The Next Frontier: Personalized Medicine and Cancer

Ken Buetow, Ph.D.
Director Computational Science and Informatics Core Program,
Complex Adaptive Systems Initiative
Arizona State University

MDx Next Spring 2012
Gaining the MDx Edge: Putting Molecular Diagnostics to Work in the Clinical Lab
The future is already here… it just not evenly distributed.

William Gibson
The Washington Post

We are using a patient’s genome to protect against heart attacks and stroke.

Each person responds differently to medicine. Using DNA, our doctors match heart patients with the right blood thinner. It’s one of the many ways we are tailoring medicine to the unique characteristics of each patient.

VanderbiltHealth.com/breakthroughs

VANDERBILT UNIVERSITY
MEDICAL CENTER

The promise of discovery
Vanderbilt University Medical Center
The Promise of Discovery

Discovery science is like "pulling back a curtain" to see what's behind it. You then find something completely new. You find something that nobody has seen before. At Vanderbilt University Medical Center, discovery science is "pulling back curtains" in the major diseases and conditions of our time.

Learn more about how Vanderbilt is reshaping healthcare.

Developing new surgical tools

New hope for people with melanoma

Fighting lung cancer with molecular medicine

Using genetics for smarter prescriptions

Learn about Vanderbilt's DNA databank
Vanderbilt BioVU
Melanoma Panel: 538 patients
67% Patients with Actionable Mutation
33% No Mutation Identified

Lung Panel: 451 patients
46% Patients with Actionable Mutation
54% No Mutation Identified

Courtesy Mia Levy
7 Cancers
- Lung
- Melanoma
- Breast
- Colon
- Thymic
- GIST
- Thyroid

22 Genes

203 Disease-Gene-Variant Relationships

Courtesy Mia Levy
<table>
<thead>
<tr>
<th>MR#</th>
<th>Patient Name</th>
<th>Actions</th>
<th>Tumor Gene Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>03</td>
<td>81 A, B M.</td>
<td>Actions</td>
<td>BRAF, NRAS, CTNNB1</td>
</tr>
<tr>
<td>03</td>
<td>56 A, P</td>
<td>Actions</td>
<td>BRAF, NRAS, CTNNB1</td>
</tr>
<tr>
<td>03</td>
<td>35 B, J A</td>
<td>Actions</td>
<td>BRAF, NRAS, CTNNB1</td>
</tr>
<tr>
<td>01</td>
<td>80 B, S A</td>
<td>Actions</td>
<td>BRAF, NRAS, CTNNB1</td>
</tr>
<tr>
<td>02</td>
<td>29 E, J E</td>
<td>Actions</td>
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</tr>
<tr>
<td>02</td>
<td>27 F, R M</td>
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<tr>
<td>02</td>
<td>77 G, T</td>
<td>Actions</td>
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<td>02</td>
<td>73 H, A</td>
<td>Actions</td>
<td>CTNNB1</td>
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<td>03</td>
<td>64 S, C</td>
<td>Actions</td>
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<td>02</td>
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<td>40 W, J E I</td>
<td>Actions</td>
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</tr>
<tr>
<td>03</td>
<td>74 W, C L</td>
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**BRAF c.1798_1799GT>AG (V600R) Not Detected**  
**BRAF c.1798_1799GT>AA (V600K) Not Detected**  
**BRAF c.1799T>A (V600E) Detected**  
**BRAF c.1799_1800TG>AA (V600E) Not Detected**  
**BRAF c.1798G>A (V600M) Not Detected**  
**BRAF c.1799T>G (V600G) Not Detected**  
**BRAF c.1799_1800TG>AT (V600D) Not Detected**
BRAF V600E (c.1799T>A) mutation in Melanoma

The V600E mutation results in an amino acid substitution at position 600 in BRAF, from a Valine (V) to a glutamic acid (E). This mutation occurs within the activation segment of the kinase domain (Fig. 2). Approximately 70-90% of V600 BRAF mutations are V600E (Rubinstein, 2010). Mutant BRAF proteins have increased kinase activity and are transforming in vitro (Davies, 2000). BRAF mutations are usually found in tumors with wildtype for NRAS, KIT, and other driver mutations.

