Personalized Cancer Treatment and Patient Stratification Using NGS and Other OMICs Data

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ESMO
Personalized Cancer Treatment and Patient Stratification Using NGS and Other OMICs Data

Your Moderator

John Sterling
Editor-in-Chief
Genetic Engineering & Biotechnology News
Personalized Cancer Treatment and Patient Stratification Using NGS and Other OMICs Data

Rolf A. Stahel, M.D.
Professor, Laboratory of Molecular Oncology
Clinic for Thoracic Surgery and Policlinic for Oncology
University Hospital of Zurich
ESMO President-Elect
From standardized to personalized treatment in oncology: The example of advanced non-small cell lung cancer

Rolf Stahel
University Hospital
Zürich
Switzerland

Zürich, December 29, 2012
Personlized therapy of lung cancer

Taking into account not only patient characteristics, but also molecular tumor characteristics and thus:

- Moving away from empiricism and serendipity to a biology-based therapy
- Matching the right drug with the right cancer type
- Defining on each patient’s tumor biomarkers of response to targeted agents
Histological classification is necessary for today’s decision making

- A diagnosis of “non-small cell lung cancer” is no longer acceptable as sufficient basis for treatment decisions:
  - Benefit of bevacizumab added to first line chemotherapy in non-squamous cell carcinoma
    Sandler, JCO 2006; Reck JCO 2009
  - Differential effect of pemetrexed in non-squamous vs squamous cell carcinoma
    Scagliotti, JCO 2008
  - Histology will help guide decision about which molecular analysis is performed
Molecular classification: Present necessities and future directions

- Adenocarcinoma of the lung is not a uniform disease and needs to be classified by additional molecular analysis
  - Present needs include EGFR mutation status and determination of EML4-ALK fusion gene
  - Emerging opportunities of targeting other oncogenic drivers and technological advances in molecular testing will lead to a shift from sequential testing of selected molecular alterations to multiplex testing and next generation sequencing

- Potential driver mutations are also being identified in squamous cell lung cancer
The situation today: ESMO Pocket Guideline (2012 edition)

SQUAMOUS CELL

METASTATIC NSCLC, PS 0–2

NON-SQUAMOUS CELL

EGFR MUTATION & ALK RE-ARRANGEMENT ASSESSMENT

ALK rearrangement: Consider crizotinib

EGFR wild type (or not done)

EGFR mutation (del 19 or L858R in exon 21)

Platinum plus
• Gemcitabine or taxanes or vinorelbine
  or
• Platinum combination plus cetuximab**

Elderly / PS 2:
• Platinum combination (preferred in fit elderly)
  or
• Monotherapy*** (preferred in unfit elderly)

Platinum plus
• Pemetrexed or taxanes and consider combination with bevacizumab* (PS 0–1)
  or
• Platinum combination plus cetuximab**

Elderly / PS 2:
• Platinum combination (preferred in fit elderly)
  or
• Monotherapy*** (preferred in unfit elderly)

EGFR TKI upfront, including elderly PS 3–4

Peters et al, 2012
IPASS: Objective RR in EGFR mutation positive and negative patients with gefitinib as compared to chemotherapy

Overall response rate (%)

71.2% (n=132) vs 47.3% (n=129)

Gefitinib
Carboplatin / paclitaxel

EGFR M+ odds ratio (95% CI) = 2.75 (1.65, 4.60), p=0.0001

EGFR M- odds ratio (95% CI) = 0.04 (0.01, 0.27), p=0.0013

Mok, ESMO 2008; NEJM 2009

Odds ratio >1 implies greater chance of response on gefitinib
First line EGFR TKI or chemotherapy for non-squamous cell lung cancer harboring activating EGFR mutation

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>N</th>
<th>RR (TKI vs Chemo)</th>
<th>PFS (HR, 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mok</td>
<td>IPASS</td>
<td>261</td>
<td>71% vs 47%</td>
<td>0.48 (0.36, 0.64)</td>
</tr>
<tr>
<td>Lee</td>
<td>First-SIGNAL</td>
<td>42</td>
<td>85% vs 38%</td>
<td>0.61 (0.31, 1.22)</td>
</tr>
<tr>
<td>Mitsudomi</td>
<td>WJTOG 3405</td>
<td>198</td>
<td>62% vs 32%</td>
<td>0.49 (0.34, 0.71)</td>
</tr>
<tr>
<td>Kobayashi</td>
<td>NEJGSG002</td>
<td>177</td>
<td>75% vs 29%</td>
<td>0.36 (0.25, 0.51)</td>
</tr>
<tr>
<td>Zhou</td>
<td>Optimal</td>
<td>165</td>
<td>83% vs 36%</td>
<td>0.16 (0.10, 0.26)</td>
</tr>
<tr>
<td>Rosell</td>
<td>EUROTAC</td>
<td>174</td>
<td>58% vs 15%</td>
<td>0.42 (0.27, 0.64)</td>
</tr>
<tr>
<td>Yang</td>
<td>LUX-Lung 3</td>
<td>345</td>
<td>56% vs 22%</td>
<td>0.58 (0.43, 0.78)</td>
</tr>
</tbody>
</table>

IPASS: Overall survival in EGFR mutation positive and negative patients

**EGFR mutation +**

- **Gefitinib (n=132)**
- **Carboplatin / paclitaxel (n=129)**

**HR (95% CI)**
1.00 (0.76, 1.33); p=0.990

**No. events**
- **G**: 104 (79%)
- **C / P**: 95 (74%)

**Median OS**
- **G**: 21.6 months
- **C / P**: 21.9 months

**EGFR mutation -**

- **Gefitinib (n=91)**
- **Carboplatin / paclitaxel (n=85)**

**HR (95% CI)**
1.18 (0.86, 1.63); p=0.309

**No. events**
- **G**: 82 (90%)
- **C / P**: 74 (87%)

**Median OS**
- **G**: 11.2 months
- **C / P**: 12.7 months

Cox analysis with covariates; a hazard ratio <1 implies a lower risk of death on gefitinib
No formal adjustment for multiple testing was made, therefore statistical significance at the traditional 5% level cannot be claimed.

