What is Immune Tolerance?

• Where the immune system ignores or fails to react to a protein, cell or tissue in our body
  – During development the immune system learns to tell the difference between things that should be ignored vs. invaders that should be attacked to protect the body

• Challenges when system gets this wrong
  Autoimmune diseases
  – Allergy & Asthma
  – Organ transplantation
Immune Tolerance Network (ITN) Mission

• Advance the clinical application of immune tolerance therapies
  – Perform high quality clinical trials of emerging therapeutics
  – Integrate with mechanism-based research assays

• Innovation and collaboration
  – Rigorous and reproducible research
  – Adherence to standardized platforms and processes
  – Use best available statistical methodology and data management practices
  – Dissemination of data and results to research community
Reproducibility of results in published literature

Figure 1 Summary of the efforts to replicate the published analyses.

Reproducible Research

• Computation is central to the scientific enterprise
  – Impossible to verify most results that computational scientists present in meetings and in papers
  – Relaxed attitudes in communicating computational details and validation of results is causing a large and growing credibility gap
  – The ability to verify previous results allows future scientists to build upon prior work
  – Sharing of raw data or processed result data is not adequate without annotated statistical code base

Integrating Research Assay Data with Clinical Outcomes

Baseline Screening

Withdrawal of Drug

Drug Administration
• Drug Levels
• Drug Effects
  • Serum Cytokines
  • Cell Populations
  • Gene Expressions

Transplant
• Graft Assessment
  • Day 0 Biopsy and Gene Expression
• Drug Levels
• Drug Effects

ISDrug Withdrawal
• Immune Response
• Cell Populations – Flow Cytometry
• T Cell Function - Drug Effects
• Rejection- Gene Expression

Immediate Post Withdrawal
• Organ Rejection - Gene Expression
• Cell Populations - Flow
• T Cell Function

Follow Up: 2-5 years
• Tolerance Marker ID
• Gene Expression
• Regulatory Cells - Flow Cytometry
• Th1/Th2 Shift
• Serum Profiles
• Other Assays

Day 0

One Year

Start of Study

End of Study

One Year

2-5 Years

Weaning Period

Baseline Screening

Drug Administration
• Drug Levels
• Drug Effects
  • Serum Cytokines
  • Cell Populations
  • Gene Expressions

Transplant
• Graft Assessment
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• Th1/Th2 Shift
• Serum Profiles
• Other Assays

End of Study
Flexible framework for rapid portal deployment

Rapidly adapt design as needed

Application framework that allows different data ‘work environments’ as needed

Data pipeline
System should address broad spectrum of users
ITN TrialShare goals and objectives

• **Data Management / Application Framework**
  - Standardized syntax and naming convention across sample sets
  - Data loading is consistent, streamlined, semi-automated
  - Extensible application framework for adding assays, analytical workflows, and tools as needed

• **Scientific / Analytical**
  - Rapid access to clinical, assay and specimen data that can be readily merged as needed
    - *Researchers need not rely on asking ITN staff for data*
  - Collaboration system for review of findings with other researchers
    - *Users provide feedback or request follow-up: Make sample, assay and/or analytical support requests*
  - Simple tools and visualizations for interpretation of data within or across studies
    - *Researchers potentially use system for hypothesis generation, study tracking, or other types of assessments*
Tools initially considered

Framework needed to tie components together. Most tools lacked context and flexibility.

Business Intelligence (BI)

Crystal Reports

Simpler interface, fewer options, but easier for novices to use immediately.

MS Reporting Services

Interactive Visualization

Tableau Spotfire ‘Custom’

Requires technical expertise, and authoring of “work book” viewer.

Difficult for novices to immediately.

MS Excel
LabKey Integrated Solution

- Standard, reporting tool functionality embedded within a portal framework
- Framework for operational workflows, Analysis, Reporting & Visualization

Publication ready analyses and report presentations (power-point)

Complex assay layout, experimental design and analysis strategies

Integration across specimen repository and data sets
Data Management, Analysis, & Dissemination

Capture
- Data extraction routines
- Standardize data elements

Reconcile
- Reconcile sample identifiers
- Account for missing samples

Analyze
- Merge datasets
- Perform QA, assess batch effects, normalize data
- Develop statistical models,
- Generate manuscript ready figures

Interpret
- Generate hypotheses
- Draft reports, manuscripts, presentations
- Design follow up experiments

Report, Collaborate
- Facilitate scientific discovery through collaboration
- Support analysis and hypothesis generation by external groups
- Solicit proposals for follow-up experiments

Portal Framework

Internal/Operational

Capture
- Data extraction routines
- Standardize data elements

Reconcile
- Reconcile sample identifiers
- Account for missing samples

Analyze
- Merge datasets
- Perform QA, assess batch effects, normalize data
- Develop statistical models,
- Generate manuscript ready figures

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Portal Framework
Layout & workflow requirements

Table for all analyses, presentation to date and associated data

Specify relevant reports of interest

Make a sample request

Search for participant characteristics

Request an Analysis
Can you check if there is an association with C4d and Tolerance?

