Clinical Trials in Organ Transplant (CTOT) Consortium

Scott Palmer, MD, MHS
Donald F. Fortin, MD Distinguished Professor of Medicine
Vice Chair for Research, Department of Medicine
Director MedicinePlus, Duke Clinical Research Institute

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

CTOT-CA

Clinical Trials in Organ Transplant (CTOT) Consortium

- CTOT is mechanism supported by NIAID to advance clinical and translational research in solid organ transplantation and includes observational and interventional studies
- CTOT emphasizes rigor around data collection and regulatory management through independently funded DCC
- The first cycles of CTOT studies were primary focused on kidney transplant
- We were funded in 2014 with a 7-year award to Duke to create the first CTOT consortium dedicated to studies in adult lung transplant
- Through our CTOT funding we completed two primary studies and 14 ancillary studies

CTOT-20: Rationale and Study Design

- Lung transplant volumes are increasing (approximately 2,500 per year in the US), but still rare condition/treatment
- Long term outcomes for lung transplant lag behind those of the other commonly transplant solid organs. The primary cause of death after lung transplantation is chronic allograft dysfunction (CLAD)
- A deeper understanding of the risk factors and mechanisms that lead to CLAD is needed to improve lung transplant outcomes
- CTOT-20 was a prospective multicenter cohort study enrolling lung transplant recipients across 5 centers with the objectives to elucidate clinical risks and biological mechanisms that lead to CLAD

Palmer PI, UO1 NIAID AI113315
ClinicalTrials.gov Identifier: NCT02631720

CTOT-20: Clinical Objective and Approach

- CTOT 20: 5 sites in North America (Duke, JHU, Toronto, CC, and UCLA) enrolling >800 new lung transplant recipients
- Subjects followed serially from transplant through CLAD onset
- Data collection from multiple sources (eCRF, PFTs labs, UNOS)
  - Rigorous data monitoring: site based and regular data reports
  - Objective approach to diagnose CLAD, confirmed by site adjudication
  - Extensive collection and banking of biosamples
    - *Blood: Plasma, Serum, RNA & DNA Paxgene*
    - *BAL: BAL fluid and cell pellet RNA (routine clinical bronchoscopy)*
- Additional funding obtained from the CFF enabled extended long term follow-up (CTOT-ES)

The Lung Transplant CTOT Program

DCRI Administration & Leadership
Scott Palmer, PI
Laurie Snyder and Jamie Todd, Co-PIs
Megan Neely, PhD Statistician
Jerry Kirchner and Courtney Frankel, PM

Clinical Sites:
Duke (Reynolds, PI)
Johns Hopkins (Shah, PI)
UCLA (Belperio, PI)
Cleveland Clinic (Budev, PI)
Toronto (Singer, PI)

Mechanistic Core Labs:
Lung Immunology (Belperio, UCLA)
Lung Genetics (Palmer, Duke)
CMV Immune Monitoring (Weinhold, Duke)
CMV Pathogenesis (Schenck, JHU)
CMV Host Defense (Kumar, Toronto)

CTOT DCC: Rho
Michelle Sever
Heather Kopetskie, Michelle Martin, Michele Cosgrove, April Cobb, Elizabeth Paynter
(previously David Ikle)

Working Groups:
Pathology, Microbiology, HLA

NIAID
Nikki Williams, Mark Robien

CTOT-20: Clinical Risk Factors and Biological Mechanisms of CLAD
CTOT-22: Immune Monitoring to Predict Risk for CMV infection

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CTOT-20: Sampling Strategy

- Prospective study visits with extensive clinical data collected, biological samples at every visit, and at every bronchoscopy for lung fluid/cells

