Our Road Towards Personalized Medicine

State of Michigan Reproductive Biology Annual Meeting
May 21st, 2010

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Director, Program of Translational Medicine
Van Andel Research Institute
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616-234-5304
Presentation Summary

• Brief Introduction to VARI/TGEN
• Development of Critical Infrastructure to Enable Efficient Translational Medicine
  ▫ Translational Informatics (XenoBase = XB-BIS)
  ▫ CLIA Certified Molecular Diagnostic Laboratory (CMM)
  ▫ Clinical Trial Network (ClinXus)
• Prospective Personalized Medicine Clinical Trials
• Application to Woman's Health research
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- **Brief Introduction to VARI/TGEN**
- **Development of Critical Infrastructure to Enable Efficient Translational Medicine**
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- **Application to Woman's Health research**
‘Impact Human Health in the 21st Century’
Jay and Betty Van Andel (1996)
May 2000: The Van Andel Institute

- Private, Independent Not for Profit Institute
- Phase I (162,000 sq. ft.)
  - ~ 250 staff
- Phase II (250,000 sq. ft extension, Dec 2009)
  - ~ 800 staff
- Education and Research Institutes
- Multiple Centers and Multiple Diseases
- Understanding of Disease at the Molecular Level and Translation to Impact Human Health in 21st Century

“Go see the human beings who are suffering, and then ask yourself, is the work I did today relevant to human suffering? Did I do something that is going to help change somebody’s life, maybe not today but sometime soon?”

Christopher Reeve, 2001
2009: VARI-TGEN Affiliation
• Four Key Stages
  ◦ Primary Data
  ◦ Reads Alignment
  ◦ Variants Called
  ◦ Interpreted Variants

• Technology Independent
  ◦ Illumina/SOLiD/454
  ◦ Complete Genomics Soon

• Analysis Super-Center Network
  ◦ TGen, UCLA, Queensland, Baylor
  ◦ Monthly calls
  ◦ Quarterly Meetings

• Developed/Refined Over the past 3 years
  ◦ 454 Data: 11/06
  ◦ Illumina Data: 6/07
  ◦ SOLiD data: 6/08

• Modular/Swappable
  ◦ Not every component must be TGen Code
  ◦ Built around common formats

• Quality Control
  ◦ Contamination (Illumina 1M)
  ◦ Recalibration
  ◦ File completeness
  ◦ Remote Access
2010
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Biomarkers and the Future of Medicine

Efficient Medical Care

Disease Severity

"Right" Drug

Monitoring

Diagnosis/Prognosis

Predisposition

Screening

Time

Health Management; Molecular Screening; Early Detection; Rapid Effective Treatment; Improved Quality of Care
How Do We **Deliver** the Right Drug to the Right Person at the Right Time?

**Pharmacopeia**

**Mechanisms of Action**

- EGFR
- TNF
- ITK
- DPP-4
- HER
- PPAR
- PPAR
- CARP
- VEGF
- IKK
- DRK
- ERK
- COX2
- MAPK
- NFKb
- CNG
- MET
- MEK
- ROS
- DPRP
- FLT
- GPR
- STYK
- FOLR
- GLP
- RXR
- GR
- ECGF

More than 324 molecular drug targets of approved drugs

Translational research is a discipline where unproven observations (hypotheses) advance to more informative studies that ultimately provide definitive information for a medical decision in routine clinical practice.
Historical Review

Long term focus on “Personalized Medicine”
Integrated Informatics
XenoBase BioIntegration Suite (XB-BIS)
Therapeutic Predictions: From the Simple...

Wang et al. Genome Biology, 2007 8:R255

RULE: IF [Eph2A] {Z-SCORE > +2} THEN [Dasatinib]
Therapeutic Predictions: 
*To the Complex (reality)*

Integrated Informatics (XB-BIS)
Data Modeling, Decision Support and Outcomes
Molecular Diagnostics Laboratory
Center for Molecular Medicine

- Joint Venture with Spectrum Health
- High Complexity CLIA certified/ CAP accredited
- Contract Research Laboratory
- Evaluation of New Molecular-Based Technologies
- FDA Approved Tests
  - AmpliChip® – Roche
    - Identifies poor metabolizers of key drugs
    - Optimize prescription dosing, circumvent ADRs
  - Cell Search CTC System – Veridex
- Homebrew Diagnostic Tests
  - Signature-based diagnostic and prognostic tests
  - Key Component of Predictive Therapeutics Trial (Affymetrix U133 2.0 Plus platform)
- Sold to Sequenom Dec 2008
Clinical Trial Alliance

• **Vision**
  ◦ A community alliance focused on the design and implementation of biomarker strategies within early phase clinical trials

• **Strategy**
  ◦ Coordination of existing and emerging expertise, infrastructure and resources
  ◦ SMO Function

• **Funding**
  ◦ MEDC 21st CJF State Grant
  ◦ Member Contributions
  ◦ Clinical Trial Revenue

• **Partnership**
  • Community alliance of committed research, educational and clinical organizations including:
    • Van Andel Research Institute
    • Spectrum Health System
    • Saint Mary’s Healthcare
    • Jasper Clinic
    • Grand Valley Medical Specialists
    • Grand Valley State University
    • Innovative Analytics
    • MPI Research
    • Cancer & Hematology Centers of West Michigan

www.clinxus.org
A consortium of industry, nonprofit institutions and regulators outlines a rolling biomarker qualification process, providing the first clear path for translation of such markers from discovery to preclinical and clinical practice.
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2005 Case Study