Yang, ESMO 2010
Comparison of survival for patients with lung adenocarcinoma in Japan before and after gefitinib approval

All patients

FGFR mut+ patients

A

No. MST (months)
After approval 200 18.1
Before approval 130 12.5

HR = 0.66 (95% CI, 0.52 to 0.84)
Log rank P < .001

B

No. MST (months)
After approval 78 27.2
Before approval 58 13.6

HR = 0.48 (95% CI, 0.32 to 0.71)
Log rank P < .001

Takano, JCO 2008
58 y/o woman with EGFR mutated lung adenocarcinoma

February 09

June 09 after 4 cycles of cis/pem/bev

March 10 on bev maintenance

July 2010 on erlotinib

January 2012 on erlotinib

April 2012 after carbo/pem

October 2012 on erlotinib

January 2013 clinical response to gemcitabine
Disease flare after discontinuation of EGFR TKI in patients with acquired resistance

- 61 pts participating in trials on patients with acquired EGFR resistance mandating TKI discontinuation:
  - 23% disease flare
  - Association with shorter time to progression
  - Association with pleural or CNS disease
- „Drug holiday not recommended"
EGFR TKI resistance (simplified)

Oncogenic driver  EGFR TKI  T790M mutation  MET amplification  HGF expression

Kosaka, J Biomed Biotechn 2011
Characteristics of tumours with acquired resistance to EGFR TKI

Pathological and molecular analysis of tumor biopsies from 37 pts with acquired resistance to EGFR inhibitors:

- Unknown mechanism (30%)
- T790M (49%)
- MET amp (5%)
- PIK3CA (5%)
- SCLC transformation (14%)

*1 pt with PIK3CA and SCLC transformation

Sequist, Sci Transl Med 2011
Identification of the transforming EML4–ALK fusion gene in non-small-cell lung cancer

Manabu Soda¹,², Young Lim Choi¹, Munehiro Enomoto¹, Shin-ichiro Fujiwara¹, Hideki Watanabe¹, Kentaro Yuichi Ishikawa⁶, Hiroyuki Aburatani⁵,⁷, Toshiro Nishikawa¹

Improvement in the clinical outcome of lung cancer is associated with EGFR mutations and ALK rearrangements, which underlie its pathogenesis. Here we show that a small intron in the first intron of the echinoderm microtubule-associated protein-like 4 (EML4) gene comprises portions of the echinoderm microtubule-associated protein-like 4, anaplastic lymphoma kinase (ALK) gene in non-small-cell lung cancer.
Responses to crizotinib for patients with ALK-positive NSCLC

Maximum change in tumor size (%)

Response rate:
- 57% (95% CI: 46, 68%)
- 63% including 5 as yet unconfirmed

PFS:
- Median not yet reached
  (median f/u for PFS of 6.4 months)

Bang, ASCO 2010: Kwak, NEJM 2010
PROFILE 1007: Randomized phase III trial of second line crizotinib or chemotherapy in ALK positive NSCLC: Response

ORR ratio: 3.4 (95% CI: 2.5 to 4.7); P<0.0001

**Crizotinib (n=173) vs Chemotherapy (n=174)**

- **ORR (%)**
  - Crizotinib: 65.3%
  - Chemotherapy: 19.5%

**Crizotinib (n=172) vs Other Treatments**

- **ORR (%)**
  - Crizotinib: 65.7%
  - Pemetrexed (n=99): 29.3%
  - Docetaxel (n=72): 6.9%

---

aRECIST v1.1; bITT population; cas-treated population
Lungscape ALK study: Flow chart

Adenocarcinoma patients with available ALK IHC data

N=1099

ALK IHC +
N=69 (6.3%)

ALK IHC -
N=1030

ALK IHC 1:2 Matched Cohort
N=207
Matching factors in order of importance:
Stage, Gender/Smoking Status,
Center/Year of surgery/ Age

ALK IHC +
N=69

22 FISH +
1 FISH +
23 FISH + (2.1%)

FISH +
38 FISH -
22 FISH +
9 FISH ND

ALK FISH 1:2 Matched sub-cohort
N=69

ALK IHC -
N=138

46 FISH -
137 FISH -
36.7% of IHC+ are FISH+
PROFILE 1007: Progression-free survival of crizotinib vs pemetrexed or docetaxel

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (n=172&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>Pemetrexed (n=99&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>Docetaxel (n=72&lt;sup&gt;a&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>100 (58)</td>
<td>72 (73)</td>
<td>54 (75)</td>
</tr>
<tr>
<td>Median, mo</td>
<td>7.7</td>
<td>4.2</td>
<td>2.6</td>
</tr>
<tr>
<td>HR&lt;sup&gt;b&lt;/sup&gt; (95% CI)</td>
<td>0.59 (0.43 to 0.80)</td>
<td>0.30 (0.21 to 0.43)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.0004</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>As-treated population: excludes 1 patient in crizotinib arm who did not receive study treatment and 3 patients in chemotherapy arm who did not receive study treatment; <sup>b</sup>vs crizotinib

Shaw, ESMO 2012
The situation tomorrow: Molecularly-based first line therapy

Adenocarcinoma
- MAP2K1
- NRAS
- AKT1
- PIK3CA
- BRAF
- HER2
- ALK fusions
- EGFR
- KRAS
- Unknown

Squamous cell carcinoma
- Unknown 37%
- FGFR1 amplification 25%
- PTEN mutation 17%
- DDR2 mutation 0%
- PTEN loss, complete 11%
- KRAS mutation 2%

Pao, Nature Med 2012
Paik, ASCO 2012
Other oncogenic driver mutations: HER2


- Response to afatinib in 3 patients with HER2 mutation. De Grève, Lung Cancer 2012

- 46 pts with HER2 mutations identified, predominantly women and never smokers. 20 pts with advanced disease received targeted therapy: 9 PR and 7 SD. Mazière, ESMO 2012
BRAF mutations

A Patient With BRAF V600E Lung Adenocarcinoma Responding to Vemurafenib

Oliver Gautschi, MD,* Chantal Pauli, MD,† Klaus Strobel, MD,‡ Astrid Hirschmann,†
Gert Printzen, MD,§ Stefan Aebi, MD,* and Joachim Diebold, MD†
ROS1 rearrangements are another target of crizotinib

