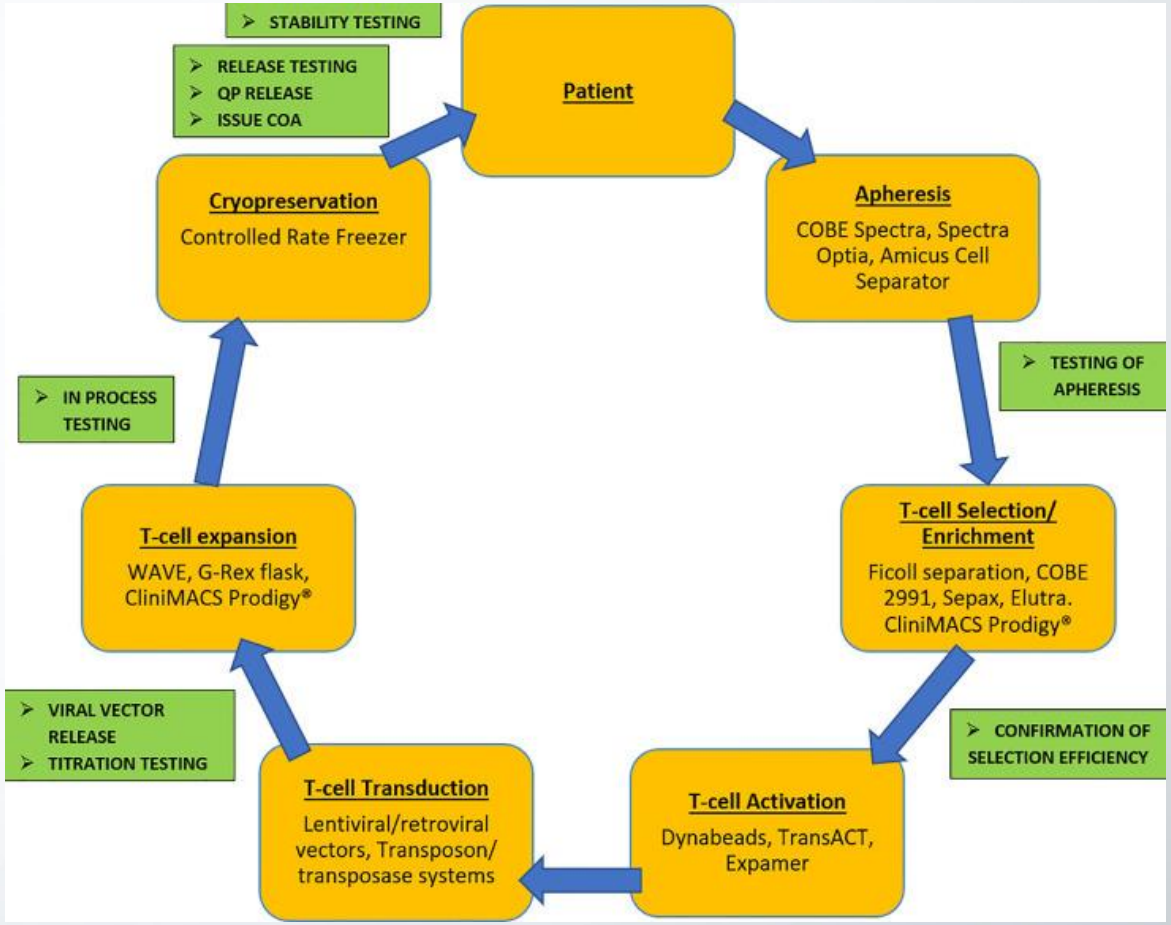


Image Credit: Roddie C, et al. *Cythother*. 2019;21:327-340. https://doi.org/10.1016/j.jcyt.2018.11.009

BUILDING BETTER CARS[6]

- Gen 1 – insufficient activity
- Gen 2 – tumor recurrence
- Gen 3 – high toxicity (CRS)
- Gen 4 – ("TRUCKs") on-target, off tumor toxicity; poor infiltration of solid tumors
- Gen 5 – JAK/STAT signaling to boost cytokine response and persistence

