



Immune Tolerance Network



ITN TrialShare: From Concept to Deployment

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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

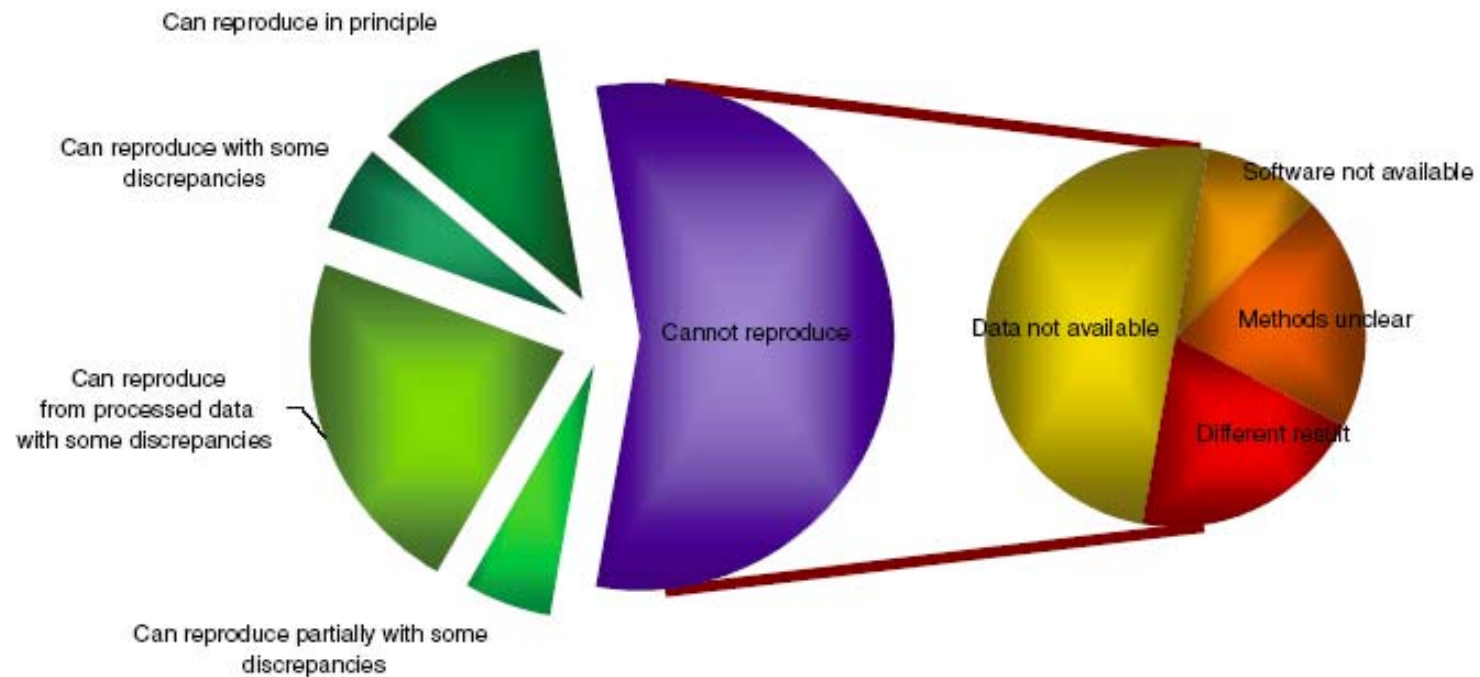


Figure 1 Summary of the efforts to replicate the published analyses.

Ionnidis, P. et al. *Repeatability of published microarray gene expression analyses. Nat Gen* , 41:2, Feb 2009

