Thymus transplantation for complete DiGeorge anomaly

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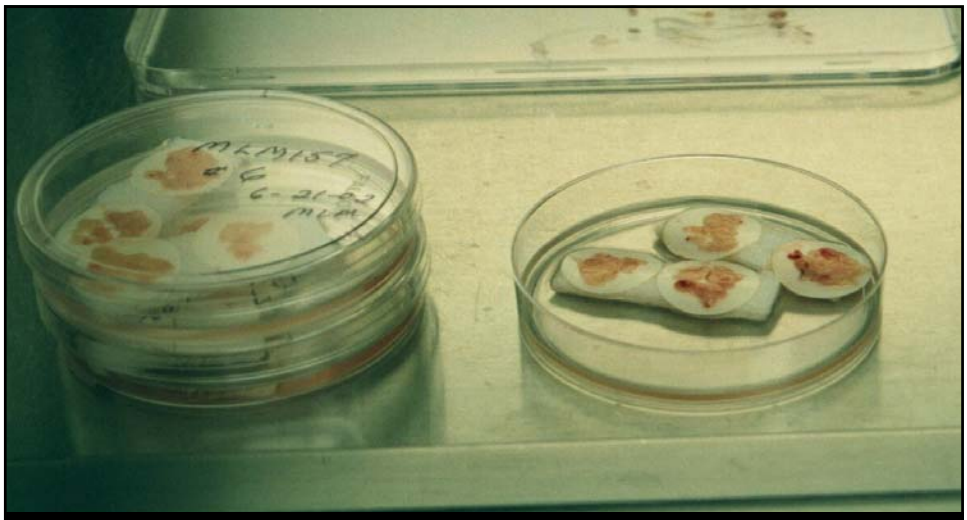
Thymus transplantation for Complete DiGeorge Anomaly

- DiGeorge Anomaly (DGA)
  - Thymus hypoplasia, low T cell counts
  - Hypoparathyroidism
  - Congenital heart disease
- Complete DGA
  - No thymus
    - Since T cells develop in the thymus, these children have no T cells.
    - Fatal condition, children usually die from infection by 2 years of age.

We transplant ***unmatched*** thymus epithelium - the school house plus teachers.

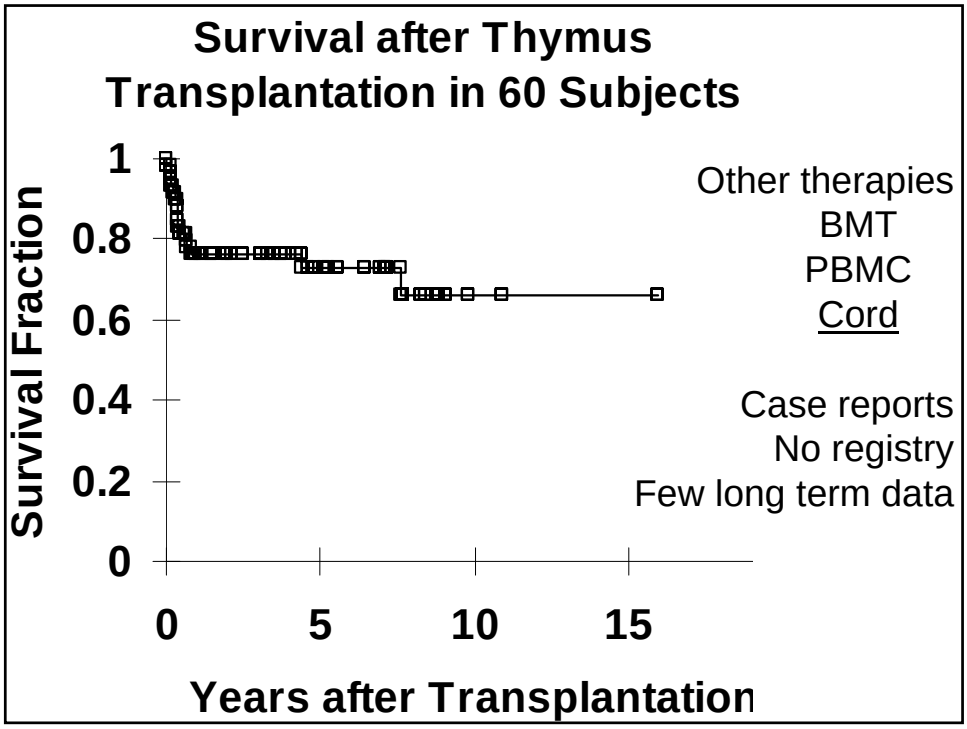
Thymus Transplantation Methods:

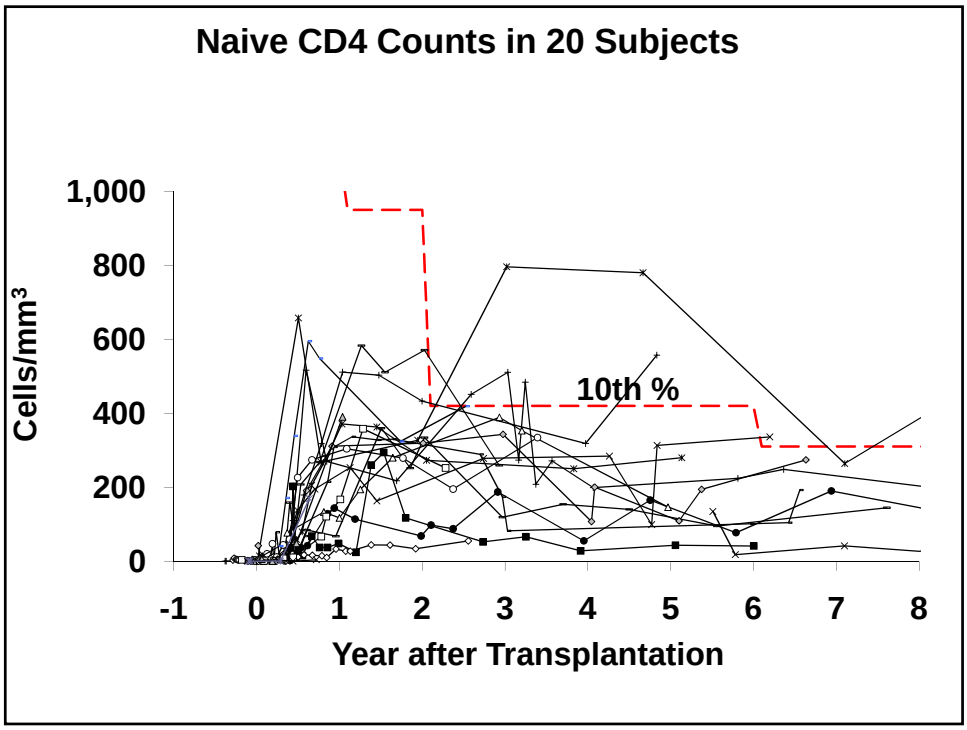
- Infant with cDGA is referred to Duke and is evaluated with immune testing and infectious disease screening.
- Thymus is obtained as “discarded tissue” in pediatric cardiac surgery cases.
  - Some thymus is removed to access the heart.
- The parent(s) of the thymus donor give(s) permission for use of the thymus and for infectious disease screening of the thymus, the donor and the birth mother.