1In the initial phase I trial, patients with metastatic melanoma whose tumor harbored a BRAF V600E mutation displayed an 81% response rate to vemurafenib (PLX4032), an orally available inhibitor of mutated BRAF. The estimated progression-free survival was > 7 months and overall survival had not been reached at the time of study publication (Hoffman, 2010). In the follow-up randomized phase III trial comparing vemurafenib to dacarbazine in previously untreated, metastatic melanoma with the BRAF V600E mutation, vemurafenib improved rates of overall survival and progression-free survival (Chapman, 2011).

2Pre-clinical data has correlated the presence of activating mutations in BRAF with sensitivity to non-ATP competitive MEK inhibitors, AZD6244 and CI-1044 (Davies, 2007; Slit, 2008). In a Phase II clinical trial of AZD6244 versus temozolomide, 5 of 42 melanoma patients with BRAF V600E mutation had confirmed partial responses (12% objective response rate) (Dummer, 2008).

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BRAF V600E mutation

Properties

- **Location of mutation**: Kinase domain (exon 15)
- **Frequency of BRAF V600E**: ~85-90% of BRAF mutant melanoma

Implications for Targeted Therapeutics

- **Response to BRAF inhibitors**: Confers increased sensitivity*
- **Response to MEK inhibitors**: Uncertain at this time#
- **Response to KIT inhibitors**: Uncertain at this time

AZD6244 versus temozolomide, 5 of 42 melanoma patients with BRAF V600E mutation had confirmed partial responses (12% objective response rate) (Dummer, 2008).

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## BRAF V600E (c.1799T>A) mutation in Melanoma

### Properties
- **Location of mutation**: Kinase domain (exon 15)
- **Frequency of BRAF V600E**: ~85-90% of BRAF mutant melanoma

### Implications for Targeted Therapeutics
- **Response to BRAF inhibitors**: Confers increased sensitivity*
- **Response to MEK inhibitors**: Uncertain at this time‡

### Treatment V600E mutation

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*Allele-specific treatment: vemurafenib for all BRAF^V600E^ patients with BRAF^V600E^ mutation has confirmed partial responses (12% objective response rate) (Dummer, 2008).

‡Data for MEK inhibitor response to BRAF^V600E^ mutation is currently limited and more research is needed.
Inhibition of mutated, activated BRAF in metastatic melanoma.

Abramson Cancer Center of the University of Pennsylvania, Philadelphia, USA. kflaherty@partners.org

Abstract

BACKGROUND: The identification of somatic mutations in the gene encoding the serine-threonine protein kinase B-RAF (BRAF) in the majority of melanomas offers an opportunity to test oncogene-targeted therapy for this disease.

METHODS: We conducted a multicenter, phase 1, dose-escalation trial of PLX4032 (also known as RG7204), an orally available inhibitor of mutated BRAF, followed by an extension phase involving the maximum dose that could be administered without adverse effects (the recommended phase 2 dose). Patients received PLX4032 twice daily until they had disease progression. Pharmacokinetic analysis and tumor-response assessments were conducted in all patients. In selected patients, tumor biopsy was performed before and during treatment to validate BRAF inhibition.

RESULTS: A total of 55 patients (49 of whom had melanoma) were enrolled in the dose-escalation phase, and 32 additional patients with metastatic melanoma who had BRAF with the V600E mutation were enrolled in the extension phase. The recommended phase 2 dose was 960 mg twice daily, with increases in the dose limited by grade 2 or 3 rash, fatigue, and arthralgia. In the dose-escalation cohort, among the 16 patients with melanoma whose tumors carried the V600E BRAF mutation and who were receiving 240 mg or more of PLX4032 twice daily, 10 had a partial response and 1 had a complete response. Among the 32 patients in the extension cohort, 24 had a partial response and 2 had a complete response. The estimated median progression-free survival among all patients was more than 7 months.

CONCLUSIONS: Treatment of metastatic melanoma with PLX4032 in patients with tumors that carry the V600E BRAF mutation resulted in complete or partial tumor regression in the majority of patients. (Funded by Plexxikon and Roche Pharmaceuticals.)
Cancer is a Complex Adaptive System

base state

malignant state

alteration

selection
Cancer is a Complex Adaptive System

- base state
- expression
- micro RNA
- glycolosis
- epigenetic
- gene
- mutation
- copy number
- malignant state
Cancer is a Complex Adaptive System

- Base state
- Angiogenesis
- Cell cycle regulation
- Telomere maintenance
- Growth factor independence
- Evade apoptosis
- Malignant state
Cancer is a Complex Adaptive System