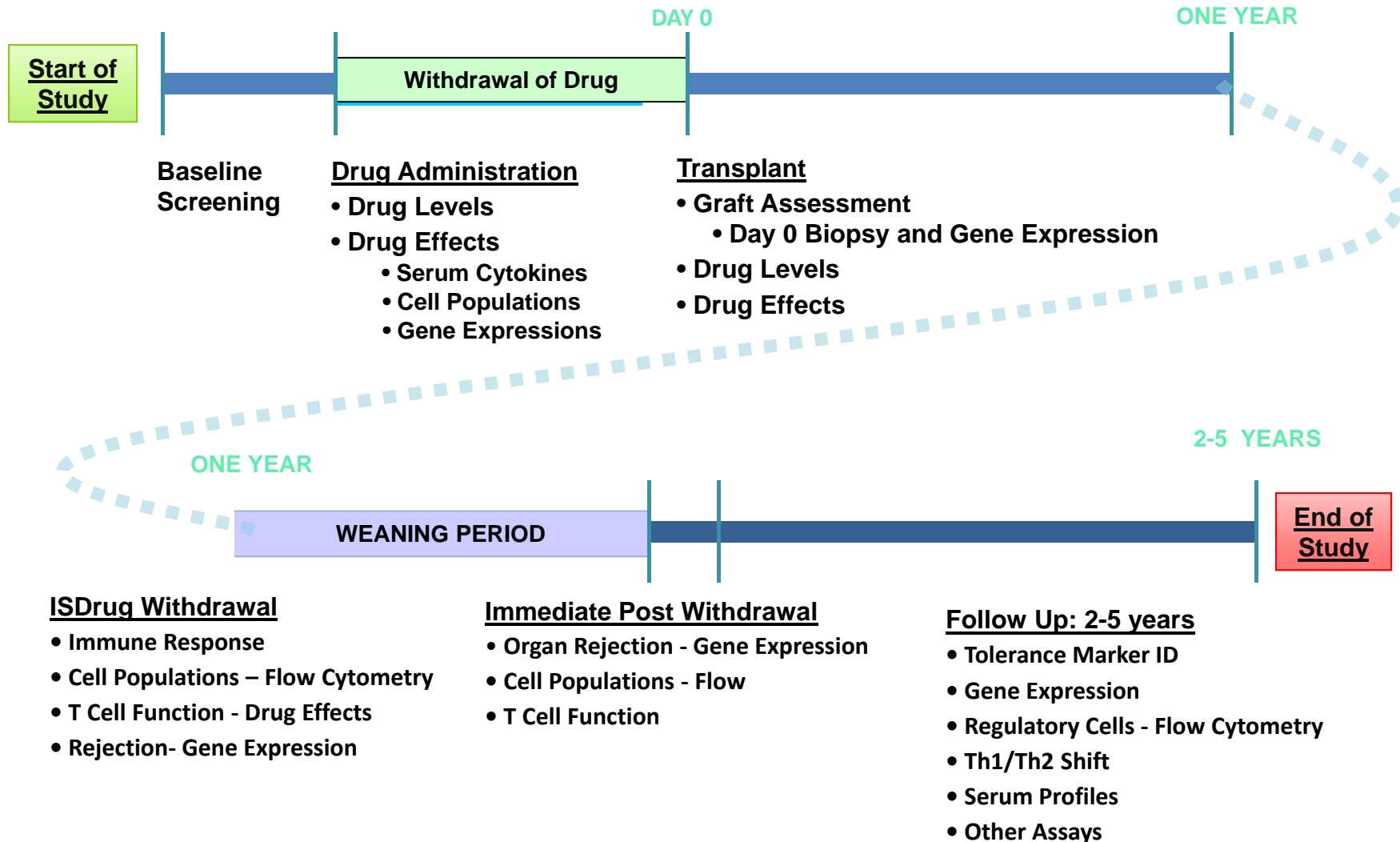
Reproducible Research

- 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

“Editorial Expression of Concern,” *Science*, Vol 327. no. 5962, p. 144, Jan 8, 2010.

D. Donoho et al., “Reproducible Research in Computational Harmonic Analysis,” *Computing in Science and Engineering*, Jan/Feb 2009(vol. 11 no. 1), pp. 8-18

Integrating Research Assay Data with Clinical Outcomes



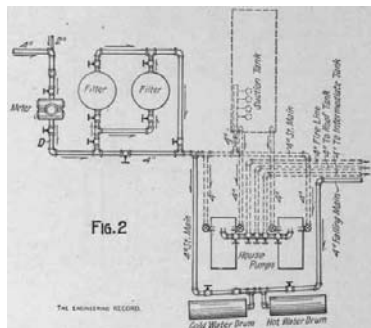
Flexible framework for rapid portal deployment