- 18/1073 (1.7%) ROS1 fusion positive tumors identified by FISH. In vitro activity and clinical response to crizotinib  
  Bergethon, JCO 2012

- Expanded experience  
  Sequist, ASCO 2012
RET rearrangements might be a target for multitargeted RET inhibitors

- Fusion of KIF5B and RET identified in an adenocarcinoma of a young non-smoker by whole-genome and transcriptome sequencing
  Young, Genome Res 2011

- 1.9% of 319 RET fusions in adenocarcinoma from Japanese and 1/80 (1.3%) from Caucasian patients.
  Activity of vandetinib
  Kohno, Nat Med 2012

- 1.7% of 633 RET fusions in adenocarcinoma from Chinese patients
  Wang JCO 2012
Personalized therapy for lung cancer

- Personalized therapy for advanced non-small cell lung cancer has become a new reality.
- As of today, up to one third of lung adenocarcinoma in Western Societies do have actionable oncogenic mutations or gene rearrangements with approved therapies (EGFR and ALK) or therapies under investigation.
- A similar picture might be emerging in lung squamous cell carcinoma.
- The multitude of actionable molecular changes is leading to a change in the diagnostic work up from sequential testing to multiplex testing and next generation sequencing.
Personalized therapy for lung cancer

- Important societal issues to resolve are:
  - Patient access to molecular testing and the targeting agents
  - Regulatory issues (ethical need from crossover, thus need for other endpoint than overall survival)

- Important research issues to resolve are:
  - How to deal with drug resistance
  - Effect of targeted therapy in earlier stages of disease
  - Both can only be successful by changing from empiricism to molecular-driven clinical trials
Personalized Cancer Treatment and Patient Stratification Using NGS and Other OMICs Data

Martin Edelman, M.D.
Professor of Medicine
University of Maryland School of Medicine
Director, Solid Tumor Oncology
Greenebaum Cancer Center
Personalization of Therapy in Advanced NSCLC: Optimization of Current and Future Drugs

Martin J. Edelman, MD
Personalization of Therapy in NSCLC

- Clearly applicable for non-squamous carcinoma
  - Histology and use of bevacizumab, pemetrexed
  - DNA sequencing for EGFR TKI, Ret
  - FISH for EML4/ALK, ROS1

- The above represents a minority of NSCLC and does not address the fact that virtually all advanced NSCLC will relapse and require additional therapy
  - Median TTP for erlotinib, crizotinib is about 10 months

- Most current approaches do not assess for tumor heterogeneity, require tissue.
Personalization for the diseases without drugs, for the drugs that exist and drugs in development

- Squamous carcinoma
- Cytotoxic chemotherapy
- Real time assessment for presence of markers of susceptibility/resistance: nuclear imaging
- Personalization of the immunotherapy
- Toxicity prevention/anticipation
SQUAMOUS CELL CANCER
New molecular targets in squamous cell lung cancer

- **Sox-2**
  - Genomic amplification in 10-20%

- **FGFR**
  - Genomic amplification in 10-20%
  - ?FGFR inhibition
  - Phase I studies with BGJ398, a pan-FGFR inhibitor (Novartis)

- **DDR2**
  - Recurrent mutations of this poorly studied tyrosine kinase in 3-4%
  - ?dasatinib
Comments: Personalization of therapy for squamous carcinoma

• Several interesting and potentially targetable pathways have been identified.
• Trials are in progress
• None are truly “actionable” at this time, i.e. you cannot write a prescription for an approved agent.
CYTOTOXIC THERAPY
Cytotoxic Therapies: Effective agents that can be made better

- Current role in curative treatment
- More sophisticated use of current agents
  - Histology (and its limitations)
  - Molecular variables (and their limitations)
- New and improved cytotoxics
  - New molecules with the same basic target
  - New molecules targeting different areas of the old target
Excision Repair Cross-complementation Group 1 (ERCC1)

- Cisplatin cytotoxicity requires creation of DNA adducts followed by covalent cross-linking between DNA strands
- Nucleotide excision important in DNA repair and cell survival
- ERCC1 is one such enzyme

Ribonucleotide Reductase M1 (RRM1)

- Regulatory subunit of RR
- Only known enzyme to convert ribonucleotides to deoxyribonucleotides, needed for DNA repair
- Likely intracellular target of gemcitabine
- High levels → improved outcome in early NSCLC
- High levels are the dominant component of gemcitabine resistance

Feasibility & Efficacy of Molecular Analysis-Directed Therapy

The MADe IT Trial

NSCLC
Stage IIIB / IV
No prior trt
PS 0 - 1
(n = 60)

Core needle biopsy, immediately frozen, laser capture microdissection
Withdrawn if tumor tissue insufficient

Real-time RTPCR and starting treatment (n = 53)

Low RRM1

High RRM1

Low ERCC1

Gemcitabine + carboplatin

High ERCC1

Docetaxel + gemcitabine

Low ERCC1

Docetaxel + carboplatin

High ERCC1

Docetaxel + vinorelbine

### Feasibility & Efficacy of Molecular Analysis-Directed Therapy

<table>
<thead>
<tr>
<th></th>
<th>MADeIT (Directed)</th>
<th>MCC-12621 (Carbo + gem)</th>
<th>E1594 (All)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (mo)</td>
<td>13.4</td>
<td>6.7</td>
<td>8.0</td>
</tr>
<tr>
<td>6-mo survival (%)</td>
<td>87</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>12-mo survival (%)</td>
<td>62</td>
<td>38</td>
<td>33</td>
</tr>
<tr>
<td>CR+PR (%)</td>
<td>42</td>
<td>24</td>
<td>19</td>
</tr>
</tbody>
</table>

**Historical comparators**

General feasibility of MADeIT design limited, due to infrastructure required.

