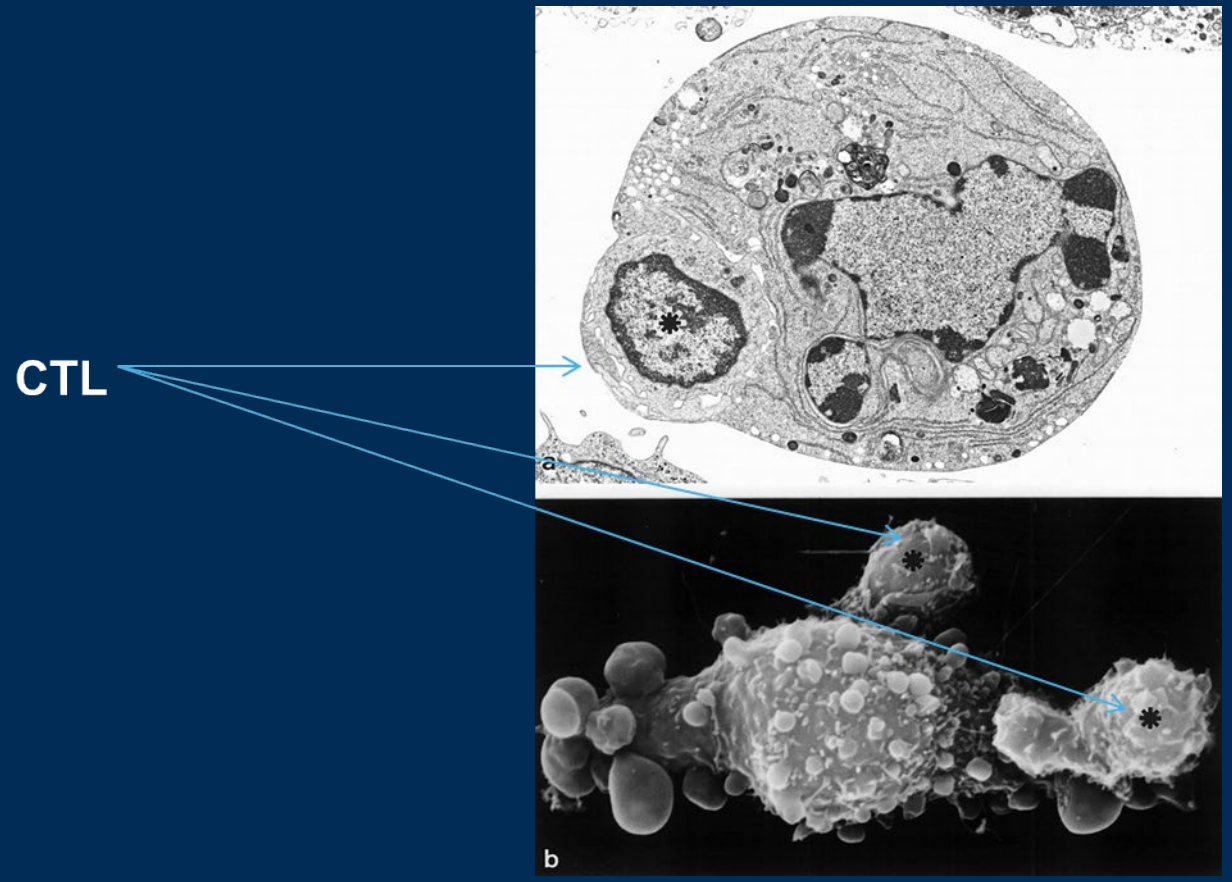
CAR T Therapy
Current Status
Future Challenges

Introduction Basics of CAR T Therapy

Cytotoxic T Lymphocytes are Specific and Potent Effector Cells



Ultrastructure of CTL-mediated apoptosis

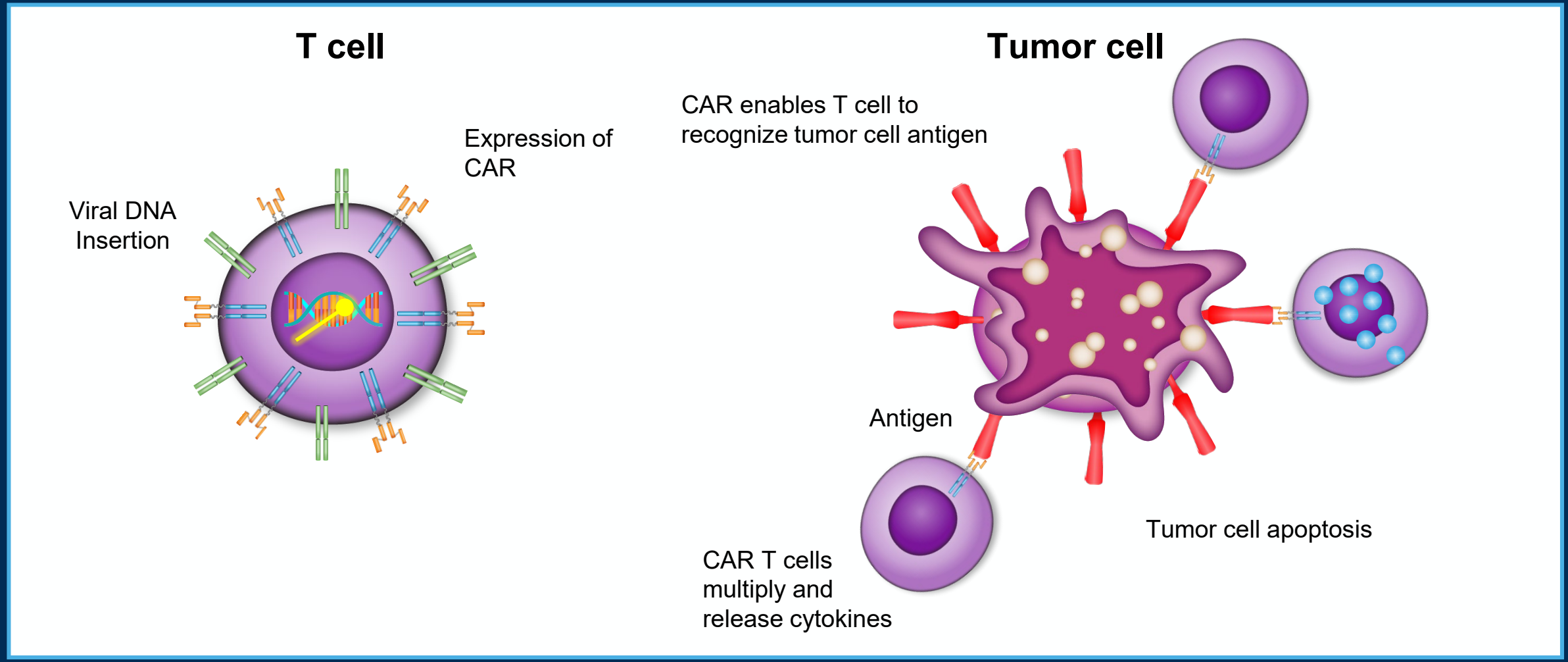
The CTL protrudes deeply into cytoplasm of melanoma cell