Rapidly adapt design as needed

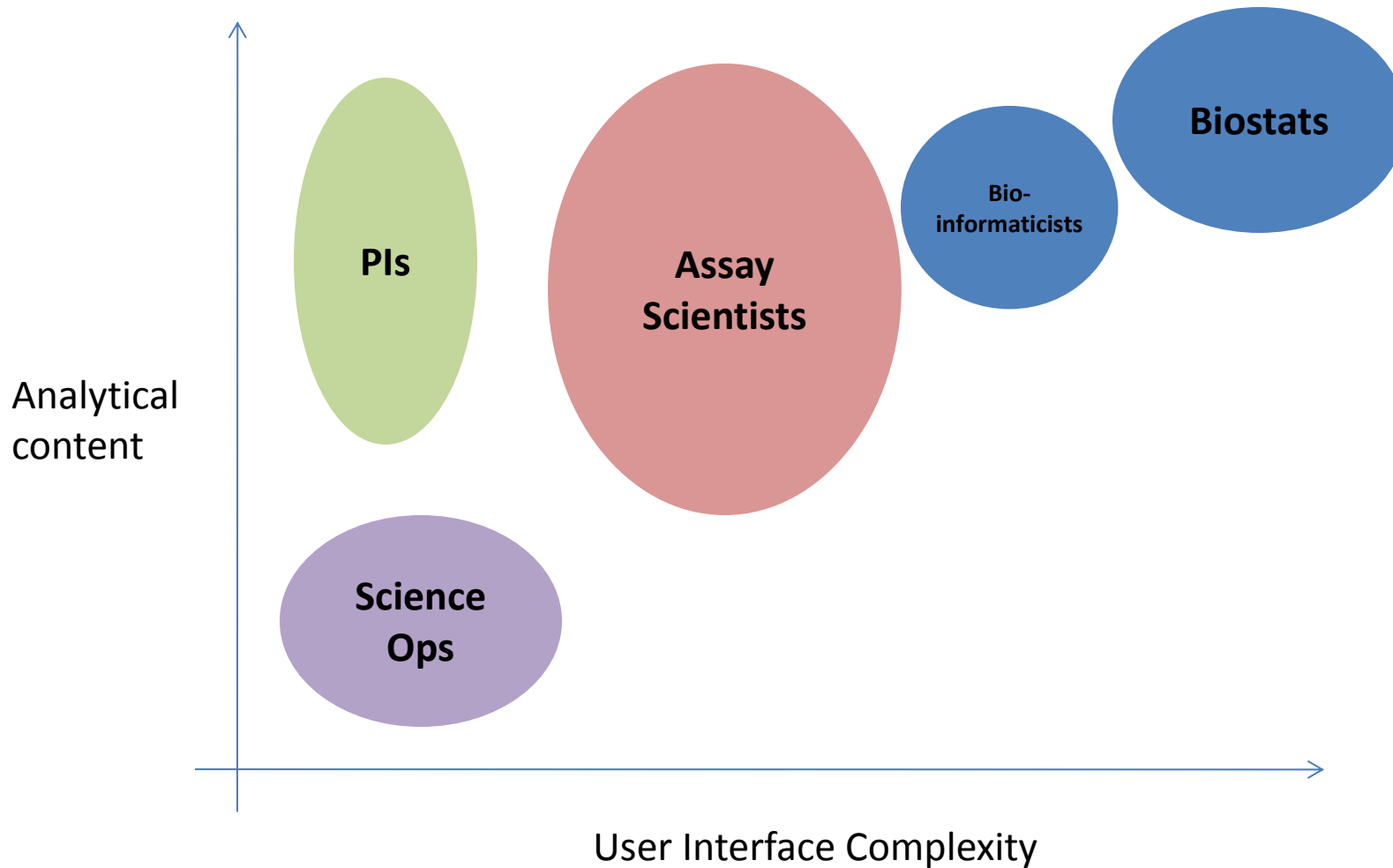


Application framework that allows different data 'work environments' as needed



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

MS Excel

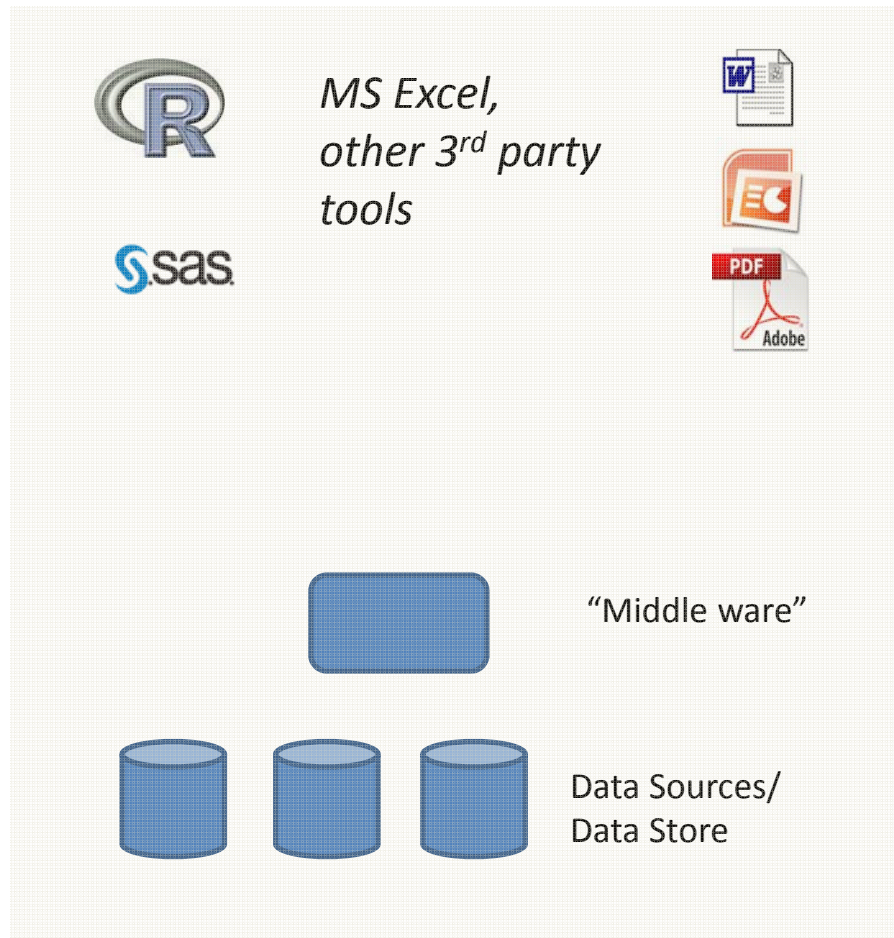
Interactive Visualization

Tableau
Spotfire
'Custom'

Requires technical expertise, and authoring of "work book" viewer.

Difficult for novices to use immediately.

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

Reconcile

Analyze

Interpret

Report, Collaborate

Internal/Operational

- Data extraction routines
- Standardize data elements

- Reconcile sample identifiers
- Account for missing samples

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

Portal Framework

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

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

Layout & workflow requirements

Immunoshare - Study Page

Description of Study
 Immunosuppression Withdrawal for Pediatric Living-donor Liver Transplant Recipients
 Protocol Chair: S. [redacted]
 This is a prospective multicenter, open-label, single-arm trial in which 20 pediatric

Abstract/Manuscripts
[ITN 10th Aniv Symp](#) [Date](#)
[ATC 2011 Abstract](#) [Date](#)

Analyses / Reports

Analysis Report	Date	Type	Data
GeneExpression	9/15/2009	Interim	<input checked="" type="checkbox"/>
Immunophenotyping	3/15/2009	Interim	<input checked="" type="checkbox"/>
C4D	3/15/2011	Interim	<input type="checkbox"/>

Participant Timeline
[Met endpoint](#)
[Did not meet endpoint](#)

Interactive Plots / Data
[Liver Function Tests](#)
[Flow Cytometry](#)
[GeneExpression](#)

Study Overview

Participant Overview

Request an Analysis
 Can you check if there is an association with C4D and Tolerance?

Specimens / Samples

External Resources
[www.rhofed.com](#) [www.mat.org](#)
[www.telepath.org](#)

Annotations:

- Table needed, for publications and Locked, "snapshot" data (points to Abstract/Manuscripts)
- Table for all analyses, presentation to date and associated data (points to Analyses / Reports)
- Minimized CRF datasets Interactive plots linked to analysis reports (points to Interactive Plots / Data)
- Specify relevant reports of interest (points to Specimens / Samples)
- Link to Rho for clinical reports, Jake's telepathology site, Charlie's MAT, GXB tools (points to External Resources)

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?