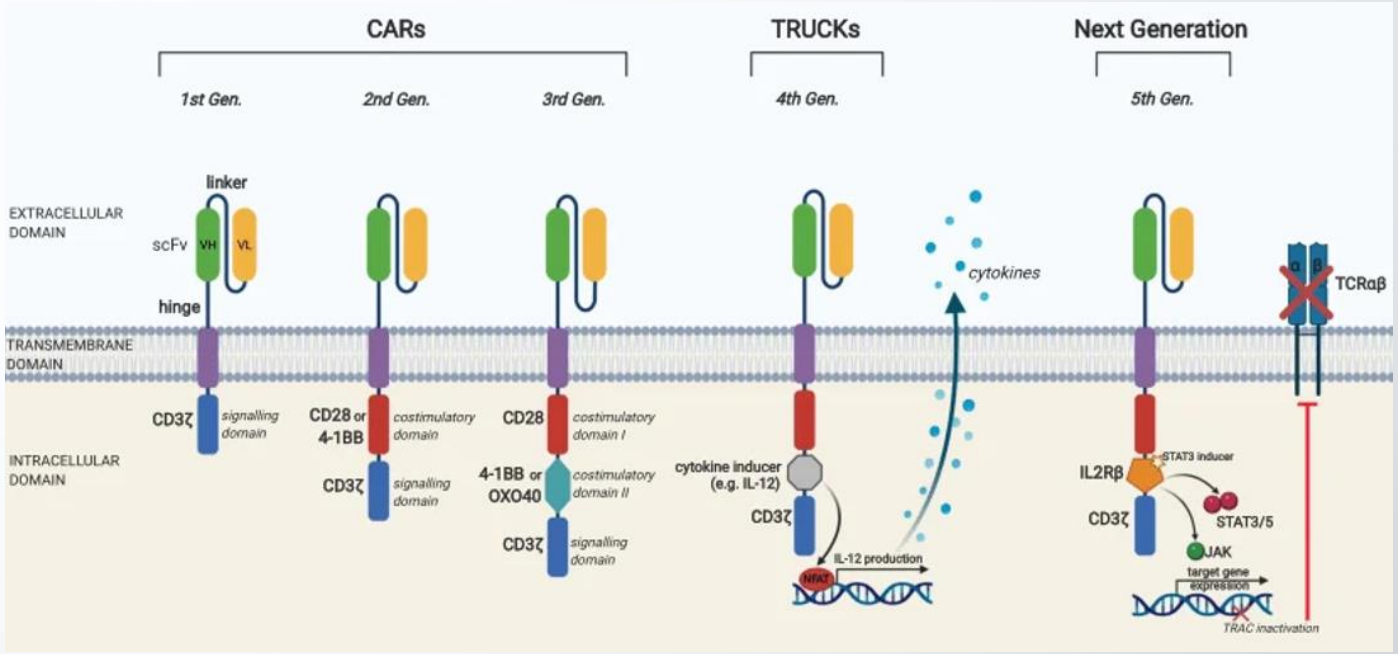


Image credit: Rallis K et al. *Anticanc Res*, 2021;41:1143-56. Doi: 10.21873/anticanres.14781.

CLINICAL ASPECTS OF CAR-T

- Approved products are still 2nd/3rd-line therapies for B cell/plasma cell disorders
- Vaccination before treatment advised
- Lymphodepleting chemotherapy a few days before infusion
- Close monitoring required for 10-14 days following infusion:
  - Cytokine release syndrome (CRS)
  - Neurotoxicity (ICANS)
- Cytopenias/transfusion common after treatment