Peter Groscurth, and Luis Filgueira Physiology 1998;13:17-21

What is CAR T Therapy?

- CAR T therapy is the name given to chimeric antigen receptor (CAR) genetically modified T cells that are designed to recognize specific antigens on tumor cells resulting in their activation and proliferation eventually resulting in significant and durable destruction of malignant cells
- CAR T cells are considered “a living drug” since they tend to persist for long periods of time
- CAR T cells are generally created from the patients own blood cells although this technology is evolving to develop “off the shelf” CAR T cells

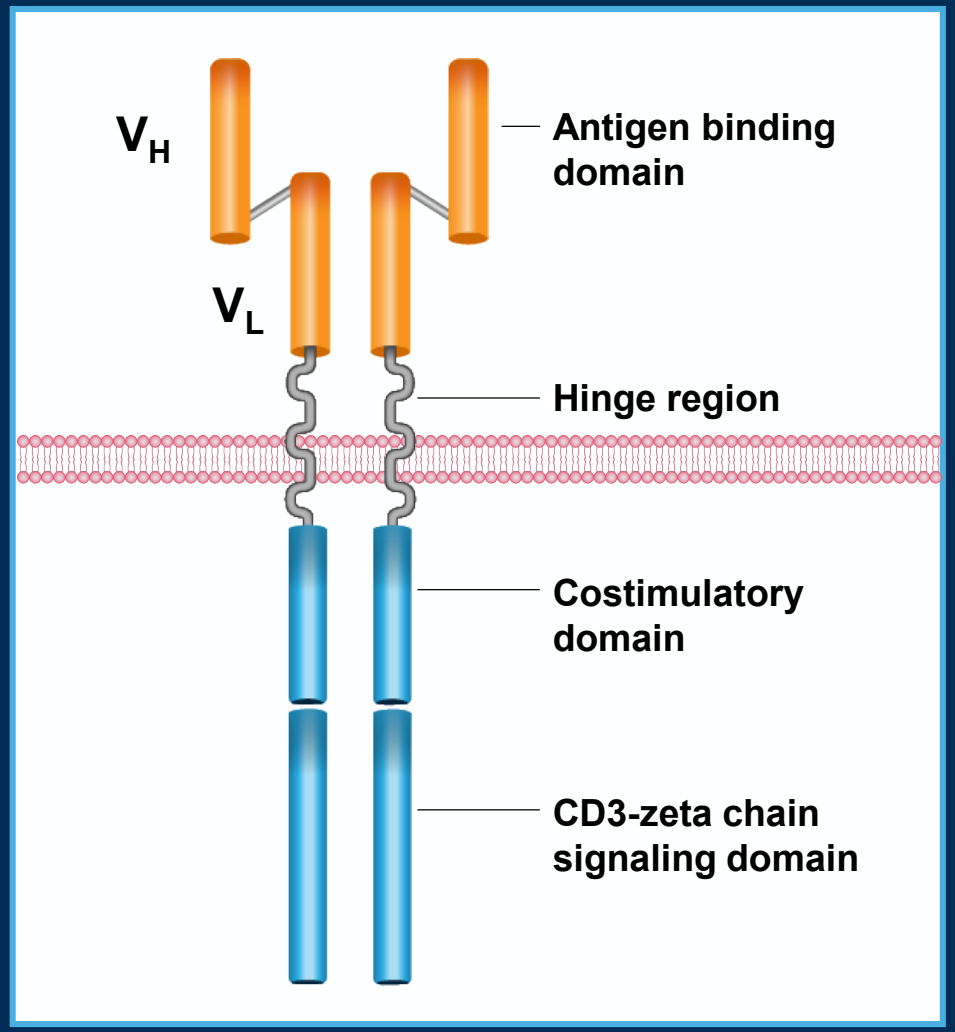
CAR T cells: Mechanism of Action



Chimeric Antigen Receptors

Antigen Binding Domain

Activation Domains



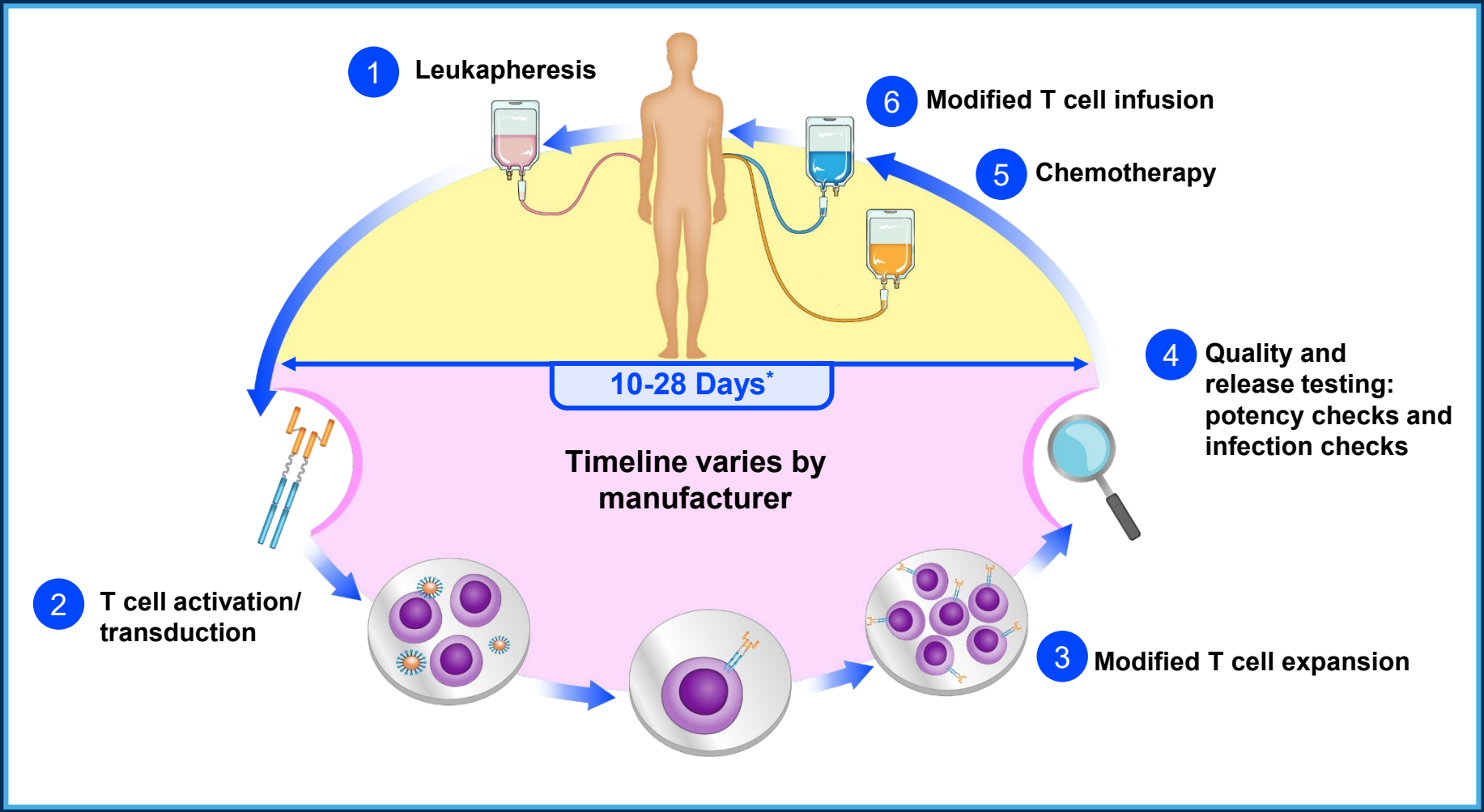
scFv
Single-chain variable fragment (scFv) bypasses MHC antigen presentation, allowing direct activation of T cell by cancer cell antigens

Hinge region
Essential for optimal antigen binding

Costimulatory Domain: CD28 or 4-1BB
Enhances proliferation, cytotoxicity and persistence of CAR T cells

Signaling Domain: CD3-zeta chain
Proliferation & activation of CAR T cells
CAR T cell-mediated killing of tumor cells