May involve making changes to Name and/or Category

I.e. the design uses some existing Names to group reports that share the same data source. But this feels wrong when it comes to "naming" a specific report list item. Maybe this becomes (or we add a field for) "Name and link to the source data set for this report"

Category seems to be used for a few different things now - to indicate status, or sometimes type of report. Could Category be used to do the grouping by data source instead?

Perhaps add a Status field for Draft or Final (or any interim stages). This means moving status (i.e. "Interim") out of Category. Status field should be a dropdown of defined status types.

There would need to be UI for this too - add/edit/delete Report Categories. Does each unique dataset or data item (.csv file, interactive plot, etc.) become a report category?

Change title from Add New List Item to Add New Report

Include a way to clone an existing report

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."

In this design, the Link and Data fields become the Link/Data associated with the snapshot data. Should tagging the data as a snapshot be optional?

(www.brighteyeweb.com)

Visualization storyboards

Chart Editor

Name: Visible By: All Just Me

Description:

ACTIONS PROPERTIES MEASURES AGGREGATES

PARTICIPANTS

- All
- Group 1
 - 700010019
 - 700010025
 - 700010032

Other side panels:

PARTICIPANTS

ANALYTES

Chart Editor

Name: Visible By: All Just Me

Description:

ACTIONS PROPERTIES MEASURES AGGREGATES

MEASURES

- Pulse from Physical Exam
- Change from LuminaAssay

ADD MEASURE REMOVE MEASURE

Divide data into Series:

- One Per Participant
- One Per Participant and

Display Duplicate Values as:

might want to specify axis for each measure here too, so axis can be set here or on the particular axis also

POST

PARTICIPANTS

- All
- Setup 1
 - 700010009
 - 700010025
 - 700010032
 - 700010048
 - 700010058
 - 700010066
 - 700010077
 - 700010081
 - 700010094
 - 700010106
 - 700010111
 - 700010122
 - 700010135
- Group 2

EDIT ADD

Other top panels/dropdowns:

ACTIONS

View Data
Export PDF
Share

PROPERTIES

Layout:

- One Chart
- One Chart for Each Participant
- One Chart for Each Dimension
- One chart for each participant group

Chart Title: Physical Exam

Use Width:

Hide Data Points

AGGREGATES

- Show individual lines
- Show aggregates
 - Mean

At some point we'll want UI to enable multiple simultaneous aggregates (min + max, median + count, mean + error bars)

System brought online within a year of development

The screenshot displays the Immune Tolerance Network (ITN) TrialShare website. At the top left, the logo for the Immune Tolerance Network Clinical Trials Research Portal is visible, alongside the text 'TrialShare INNOVATION • COLLABORATION' and 'A clinical research consortium funded by NIAID'. A central banner image shows three researchers in a lab setting. To the right of the banner, the text reads 'The Immune Tolerance Network' with the website 'immunetolerance.org' and the tagline 'Accelerating clinical development of immune tolerance therapies and biomarkers'. Below the banner, the page is divided into two main sections. The left section, titled 'WHAT'S NEW - SEP 16TH, 2012', contains two sub-sections: 'Study Data Updates' and 'New Dataset Status', each with a bulleted list of recent updates. The right section, titled 'SIGN IN', features a 'REQUEST AN ACCOUNT' button, input fields for 'Username' and 'Password', a 'Forgot password?' link, and a 'SIGN IN' button. A 'Terms of Use' section follows, stating that users have previously agreed to the terms and providing a link to the full terms. A checkbox for 'I agree to these terms' is present, along with a link to the 'Privacy Policy'.

WHAT'S NEW - SEP 16TH, 2012

Study Data Updates

- AWISH Study Data and Reports are now available for review along with associated graphical representations.
- IL2 (Greenbaum) has ancillary assays included, such as cytokine and methylation data.

New Dataset Status

- All Datasets now display with a Status icon of Unlocked, Locked, or Final. Unlocked conveys the possibility of future changes to the dataset. Locked displays for clinical datasets once the clinical database has been locked. Final indicates that a dataset has been used for a specific publication, abstract or presentation analysis/figure.

SIGN IN [REQUEST AN ACCOUNT](#)

Username *

Password * [Forgot password?](#)

You have previously agreed to the Terms of Use

The information contained on the ITN TrialShare Site is made available as a service by the ITN in order to foster rapid dissemination of scientific information and promote transparent access to ITN research data. As a Site user, you are obligated under the ITN TrialShare Terms of Use to comply with all terms and conditions therein including, without limitation, a lawful use of the Site in accordance with all applicable laws and regulations. Please review the complete [Terms of Use](#).

By clicking "I Agree" below you are confirming that you have read and accept all the terms and conditions without limitation.

I agree to these terms

Your privacy is important to us and we encourage you to read our [Privacy Policy](#).

[SIGN IN](#)

Dashboard

https://access.rii.munetolerance.org/project/home/begin.view? Google

Most Visited Getting Started Latest Headlines Bookmarks

Immune Tolerance Network **TrialShare** **INNOVATION · COLLABORATION**
 Clinical Trials Research Portal A clinical research consortium funded by NIAID

Search ITN TrialShare Admin | Home | Help | aasare@immunetolerance.org

ITN TrialShare

Highlights

- Welcome
- Getting Started
- Highlights
- Study Catalog
- Manuscripts & Abstracts

RAVE: Rituximab for ANCA-Associated Vasculitis

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

Days	Cyclophosphamide, MPO	Cyclophosphamide, PR3	Rituximab, MPO	Rituximab, PR3
0	240	210	210	210
30	10	10	10	10
61	10	10	10	10
122	10	10	10	10
183	10	10	10	10
274	10	10	10	10
305	10	10	10	10
456	10	10	10	10
548	10	10	10	110

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.

