Consortium of Pediatric Cellular Therapeutics

U01 Meeting

August 17, 2017

General Objectives

- Accelerate the development of novel cellular immunotherapies for pediatrics
- Disseminate access to these novel therapies

- Utilize CTSA infrastructure to maximize implementation success
- Share patient resources
- Share biologic specimens
- Share data

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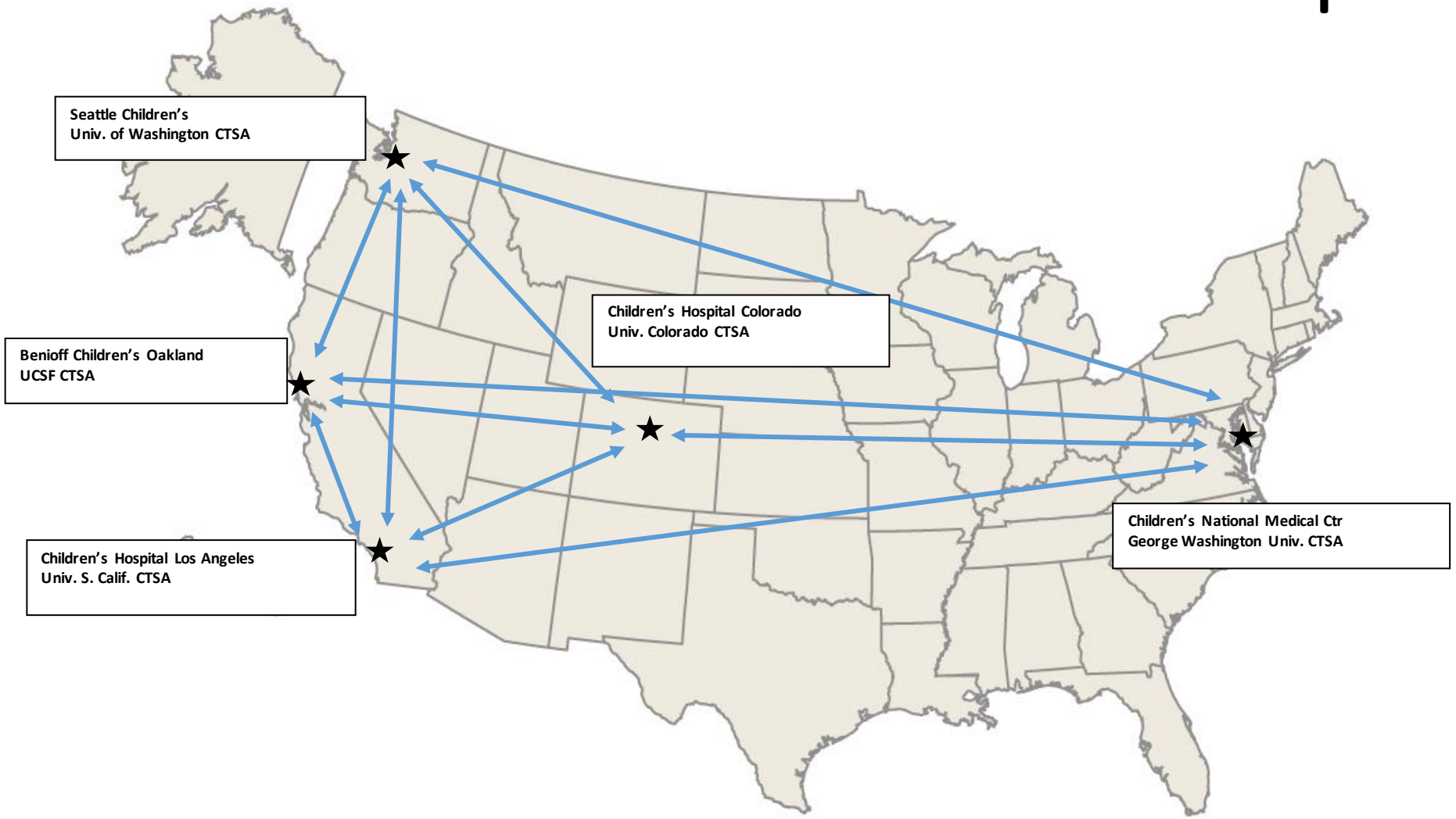


Figure 1. Consortium of Pediatric Cellular Therapeutics.
The bidirectional arrows depict the collaborative nature of this consortium where each program will bring unique expertise and pre-clinical programs (Table 1) for eventual clinical protocols within the consortium.