Overview of CAR T Therapy

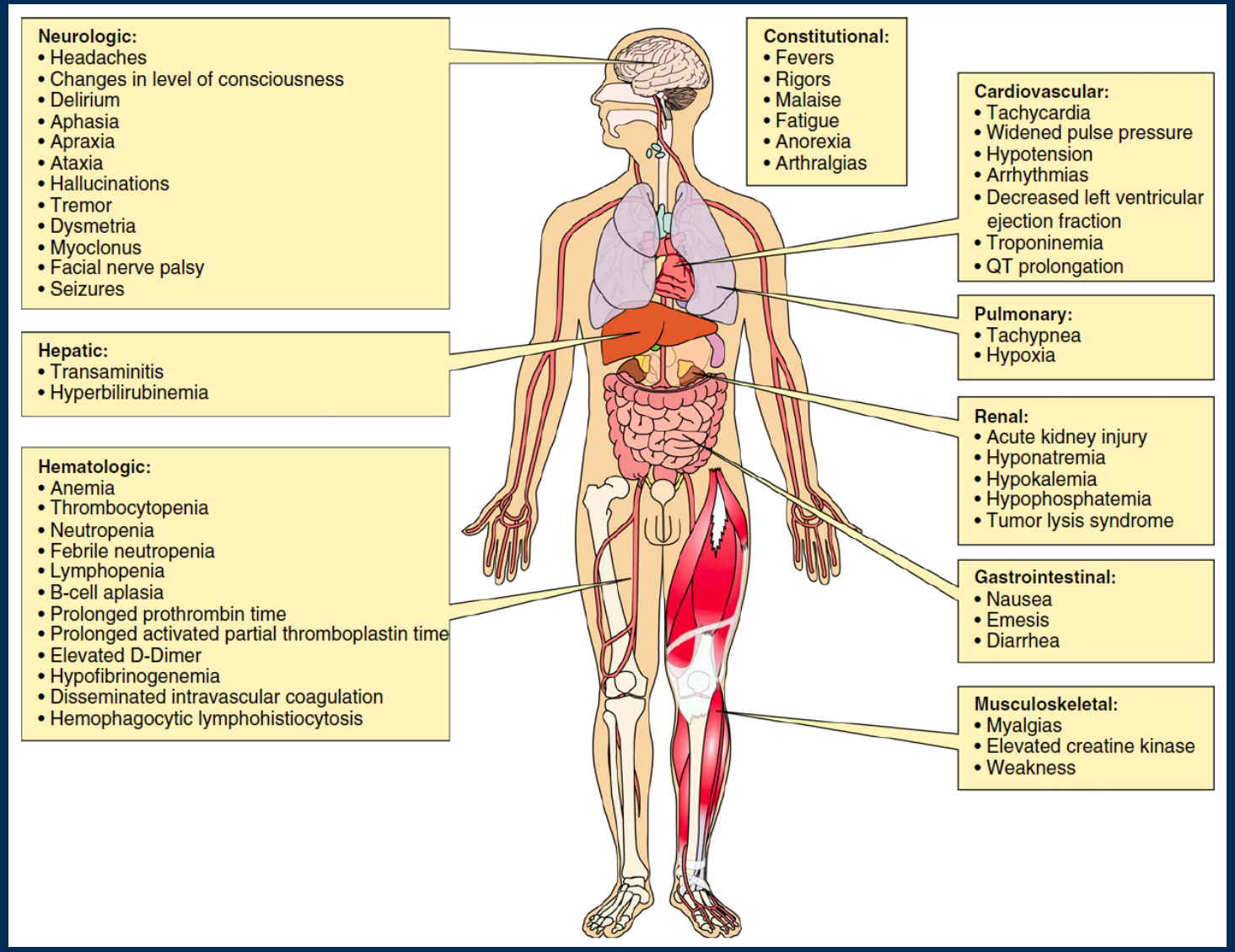


*Personal communication

CAR T Therapy: Toxicity

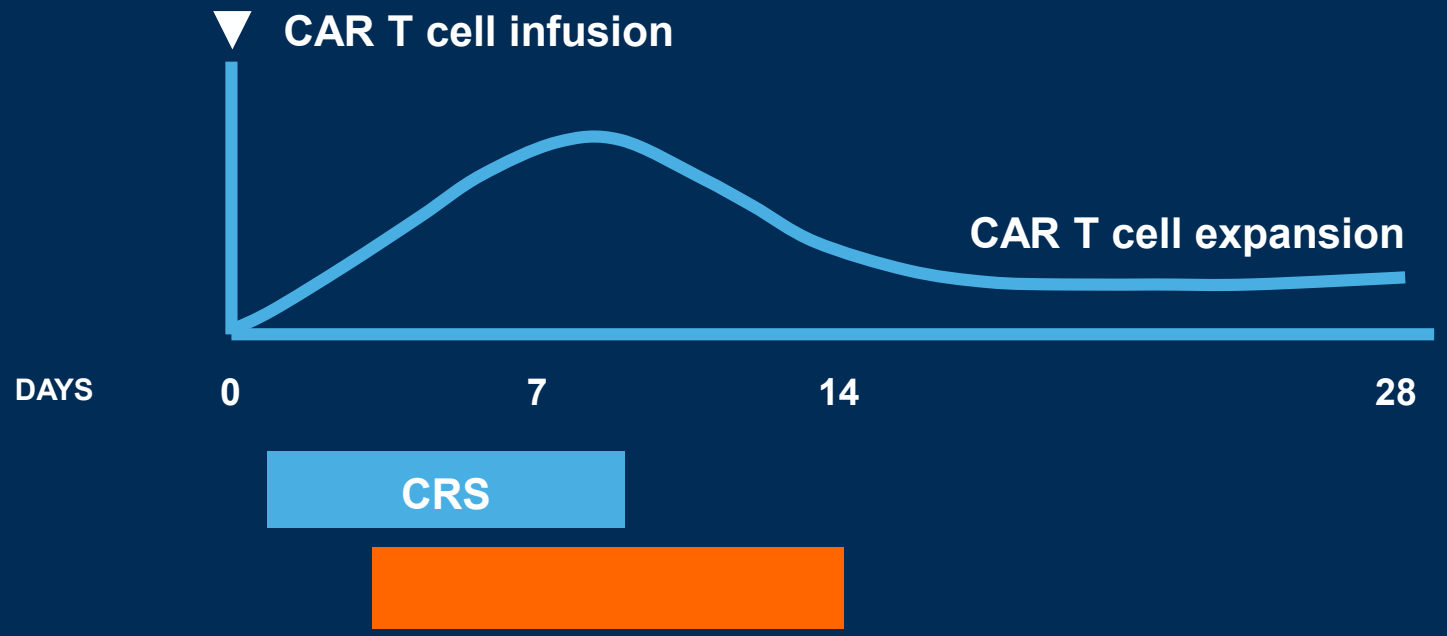
- No significant acute infusional toxicity
- Tumor Lysis Syndrome
  - Rarely occurs; effector cell expansion requires time negating massive tumor lysis
- Cytokine Release Syndrome (CRS)
  - Life-threatening if not managed by expert multidisciplinary team
  - May include cardiac events, hepatotoxicity, or renal toxicity
- Neurologic Toxicity