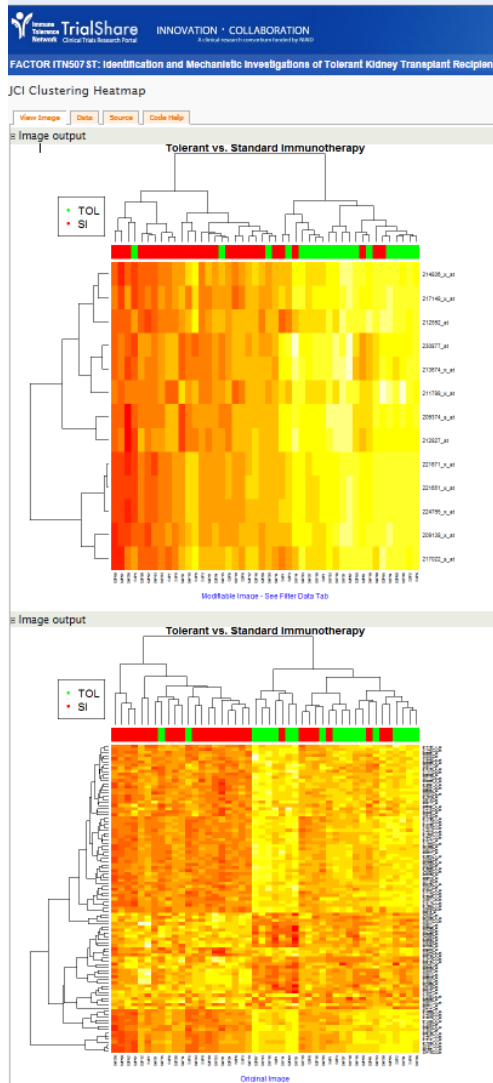
View Studies

- Type I Diabetes
 - Herold II
 - AbATE ITN027AI
 - IL2-RAPA ITN018AI
- Autoimmune
 - RAVE ITN021AI Reviewer
 - RAVE ITN021AI
 - Overview
 - Data and Reports
 - Participants
 - RAVE ITN021AI Operational
- Transplant
 - FACTOR ITN5075T Public
 - FACTOR ITN5075T
 - AWISH ITN0305T
 - WISP-R ITN0295T
- Other Places
 - Dashboard
 - My Account
 - Help
 - Quick Start Guide
 - User Guide
 - Support
 - Mech Ops
 - Admin Console
 - Administration Area
 - Clear Local Storage

Study Access

Viewable information is based on whether or not study results are available for public dissemination. If you have questions about access to any of the information on this site, contact the TrialShare Support.

Manuscript Figures using R-console



FactorITN507ST: Identification and Mechanistic Investigations of Tolerant Kidney Transplant Recipients

Overview Data & Reports Participants Manage

JCI Clustering Heatmap

View Image Data Source Code Help

Download input data?

Probe	Symbol	Description	Uni Gene	OMIM	Pathway	Raw P	Fdr P	Log2ratio	Ratio	FC
200811_at	CIRBP	cold inducible RNA binding protein	Hs.634522	602649	---	0.0024	0.19733501	0.321199343	1.249368744	1.249368744
200972_at	TSPAN3	tetraspanin 3	Hs.5062	---	---	0.0022	0.189720599	0.628052513	1.545477352	1.545477352
200973_s_at	TSPAN3	tetraspanin 3	Hs.5062	---	---	0.0016	0.164996779	0.557432298	1.471647653	1.471647653
202154_x_at	TUBB3	tubulin, beta 3	Hs.511743	602661	Circadian_Exercise // GenMAPP // Circadian_Exercise // GenMAPP	0.0003	0.102969119	-0.686292857	0.621448672	-1.609143353
202548_s_at	ARHGEF7	Rho guanine nucleotide exchange factor (GEF) 7	Hs.508738	605477	---	0.001	0.134685505	0.329969562	1.256986855	1.256986855
202724_s_at	FOXO1	forkhead box O1	Hs.370666	136533 // 268220	---	0.0023	0.1933591	0.430510448	1.347803753	1.347803753
203221_at	TLE1	transducin-like enhancer of split 1 (E(spl) homolog, Drosophila)	Hs.197320	600189	---	0.0023	0.1933591	0.682530102	1.604951945	1.604951945
203717_at	DPP4	dipeptidyl-peptidase 4 (CD26, adenosine deaminase complexing protein 2)	Hs.368912	102720	---	0.0013	0.151214086	0.636200135	1.55423013	1.55423013
203865_s_at	ADARB1	adenosine deaminase, RNA-specific, B1 (RED1 homolog rat)	Hs.474018	601218	---	0.0003	0.102969119	0.749622179	1.681352451	1.681352451
204141_at	TUBB2A	tubulin, beta 2A	Hs.654543	---	---	<.0001	0.023520644	-2.877084207	0.136116682	-7.346638094
205513_at	TCN1	transcobalamin I (vitamin B12 binding protein, R)	Hs.2012	189905	---	0.0019	0.174604019	-1.142359062	0.453018207	-2.2074168
205557_at	BPI	beta-defensin 1	Hs.2012	189905	---	0.0019	0.174604019	-1.142359062	0.453018207	-2.2074168
205671_s_at	HLA-DOB	HLA class II DOB chain	Hs.2012	189905	---	0.0019	0.174604019	-1.142359062	0.453018207	-2.2074168

FactorITN507ST: Identification and Mechanistic Investigations of Tolerant Kidney Transplant Recipients