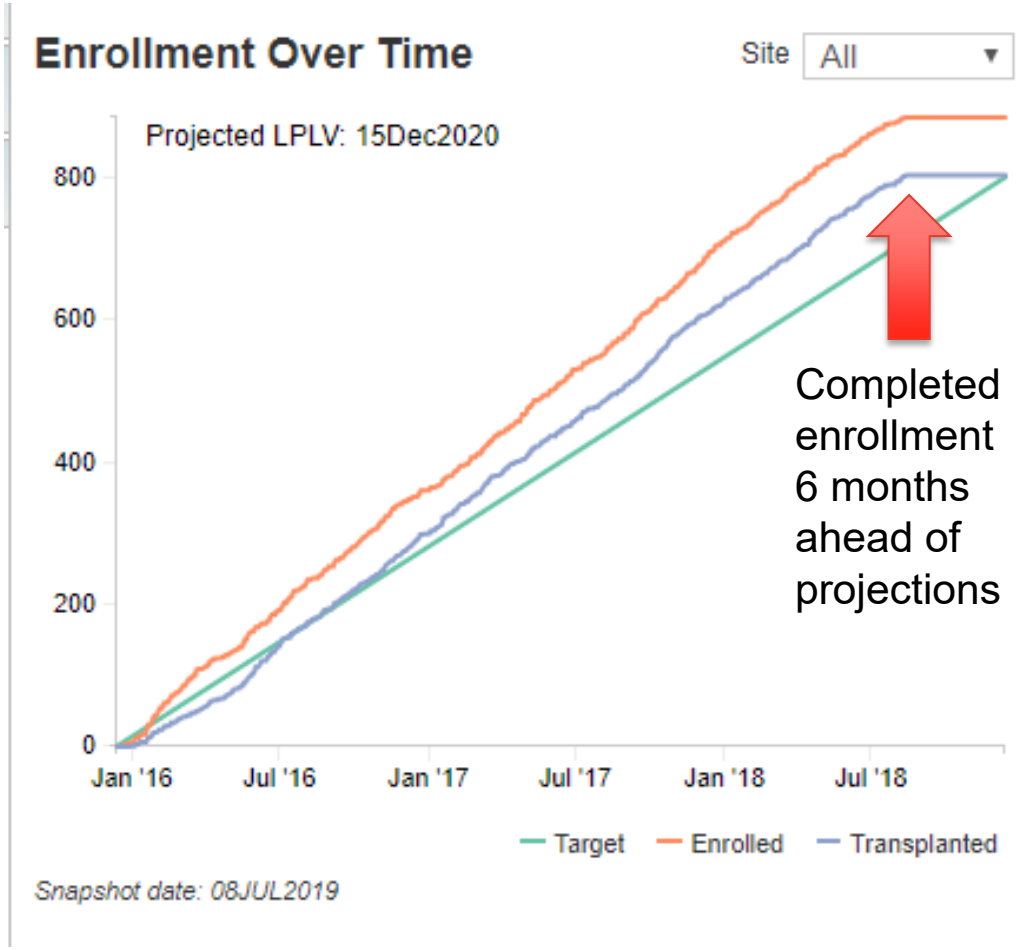
Pre-LTX LTX Yr1 Yr2 Yr3 Yr4

Phase	Pre-LTX	LTX	Post LTX Yr 1					Post LTX Yr 2		Post LTX Yr 3		Post LTX Yr 4	
Month	-6 to 0	0	1	3	6	9	12	18	24	30	36	42	48
Blood *	x		x	x	x	x	x	x	x	x	x	x	x
BAL**			x	x	x	x	x		x		x		x
PFTs			x	x	x	x	x	x	x	x	x	x	x
Clinical Data Extraction (micro, path, HLA, donor factors, meds)	x	x	x	x	x	x	x	x	x	x	x	x	x
QOL	x		x	x	x	x	x	x	x	x	x	x	x