  - 3 subtypes: acute, delayed, idiosyncratic
- Cytopenias
  - Macrophage Activation Syndrome (MAS) or HLH is a very rare and severe form
- B cell aplasia and hypogammaglobulinemia

CRS Toxicities by Organ System



Brudno JN and Kochenderfer JN. *Blood* 2016; 127(26):3321-3330

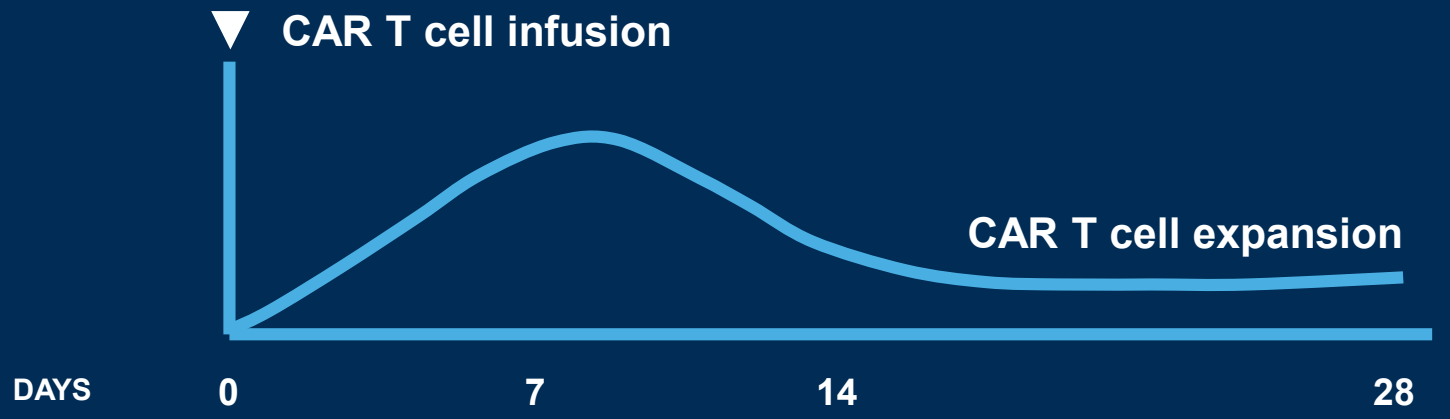
Typical Onset and Resolution of CRS and Neurologic Events



May occur within minutes or hours but generally appears within days or weeks
Coincides with maximal T-cell expansion

Lee DW et al. Blood. 2014;124(2):188-195.