Overview Data & Reports Participants Manage

JCI Clustering Heatmap

View Image Data Source Code Help

```
### read in top gene table (SI vs. TOL)
#####
toptable<-labkey.data;
#dim(toptable);
#toptable;
topgenes<-as.character(toptable$probe);
#topgenes;
library(Rlabkey)
toptabq<-labkey.selectRows(labkey.url.base,labkey.url.path,schemaName="lists",queryName="Genelist",colNameOpt="rname")
topgenq<-as.character(toptabq$probe);

#####
### load filtered expression data and pData
#####
load("D:/Program Files/Labkey Server/files/Studies/ITN507ST/Study
Data/@files/assaydata/Newell_20081202_VO_badEx_nodup_DMHC_RMA_expression_filtered_grpCor.Rdata");
load("D:/Program Files/Labkey Server/files/Studies/ITN507ST/Study
Data/@files/assaydata/Newell_20081202_VO_badEx_nodup_DMHC_grpCor_phenoData.Rdata");

#expression2.filtered.grpCor[1:5,];
#dim(expression2.filtered.grpCor);

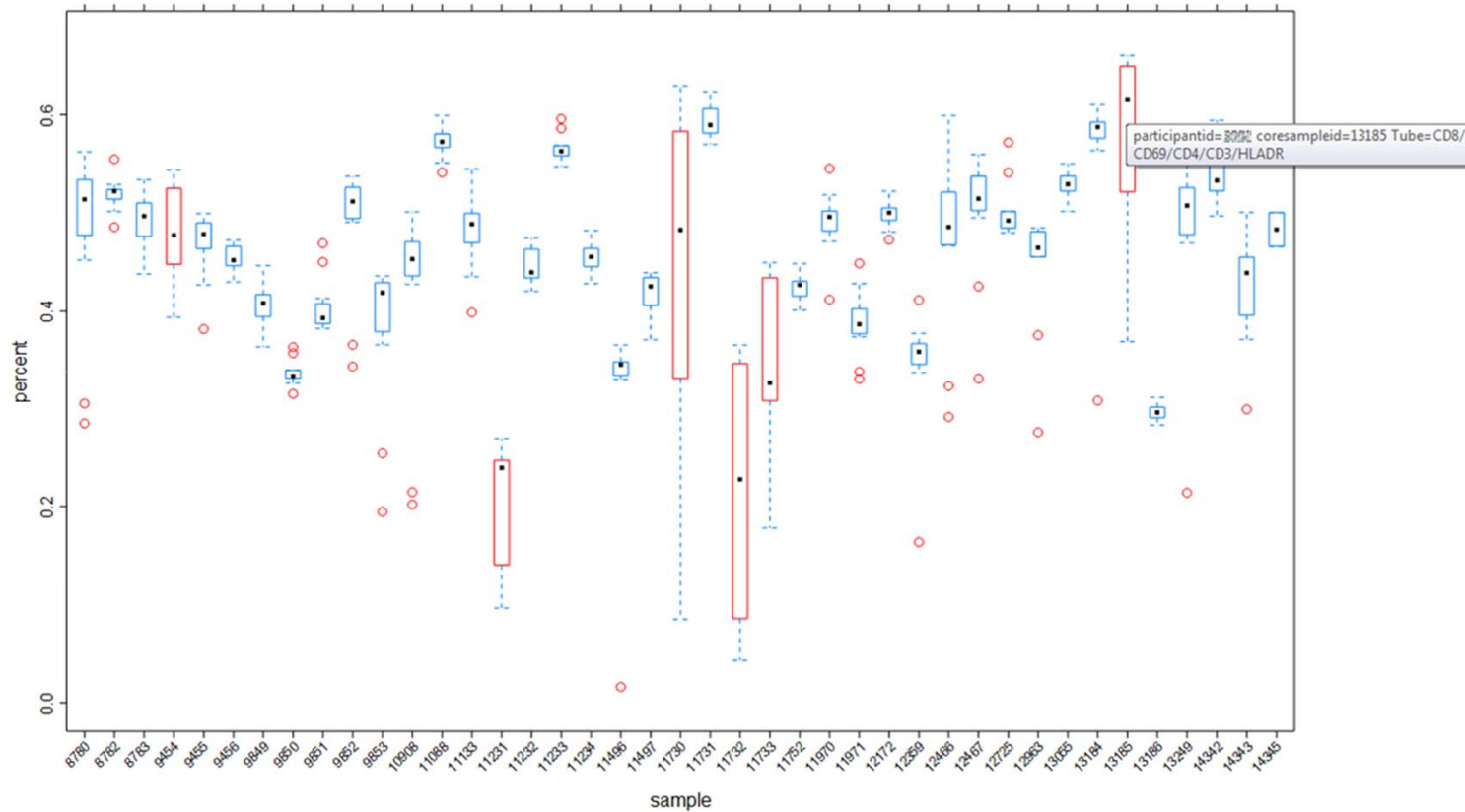
#pd;
#dim(pd)

 Toggle editor
 Make this view available to all users
 Show source tab to all users
 Make this view available in child folders?
 Run this view in the background as a pipeline job
```