Hype and Hope: The Problem of Single Center Studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Phase</th>
<th>Response Rate (%)</th>
<th>MST (mo)</th>
<th>1-yr Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langer et al</td>
<td>II</td>
<td>62</td>
<td>12</td>
<td>54</td>
</tr>
<tr>
<td>Natale et al</td>
<td>I-II</td>
<td>62</td>
<td>10.5</td>
<td>43</td>
</tr>
<tr>
<td>Belani et al</td>
<td>III</td>
<td>23</td>
<td>7.7</td>
<td>32</td>
</tr>
<tr>
<td>Schiller et al</td>
<td>III</td>
<td>15</td>
<td>8.2</td>
<td>35</td>
</tr>
<tr>
<td><strong>Langer C+T+Herceptin</strong></td>
<td><strong>II</strong></td>
<td><strong>21</strong></td>
<td><strong>10.1</strong></td>
<td><strong>43</strong></td>
</tr>
</tbody>
</table>

Belani et al. PASCO, 1998  Schiller et al. PASCO 2000
Referral Populations

- Referral populations inherently do better.
- Possible reasons:
  - Socioeconomics
  - Nutrition
  - Inherent biology

Lamont, JNCI, 2001
Clinical Trial of Molecular Analysis-Directed Therapy: MADe IT Phase III

Stage IIIB / IV NSCLC, PS 0-1 Tumor block available
N = 267

Randomization 2:1

Treatment Selection by AQUA

Low RRM1

Low ERCC1

Gemcitabine + carboplatin

High RRM1

High ERCC1

Docetaxel + carboplatin

Docetaxel + gemcitabine

Standard of care
Gemcitabine + carboplatin

Docetaxel + vinorelbine

TS: Mechanism of Resistance to Fluoropyrimidines

- Pemetrexed: multitargeted antifolate agents
  - Inhibit TS, DHFR, GART
- TS is involved in DNA biosynthesis. In NSCLC
  - Increased expression significantly correlated with pemetrexed resistance in NSCLC cell lines
  - TS expression significantly higher in SCC compared with adenocarcinoma
- Higher TS expression may be biologic mechanism for reduced efficacy of cisplatin/pemetrexed in SCC versus adenocarcinoma

TS and TTF-1 to Predict Response to Pemetrexed

Comments: Personalization of cytotoxic therapy

• Numerous potential targets of sensitivity and resistance for cytotoxics have been described.
• None have yet been validated and can be utilized in routine practice.
  – No standardized tests: e.g. ERCC1 expression varies with antibody used and may not be reproducible.
  – No randomized controlled trial has demonstrated benefit
IMAGING AND PERSONALIZATION: THE EXAMPLE OF EC145
EC145 targets cancer cells; avoids normal cells

1. Folate SMDC binds to the high affinity folate receptor.

2. Upon binding to the folate receptor, the folate SMDC is internalized via endocytosis.

3. The SMDC is cleaved inside endosome.

4. Drug payload escapes endosome and exerts activity on cell.

5. Folate receptor recycles to the cell surface.

The reduced folate carrier binds with low affinity. SMDCs will not enter cell through the reduced folate carrier.
EC145: A folate-\textit{Vinca} alkaloid conjugate

**Drug** (Vinca alcaloid)

**Spacer Linker System**

**Targeting Ligand (Folate)**

Linker self-annihilates releasing intact drug

Patient with RECIST PR

<table>
<thead>
<tr>
<th>Target Lesion</th>
<th>EC20 Scan</th>
<th>CT Baseline Size</th>
<th>CT 8 Week Size</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Positive</td>
<td>34mm</td>
<td>15mm</td>
<td>-56%</td>
</tr>
<tr>
<td>T2</td>
<td>Positive</td>
<td>25mm</td>
<td>10mm</td>
<td>-60%</td>
</tr>
</tbody>
</table>

WCLC 2009 Abstract 3.4.4
Open-Label Randomized Phase 2 for FR(++) NSCLC Patients

- **Primary Endpoint**: PFS
  - 75% Power for 50% Improvement (from 3 months to 4.5 months)
  - 1-Sided Alpha= 0.10
  - Futility Interim at 50% PFS events

- **Secondary Endpoints**
  - ORR, DCR, OS

- **Interim Safety Analyses**
  - After 5 and 15 patients in Arm B

**Second Line NSCLC [FR(++)]**

- 99mTc-EC20 scan
- Randomization- 1:1:1

**Arm A:**
- EC145 (n=60)
- 2.5 mg Days 1, 4, 8 and 11 (Wks 1 and 2 q 3 wks)

**Arm B:**
- EC145+Docetaxel (n=60)
- As per Arm A and Arm C schedules

**Arm C:**
- Docetaxel (n=60)
- 75 mg/m² IV Day 1 (q 3 weeks)

PD or unacceptable toxicity
IMMUNOTHERAPY: PD-1 AND CTLA4
What is PD-1?
- Involved in T cell regulation
- Expressed by activated memory and regulatory T cell
- Down regulates T cell by binding to PD-L1/L2
Clinical Activity of BMS-936558 in NSCLC Patients

- ORR was assessed using modified RECIST v1.0

<table>
<thead>
<tr>
<th>Pop</th>
<th>Dose (mg/kg)</th>
<th>Pts n</th>
<th>ORR n (%)</th>
<th>Duration of Response (mo)</th>
<th>SD ≥24 wk n (%)</th>
<th>PFSR at 24 wk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL NSCLC</td>
<td>1-10</td>
<td>76</td>
<td>14 (18)</td>
<td>1.9+ to 30.8+</td>
<td>5 (7)</td>
<td>26</td>
</tr>
<tr>
<td>NSCLC</td>
<td>1</td>
<td>18</td>
<td>1 (6)</td>
<td>9.2+</td>
<td>1 (6)</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>19</td>
<td>6 (32)</td>
<td>1.9+ to 30.8+</td>
<td>2 (11)</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>39</td>
<td>7 (18)</td>
<td>3.7 to 14.8+</td>
<td>2 (5)</td>
<td>24</td>
</tr>
</tbody>
</table>

Brahmer, NEJM, 2012
Activity in NSCLC: 10 mg/kg

History: 60 y/o diagnosed with Large cell NSCLC in 2002

- Multiple prior chemotherapy regimens
- Prior radiation

Screening - 12/17/09

Cycle 2 – 4/26/10

J Brahmer, SKCCC at Johns Hopkins
Tumor PD-L1 / B7-H1 Expression

- Potential way tumor cells evade immune system (self-defense)
- Poor prognosis in multiple tumor types including NSCLC
- More commonly seen in Adeno vs. Squamous
- NSCLC- membranous staining

1 Mu CY et al Med Oncol 2010, Taube J personal communication
• Anti-PD-1 and anti PD-L1 are unique and likely to become validated targets.