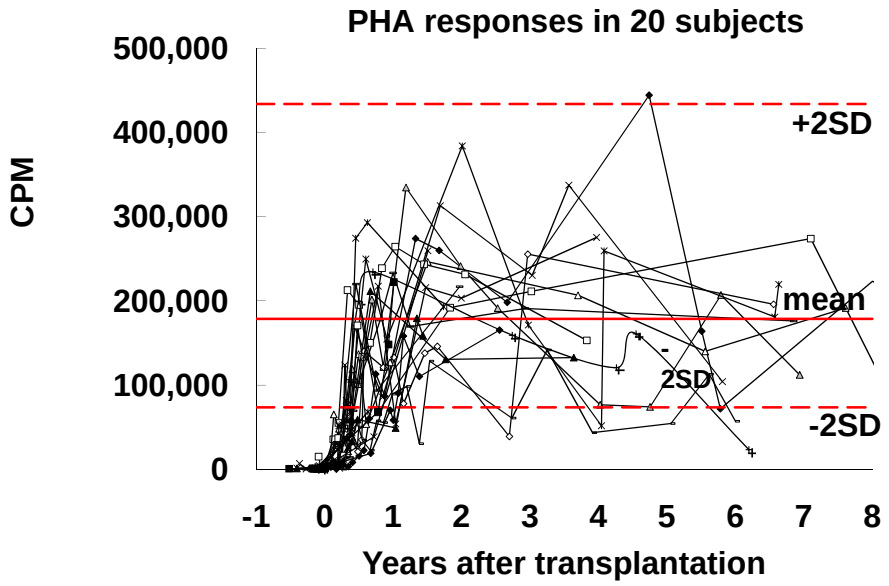
Risks:
- Infection transmission from donor
- Infection while waiting the 4 to 5 months until T cells appear in the circulation
- Unanticipated adverse events

Benefits:
- Survival
- Development of naïve T cells with diverse T cell repertoire


Survival after Thymus Transplantation in 60 Subjects
Survival Fraction
1
0.8
0.6
0.4
0.2
0
0
5
10
15
Years after Transplantation
Other therapies
BMT
PBMC
Cord
Case reports
No registry
Few long term data


Naive CD4 Counts in 20 Subjects
Cells/mm³
1,000
800
600
400
200
0
10th %
-1
0
1
2
3
4
5
6
7
8
Year after Transplantation

Although T cell numbers are low, function is normal.



Phase I Challenges

- Principal investigator = sponsor
- Clinical investigation
  - Comply with FDA, IRB requirements
  - ClinTrials.gov
- Manufacture of the tissue
  - Comply with FDA, CLIA regulations

Challenges : Clinical

- Phase I trials
  - Unpredictability of recruitment.
    - Only 10 – 20 infants with complete DiGeorge anomaly born per year in US
    - Different phenotypes require different adjunctive treatments
    - Competition for patients by sites with other treatment options
  - Time required to obtain insurance/Medicaid approval for a “research” procedure

Challenges with data impacting clinical trial design

- Data collection
  - Small numbers of subjects
  - Small blood volumes allowed
    - Limitation on studies
  - Timing of samples is variable
  - Dependence on local physicians
- Data analysis
  - Insufficient funding for data management programs

Strategies to bridge gaps

- Need specialized resources to identify sources of support for rare diseases
  - Manufacturing expertise
  - Shared manufacturing facilities
  - Industry sponsorship
    - No NIH or FDA regulatory support possible
- Perform research to expand indications so that industry will be interested.

Clinical challenges in Phase I: Insufficient regulatory funding in FDA, NIH grants

- Clinical regulatory costs
  - IRB revisions, annual reports, SAE reports
  - Clinical SOPs
  - DSMB preparation of materials, AE reporting, preparation of minutes
  - ClinicalTrials.gov
  - FDA IND yearly reports
  - Audits/monitoring
  - Institutional requirements

Manufacturing barriers in Phase I

- Appropriate facility
- Insufficient funding for manufacturing regulatory affairs
  - Compliance with cGMP and cGTP
    - Manufacturing SOPs
    - Training
    - Audits
  - IRB for tissue procurement
- Difficulty in recouping costs of manufacturing using “cost recovery”

Pre-Biologic License Application (BLA) barriers for investigator/sponsors

- In addition to the challenges for Phase 1:
- No NIH or FDA regulatory support is possible
  - NIH says the procedure is “standard of care” and will not pay for any regulatory effort.
  - There is no support for long term follow up.
- No private company sponsorship
  - With low patient numbers, economic feasibility is questionable.
- Academic pressure to have grants