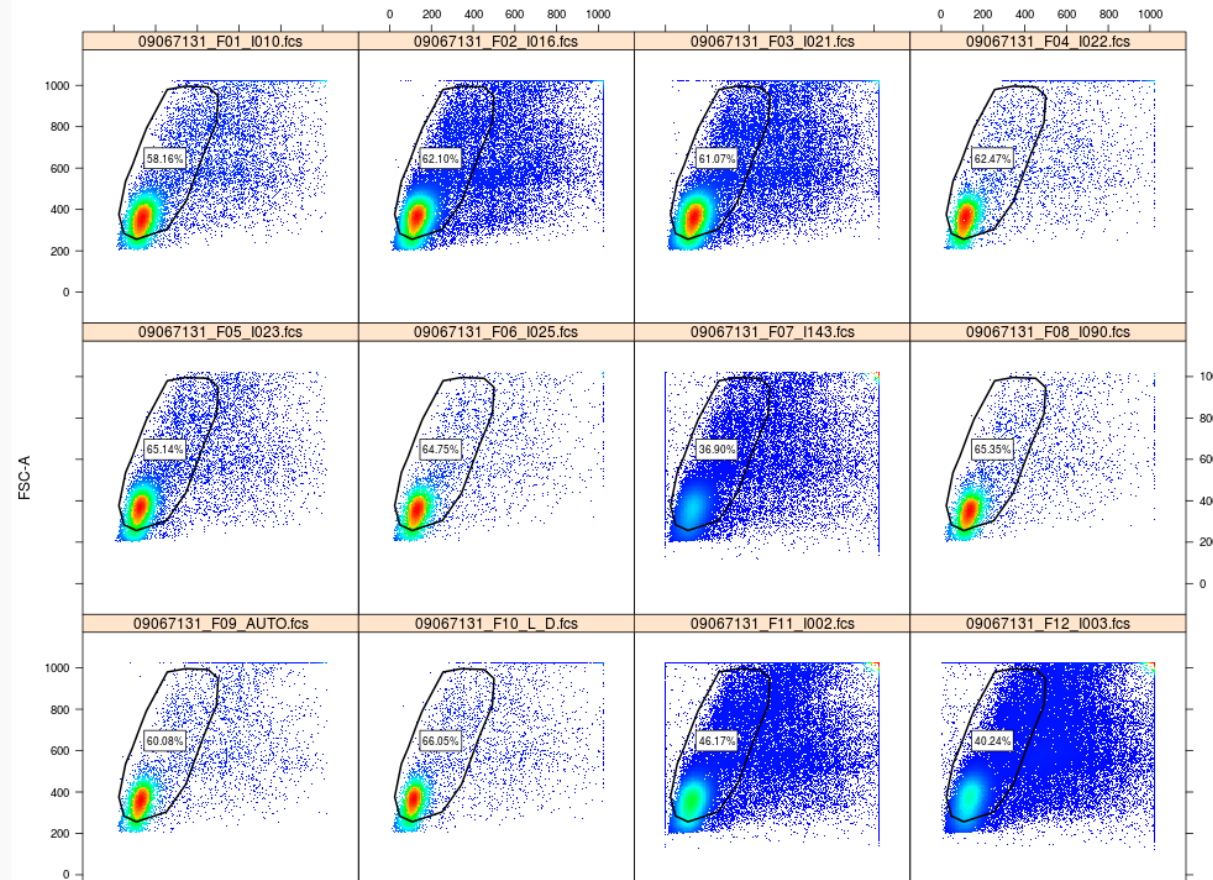
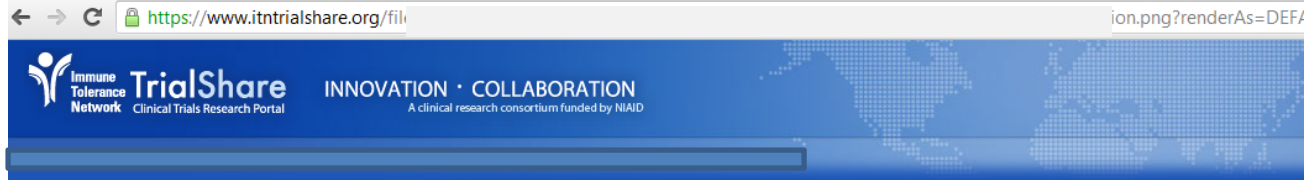
Specialized statistical pipeline work

https://www.itntrialshare.org/reports/Studies/ITN029ST/Study%20Data/download.view?entityId=CB829748-2B5B-102F-ADAD-A030294FD640&name=aliquot_boxplot_for