CRS Response to Tocilizumab is Biphasic



CRS → First phase is highly responsive to tocilizumab

Neurologic events → Second phase may be less responsive to tocilizumab

Lee DW et al. Blood. 2014;124(2):188-195.

Current Status

Current Status

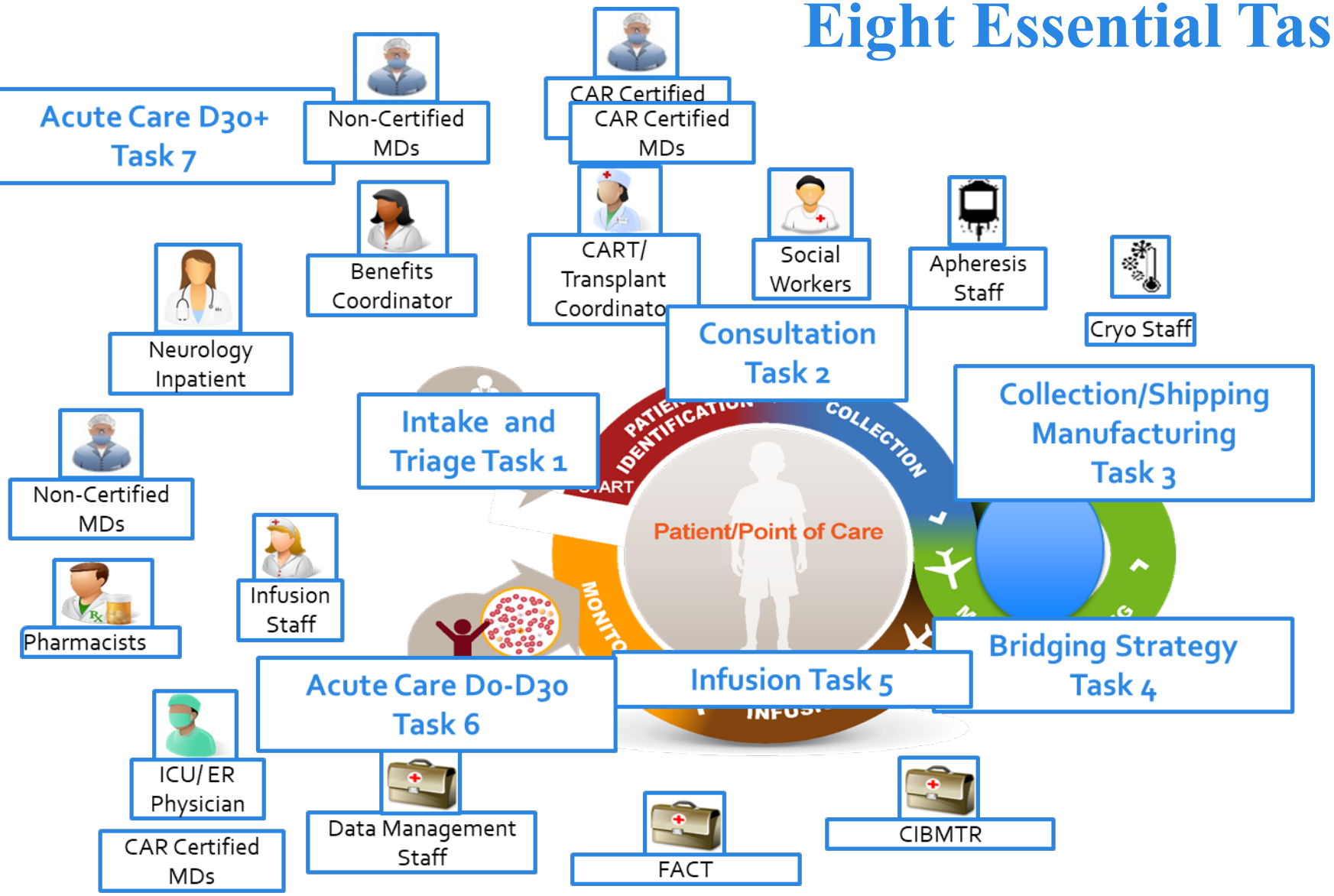
THREE PRODUCTS APPROVED

- Three products FDA Approved
- Kymriah
  - RR Acute Lymphoblastic Leukemia – Less than 25 years of age
  - Diffuse Large B Cell Lymphoma
- Yescarta
  - Diffuse Large B Cell Lymphoma
- Tecartus
  - Mantle Cell Lymphoma