- Angiogenesis
- Cell cycle regulation
- Telomere maintenance
- Base state
- Malignant state
- Growth factor independence
- Apoptosis evasion

ASU Complex Adaptive Systems Initiative
Cancer is a Complex Adaptive System

- base state
- angiogenesis
- growth factor independence
- evade apoptosis
- cell cycle regulation
- telomere maintenance
- malignant state

Cancer cells adapt and evade normal cellular processes such as cell cycle regulation, telomere maintenance, and growth factor independence, among others.
Cancer is a Complex Adaptive System

- Chemical
- Virus
- Hormone
- Nutrition

Base state

Genetic constitution

Malignant state

- Angiogenesis
- Cellular matrix
- Immune response
Multiple systems technologies are needed to triangulate molecular state of disease.
TCGA Ovarian Cancer
Chromosomal Amplifications and Deletions
TCGA Glioblastoma Multiforme

TCGA: Nature 2008
Patient selection for HER2 Tx required tissue screen and allowed only 1 of 4 women to participate.

<table>
<thead>
<tr>
<th>Calculated Sample Size And Study Duration</th>
<th>Hypothetical HER2+ Prevalence</th>
<th>Required “Screened” Population</th>
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<tbody>
<tr>
<td>1250 → 52 mos</td>
<td>100%</td>
<td>1250</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>2500</td>
</tr>
<tr>
<td></td>
<td>25%</td>
<td>5000</td>
</tr>
</tbody>
</table>

* Need a obtain a suitable specimen, wait for test results. (Results were obtained in days to weeks)
* Need to screen many patients.

Courtesy H. Kim Lyerly, M.D.,
## Size of Population with “Pathway” to Inhibit

<table>
<thead>
<tr>
<th>Population fraction containing signature</th>
<th>100%</th>
<th>50%</th>
<th>25%</th>
<th>12.5%</th>
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</thead>
<tbody>
<tr>
<td>No Pathway Defect</td>
<td>Phenotype A</td>
<td>Phenotype A1</td>
<td>Phenotype A2</td>
<td>Phenotype 1</td>
</tr>
<tr>
<td></td>
<td>Phenotype B</td>
<td>Phenotype B1</td>
<td>Phenotype B2</td>
<td>Phenotype 2</td>
</tr>
</tbody>
</table>

| Size of Population Needed To Screen    | 1,250 | 2,500 | 5,000 | 10,000 |

*Courtesy H. Kim Lyerly, M.D.*
Biomedicine: “fallen and I can’t get up”

- Impending “Pharmageddon”*: Declining R&D Productivity with Rising Costs
- Healthcare ecosystem is broken
- Poor understanding of the underlying biological complexity – current dominance of reductionist paradigm
- Vertically integrated development model (FIPCo) vs networked model (FIPNet) that dominates other sectors
- Exponential fragmentation of health information

need to embrace biomedicine as SYSTEM

* from M. King Jolly, Pharm.D. Quintiles, Inc. DIA 2011
Biomedicine: a Complex Adaptive System
“the whole is more than the sum of the parts”

- Diverse stakeholders: multidimensional, interacting “ecosystem”
  - Industry, Academe, Government, NGOs
  - Physicians, Regulators, Researchers, Payors, Consumers, Public Health Officials
  - Biology, Chemistry, Medicine, Business, Sociology, Anthropology
- Adaptive behaviors (dynamic as opposed to static)
- Emergent properties (or unintended consequences)
- Interdependencies
  - Resources
  - Information
Strategies for “Managing” Complexity

• Networking
  – **Differentiated functions** connected though well-defined **interfaces** – e.g.
    • Biologic processes
    • Manufacturing

• Layering
  – **Abstracted combinations of functions** into hierarchical/multidimensional strata which connect through well defined **interfaces** – e.g.
    • Quantum physics – Newtonian physics
    • Biologic complexity: cell, organism, society
    • Organizational hierarchies
Clinical Continuum

Diagnosis → Treatment Selection → Treatment Plan Management → Treatment Response Assessment
Clinical Biomarkers

- Diagnosis
- Treatment Selection
- Treatment Plan Management
- Treatment Response Assessment

Risk Biomarker
Diagnostic Biomarker
Prognostic Biomarker
Predictive Biomarker
Response Biomarker
Evidence Generation “System”

Standards for Biospecimen (by Analyte) → Evidence Threshold for Qualification → Validation