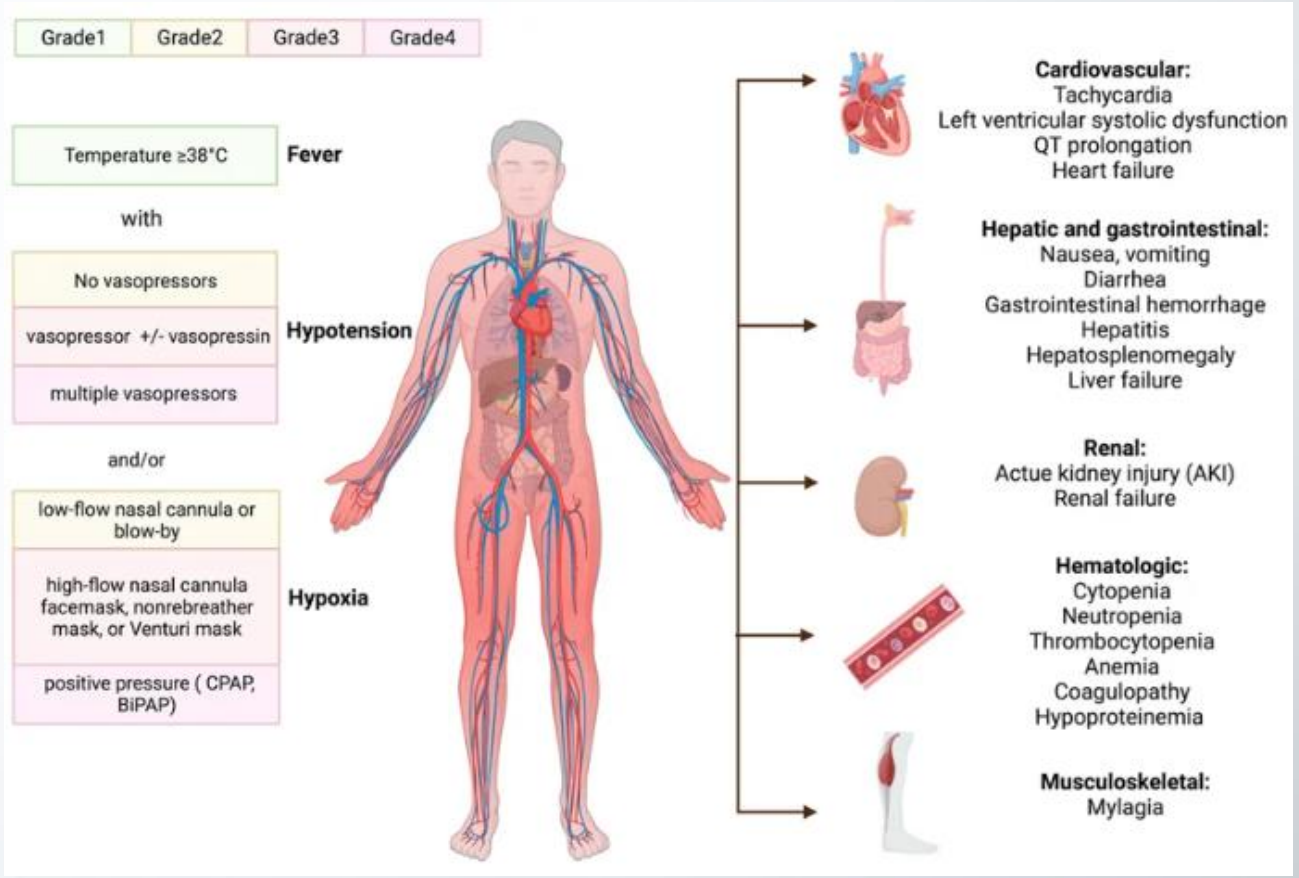


Image credit: Zhang Y et al. *J Clin Med*, 2023;12:6124. Doi: 10.3390/jcm12196124.

BENEFITS OF CAR-T FOR MULTIPLE MYELOMA

- CARTITUDE-4 Trial[7] (ciltacabtagene autoleucel)
- Relapsed/refractory MM after at least 1 line of therapy
- CAR-T group:
  - 40% less likely to progress
  - Triple the complete response rate
  - Death 45% less likely in at 33 months post infusion

- KarMMa-3 Trial[8] (idecabtagene vicleucel)
- Relapsed/refractory MM after at least 2 lines of therapy
- CAR-T group:
  - Half as likely to progress/die at 13 months post infusion
  - 8 times as many patients had a complete response
  - Higher rate of severe adverse events

FDA-APPROVED CANCER CELLULAR IMMUNOTHERAPIES – APRIL, 2026

Year Approved	Type	Drug Name	Trade Name	Target	Approved Disease(s)
2010	Dendritic cell Vaccine	Sipuleucel-T	PROVENGE	PAP	Prostatic carcinoma
2017	CAR-T	Tisagenlecleucel	KYMRIAH	CD19	B cell ALL, B cell lymphomas
2017	CAR-T	Axicabtagene ciloleucel	YESCARTA	CD19	B cell ALL, B cell lymphomas
2020	CAR-T	Brexucabtagene autoleucel	TECARTUS	CD19	B cell ALL, B cell lymphomas
2021	CAR-T	Idecabtagene vicleucel	ABECMA	BCMA	Multiple myeloma
2021	CAR-T	Lisocabtagene autoleucel	BREYANZI	CD19	B cell ALL, B cell lymphomas
2022	CAR-T	Ciltacabtagene autoleucel	CARVYKTI	BCMA	Multiple myeloma
2024	CAR-T	Obecabtagene autoleucel	AUCATZYL	CD19	B cell ALL
2024	TIL	Lifileucel	AMTAGVI	--	Melanoma

ACTIVE CAR-T TRIALS IN 2026[9]

- 893 trials related to "CAR-T"
- 20 in Phase 3
- 12 in the US
  - 8 evaluating use of drug
  - 2 regarding long term follow up of CAR-T recipients
  - 1 regarding telemonitoring
  - 1 regarding lymphodepletion regimen in children

Study	Disease	Target(s)
Rondecabtagene autoleucel vs. Other CD19 CAR-T	Large B cell lymphoma	**CD19 + CD20**
Mivocabtagene autoleucel vs. SOC	**Myasthenia gravis**	CD19
"Descartes-08" (**mRNA CAR-T**) vs. Placebo	**Myasthenia gravis**	BCMA
AZD0120 (CAR-T) vs. SOC	Multiple myeloma	**BCMA + CD19**
Arlocabtagene autoleucel vs. SOC	Multiple myeloma	**GPRC5D**
Axicabtagene ciloleucel as **1st line** vs. SOC	Large B cell lymphoma	CD19
CABA-201 (CAR-T)	**Idiopathic inflammatory myositis (IIM)**	CD19
Anitocabtagene autoleucel vs. SOC	Multiple myeloma	BCMA