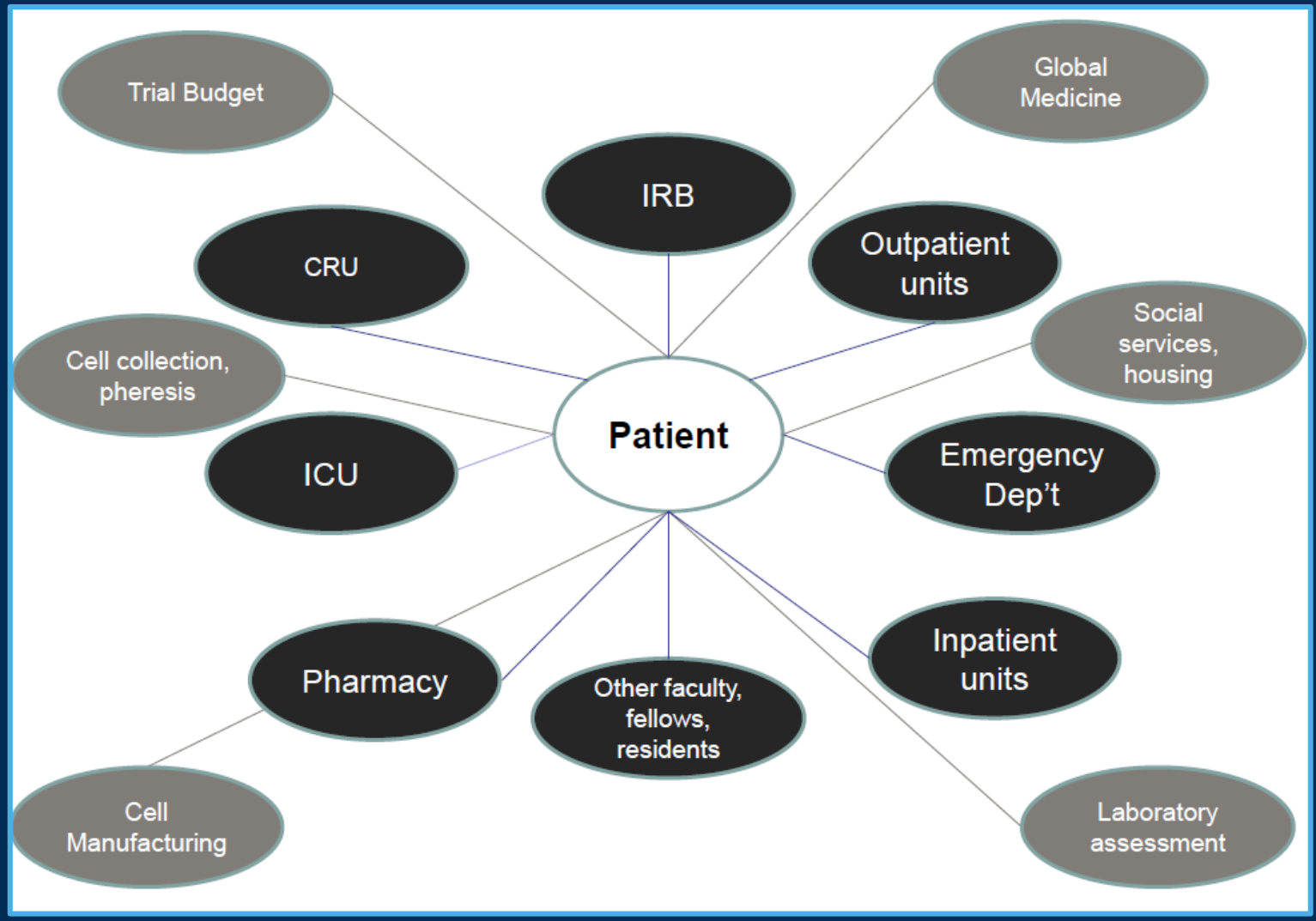
ISSUES

- Apheresis resources are currently being stretched thin
- Products can only be infused in FACT accredited programs. Patients require caregivers and to stay locally for 4 weeks. Thus access is a major issue
- Toxicities require hospitalization. Inpatient beds are becoming an increasing issue for large programs
- Significant investment in developing the infrastructure and resources needed to start a CAR T program.
- Limited trained medical, and non medical personnel to staff programs

Eight Essential Tasks



Best Practices: Ensure Crosstalk between Clinical, Nursing, Financial, and Coordination Teams



Cellular Immunotherapy Data Resource (CIDR) Updates and Governance

CIDR Stakeholders' Council

October 4th, 2019

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The CIBMTR® (Center for International Blood and Marrow Transplant Research®) is a research collaboration between the National Marrow Donor Program® (NMDP)/ Be The Match® and the Medical College of Wisconsin (MCW).

CIDR
CELLULAR IMMUNOTHERAPY DATA RESOURCE

Overview of CIDR Objectives

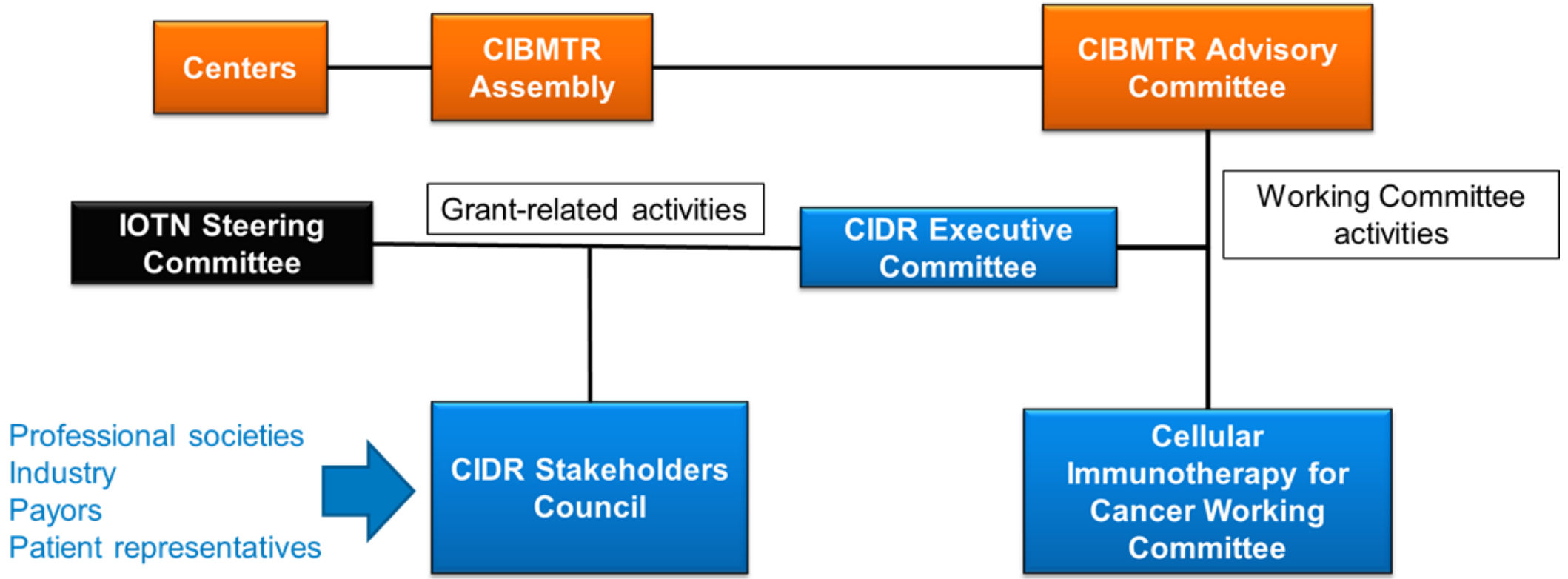
CIDR
CELLULAR IMMUNOTHERAPY DATA RESOURCE