“Fit for Purpose”
- Stratify
- Prognosis
- Diagnostic

(each requires different evidence)
Evidence Generation “System”

- Standards for Biospecimen (by Analyte)
  - Evidence Threshold for Qualification
    - Validation
      - Stratify
      - Prognosis
      - Diagnostic
  (different designs for each class)
20th Century Research > Care Paradigm

Discovery
- Biological pathways
- Target identification and validation

Product Development
- Candidate selection and Optimization
- Pre-clinical testing
- Phase I, II, III
- New Drug application and Approval

Clinical Care
- Product launch
- Clinical adoption

Outcomes & Surveillance
- Reporting of serious/fatal ADRs
- Re-labeling (or recall) as needed
- Additional indications as warranted
21st Century Learning Health System

- Analysis and Learning
- Outcomes & Surveillance
- Discovery
- Product Development
- Clinical Care
BRAF V600E (c.1799T>A) mutation in Melanoma

**Properties**
- Location of mutation: Kinase domain (exon 15)
- Frequency of BRAF V600E: ~85-90% of BRAF mutant melanoma

**Implications for Targeted Therapeutics**
- Response to BRAF inhibitors: Confers increased sensitivity*
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The V600E mutation results in an amino acid substitution at position 600 in BRAF, from a Valine (V) to a Glutamic acid (E). This mutation occurs within the activation segment of the kinase domain (Fig. 2). Approximately 70-90% of V600 BRAF mutations are V600E (Rubin, 2010). Mutant BRAF proteins have increased kinase activity and are transforming in vitro (Davies, 2000). BRAF mutations are usually found in tumors wildtype for NRAS, KIT, and other driver mutations.

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**Title**
A Phase Ib, Open Label, Dose-Escalation, Study Evaluating the Safety, Tolerability and Pharmacokinetics of RO5185426 in Combination with GDC-0973 when Administered in Patients with BRAFV600E-Positive Metastatic Melanoma Who Have Progressed After Treatment with RO5185426

**Principal Investigator(s)**
Igor Puzanov

**Description**
The purpose of this study is to test the combination of the investigational drugs RO5185426 (BRAF inhibitor) and GDC-0973/XL518 (MEK inhibitor) in order to find a safe and tolerated dose when taking these drugs together.

**Eligibility**

**Details**

**Learn more**
- Call toll-free number: 1-800-811-8480
- Use our Online self-referral form
- Print this page for your doctor

**Melanoma (1)**

**Tennessee (4)**

**United States (13)**

**Internationally (12)**
# BRAF Mutation Directed Melanoma Clinical Trials

## United States (13)

<table>
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<th>Protocol No.</th>
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<tr>
<td>NCT01271803</td>
<td>A Study of RO5185426 And GDC-0973 in Patients With BRAF-Mutation Positive Metastatic Melanoma</td>
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<tr>
<td>NCT01350401</td>
<td>Phase I/II Study to Assess the Safety and Activity of Enhanced TCR Transduced Autologous T Cells in Metastatic Melanoma</td>
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<td>NCT01390818</td>
<td>Trial of MEK Inhibitor and PI3K/mTOR Inhibitor in Subjects With Locally Advanced or Metastatic Solid Tumors</td>
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<td>NCT01136967</td>
<td>An Open-Label, 2-Cohort, Multicenter, Study of E7080 in Previously Treated Subjects With Unresectable Stage III or Stage IV Melanoma</td>
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<td>NCT00866177</td>
<td>Phase II Study of MEK Inhibitor AZD6244 in Patients With BRAF-Mutated or NRAS-Mutated, Unresectable Stage III or IV Melanoma</td>
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<td>NCT00948467</td>
<td>Study of TAK-733 in Adult Patients With Advanced Nonhematologic Malignancies</td>
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<td>NCT01248936</td>
<td>A Study of RO5185426 in Patients With Metastatic Melanoma</td>
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<td>NCT01266967</td>
<td>A Study of GSK2118436 in BRAF Mutant Metastatic Melanoma to the Brain</td>
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<tr>
<td>NCT01072175</td>
<td>Investigate Safety, Pharmacokinetics and Pharmacodynamics of GSK2118436 &amp; GSK1120212</td>
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Trial of MEK Inhibitor and PI3K/mTOR Inhibitor in Subjects With Locally Advanced or Metastatic Solid Tumors

This study is currently recruiting participants.
Verified on July 2011 by EMD Serono
First Received on April 18, 2011. Last Updated on July 8, 2011

Purpose

This research trial is testing a combination of two experimental drugs, MSC1936369B (Mitogen-activated protein extracellular signal-regulated kinase (Mek) Inhibitor) and SAR245409 (Phosphatidylinositol 3-kinase (PI3K)/Mammalian Target of Rapamycin (mTOR) inhibitor), in the treatment of locally advanced or metastatic solid tumours. The primary purpose of the study is to determine the maximum tolerated dose of the drug combination.