IEC EXPERIENCE IN NORTH DAKOTA

SANFORD HEALTH – FARGO

2023-2026

IMMUNOTHERAPIES OFFERED

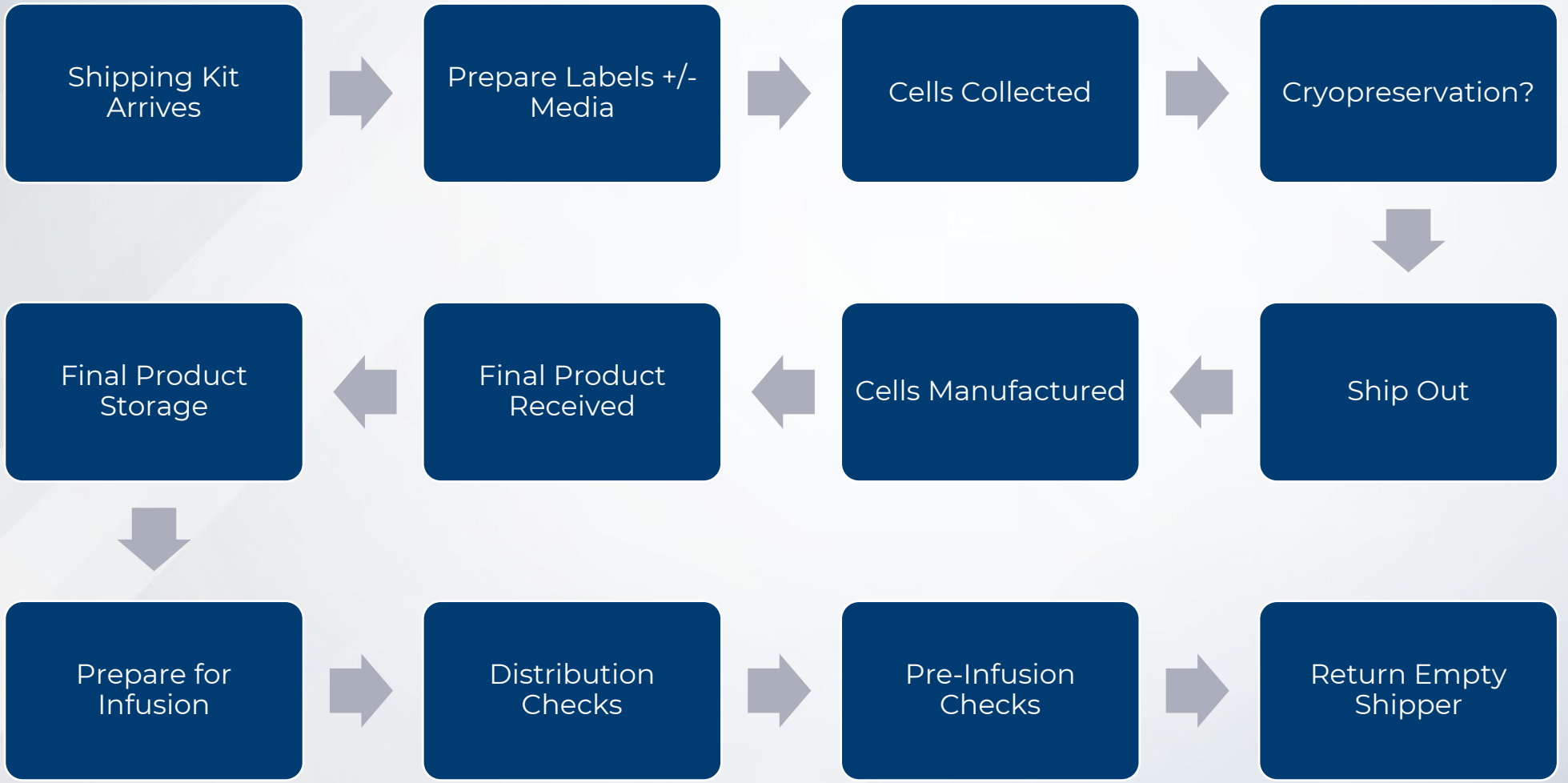
Manufacturer	Year Added	Type	Drug Name	Products Manufactured	Disease(s)
A	2023	CAR-T (CD19)	Axicabtagene ciloleucel	15	B cell ALL, B cell lymphomas
A	2023	CAR-T (CD19)	Brexucabtagene autoleucel	6	B cell ALL, B cell lymphomas
B	2024	CAR-T (BCMA)	Idecabtagene vicleucel	0	Multiple myeloma
B	2024	CAR-T (CD19)	Lisocabtagene autoleucel	9	B cell ALL, B cell lymphomas
C	2025	CAR-T (CD19)	Tisagenlecleucel	0	B cell ALL, B cell lymphomas
D	2025	CAR-T (BCMA)	Ciltacabtagene autoleucel	17	Multiple myeloma
E	2025	TIL (clinical trial)	Lifileucel	1	Non-small cell lung carcinoma