Specific Aims

- **Old SA1.** Expand cGMP cellular therapeutics manufacturing programs focused on single center trials to provide capacity and expertise to ensure state-of-the-art cellular immunotherapy for multi-center clinical trials.
  - Rev SA1. Expand cellular immunotherapy GMP therapeutics for treatment of pediatric disease
- **Old SA2.** Successfully initiate and conduct high quality, safe and efficient multi-center cellular immunotherapy trials enabled by a robust consortium governance structure and central coordinating center.
  - Rev SA2. Provide access of cellular immunotherapeutics to a diverse pediatric patient population
- **Old SA3.** Develop consortium reference laboratories for the receipt, processing, bio-banking and conduct of correlative immunobiology studies and analytic assays pertaining to consortium clinical trial outcome endpoints to assist in future trial designs and to develop biomarkers of safety and efficacy.
  - Rev SA3. Enhance assessment of safety and outcomes of cellular therapeutics in pediatric patients
- **Old SA4.** Develop infrastructure and collaborations to facilitate sustainable access to the most promising cellular immunotherapies for children.
  - No change

Old SA1: Expand cGMP cellular therapeutics manufacturing programs

- *SA1A. Develop a work flow that can be scaled to provide cellular products across the consortium.*
- *SA1B. Produce a series of standard operating procedure (SOP) covering the manufacture and shipment of cellular products.*
- *SA1C. Provide consultation to enhance the transfer of cGMP technology to other sites for use in establishment of additional cGMP facilities.*

Rev SA1: Expand cellular immunotherapy GMP therapeutics for treatment of pediatric disease

- *SA1A. Define and align best practices across GMP facilities*
  - *GAP analysis/Consensus meeting, development of consensus SOP, training workforce (will include process development)*
- *SA1B. Enhance distribution of cellular therapeutics to sites of patient care*
  - *Develop logistics of procurement, shipment and receipt of cellular products.*
  - *Allows access at point of care*
- *SA1C. Expansion of available GMP facilities across CTSA to maximize distribution*
  - *Provide consultation to enhance the transfer of cGMP technology to other sites for use in establishment of additional cGMP facilities.*
    - *Describe what this might look like? What issues would need to be resolved?*
      - *Cost analysis, GMP requirements, minimum personnel requirements*

SA1: Metrics

- Production and distribution of cGMP cellular products to each of the consortium sites to support the planned clinical trial pipeline. The key metrics will be:

1. Develop consensus best practices for “x” processes
2. Cross site best practices assessment
    1. Deficiencies will drive subsequent education modules
3. At least 2 consortium sites will have capabilities for multi-institutional distribution
    1. Outcome (or activity) will be to measure recover, viability (is this cross site practices)?
4. Have some statement about tracking number of cGMP facilities

Old SA2: Initiate trials enabled by a robust consortium governance structure and central coordinating center

- *SA2A: Create a highly engaged partnership across consortium institutions to develop a specialized training program that will produce a dedicated workforce for the implementation of pediatric cellular based immunotherapy trials within the consortium and then disseminated across CTSA Hubs.*
- *SA2B: Support the development of novel study designs and outcome measures and create a standardized platform for data collection, safety monitoring and statistical analysis across consortium trials.*
- *SA2C: Develop rigorous and efficient study development processes that can be implemented across a geographically and socio-economically diverse patient referral base.*

Rev SA2: Provide access of novel therapeutics to a diverse pediatric patient population