Condition | Intervention | Phase
--- | --- | ---
Locally Advanced Solid Tumor | Drug: MSC1936369B and SAR245409 | Phase I
Metastatic Solid Tumor

Study Type: Interventional
Study Design: Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: An Open-Label, Phase Ib Dose Escalation Trial of Oral Combination Therapy With MSC1936369B and SAR245409 in Subjects With Locally Advanced or Metastatic Solid Tumors

Resource links provided by NLM:
- MedlinePlus related topics: Cancer
- Drug Information available for: Sirolimus, Everolimus, CCI 779
- U.S. FDA Resources

Further study details as provided by EMD Serono:
The I-SPY TRIAL (Investigation of Serial studies to Predict Your Therapeutic Response with Imaging And molecular analysis):

A national study to leverage biomarkers in predicting response to combinatorial therapy for women with Stage 3 breast cancer.

(PI Laura Esserman, UCSF)
UCSF I-SPY 2 study
I-SPY Adaptive Trial:
Introduce several new agents for a given profile

*Or Equivalent
I-SPY Adaptive Trial:
Introduce several new agents for a given profile

On Study

Randomize

HER 2 (+)

Taxol + Trastuzumab*

Taxol + Trastuzumab* + New Agent A

Taxol + Trastuzumab* + New Agent B

Taxol + Trastuzumab* + New Agent C

Taxol + Trastuzumab* + New Agent F

Taxol + New Agent F

Taxol + New Agent D

Taxol + New Agent G

HER 2 (-)

Randomize

AC → Surgery

Learn, Adapt from each patient

Surgery

*Or Equivalent
I-SPY TRIAL IT Infrastructure

Research Environment
- SNPArray Data
- Expression Array Data
- Patient Samples

Clinical Care Environment
- Clinical Data
- Radiological Data

caBIG® Applications
- caTissue
- caArray

Data Mart
- API

caExchange - Hub
- API

caBIG® Services to Local System
- Tolven
Network-centric “warfare”

A military doctrine or theory of war pioneered by the United States Department of Defense. It seeks to translate an information advantage, enabled in part by information technology, into a competitive warfighting advantage through the robust networking of well informed geographically dispersed forces. This networking, combined with changes in technology, organization, processes, and people - may allow new forms of organizational behavior.

Specifically, the theory contains the following four tenets in its hypotheses:
– A robustly networked force improves information sharing;
– Information sharing enhances the quality of information and shared situational awareness;
– Shared situational awareness enables collaboration and self-synchronization, and enhances sustainability and speed of command; and
– These, in turn, dramatically increase mission effectiveness.

(Wikipedia)
“Network-centric” Biomedicine

- Research Center
- Clinical Trials
- Analytical Tools
- Microarray Data
- Biospecimens
- Medical Center
- Index Service
- Vocabularies & Ontologies
- GME Schema Management
- Common Data Elements
- Workflow Management Service
- Federated Query Service
- Security
- Advertisement / Discovery
- Metadata Management
- Dorian GTS
- Research Unit

Medical Center

Research Center

Research Unit

Array Data
“Network-centric” Biomedicine

Virtual Community
(Services Infrastructure)
"Network-centric" Biomedicine

Virtual Community (Services Infrastructure)

Common Data Elements
Vocabularies & Ontologies
Research Center
Medical Center
VGMESchema
Workflow Management
Federated Query Service
Metadata Management
Federated Query Workflow
Research Unit
Medical Center
Virtual Community (Services Infrastructure)

"Network-centric" Biomedicine

Security
Discovery
Summary

- The future is already here for biomarker-based biomedicine.

- The biomedical ecosystem is ill prepared to address the complexity of common diseases such as cancer.

- Approaching biomedicine as a Complex Adaptive System may help address some of the challenges it currently faces.

- It is technically feasible to create and deploy technology to exchange information within and between members of the ecosystem.

- A multi-stakeholder, multidimensional community will be necessary to create a sustainable ecosystem.