• Significant questions
  – What will be the precise role? (refractory, in combination with chemotherapy, adjuvant etc).
  – Can this modality be combined with radiotherapy? (pneumonitis).

• Drugs are currently being evaluated in phase III trials
  – Correlative studies may define the role of predictive markers.
PERSONALIZATION AND TOXICITY
Toxicity: Germline Analysis

- There is clear evidence that germline polymorphisms (e.g. drug metabolism enzymes) can predict toxicity (and also outcome).
- “Common arm” analysis of clinical trials
- Examples
  - Irinotecan
    - Marked differences in toxicity and outcome in trials between US and Japan
  - Sunitinib
    - CYP3A5*1 (rs776746) high metabolising allele associated with dose modifications for toxicity in renal cancer

PERSONALIZATION: A NOTE OF CAUTION
Lung Cancer is Genetically Very Complex

- Carcinogen associated epithelial cancer (colon, lung, melanoma) are exceedingly complex.
- Single “determinants” of benefit are likely to be useful for only a part of the tumor population.
Personalized Cancer Treatment and Patient Stratification Using NGS and Other OMICs Data

Yuri Nikolsky, Ph.D.
Vice President, Research & Development
Intellectual Property & Science
Thomson Reuters
Methods of functional analysis of OMICs data for personalized & translational medicine

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VP Research & Development
858 756 7996
Yuri.nikolsky@thomsonreuters.com
CANCER DRUG RESPONSE MARKERS

• Current state of art
  – Individual drug response markers at DNA and RNA level
    • EGFR mutations for gefitinib in lung adenocarcinoma
    • KRAS mutations for sorafenib (Kim E.S., et al., Cancer Disc., 2011, 1, 44-53)
    • BRAF V600 mutation for zelboraf in melanoma (Bollag G. et al., Nature, 2010, 467, 596-599)
  – Prognostic markers for cancer progression
    • 21, 70-gene expression gene signatures for breast cancer
    • Other ones?

• Near future
  – Clinical cancer re-sequencing: whole genome and exome
  – Sequence variants, amplifications, deletions, fusion genes
  – RNA-Seq: highly diverse quantitatively, splice variants
  – ENCODE data
DATA AND OMICS ASSAYS IN ONCOLOGY

DNA
- Epigenetics
  - Methylation
  - Histones
  - Nucleosomes
- Germline abberations
- Somatic mutations
- Amplifications
- Deletions

RNA
- Gene expression:
  - mRNA: abundance, splicing
  - miRNA

Protein
- Protein changes:
  - Mutated
  - PTMs

Metabolites
- Metabolites:
  - Major misbalances
  - Energy
  - Protein synthesis

Effect

Signaling
ISSUES WITH OMICS DATA ANALYSIS

• No single level data can generate sufficiently accurate descriptors (biomarkers) or explain cancerogenesis mechanisms
  - Poor performance of single feature markers
  - Growing evidence that multi-variant markers (gene signatures) perform poorly in large datasets, more complex endpoints

• Datasets assayed at different levels generally do not overlap at gene level: mutations – amplifications, methylation – expression, expression – proteomics, DNA – metabolism

• Statistical correlation between data of different types is based on independent variables and works poorly
SYSTEMS (PATHWAY) ANALYSIS IS THE ENGINE FOR TRANSLATIONAL RESEARCH

From bench to bedside:
- Animal Models
- Cell Lines

From bedside to bench:
- Basic Biomedical Research
- Research in Clinical Setting
- Human Model
- Clinical Samples

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Hartwell et al (1999) article proposed study of “modules” instead of genes

From molecular to modular cell biology

Leland H. Hartwell, John J. Hopfield, Stanislas Leibler and Andrew W. Murray

Cellular functions, such as signal transmission, are carried out by ‘modules’ made up of many species of interacting molecules. Understanding how modules work has depended on combining phenomenological analysis with molecular studies. General principles that govern the structure and behaviour of modules may be discovered with help from synthetic sciences such as engineering and computer science, from stronger interactions between experiment and theory in cell biology, and from an appreciation of evolutionary constraints.
What network properties are required for reconstruction of real biological pathways?

Binary relationships between proteins (interactions) can be depicted as edges on pathways.
SIGNALING PATHWAYS IN NETWORK

What network properties are required for reconstruction of real biological pathways?

Nodes should reflect the molecular function of corresponding biomolecule (receptor, phosphatase etc.)
MUTATIONS IN PATHWAYS, NOT INDIVIDUAL GENES DEFINE CANCEROGENESIS

An Integrated Genomic Analysis of Human Glioblastoma Multiforme
D. Williams Parsons,1,2* Siân Jones,1* Xiaosong Zhang,1* Jimmy Cheng-Ho Lin,1* Rebecca J. Leary,1*

RESEARCH ARTICLES

The Genomic Landscapes of Human Breast and Colorectal Cancers
Laura D. Wood,3* D. Williams Parsons,3* Siân Jones,3* Jimmy Lin,3* Tobias Sjöblom,3*†

Published in final edited form as:

The genetic landscape of the childhood cancer medulloblastoma
D. Williams Parsons1,2,*, Meng Li1,*, Xiaosong Zhang1,*, Siân Jones1,*, Rebecca J. Leary1,*,
Different linear unidirectional multistep pathways that connect all levels of cellular life and are widely accepted and supported by the literature are considered Canonical Pathways (~200,000). Groups of such pathways that may share the same signaling theme or same cascade regulators or effectors are represented on GeneGo Maps (~nearly 1000 used for enrichment analyses).
Application: comparison of different types of OMICs data

Enrichment analysis:
- Concordance in distributions
- Synergy in distributions

Interactome:
- 1-step Interactions cross-set
- Overconnected proteins

“Hidden nodes”:
- Topology-based
- Prioritized regulators

Pathway reconstruction:
- Pathway-based networks
- Restores most likely linear pathways between datasets
TOPOLOGICAL SCORING AND CAUSAL NETWORKS