MNC % Consistency Across sample aliquots

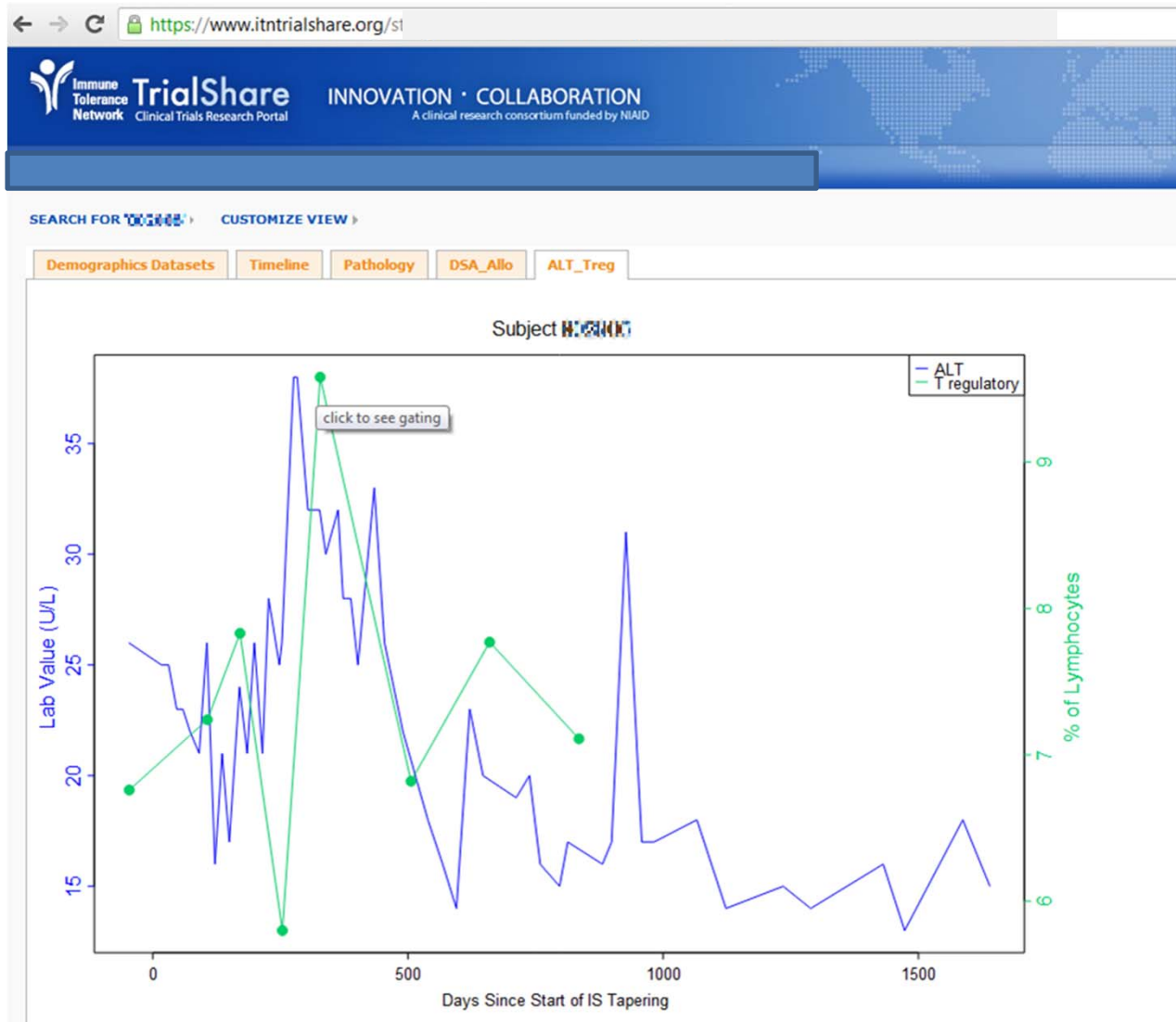


Review of underlying flow gating



Domain experts with no expertise in R can review plots rapidly

Link plots to “flow assay module”



Click on results

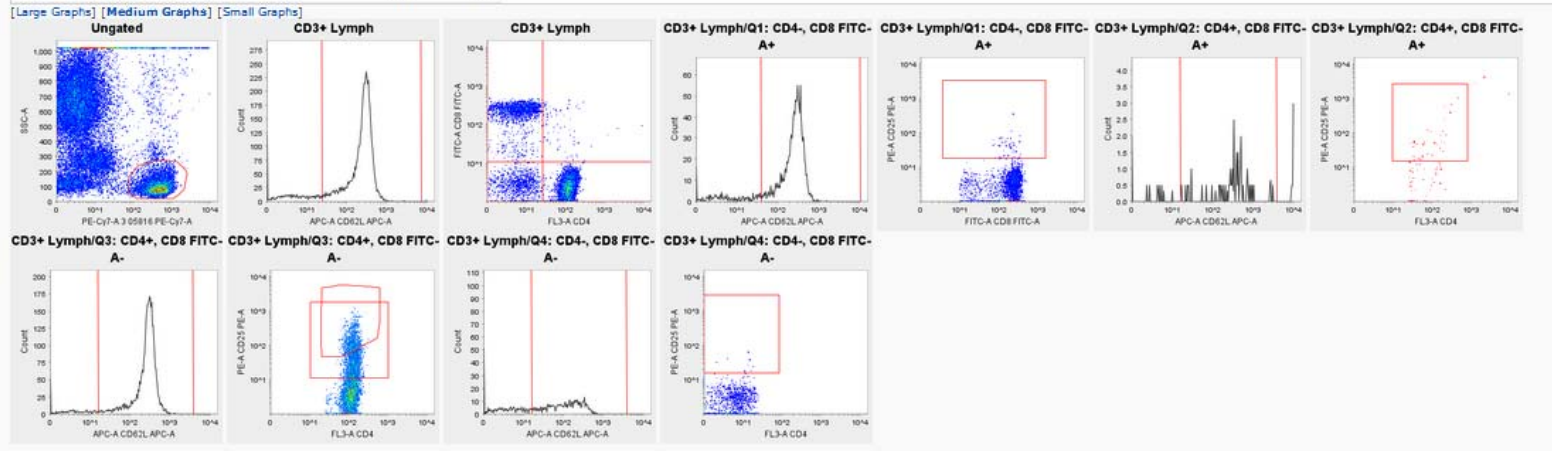
Flow

Flow Dashboard

Run Name: XXXXXXXXXX
 Analysis Folder: XXXXXXXXXX
 Well Name: 20080219170_F01_I010.fcs
 FCS File: 20080219170_F01_I010.fcs
 Well Comment:
 Analysis Script: workspaceScript472

Population	Count	%P
CD3+ Lymph	13,797	27.6%
CD26L-APC	12,043	87.3%
Q1: CD4-, CD8 FITC-A+	3,097	22.4%
activated	349	11.3%
CD25+	48	1.5%
CD62L+	2,748	88.7%
Q2: CD4+, CD8 FITC-A+	84	0.6%
activated	18	21.4%
CD25+	35	41.7%
CD62L+	66	78.6%
Q3: CD4+, CD8 FITC-A-	8,717	63.2%
activated	647	7.4%
CD25+	2,439	28.0%
CD25bright	835	9.6%
CD62L+	8,070	92.6%
Treg	791	9.1%
Q4: CD4-, CD8 FITC-A-	1,899	13.8%
activated	621	32.7%
CD25+	19	1.0%
CD62L+	1,278	67.3%

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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Digestive & Kidney Diseases



Food
Allergy
Initiative