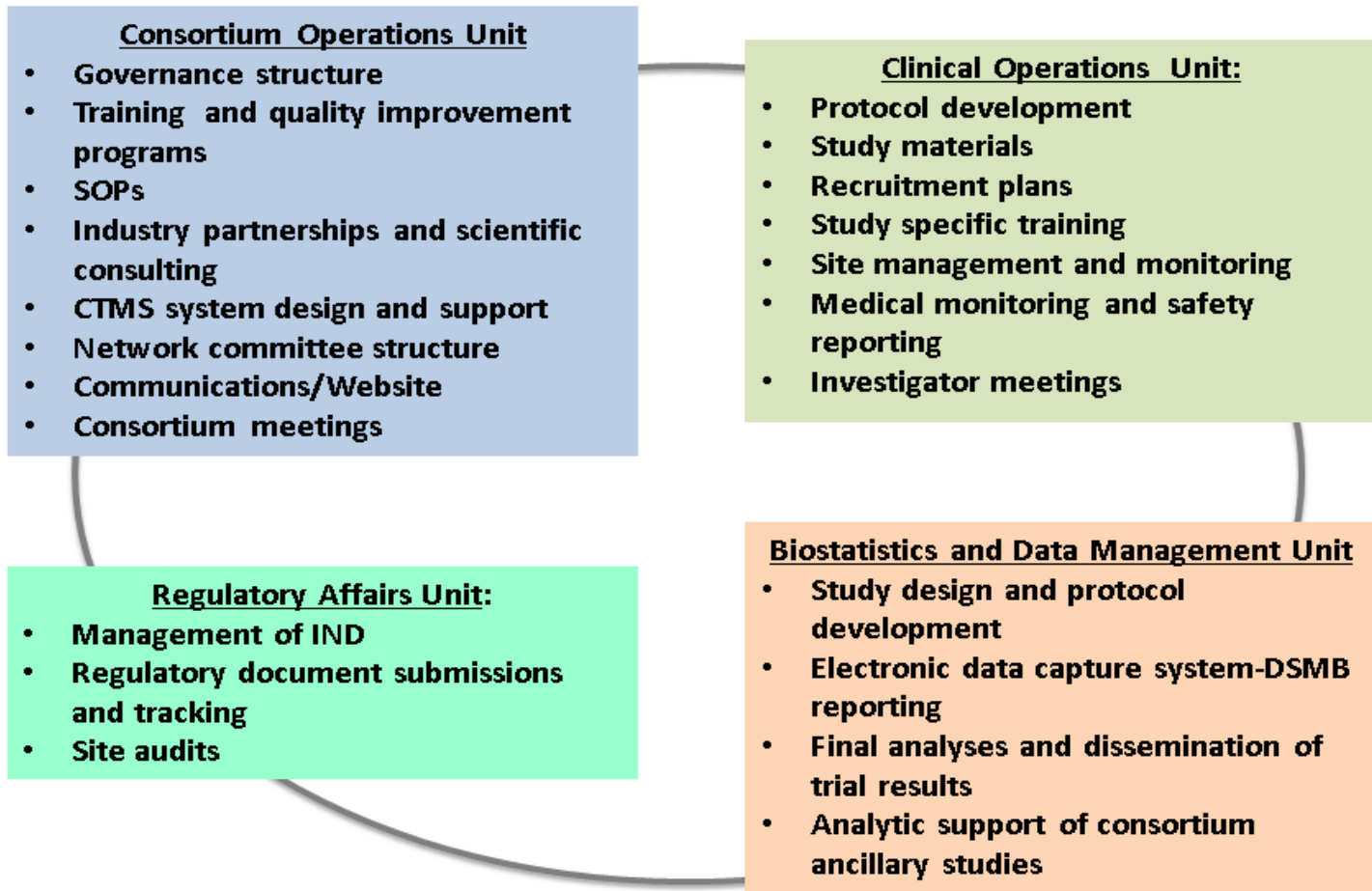
- *SA2A: Establish the training and infrastructure to promote development and implementation of clinical immunotherapy trials in pediatric patients*
  - *Develop a specialized training and safety program that will produce a dedicated workforce for the implementation of pediatric cellular based immunotherapy trials within the consortium and then disseminated across CTSA Hubs.*
  - *Develop a clinical trials coordinating center with expertise in the development of cellular immunotherapy clinical trials (Metric study development process)*
- *SA2B: Utilize clinical trial designs that realize the unique constraints of rare disease-focused clinical trials in pediatric populations*
  - *Designs will recognize limitation in patient accrual and also minimize complexity (for the patient) so as to increase feasibility of implementation across diverse SES and racial referral base*
  - *Reference collaboration with ITHS: Integrating Special populations*

SA2 Metrics

- We will develop an infrastructure to promote efficient and effective implementation of clinical trials, unsurpassed multidisciplinary care, education of site medical personnel to ensure safe implementation of cellular immunotherapy clinical trials.

1. Develop cellular therapeutic-specific training modules for x processes (principles of GCP)
2. Monitoring metric (GCP)
3. Open x multi-site clinical trials (how to assess diversity?)