**Blood: Plasma, Serum, RNA PAXgene, DNA*

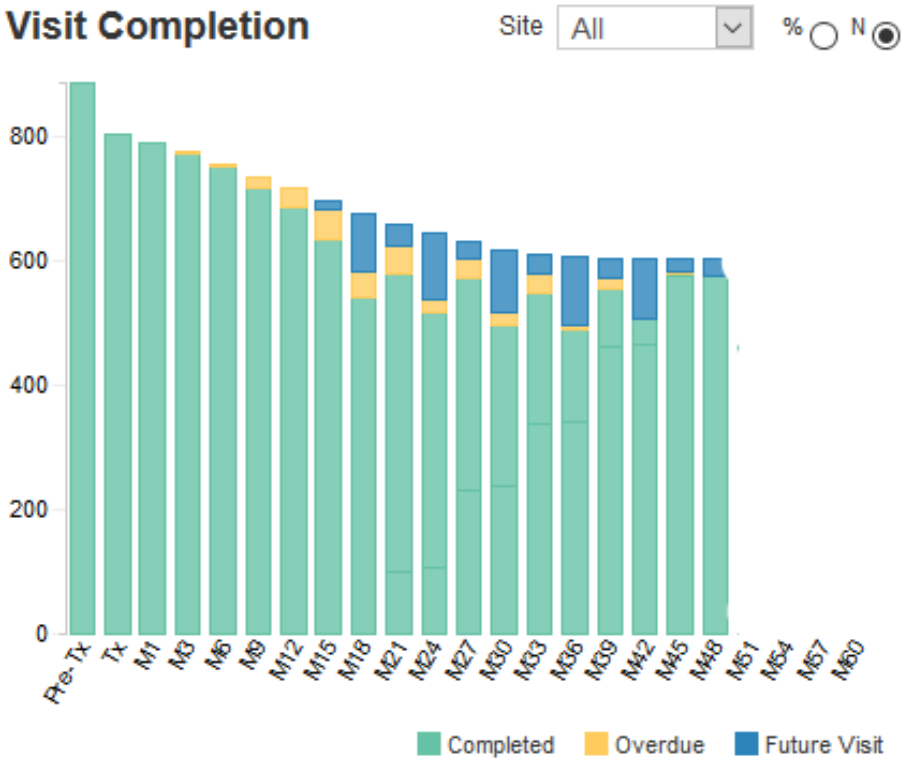
***BAL: BAL fluid and cell pellet RNA*

CTOT-20: Enrollment of 803 Lung Transplant Recipients



Site	Transplants
Duke	210
Hopkins	58
Cleveland	205
Toronto	200
UCLA	130
TOTAL	803

CTOT-20: Completeness of Clinical Data

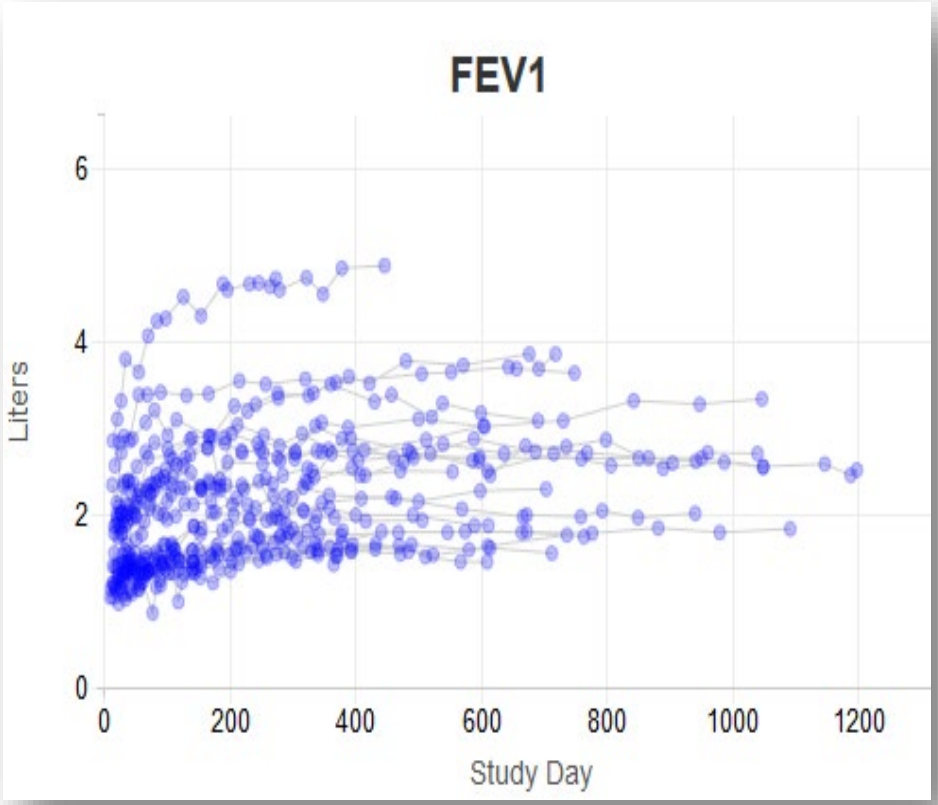


Site	CRFs Completed
Cleveland Clinic	9,771
Johns Hopkins	3,515
Toronto	7,752
UCLA	5,160
Duke	12,131
Total	**38,329**