PREPARING TO OFFER IEC PRODUCTS

- Contract signed

- Pre-implementation work:
  - Review 3rd party SOPs
  - Provide tour and explanations of key processes (e.g. shipping and storage)
  - Update forms or SOPs to satisfy 3rd party
  - Training on 3rd party SOPs, online portal, shipping

(LAB-FOCUSED) IEC PROCESS OVERVIEW



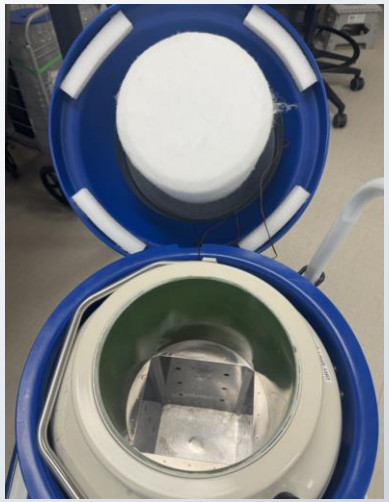
Each step: Document!

SHIPPING CONTAINER ARRIVES

- Nanocool
- Credo Cube
- Dry Shipper

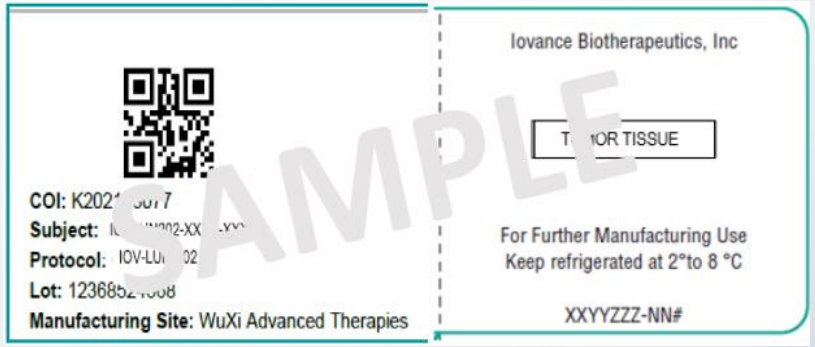
- Chain of Identity (COI) check
  - In portal
  - Waybill

https://www.pelibiothermal.com/product/credo-cube/



PRODUCT LABEL

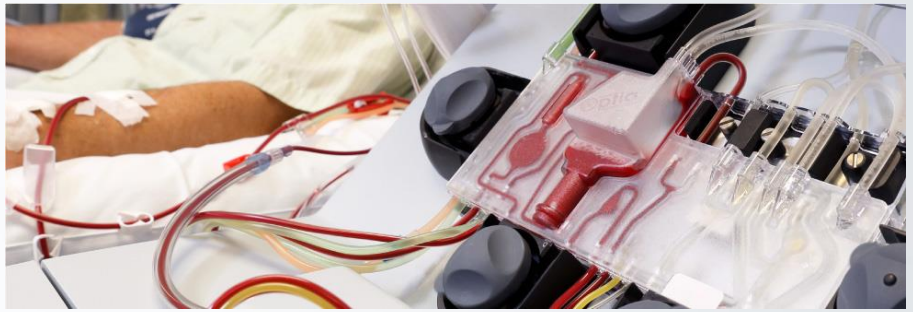
- Collection Facility Label
  - ISBT-128 label format
- Identifiers
  - DIN
  - Donor/Recipient Name + DOB
  - COI
  - Lot number
  - Order number
- 3rd Party-Specific Label?
  - Access through portal and print
  - Sent with shipper



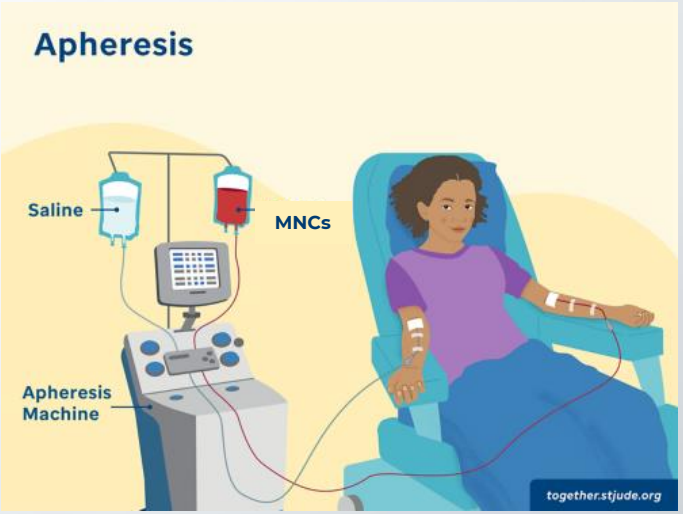
APHERESIS COLLECTION

- Performed by RN's
- Centrifuge whole blood
  - Collect mononuclear cell layer
  - Contains primarily lymphocytes and monocytes
- Amount collected varies per manufacturer
  - 2 to 5 hours collection time