• 44-year old male patient with metastatic mesenchymal chondrosarcoma
• Refractory to multiple lines of treatment
• Could (should) molecular information derived from patients tumor be used to assist physicians in treatment planning?
  ▫ Standard of care options?
  ▫ Experimental protocols?
  ▫ Off-label use?
Patient’s Outcome
Grand Rapids Proof-of-Feasibility Trial
50 Patient Feasibility Study

- 50 refractory patients enrolled
- Both pediatric and adult patients (age range 3-80 years old at enrollment)
- 11 process failures (SOP’s now finalized)
- 24/34 cases utilized report information
- 9/24 responses observed

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Multidisciplinary Team

- Helen DeVos Children’s Hospital
  - Deanna Mitchell, MD
  - David Dickens, MD
  - Al Cornerlius, MD
  - Richard Axtel, MD
  - Jim Fahner, ND

- Cancer Hematology Centers of West Michigan
  - Timothy O’Rourke, MD
  - Alan Campbell, MD
  - Mark Campbell, MD

- Oncology Care Associates
  - Eric Lester, MD

- Spectrum Health Research Department
  - Marcy Ross, BS
  - Brian Hilary, BA
  - Kim Mohr, RN
  - Tracy Waldherr, RN
  - Debbie Ritz-Holland, RN
  - Sara Finton, RN
  - Bethany Stanisiewski, MBA

- Spectrum Health Pathology Department
  - Sandra Cottingham, MD
  - Barbara Fulton, MD
  - Alyson Booth, MD
  - Gloria Kohut, MD
  - Kim Mills MD
  - Sarla Puri, MD
  - Said Ismail, MD
  - Roberta Clark
  - David Chesla

- Spectrum Health Pharmacy
  - Jennifer Zimmer-Young, PharmD
  - Jeff Barletta, PharmD
  - Polly Kintzel, PharmD

- Advanced Radiology Services
  - Joe Junewick, MD
  - Mike Knox, MD
  - Kenneth Gritter, MD
  - Bryan Mustert, MD
  - Jeffery Van Erp, MD
  - Barbara Thornburg, MD

- Medical Specialty Associates
  - Larry Pawl, MD

- Academic Surgical Associates
  - Marianne Lange, MD
  - Jane Pettinga, MD

- Spectrum Health Laboratories
  - Michael Warzynski, PhD
  - John Roys, MS
  - Susan Mammina, PhD

- Center for Molecular Medicine
  - Dan Farkas, PhD
  - Lyle Rawlings, PhD

- Others
  - Alan Davis, PhD (GRMERG)
  - Martin Luchtefeld, MD (MMPC)
  - Mathew Chung, MD (MMPC)
  - Sean Vance (MSU CHM)
PTOCA-0006: 63 year old Male with Metastatic NSCLC
PTSH-0005: 5 year old male with Clear Cell Sarcoma of Kidney

Pre-Treatment Baseline Scan

Post-Treatment (3 month) (Bevacizumab + Celecoxib) Scan
Conclusions of Our First Study

• Molecular profiling of patient tumors in a real time clinical environment (5 day turnaround) is feasible
• Information provided to physician was deemed useful in steering treatment decisions
• Anecdotal evidence provides impetus to test hypothesis that molecular information improves patient outcomes
Current Activities in Oncology

- Continued refinement of predictive methods and introduction of additional “omic” technologies
  - Next-Gen transcriptome sequencing
  - OncoCarta SNP genotyping
- Application to “Tumor Stem Cell” targeting
  - Pancreatic Cancer and GBM
- Pediatric Neuroblastoma Trial (5 patients)
  - NMTRC sponsored multi site feasibility trial
- SOLID Trial – 3rd Line Metastatic Breast Cancer (152 Patients)
- Registry Trial – utility assessment in late stage cancer patients – Third Party Payer Support (100 patients)
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Genomic Markers of Endometriosis
Underlying Biology of Endometriosis

Mid Secretory
FC=3; p<0.001
112 genes
Composite Diagnostic for Endometriosis?
### Personalized Medicine Report

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Partners

- Ben and Catherine Ivy Foundation
- MMRF
- Spectrum Health Foundation
- Hope on the Hill Foundation
- Michigan Economic Development Corporation
- Henry Ford
- Spectrum Health
- Helen DeVos Children's Hospital
- Advanced Radiology Services
- Saint Mary’s Healthcare
- Children’s Memorial Research Center
- NIH
- New York University
- Karmanos Cancer Institute
- Oncology Care Associates
- Academic Surgical Associates
- Cancer Hematology of West Michigan
- Michigan Medical PC
- Pfizer
- Schering Plough Research Institute
- Qiagen
- GeneGo
- Center for Molecular Medicine (Sequenom)
- ClinXus
- Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC)
- MSU CHM
The Program of Translational Medicine

- Hailey Jahn (Lab Technician)
- Sujata Srikanth (Molecular Technologist)
- Patrick Richardson (Biostats)
- Kathy Koehler (Admin)
- David Monsma (Preclinical Services)
- Dawna Dylewski (Preclinical Technician)
- Emily Eugster (Molecular Technologist)
- Stephanie Scott (Lab Technician)
- Jeremy Miller (Dev. Informatics, XB)
- Theresa Wood (Business Analyst/Project Manager)

- Phil Dumas (Student Intern, Ferris)
- David Cherba (Informatics and Diagnostics)
- Craig Webb (Director)
- Rick McUmber (XB-Software Development)
- Brian Berns (XB-Software Development)
- Chris Mazzanti (XB-Software Development)
- Frank DuPont (XB-Software Support)