TGF-beta receptor type I

NF-kB – overconnected transcription factor

“hidden node”
TRANSLATIONAL BIOMARKERS: DELIVERABLES FOR A SINGLE REGIMENT DRUG

MECHANISM OF RESISTANCE

MECHANISM OF SENSITIVITY

THOMSON REUTERS
CAUSAL NETWORKS FOR PERSONALIZED CANCER TREATMENT

• Expression data from 1 patient cancer sample were processed by GC-RMA along with 64 Normal pancreas samples from 3 different GEO datasets (provided at the same array Affy u133 plus2)

1 Pancreatic Cancer Sample  64 Pancreatic Normal Samples

276 DEGs

• For each feature ID (EntrezGene) from Patient Sample a Fold Change and p-values were calculated (Patient Cancer Sample versus 64 Normal Pancreas Sample)

• 276 IDs are differential expressed (DEGs) in Patient Sample with p-value<0.05
DRUG TARGETS FROM CAUSAL MODEL

- Upstream Regulators and corresponding pathways that may activate overconnected TFs were identified

<table>
<thead>
<tr>
<th>Object</th>
<th>Drug</th>
<th>Tested at</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGF receptor</td>
<td>Tivantinib (therapeutic)</td>
<td>Pancreatic Neoplasms</td>
<td>Possibly induce signal transduction by several major pathways such as MAPK and PI3K/AKT pathways; associated with anti pancreatic cancer drug</td>
</tr>
<tr>
<td>TGF-beta 2</td>
<td>Trabedersen (therapeutic)</td>
<td>Pancreatic Neoplasms</td>
<td>Possibly induce signal transduction by proinflammatory and proliferation pathways; associated with anti pancreatic cancer drug</td>
</tr>
<tr>
<td>IL1-Receptor</td>
<td>Estradiol (secondary)</td>
<td>Prostatic Neoplasms</td>
<td>Induce signal transduction by PI3K/AKT pathway; not associated with primary anti solid tumor drugs</td>
</tr>
<tr>
<td>IL6-Receptor (gp130 subunit)</td>
<td>Tocilizumab (therapeutic)</td>
<td>Multiple Myeloma</td>
<td>Induce signal transduction by proinflammatory and proliferation pathways; not associated with anti solid tumor drugs</td>
</tr>
<tr>
<td>Activin A</td>
<td>-</td>
<td>-</td>
<td>Induce signal transduction by proinflammatory and proliferation pathways; not associated with any drug</td>
</tr>
</tbody>
</table>

- **HGF receptor** and **TGF-beta2** – are the most suggestive targets for anti cancer therapy
### METAMINER ONCOLOGY DELIVERABLES

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Number of Maps</th>
<th>Number of Associated Genes</th>
<th>Associated Gene Variants (e.g. SNP, deletions)</th>
<th>Number of OMICs datasets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>25</td>
<td>1,231</td>
<td>774</td>
<td>18</td>
</tr>
<tr>
<td>Gastric Cancer</td>
<td>25</td>
<td>2,401</td>
<td>1,848</td>
<td>11</td>
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<tr>
<td>Pancreatic Cancer</td>
<td>26</td>
<td>1,315</td>
<td>1,122</td>
<td>11</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>27</td>
<td>783</td>
<td>475</td>
<td>5</td>
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<tr>
<td>Lung Cancer</td>
<td>28</td>
<td>2,767</td>
<td>4,288</td>
<td>17</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>25</td>
<td>3,004</td>
<td>6,285</td>
<td>10</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>25</td>
<td>2,586</td>
<td>6,174</td>
<td>0</td>
</tr>
<tr>
<td>Melanoma</td>
<td>25</td>
<td>854</td>
<td>1,227</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>206 (unique)</strong></td>
<td><strong>6,119 (unique)</strong></td>
<td><strong>16,549 (unique)</strong></td>
<td><strong>72 (unique)</strong></td>
</tr>
</tbody>
</table>
ZINC DEFICIENCY IN PROSTATE CANCER: MECHANISTIC LEVEL

In prostate cancer, the malignant cells undergo a metabolic transformation from citrate-producing to citrate-oxidizing cells. This results from the lost ability of the malignant cells to accumulate zinc. The absence of high mitochondrial zinc levels removes the inhibition of m-aconitase activity. Citrate is then oxidized via a functional Krebs cycle, and the typical complete oxidation of glucose restores the efficient ATP production.

The diagram illustrates the mechanisms involved in zinc deficiency in prostate cancer, including the roles of SLC39A1 (ZIP1), TR, IkappaB-alpha, IkappaB-beta, NF-kB, SP1, CREB1, MMP-9, ICAM1, VEGF-A, c-IAP2, IL-6, IL-8, and the effects on extracellular matrix remodeling, cell adhesion, angiogenesis, inhibition of apoptosis, proliferation, and increased production of ATP, leading to tumor invasion and dissemination and tumor growth.
ZINC DEFICIENCY IN PROSTATE CANCER: ASSOCIATIONS

1) Decrease of expression level
2) Decrease of abundance

Increase of abundance

1) Single Nucleotide Polymorphism (SNP)
2) Increase of expression level
3) Increase of abundance

Decrease amount

Increase of activity

Decrease amount

Decrease amount

Increase amount

Increase amount

Zinc deficiency in Prostate Cancer. Causal gene-disease associations
CAUSAL ASSOCIATIONS IN METAMINER

Table of Content

- DNA level
  - Amplification
  - Fusion genes
  - Rearrangement
  - Locus change
  - Haplotype/SNP
  - Epigenetics

- RNA level
  - Alternative transcript
  - Major transcript

- Protein level
  - Isoform
  - Mutant protein
  - Phosphorylation
  - Other PTM
  - Posttranscriptional modification
  - Peptide
  - Protein
  - Protein complex
  - Protein group

- Endogenous compounds
- Unspecified associations

- Disease-specific Characteristics
  - Abundance
  - Gain/Lost of function
  - Activity
  - Organ or Tissue distribution
  - Subcellular Localization change
## CANCER-SPECIFIC GENE AMPLIFICATIONS