- Adverse effects:
  - Pain and complications from peripheral access or central line
  - Hypotension
  - Thrombocytopenia
  - Citrate toxicity (hypocalcemia)



https://www.terumobct.com/spectra-optia



https://together.stjude.org/en-us/diagnosis-treatment/treatment/bone-marrow-transplant/autologous-stem-cell-bone-marrow-transplant.html

TUMOR INFILTRATING LYMPHOCYTE HARVEST

- Surgical excision of lymph node or metastatic tumor
- Need 1-4 cm^3 of viable tumor, cut into fragments
- Placed in sterile transport media in OR
  - Media may be prepared fresh by lab in BSC on harvest day

PRODUCT PICKUP

- Read off with RN
- Sign chain of custody
  - Chain of custody
  - Sign-off in portal
  - Package insert
- Product transported in validated cooler

SANFORD
ROGER MARIS
CANCER CENTER

Blood Disorders & Bone Marrow Transplant
Cell Therapies Laboratory

Donor Name: _____
Donor DOB: _____
Donor MRN: _____
3rd Party/Study ID: _____
Recipient Name/ID: ☐ N/A _____
Recipient MRN: ☐ N/A _____

CTL-608-1 PRODUCT CHAIN OF CUSTODY FORM

FROM: _____
Sanford Roger Maris Cancer Center
801 Broadway North
Fargo, North Dakota 58102

TO: Dr. Nicholas Gau 701-234-2234
Cell Therapies Laboratory at Sanford Health System
737 Broadway North - Room 4C180
Fargo, North Dakota 58122

☐ **ISBT DIN:** ☐ N/A _____ **3rd Party/Study Lot:** ☐ N/A _____
☐ **COI:** ☐ N/A _____ **Donor Identity Confirmed by:** _____
Collection Date: ____/____/____ **Collection End Time:** _____ **Collected By:** _____
Product Labeled by: _____ **Label Verification (2nd Staff):** _____

Label Reconciliation: **No. DIN Labels received:** _____ **Used:** _____ **Discarded:** _____ ☐ **N/A**
No. Base labels received: _____ **Used:** _____ **Discarded:** _____ ☐ **N/A**
(Includes ISBT-128 HPC, concurrent plasma, MNC, or other product type container label)
No. 3rd Party/Study labels received: _____ **Used:** _____ **Discarded:** _____ ☐ **N/A**

Biohazard Warning Labels Applied to Product (if applicable); Check appropriate boxes ☐ **N/A**
☐ **#1 NOT EVALUATED FOR INFECTIOUS SUBSTANCES**
☐ **#2 WARNING: REACTIVE TEST RESULTS FOR:_____; BIOHAZARD LABEL**
☐ **#3 WARNING: ADVISE PATIENT OF COMMUNICABLE DISEASE RISK; BIOHAZARD**

*** Press **MAX/MIN, RESET, MAX/MIN, RESET** on the Humidity/Temperature monitoring device to clear history ***

Product Release By: _____ **Date/Time:** _____
Product Released To: _____ **Date/Time:** _____
Product Release By: _____ **Date/Time:** _____
Product Released To: _____ **Date/Time:** _____
Product Release By: _____ **Date/Time:** _____
Product Released To: _____ **Date/Time:** _____

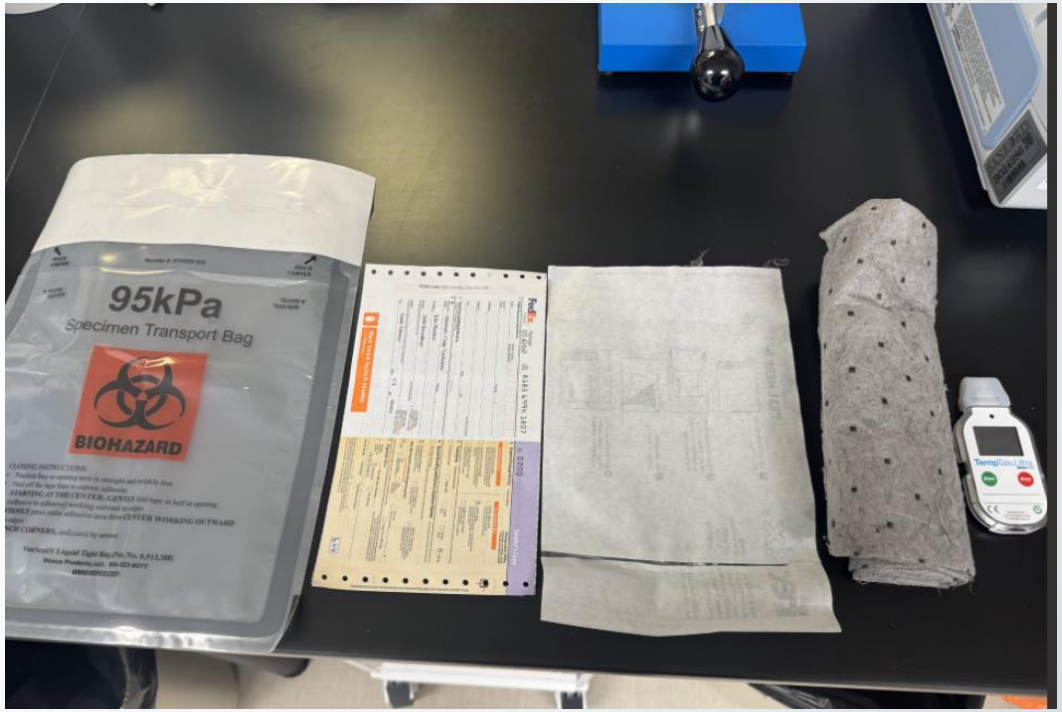
General Handling Instructions: Keep container upright, Protect from exposure to extreme temperatures, DO NOT leave unattended, Transport to destination as soon as possible.
Special Handling Instructions: Human Cells – Handle with Care; **Do Not X-Ray or Irradiate.**