Figure 2. Overview of the Consortium Coordinating Center



Each box represents the 4 functional units of the coordinating center. Listed within each box are the key functions of the unit. The unit managers will meet weekly with Drs. Ramsey and Hamblett to review progress.

Old SA3: Establish consortium reference laboratories for the discovery of novel biomarkers and outcome measures

- *SA3A: Establish a specimen processing and biorepository for pediatric clinical samples to promote future translational research*.
- *SA3B: Establish clinical trial correlative assays to measure safety, efficacy and promote rapid translation of findings*.
- *SA3C: Develop a web-based data integration platform for the integration, analysis visualization and sharing of data across sites*.

Rev SA3: Expedite the assessment of safety and outcomes of cellular therapeutics

- *SA3A: Develop reproducible sample collection and process standards for use across consortium trials*.
  - Distribute analyses based on expertise in correlative analyses and trials
- *SA3B: Apply a web-based data integration platform for the integration, analysis visualization and sharing of data across sites*.
- *SA3C: Establish biologic measures (outcomes) to assess safety, efficacy and promote rapid translation of findings*.

SA3 Metrics

- We will develop an infrastructure to promote accurate and timely analyses of correlative studies to inform safety, efficacy and future study development.

1. Develop GLP standards for “x” processes.
2. Implement GLP/cross validation testing?
3. Implement LabKey for “x” multi-site trials that will facilitate the analyses of key outcome measures

Old SA4. Facilitate sustainable access to the most promising cellular immunotherapies for children

- SA4A. *Development relationship with pharmaceutical partners to facilitate the development and implementation of novel immunotherapies*
- SA4B. *Develop the CureWorks cooperative*

Rev SA4. Facilitate sustainable access to the most promising cellular immunotherapies for children

- No specific subaims, an overview planned avenues
  - SA4A. *Development relationship with pharmaceutical partners to facilitate the development and implementation of novel immunotherapies*
    - *Would need infrastructure support beyond individual clinical trial and only be included if we can obtain Letter of support for the grant*
  - SA4B. *Develop the CureWorks cooperative*

SA4 Metrics

- Identify pharmaceutical partners?
- Initiate CureWorks?

Additional Items for investigators to address

- Site PI's to complete pipeline table
  - Hashed = single institution trial
  - Solid = multi-institutional trial (at least one additional site)
- Table for Site contributions
  - To be completed by Pis
- Finalize Global Org/Governance structure

Clinical Trial Pipeline

Clinical Trial	2018	2019	2020	2021	2022
PLAT-02 CD19					
PLAT-05 CD19xCD22					
STrIVe					
Brain Child					

Hospital/CTSA	PI/Subinvestigators	Technology/Applications	CTSA Contributions?
Children's Hospital Los Angeles/USC	Alan Wayne, MD Nora Heistekamp, PhD Michael Pulsipher, MD	APC aNK-derived Exosomes, CAR T Cells/Leukemia, NB Activated NK Cells +mABs/Leukemia CAR T Cells/Leukemias incl. AML Pediatric Oncology Phase I Program	
Benioff Children's Hospital Oakland/UCSF	Mark Walters, MD Elliot Vinchinsky, MD Anu Agrawal, MD	HSC Gene Repair – Sickle Cell Disease, Thal major	
Children's Hospital Colorado/UC	Lia Gore, MD Giller et al C. Baker, MD	CD19CAR T cells Pediatric Oncology Phase 1 Program EBV and CMV specific T cell adoptive therapy Umbilical endothelial stem cells- bronchopulmonary dysplasia	
Seattle Children's Hospital/UW	Michael C. Jensen, MD Andrew Scharenberg, MD David Rawlings, MD Thor Wagner, MD Leslie Kean, MD, PhD Julie Park, MD	CAR T Cells/Gene Editing – Peds Immuno-oncology T Cell and HSC Genetic Editing – Inherited Immunodeficiency Gene Modified Tregs – Autoimmune Diseases CAR T Cells/Gene Editing – HIV Immunotherapy Gene Modified Tregs – Graft Tolerance Pediatric Oncology Advanced Therapeutics Program	
Children's National Medical Center/GWU	Catherine Bollard, MD Kirsten Williams, MD		

Cellular Immunotherapy Consortium Governance

Steering Committee (PI's)

Development/Communications

Protocol Review Committee

Manuscript Committee

External Advisory Committee - quarterly