<table>
<thead>
<tr>
<th>No.</th>
<th>Gene</th>
<th>Amplification name (GeneGo name)</th>
<th>Activity/Gain/Loss of Function</th>
<th>Examined tissue or organ</th>
<th>Supported articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ABCB1</td>
<td>ABCB1_HUMAN_Amplification</td>
<td>up</td>
<td>prostate cancer</td>
<td></td>
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<tr>
<td>2</td>
<td>AR</td>
<td>AR_HUMAN_Amplification</td>
<td>up</td>
<td>prostate cancer, Prostate</td>
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<tr>
<td>3</td>
<td>AR</td>
<td>AR_HUMAN_Amplification</td>
<td>up</td>
<td>prostate cancer</td>
<td></td>
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<tr>
<td>4</td>
<td>ASAP1</td>
<td>ASAP1_HUMAN_Amplification</td>
<td>up</td>
<td>Tumours</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>BAG1</td>
<td>BAG1_HUMAN_Amplification</td>
<td>up</td>
<td>prostate carcinoma</td>
<td></td>
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<tr>
<td>6</td>
<td>C8orf7</td>
<td>C8orf7_HUMAN_Amplification</td>
<td>up</td>
<td>prostate cancer</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>CHRAC1</td>
<td>CHRAC1_HUMAN_Amplification</td>
<td>up</td>
<td>prostate cancer</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>CREB3L4</td>
<td>CREB3L4_HUMAN_Amplification</td>
<td>up</td>
<td>prostate cancer</td>
<td></td>
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<tr>
<td>9</td>
<td>CTSZ</td>
<td>CTSZ_HUMAN_Amplification</td>
<td>up</td>
<td>prostate cancer, Prostate</td>
<td></td>
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<tr>
<td>10</td>
<td>DKC1</td>
<td>DKC1_HUMAN_Amplification</td>
<td>up</td>
<td>prostate carcinoma</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>EGFR</td>
<td>EGFR_Amplification</td>
<td>up</td>
<td>prostate carcinoma</td>
<td></td>
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<tr>
<td>12</td>
<td>EGFR</td>
<td>EGFR_HUMAN_Amplification</td>
<td>up</td>
<td>prostate carcinoma</td>
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<td>13</td>
<td>ERF</td>
<td>ERF</td>
<td>up</td>
<td>prostate cancer</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>ER</td>
<td>ER</td>
<td>up</td>
<td>prostate cancer</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>ER</td>
<td>- drug target</td>
<td>up</td>
<td>prostate cancer</td>
<td></td>
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<tr>
<td>16</td>
<td>EZH2</td>
<td>EZH2</td>
<td>up</td>
<td>prostate cancer, Prostate</td>
<td></td>
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<tr>
<td>17</td>
<td>FGFR2</td>
<td>FGFR2_HUMAN_Amplification</td>
<td>up</td>
<td>prostate cancer, Prostate</td>
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<tr>
<td>18</td>
<td>FGFR3</td>
<td>FGFR3_HUMAN_Amplification</td>
<td>up</td>
<td>prostate cancer, Prostate</td>
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<tr>
<td>19</td>
<td>FGFR4</td>
<td>FGFR4_HUMAN_Amplification</td>
<td>up</td>
<td>prostate cancer, Prostate</td>
<td></td>
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<tr>
<td>20</td>
<td>HRAS</td>
<td>HRAS_HUMAN_Amplification</td>
<td>up</td>
<td>prostate cancer, Prostate</td>
<td></td>
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<tr>
<td>21</td>
<td>IGFBP</td>
<td>IGFBP_HUMAN_Amplification</td>
<td>up</td>
<td>prostate cancer, Prostate</td>
<td></td>
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<tr>
<td>22</td>
<td>IL12A</td>
<td>IL12A_HUMAN_Amplification</td>
<td>up</td>
<td>prostate cancer, Prostate</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>INSR</td>
<td>INSR_HUMAN_Amplification</td>
<td>up</td>
<td>prostate cancer, Prostate</td>
<td></td>
</tr>
</tbody>
</table>

**Function:**

The protein encoded by this gene is a transmembrane glycoprotein that is a member of the protein kinase superfamily. This protein is a receptor for members of the epidermal growth factor family. EGFR is a cell surface protein that binds to epidermal growth factor. Binding of the protein to a ligand induces receptor dimerization and tyrosine autophosphorylation and leads to cell proliferation. Mutations in this gene are associated with lung cancer. [provided by RefSeq]
ZINC DEFICIENCY IN PROSTATE CANCER: CAUSAL LEVEL

In prostate cancer, the malignant cells undergo a metabolic transformation from citrate-producing to citrate-oxidizing cells. This results from the lost ability of the malignant cells to accumulate zinc. The absence of high mitochondrial zinc levels removes the inhibition of m-acinaticase activity. Citrate is then oxidized via a functional Krebs cycle, and the typical complete oxidation of glucose restores the efficient ATP production.
## DISEASE MAPS RANKED BY MM BIOMARKERS