Arrival Date/Time	Current Temp (C)	Current Humid. (%)	Max. Temp (C)	Max. Humid. (%)	Min. Temp (C)	Min. Humid. (%)	Inspection (Pass/Fail)	Tech

Release time to arrival time must be ≤30 min. Acceptable HPC temp: 15-30°C. Acceptable humidity: 5-80%.
See 3rd party/study protocol for acceptable transport temps where applicable.
Examine product for leaks, clots, hemolysis, or discoloration & for intact labeling upon arrival.

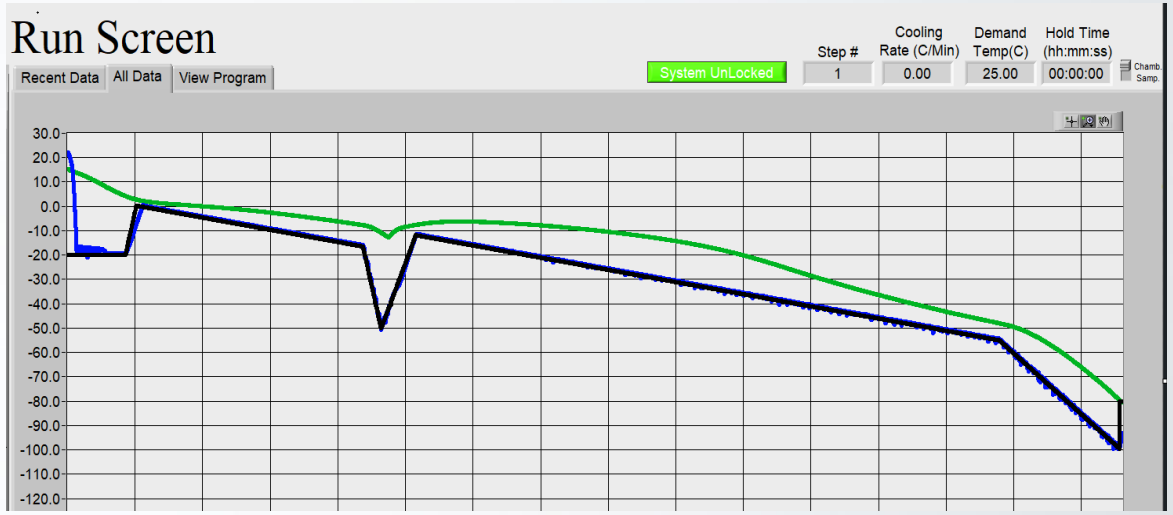
PREPARATION FOR SHIPMENT

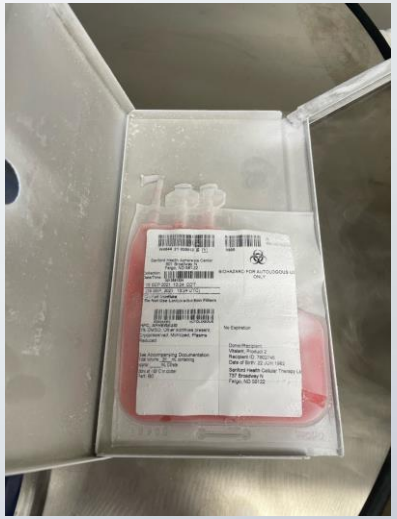
- Product inspection
- Label check
- Release criteria check
- COI checks
  - Portal sign-off
- Product tracking form



