Biomarker Development to Improve Decision Support for the Treatment of Organ Failures: How Far Are We Today?

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Outline

• **Part I: Clinical side**
  - PROOF Centre Biomarker Programs
  - Sample and data handling, workflows, QC/QA
  - Statistical analysis
  - Pre-qualification, qualification, validation

• **Part II: Informatics side** – connecting the dots
  - Tracking Chronic Kidney disease: process management
  - Secure search of clinical information
  - Exploring experimental correlation networks and enriching with public knowledge
  - Creating and applying combinatorial biomarker profiles
  - Decision support for organ failure risk assessment

• **Summary**
  - Where are we now, where do we go next?
PROOF Centre Mission

Discover
Develop
Commercialize
Implement

BIOMARKER SOLUTIONS
Prevent
Predict
Diagnose
Manage
Treat

Heart failure
Lung failure
Kidney failure
Integration of genomics and proteomics is important due to different biomarker “compartments”
PROOF Centre Biomarker Programs

Clinical Question Biomarker Discovery Biomarker Development Clinical Implementation

Chronic Kidney Disease
Levin, Gill, Beaulieu, Gill, Landsberg, Johnston, Djurdjev

Chronic Obstructive Pulmonary Disease
Sin, Hogg, Paré

Heart Failure
Ignaszewski, Ramanathan, Cheung, Oudit, Anderson, Dyck, Arnold

Biomarkers in Transplantation
Co-Leads: McManus, McMaster, Keown, Ng

“Cured” Organ Failure

New Biomarker Technology
Borchers, Hill, Francis, Walley, Granville

Lecture at ADAPT 2010, Arlington, VA, Sept.15, 2010
Current Diagnostic Approaches for Heart and Kidney Transplantation

Tissue biopsies remain the gold standard for diagnosis of acute rejection.

- Highly invasive
- Not timely
- Expensive
- Diagnostic only, not prognostic
- Uncomfortable and fear-evoking
- Prone to sampling error
- Subject to interpretative variability
Need for Improved Diagnostics

*The Driver of Biomarkers in Transplantation*

- Identify effective, minimally invasive, and widely applicable markers that…
  - *diagnose* acute and chronic rejection
  - *predict* rejection or immune accommodation of solid organ transplants
  - *forecast the response to therapies* that individual transplant recipients receive

- Discover plausible new targets for drug discovery
BiT Biomarker Discovery Strategy
“Omics” Tools and Approaches

**TRANSCRIPTOMICS**
- PAXgene Whole Blood
  - RNA Extraction
    - Affymetrix Microarray Analysis
      - Microarray Core Laboratory, Children’s Hospital, LA, CA

**PROTEOMICS**
- Plasma
  - Plasma Depletion
    - ABI 4800 iTRAQ Analysis
      - UVic-Genome BC Proteomics Platform, Victoria, BC

**METABOLOMICS**
- Serum and Urine
  - NMR & Mass Spec Analysis
    - U of Alberta Metabolomics Platform, Edmonton, AB

**QA/QC** – All sample collection and processing is done to SOP

Lecture at ADAPT 2010, Arlington, VA, Sept.15, 2010
BiT Analysis Strategy

Pre-processing
- Genomics
  - Affymetrix U133 plus 2.0 microarrays
  - RMA Normalization
  - Pre-filtering
- Proteomics
  - iTRAQ Mass Spectrometry
  - Protein Group Assignment
  - Pre-filtering

Statistical Analysis
- Differential Expression with Accommodation of Batch Effect
- Statistically Significant Probe Set List (False Discovery Rate)
- Relative Abundance
- Relative Frequency
- Statistically Significant Protein List

Bioinformatic Tools
- IO Informatics Knowledge Explorer
- GOstats
- MetaCore
- Gene Set Enrichment
E.g., Diagnostic Genomics Panel for Acute Renal Rejection

Biomarkers in Transplantation

Moving from development to clinic

- **2009**
  - External qualification of genomic and proteomic blood-based biomarkers for heart and kidney rejection
  - **International Biomarker Trial (BiT2)** - 350 kidney transplant patients and 150 heart transplant patients
  - **Biomarker Panel Refinement** – improved AUCs to >0.90 for acute kidney and heart rejection
  - **Assay Development**

- **2011**
  - In vitro diagnostic regulatory submissions

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Part II: Informatics side

• Connecting the dots …
  • Tackling end-stage kidney diseases: manage and synchronize tasks
  • Secure search of patient and clinical information
  • Exploring experimental correlation networks and enriching with public knowledge: does it make sense mechanistic-biologically?
  • Creating and applying combinatorial biomarker profiles: decision support to assess risk of pre-symptomatic organ failure
Workflow End-Stage Kidney Failure

Manage and synchronize tasks
From sample processing to analysis and reporting
Web-based workflow management
Secure Patient Search

- Track Immunosuppressant treatments at various times after organ transplantation

Compliant web-based query
Biomarkers: From Data to Knowledge

- Applied Semantic Knowledgebase (ASK) for predictive biology
- Capture combinatorial marker patterns in ‘SPARQL Arrays’
- Create semantic networks to visualize and explore biomarkers
- Test hypotheses, qualify & validate model
- Unify & analyze data
Combinatorial Marker Network

- Explore significantly affected genes and proteins for a control patient
Create Profiles visually
• Set ranges for each marker and refine hypothesis and model iteratively
Physician’s view

- Logon the web and select the knowledge arrays for Organ Failure
Physician’s view
- Search for matching patients
Physician’s view

• Review hits on each rejection profile
Physician’s view
• Get matching patient’s biomarker values and confidence scores
Physician’s view
• Review goodness of fit graphically
Patient screening – mobile

Physician’s view
• Ability to securely screen patients via mobile devices
Result: Applicable Knowledge

Confident decision support under complex biological conditions via web, in real-time
Summary

• Today
  • Building combinatorial biomarker panels for transplant rejection is complex
  • It requires meaningful integration of genomics, proteomics and clinical data.
  • Data integration and knowledge building using a semantic systems-approach has led to better understanding of the complex biological mechanisms involved in organ failure

• And in the future?
  • Widespread use of biomarker panel-based screening profiles to pro-actively manage organ failures of kidney, lung and heart.
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