Enabling Personalized Medicine Through Public-Private Partnerships

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Goal: To identify biomarkers of tumor progression

Pooling Progression Experiment

<table>
<thead>
<tr>
<th>Normal</th>
<th>Adenoma</th>
<th>Cancer</th>
<th>Mets</th>
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<td>N = 10</td>
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Focus on genes whose expression progressively increased with advancing tumor stage
The Director’s Challenge:
To form collaborations to determine if human tumors could be globally profiled with the extraction of meaningful biology

The early days of molecular profiling...

Molecular Staging for Survival Prediction of Colorectal Cancer Patients

JCO, 2005

Steven Eschrich, Ivana Yang, Greg Bloom, Ka Yin Kwong, David Boulware, Alan Cantor, Domenico Coppola, Mogens Kruhøffer, Lauri Aaltonen, Torben F. Orntoft, John Quackenbush, Timothy J. Yeatman
Colon Classifier

• 43 gene signature
• Classifier genes discriminate well while Dukes’ does Not
• SPP1 one of the key classifier genes

Validation of classifier with independent Danish test set

• Cross-platform classification discriminates populations
• Loss of accuracy X-platform
• Only 50% of cDNA classifier genes on U133A GeneChip
• Need for larger, single platform datasets

Emerging Needs

• Molecular profiling showed promise but…
  – Larger datasets were needed to permit independent testing and avoid “over-fitting” of data
  – Signal & tumor biology (heterogeneity) needed to be separated from noise
  – Larger collaborations needed to achieve “Big Science” goals
Moffitt’s Total Cancer Care (TCC) Initiative in Personalized Medicine

A Cancer Patient’s Life Journey

Total Cancer Care protocol:
1. How can we follow you throughout your lifetime?
2. Can we treat your tumor with precision technology?

History of Merck/MCC Partnership

– Shared vision between MCC & Merck leadership for development of a large clinical and molecular database
– Vision for use of the data by multiple stakeholders for new scientific discoveries
– Desire to produce thousands of molecular profiles to create molecular signatures of response to therapy
– Vision to develop evidence based guidelines & develop treatment plans for practicing physicians

“Partnership” Goals

• Collaboration established with “objectives, milestones, & deliverables”
  – Tissue & data deliverables
  – Global genome wide surveys
  – Specific “joint scientific” projects
• Acquire & profile ~20,000 high quality tumors
• Acquire deep clinical data sets (>100 elements)
• Develop R & NR signatures to SOC therapies
• Perform clinical trials using data from the database to find the right patients
The TCC® Consortium

Partners In The Fight Against Cancer
Total Cancer Care® Consortium

18 Partners...Focused mission

New Architecture: Relational DB

Information will be aggregated, stored and delivered by means of stringent standard operating procedures (SOP’s) to ensure high quality.
Four Portals to Total Cancer Care™

- **Researcher View**
  - Cohort Identification
  - Molecular Profiling
  - Comparative Effectiveness Research

- **Patient View**
  - Personal Health Record
  - Longitudinal Follow-up
  - Personalized Search

- **Administrators View**
  - Operational Dashboards
  - Quality & Safety Monitoring
  - Meaningful Use

- **Clinician View**
  - Decision Support
  - Clinical Pathways
  - Clinical Trial Matching
  - Access for Affiliate Network

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**M2Gen**

- M2Gen ("Moffitt 2nd Generation")
- Moffitt Cancer Center’s wholly owned subsidiary
- Created by State of FL as an “economic multiplier” opportunity
- Highly focused entity; developing multiple business/service lines to serve the pharmaceutical/biotech space
- Currently executes on projects run for Merck & Moffitt’s Total Cancer Care (TCC®) Initiative
- Operating with funding, from Clients & Government Sources

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**M2Gen Offices, Laboratories, Bio-repository & Data Warehouse**

100,000 sq ft in Tampa, FL
Project Milestones

- Initiated TCC 2006
- Initiated M2Gen 2007
- Developed TCC Consortium of 20 sites 2007-2008
- Developed MCC data warehouse & M2Gen database, EDC solution, and defined data set with definitions 2009
- Consented > 85,000 patients to date
- Acquired ~30,000 tumor samples
- Assessed > 20,000 tumors on GeneChips
- ~500 whole exomes
- ~4000 targeted resequencing
- CNV/SNP; Sequenom; Xenografts; Targeted resequencing
- Extracted >8,000 DNA samples for future sequencing

Multi-centric, Integrated Analyses: Biomarker Discovery Engine

- 110 Frozen Tumors
- Formalin-fixed, Paraffin-embedded Tissue (FFPET)
- Tissue Milling & Division (TMAD)

Cell Probes
- mRNA
- miRNA
- DNA
- Protein

Molecular Pathology
- RNA
- TRA

Imaging
- Qualitative Response
- Quantitative Response
- Imaging
- TRA Analysis
- Image Analysis

Volumetric Image Analysis

TMA

Amalga – Clinical

Comprehensive Molecular Profiling

Comprehensive Patient Portrait

UNDUPERVISED ANALYSIS:

1ST PRINCIPAL COMPONENT ROBUSTLY IDENTIFIES 2 INTRINSIC SUBPOPULATIONS IN COLON CANCER

MCC Cases

EXPO Cases
GENES & SIGNATURES: PC1 STRONGLY CORRELATES WITH (EPITHELIAL MESENCHYMAL TRANSITION) EMT

PC1 most closely resembled EMT among hundreds tested

EMT SCORE DERIVED FROM GED FROM 93 LUNG CANCER CELL LINES

EMT is the Dominant Program in Human Colon Cancer
BMC Genomics, 2011

A GLIMPSE INTO THE FUTURE OF PERSONALIZED MEDICINE

Leveraging the TCC Database for clinical trials
Today’s Oncology Challenge

- Trial accrual too slow, too expensive
- Patients do not want to leave home
- 80% of cancer care delivered locally
- Existing matching programs send patients to trial opportunities outside their communities

Early Concept: Visit the Gene Expression Library

Tumor Biopsy

Central Library

Diagnosis: Colon Cancer

Clinical Data

Chemotherapy: ILF Sensitive 95%

Prognosis: Poor

Paradigm Shift

TODAY
 Trials searching for patients

TOMORROW
 Trials designed for and directed to patients
Modern View: “Gene Based Trial Matching”

Key element: network willing to share clinical data

How GBTM Can Streamline Clinical Trials

Traditional Clinical Trials
- Broad Patient Population
- 10-12 Years

TurboTrial
- Molecularly defined population
- 3-5 Years

Ways to Fix the Clinical Trial

- Recruit early
- Skip animals
- Use models
- Alter course

Clinical trials are crumbling under modern environmental and scientific pressures. Nature looks at ways they might be renewed.
Conclusions

- Technology has evolved to permit comprehensive human tumor assessments for individual genes and pathways
  - Microarrays
  - Sequencing
  - Informatics
- Molecular profiles may be diagnostic, prognostic, and predictive
- Science suggests Gene Based Trial Matching is feasible if biomarker hypothesis is correct
- Networks and larger collaborations are necessary to achieve the vision

Conclusions

- Challenges are largely operational
  - Assembling, integrating and querying the data
  - Communicating with patients and physicians in real time
  - Buy-in from Pharma
    - Re-thinking trial design and execution
    - Smaller, more effective trials
    - Costs of biopsies & profiling
- “Gene based trial matching” offer promise to revolutionize trial designs and efficiency

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