- Build the CT registry for cancer as a resource to the medical community
- Incentivize projects that will build the infrastructure
- Create systems and initiatives to maximizes its use
- Leverage the relationship with IOTN and other partners to sustaining the programs and broadening its reach.

CIDR Governance

CELLULAR IMMUNOTHERAPY DATA RESOURCE

CIBMTR Existing Governance Structure



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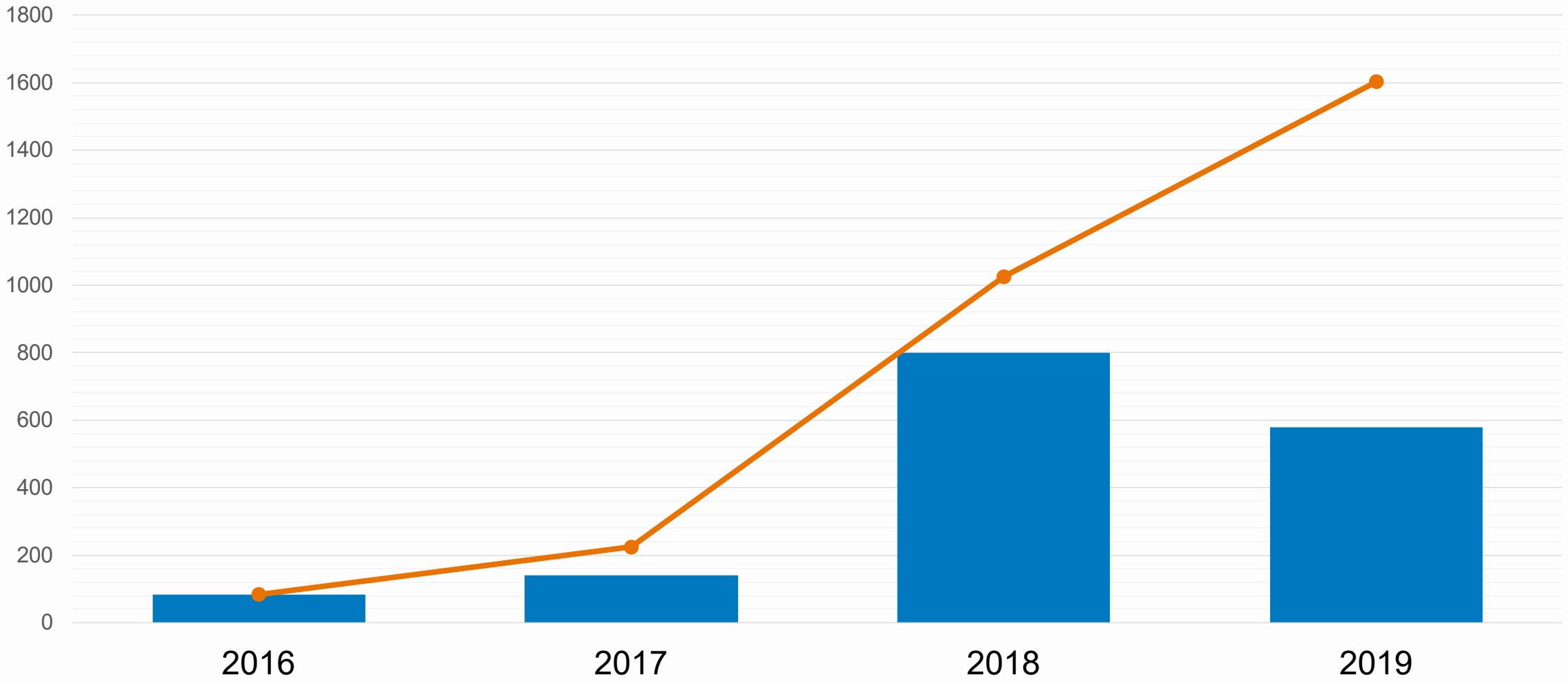
Number of CAR T cell infusions: 2016-2019 (1,603 patients)

CELLULAR IMMUNOTHERAPY DATA RESOURCE



Cumulative

Data Incomplete for 2019

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Active Projects utilizing the CT Registry

CELLULAR IMMUNOTHERAPY DATA RESOURCE

Project	Sponsor	Objective	Timeline/Duration
Yescarta LTFU (Axicabtagene ciloleucel)	**Kite**	Safety and efficacy outcomes (PASS) **N=1,500** **Diseases: NHL**	**5** years of accrual **15** years of follow up
Kymriah LTFU (Tisagenlecleucel)	**Novartis**	Safety and efficacy outcomes (PASS) **N=2,500** **Diseases: NHL and ALL**	**5** years of accrual **15** years of follow up

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CIDR Year 2 and beyond

CELLULAR IMMUNOTHERAPY DATA RESOURCE

- Ongoing Data Quality Initiatives
  - –Metrics for data submission (CPI), updating forms, site training and Data Audit
- Implementation of PRO
- REMS reporting tool
- Post marketing studies