PRODUCT CRYOPRESERVATION

- Some products may require or allow on-site freezing before shipment to 3rd party
- Follow Cellular Therapy autologous freezing protocol
  - Take sample for cultures (pre and post processing) and cell counts
    - Need CD3+ count by flow cytometry
  - DMSO-based cryoprotectant
  - Use controlled rate freezer to bring cells to –80C
  - Transfer to vapor phase nitrogen storage (-130 to –196C)





SHIP TO 3RD PARTY FOR MANUFACTURE

- Waybill sign off
- Internal chain of custody
- Pharmaceutical companies typically subcontract shipping to courier services

CAR-T MANUFACTURING

- Activate/genetically modify T-Cells
- Culture activated/modified cells
  - Usually mixed T cells, but may be separated into CD4+ and CD8+
- Cryopreserve
  - Bags or vials
- Label (drug label if FDA-approved)
- Release criteria met
  - Dose, purity, viability, sterility
- Return to treatment facility

CAR-T PRODUCT RETURNED

- Chain of custody
  - Internal form
  - Waybill
- Check temperature
  - Website
  - QR code
  - Button
- COI checks
  - Tamper evident zip tie
  - Confirm correct product sent
  - Document in portal
  - Transfer to long term storage
- Internal documents
  - Product tracking form
  - Product summary and request for infusion

INFUSION

- Prepare internal infusion paperwork
  - Product Summary and Request for Infusion form
  - Infusion Summary and Adverse Reactions form
  - Final Product Release Criteria Checklist
  - Update Product Tracking form
- Add supplemental label (tie tag) for pre-infusion checks
- Make sure irradiation is added to patient blood requirement in blood bank software
- Issue product from lab
  - Includes COI checks

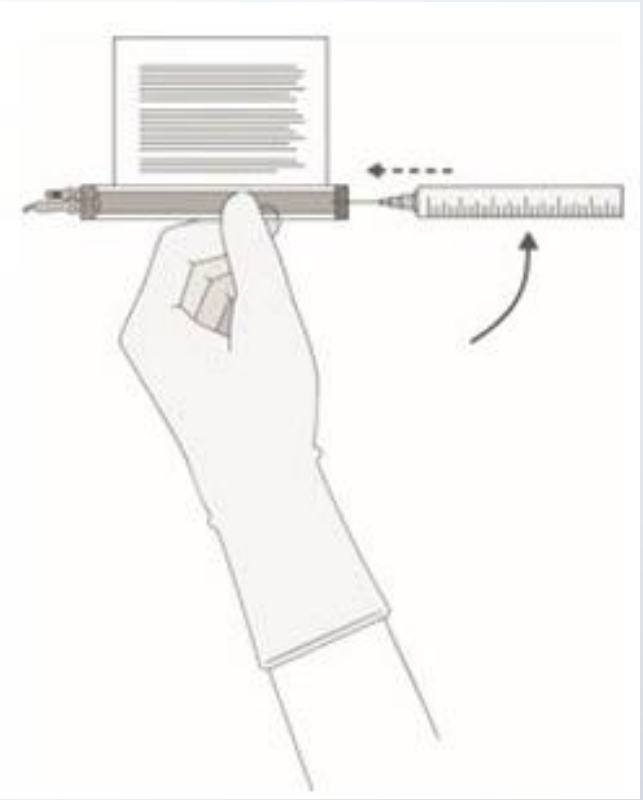
Product image for download (Photo: Bristol Myers Squibb)

BAG INFUSION

- CTL staff performs patient safety checks with RN and thaws each product bag
- 1 bag is thawed and infused before the next bag is thawed

VIAL INFUSION

- CD8
  - Up to 4 vials
- CD4
  - Up to 4 vials
- Thaw at room temp
  - 2-hour expiration
- Draw product into syringes in BSC
  - Label with Manufacture specific label
- CTL performs COI checks with RN at bedside



EXPANDED ACCESS PROTOCOL (EAP)

- Manufactured product does not meet release criteria
- Provider approval required
  - May accept product due to urgent medical need
- If accepted, additional documentation required
  - Patient essentially enrolled in a clinical trial evaluating drug at lower dose

PAIN POINTS FOR THE CLINICAL LAB

- Maintaining competency with SOPs for growing number of 3rd parties
  - SOPs divided in different ways between apheresis, lab, and clinical program
  - Maintaining document control over 3rd party SOPs
  - Updating internal worksheets to accommodate 3rd parties
- Remembering 5 different logins for 3rd party portals!
- Ensuring couriers follow protocol
  - Have left cells unattended at loading dock!!!
- Effort put into SOPs, training to support temporary clinical trial protocols

STANDARDIZATION COMING?

- FACT 9th Edition Standards require all accredited sites use ISBT-128 "split label" and assign COI
- Attempt to force pharmaceutical companies to adopt similar practices for fresh product labeling
- Pharmaceutical companies have begun contracting with non-FACT centers in recent years—will standardization happen???

QUESTIONS?

SANFORD HEALTH

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THANK YOU

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