<table>
<thead>
<tr>
<th>Name</th>
<th>p-Value</th>
<th>Gene/Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role of DNA methylation in progression of multiple myeloma</td>
<td>1.85E-27</td>
<td>APC</td>
</tr>
<tr>
<td>Inhibition of apoptosis in multiple myeloma</td>
<td>1.38E-19</td>
<td>BCL2</td>
</tr>
<tr>
<td>Suppression of p53 signaling in multiple myeloma</td>
<td>2.32E-18</td>
<td>APAF1</td>
</tr>
<tr>
<td>Role of osteoblasts in bone lesions formation in multiple myeloma</td>
<td>1.82E-17</td>
<td>ALPL</td>
</tr>
<tr>
<td>Influence of multiple myeloma cells on bone marrow stromal cells</td>
<td>3.88E-16</td>
<td>CD40</td>
</tr>
<tr>
<td>Transition of Monoclonal gammopathy of undetermined significance to active multiple myeloma (schema)</td>
<td>2.00E-15</td>
<td>CCL3</td>
</tr>
<tr>
<td>NF-κB pathway in multiple myeloma</td>
<td>2.15E-13</td>
<td>BCL2</td>
</tr>
<tr>
<td>Influence of bone marrow cell environment on progression of multiple myeloma</td>
<td>1.25E-11</td>
<td>Ca('2+)</td>
</tr>
<tr>
<td>Transition of Smoldering multiple myeloma to active myeloma (schema)</td>
<td>3.49E-11</td>
<td>CCL2</td>
</tr>
<tr>
<td>Multiple Myeloma (general scheme)</td>
<td>5.40E-11</td>
<td>CCL4</td>
</tr>
<tr>
<td>Mechanisms of drug resistance in multiple myeloma</td>
<td>6.68E-11</td>
<td>ABCB1</td>
</tr>
<tr>
<td>IL-6 signaling in multiple myeloma</td>
<td>2.74E-10</td>
<td>AKT1</td>
</tr>
<tr>
<td>DKK1 signaling in multiple myeloma</td>
<td>1.35E-09</td>
<td>ALPL</td>
</tr>
<tr>
<td>Main signaling cascades in myeloma cells</td>
<td>1.44E-09</td>
<td>AKT1</td>
</tr>
<tr>
<td>Mechanisms of CAM-DR in multiple myeloma</td>
<td>1.56E-09</td>
<td>BCL2L11</td>
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<tr>
<td>Interleukin-6 signaling in multiple myeloma</td>
<td>4.49E-09</td>
<td>AKT1</td>
</tr>
<tr>
<td>Role of IGH translocations in multiple myeloma</td>
<td>6.24E-08</td>
<td>CCND1</td>
</tr>
<tr>
<td>VEGF signaling in multiple myeloma</td>
<td>9.71E-07</td>
<td>ABCB1</td>
</tr>
<tr>
<td>Rb proteins signaling in multiple myeloma</td>
<td>1.25E-06</td>
<td>CCND1</td>
</tr>
<tr>
<td>IGF-1 signaling in multiple myeloma</td>
<td>2.72E-06</td>
<td>AKT1</td>
</tr>
<tr>
<td>Activation of osteoclast differentiation in bone lesions formation in multiple myeloma</td>
<td>7.48E-06</td>
<td>CCL3</td>
</tr>
</tbody>
</table>
Pathways classifiers in GWAS studies

Pathway and network-based analysis of genome-wide association studies in multiple sclerosis

Sergio E. Baranzini1,*, Nicholas W. Galwey2, Joanne Wang1, Pouya Khankhanian1, Raija Lindberg3,4, Daniel Pelletier1, Wen Wu2, Bernard M.J. Uitdehaag5, Ludwig Kappos3,4, GeneMSA Consortium, Chris H. Polman5, Paul M. Matthews2, Stephen L. Hauser1, Rachel A. Gibson2, Jorge R. Oksenberg1 and Michael R. Barnes2

1Department of Neurology, UCSF, San Francisco, CA, USA, 2GlaxoSmithKline Research and Development, Harlow, UK, 3Department of Neurology and 4Department of Biomedicine, University Hospital Basel, Basel, Switzerland and 5Department of Neurology, Vrije Universiteit Medical Center, Amsterdam, The Netherlands

Received November 15, 2006; Revised and Accepted March 11, 2008

Genome-wide association studies (GWAS) testing several hundred thousand SNPs have been performed in multiple sclerosis (MS) and other complex diseases. Typically, the number of markers in which the evidence for association exceeds the genome-wide significance threshold is very small, and markers that do not exceed this threshold are generally neglected. Classical statistical analysis of these datasets in MS revealed genes with known immunological functions. However, many of the markers showing modest association may represent false negatives. We hypothesize that certain combinations of genes flagged by these markers can be identified if they belong to a common biological pathway. Here we conduct a pathway-oriented analysis of two GWAS in MS that takes into account all SNPs with nominal evidence of association ($P < 0.05$). Gene-wise $P$-values were superimposed on a human protein interaction network and searches were conducted to identify sub-networks containing a higher proportion of genes associated with MS than expected by chance. These sub-networks, and others generated at random as a control, were categorized for membership of biological pathways. GWAS from eight other diseases were analyzed to assess the specificity of the pathways identified. In the MS datasets, we identified sub-networks of genes from several immunological pathways including cell adhesion, communication and signaling. Remarkably, neural pathways, namely axon-guidance and synaptic potentiation, were also over-represented in MS. In addition to the immunological pathways previously identified, we report here for the first time the potential involvement of neural pathways in MS susceptibility.
Can “pathway classifiers” work any better than gene-based classifiers?

- A common sense expectation is “yes”
- Similar performance for pathway and gene content descriptors in MAQCII
- However larger datasets, multiple studies are needed for fair tests
PATHWAY BARCODING OF PHENOTYPES

Pharmacological Mechanisms of Action (targets and drugs)

Applications:
- New target hypotheses
- Drug repositioning
- Targets for combination drugs
- Market intelligence
- Personalized medicine
- Translational medicine

- Scoring,
- Ranking,
- Prioritization
- Reporting

Normal Pathways

Pathology Pathways
## PATHWAY-BASED DISEASE SIMILARITIES

<table>
<thead>
<tr>
<th>Mental disorders</th>
<th>Neurodegenerative</th>
<th>Neoplasms</th>
<th>Autoimmune diseases</th>
<th>Inflammatory diseases</th>
<th>Obesity; Diabetes II; etc</th>
<th>Cardiovascular</th>
</tr>
</thead>
</table>
PATHWAY (FUNCTIONAL GROUPS) CLUSTERING

Patients (samples) in one cohort, say Breast cancer study of 400 patients

Individual profiling based on EA in multiple ontologies

Pathway-based similarity tree

Clustering based on tree A.B,C.. – individual samples
Rolf A. Stahel, M.D.
Professor, Laboratory of Molecular Oncology
Clinic for Thoracic Surgery and Policlinic for Oncology
University Hospital of Zurich
ESMO President-Elect
Martin Edelman, M.D.
Professor of Medicine
University of Maryland School of Medicine
Director, Solid Tumor Oncology
Greenebaum Cancer Center
Personalized Cancer Treatment and Patient Stratification Using NGS and Other OMICs Data

Yuri Nikolsky, Ph.D.
Vice President, Research & Development
Intellectual Property & Science
Thomson Reuters
Thank you for attending
Personalized Cancer Treatment and Patient Stratification Using NGS and Other OMICs Data

Broadcast Date: Thursday, January 31, 2013
Time: 11am ET, 8am PT

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