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Future State

Likely FDA Approvals for 2021

NEW INDICATIONS & PRODUCTS

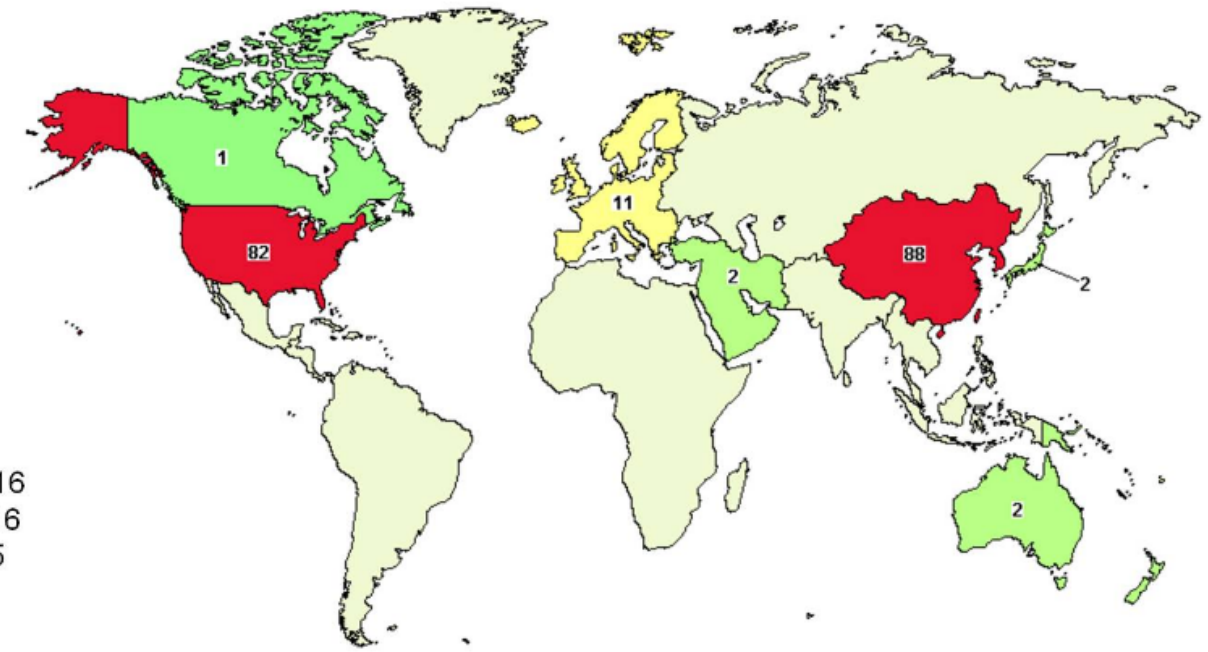
- Myeloma
  - IdeCel-Likely Q1 2021 – 1000+ infusions a year for RRMM
  - J&J BCMA CAR
  - JUNO BCMA CAR
- Adult ALL CD19 CAR
- CLL

ISSUES/COMPETITORS

- Access and resources will be major issues as volume increases
- Off the shelf CAR T not ready for prime time but being developed
- BITE will soon become commercially available. These are “off the shelf” products that will directly compete with CAR T therapy.
- How they will be used or sequenced uncertain but likely will be used frequently in community practices

CAR T Therapy is a Rapidly Growing Technology

CAR T Cell Trials Are Now Global



123 – May 19, 2016
102 – Feb 26, 2016
88 – Dec 10, 2015
77 – Sept, 2015
<5 - 2010

Clinical trials.gov search term "chimeric antigen receptor"
183 trials ongoing as of April 23, 2017

June CH. 2017 ASCO Annual Meeting. Adoptive T Cell Therapy: Ready for Prime Time?

Ongoing CAR Trials in Hematologic Malignancies

	Number of Clinical Trials			Targets Currently Being Investigated
	Total	Phase 1	Phase 2	
Lymphoma	105	89	44	
B cell Lymphoma	56	47	25	CD19, CD20, CD22, CD30
ALL	43	37	17	CD19, CD22, CD7
CLL	36	30	18	CD19, CD20, CD22
Non-Hodgkin Lymphoma	67	58	29	CD19, CD30, CD22, CD20
DLBCL	24	20	14	CD19, CD20, CD22
MCL	16	14	11	CD19, CD20, CD22
FL	15	13	9	CD19, CD20, CD22
Burkitt Lymphoma	14	13	5	CD19, CD20, CD22
Hodgkin Lymphoma	11	9	3	CD19, CD30, NY-ESO
Leukemia	90	76		
B cell Leukemia	36	30	17	CD19, CD5, CD20, CD22, CD30, CD33, CD123, BCMA
AML	12	9	3	CD7, CD33, CD123
MM	13	11	4	CD19, BCMA, CD138, NY-ESO

www.clinicaltrials.gov. Search term “chimeric antigen receptor”. Accessed 5.18.2017

Ongoing CAR Trials in Solid Tumors

	Number of Clinical Trials	Targets Currently Being Investigated
Astrocytoma	7	HER2, EGFRvIII, IL13Rα2
Glioblastoma	7	HER2, EGFRvIII, IL13Rα2, NY-ESO
Breast	13	HER2, EpCAM, cMET, Mesothelin, ROR1, MUC1, CEA, CD70, CD133, NY-ESO
Colorectal	9	CEA, EGFR, MUC1, HER2, CD133,
HCC	11	Glypican-3 (GPC3), MUC1, EPCAM, NY-ESO
NSCLC	5	PD-L1, MUC1, ROR1, CEA, NY-ESO
Melanoma	3	cMET, GD2, CD70, NY-ESO
Mesothelioma	4	FAP, mesothelin
Neuroblastoma	8	GD2, CD171, NY-ESO
Ovarian	7	Mesothelin, CD70, HER2, CD133, CEA, NY-ESO
Pancreatic	13	Mesothelin, Prostate Stem Cell Antigen (PSCA), CD70, MUC1, HER2, CD133, NY-ESO
Stomach	8	EPCAM, CEA, MUC1, HER2, NY-ESO
Thoracic	5	MUC1, ROR1, PD-L1

www.clinicaltrials.gov. Search term “chimeric antigen receptor”. Accessed 5.18.2017

Summary

- CAR T cells are a major therapeutic breakthrough for lymphoid malignancies (NHL, ALL and Myeloma)
- There use is associated with unique toxicities and require specialized resources and personnel.
- There cost are likely to be a major problem that has yet to be addressed.
- Access will depend on supporting the development of specialized centers across the country with adequate personnel and resources.