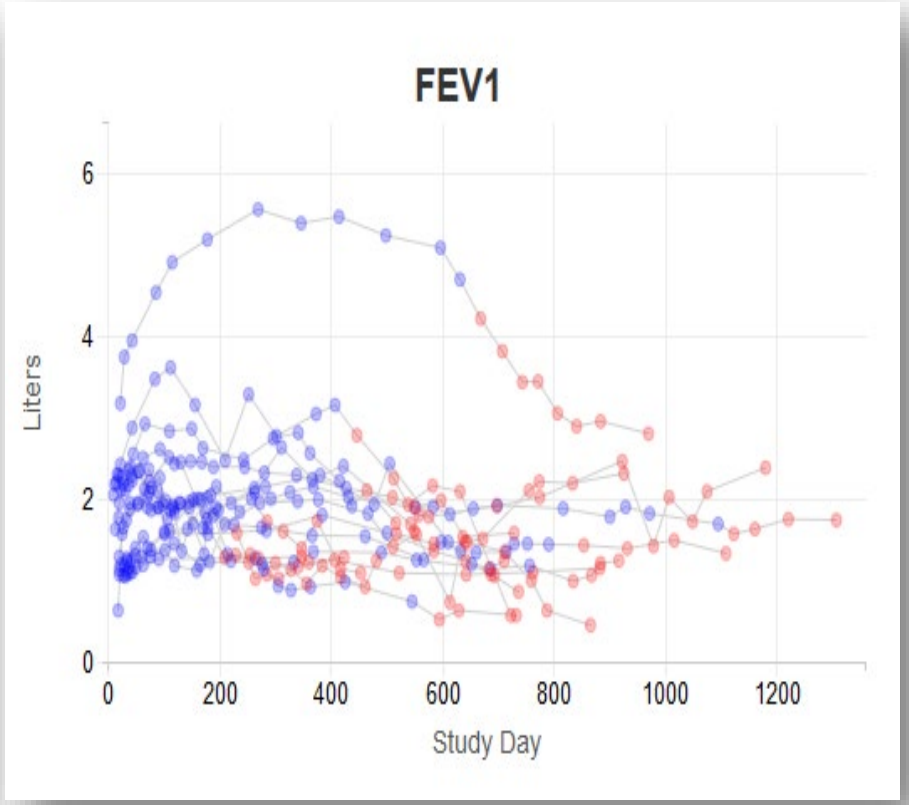
CTOT-20: Electronic PFT Collection

- PFTs used for assessment of primary outcome (CLAD)
- Created a mechanism for the electronic transfer of PFTs data from each site directly from PFT lab
  - >15,000 **PFTs** in database
  - > 19 PFTs per patient
- Multiple QI steps in process from transfer to ascertainment of CLAD
- Automated CLAD calculator triggered further site adjudication of CLAD once prompted by sustained PFT decline meeting CLAD criteria

CTOT-20: PFT TRAJECTORIES



Trajectory of PFTs in CLAD free patients



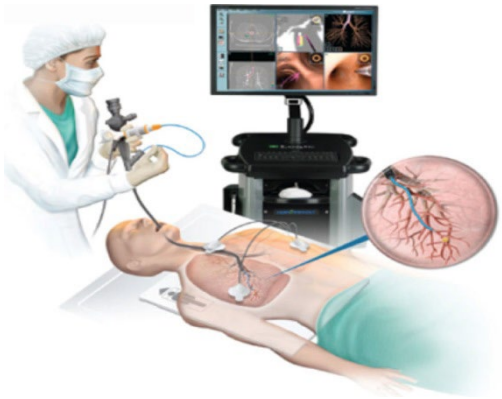
Trajectory of PFTs in CLAD patients (sustained drop in lung function in red)

CTOT-20: BIOSPECIMEN COLLECTION

BLOOD

- **>13,000 blood samples including**
  - DNA (one pre and one post)
  - RNA (serial all time points)
  - Plasma (serial all time points)
  - Serum (serial all time points)

BAL (lung fluid)



- **4,400 BAL samples including:**
  - BAL fluid
  - BAL cell pellet

  (collected at time of bronchoscopy)

100,000 sample aliquots across all compartments generated in CTOT 20

CTOT-ES

- CFF supported additional dedicated collection of clinical data and bio-samples in patients enrolled in CTOT20 for two additional years
  - Extended post-transplant f/u of participants vs. CTOT20
    - Minimum 3 years, maximum 5.5 years
  - Collected additional biospecimens (BAL, blood)
    - BAL supernatant - 1,445 aliquots
    - BAL cell pellet – 224 aliquots
    - Plasma (EDTA) – 1,329 aliquots
    - Serum – 768 aliquots
    - PAXgene RNA – 281 samples
- Collected annual PROs, clinical data, adjudicated CLAD
  - Increased total number of probable and definite CLAD events
- CFF also supported targeted long-term clinical outcome assessment for three additional years (ends spring 2024)

Progression from CTOT-20 to CTOT-CA

- Data and samples from CTOT-20 and CTOT-ES have contributed to over 12 publications and 25 abstracts
- With this prior CTOT experience and data in hand, we were able to successfully compete for a new CTOT-CA (children-adult) consortium awarded in Aug 2021 to conduct an interventional study in CLAD prevention using Rezurock
- CFF has issued two rounds of RFAs for studies that collaboratively use samples and data collected through CTOT-20 and CTOT ES creating a resource for the community

Summary of CTOT experience

- An observational cohort study can bring centers together, generate high priority targets laying foundation for interventional trials
- Independent and experienced DCC increases rigor of study
- Create approaches to data collection (PFT transfers)
- Extensive sample banking and core labs support translational mechanistic studies and/or future ancillary studies to extend impact of the primary study
- Incorporated like minded investigators from multiple centers, included junior faculty, and broad range of disciplines (medicine, surgery, ID, pathology, HLA laboratory)