Notify

Category

External Resources
www.rhofed.com
www.mct.org
www.telepathy.org

Interactive Plots / Data
Liver Function Tests
Flow Cytometry
Gene Expression

Participant Timeline
Mat endpoint
Did not meet endpoint

Interactive plots linked to analysis reports

Minimized CRF datasets

Table needed, for publications and locked, "snapshot" data

Link to Rho for clinical reports, Jake’s telepathology site, Charlie’s MAT,6XB tools

Description of Study
Immunosuppression Withdrawal for Pediatric Living-donor Liver Transplant Recipients
Protocol Chair: Submitted

This is a prospective multicenter, open-label, single-arm trial in which 20 pediatric

Analyses / Reports

Gene Expression
Analysis Report
Date
Type

3/20/2009
Interim

3/25/2011
Interim

ImmunePhenotyping

C4d

Abstract/Manuscripts

ITN 10th Annu. Symp Data
ATC 2011 Abstract Data

Study Overview

Participant Overview

Specimens / Samples

LabKey User Conference 2012
Storyboard design mock-ups: Report management

Auto-rotation and/or pagethru “Highlights” webpart
Accommodates variable R plot sizes, variable numbers of charts in each tab, ~1000px page width, persistent View Studies widget

How does the design impact adding a new list item?

- Change title from Add New List Item to Add New Report
- Include a way to clone an existing report
- Perhaps add a Status field for Draft or Final (or any interim stages). This means moving status (i.e. “draft”) out of Category. Status field should be a drop-down of defined status types.
- Make tooltips more helpful. i.e. “Data source for the report. You can choose this to be a snapshot of the data as it existed at the time the report was created.”

(www.brighteyeweb.com)
Visualization storyboards
System brought online within a year of development
RAVE: Rituximab for ANCA-Associated Vasculitis

Protocol Chairs: John H. Stone, MD, MPH and Ulrich Specks, MD

The median of peripheral-blood B-cell counts in the rituximab and control groups according to antineutrophil cytoplasmic antibody (ANCA) type. MPO denotes ANCA directed against myeloperoxidase, and PR3 ANCA directed against proteinase 3.
Manuscript Figures using R-console

[Images of heatmaps and R console output]
Specialized statistical pipeline work

[Diagram: Boxplot showing MNC % Consistency Across sample aliquots]
Review of underlying flow gating

Domain experts with no expertise in R can review plots rapidly.
Link plots to “flow assay module”

Click on results
Clicking on r-report generates full flow-Jo gating strategy using GATE-ML standard
LabKey functionality sponsored by ITN

- Report management
  - Data report browser layout, design
- Participant sub-setting
  - Participant groups, categorization in drop-downs
- Visualization
  - Enhancements to Time-charts
  - Box-plots
  - Scatter plot overlays
- Flow Cytometry module
  - GATING-ML standard for FlowJo data parsing
- “Publishing” studies
  - Enhancement to snapshot tool, de-identification for public dissemination
ITN data & software development work

- All upstream data management, cleaning, transformations
- Automated loading
- Dashboard log-in messaging, configuration
- Specimen workflow UI enhancements
- Automated public-account registration
- R-plot configuration design and workflows
Next steps

• Public Launch October 2012
• Continue refining workflows
  – Use focus groups and surveys to assess investigator pressure points and areas for further enhancement
• Work with LabKey to add additional functionality within the core system
• Expand out into customized applications and modules
Conclusions

• LabKey allows rapid application development and prototyping for TrialShare
• Minimized creating core components from scratch
  – “Modules”, web-parts or frames could be inserted and laid out for workflows as needed
• Potentially a standard framework for other clinical trial consortia to consider in dissemination of research assay data
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Alan Vezina
Cory Nathe
Kim Carson
others...

LabKey User Conference 2012
F U N D E D  B Y:

NIAID
National Institute of Allergy & Infectious Diseases

JDRF
National Institute of Diabetes & Digestive & Kidney Diseases

Food Allergy Initiative