European Perspectives in Personalised Medicine

Personalised Medicine – Opportunities and Challenges

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EPFL, Lausanne, FIMM, Helsinki, Caris Life Sciences, Dallas and Lausanne

Brussels 12-13 May 2011
The opportunity - What is New?
Past and Future Practice of Medicine

The past 1000s of years
Diagnosis and treatment based on what could be seen, smelled, tasted, palpated or intuited (anatomical)

The last 100 years
Diagnosis and treatment based on increasing knowledge about biochemistry and cellular processes (cellular)

Today
Diagnosis and treatment increasingly based on rapidly growing insights into molecular biology and genetics (molecules, genes and pathways)

Tomorrow
Patient management based on individualized computer prediction of optimal and necessary therapies for individual patients (systems view)
Past Success creates future challenge

We have been very successful in creating many new effective medicines –

Over 7500 different medicines available worldwide

The future will need to be different!
Economic and Social Pressures: Step-Change Needed in Efforts to Create New Therapies

Sources: FDA/CDER Data, PhRMA data, Price Waterhouse Coopers analysis, Pharma 2020
How can we better identify the patients who need each Therapy?

Spears et al., Trends Mol Med, 2001; 2 Lazarou et al., JAMA, 1998
Personalized Healthcare

Use of Molecular Insights and Diagnostic Tests to Better Tailor Medicines and Manage a Patient’s Disease

Today Most Patients are Treated the Same

- 25-80% of patients receive effective treatment\(^1\)
- >100,000 deaths/yr from adverse drug reactions in US\(^2\)

Molecular diagnosis

How can we encourage the development and use of New Diagnostic tools?

Increasingly, treatment will be tailored to **selected patient groups** defined by molecular diagnostics

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1 Spears et al., Trends Mol Med, 2001
2 Lazarou et al., JAMA, 1998
The road to new effective therapies for all diseases

1. Stratified Medicine
   New Classes of Patient subgroups

2. Personalized Medicine
   Individual often novel combinations for each patient
How can we better bring together those who understand (human) molecular biology and those who understand medicine to help patients?
Driver Gene Classification

3142 genes mutated in human cancers

286 Tumor Suppressor Genes

33 Oncogenes

90% of drivers are suppressors

Virtually all are components of 12 core pathways
The pioneer – Cancer

Genetic lesions in **melanoma**: targeting BRAF gain of function mutation

Shepherd C. Curr Oncol Rep 2010, 12 p146
How can we accelerate the design and implementation of stratified therapy trials through pre-stratification of patients?

How can we ensure the rapid and universal uptake of diagnostics required for stratified medicines?
The road to new effective therapies

1  Stratified Medicine
New Classes of Patients subgroup

2  Personalized Medicine
Individual, often novel, combinations for each patient
Practical Personalised Medicine Today: Highlights from the Bisgrove Study

- 97% of patients yielded a target by IHC/FISH, and 94% of patients yielded a target by MA
- Molecular profiling identified agents that would not have been the oncologist’s first choice
  - There was no relationship between the therapy the clinician would have selected before molecular profiling and what the molecular profiling results suggested. More specifically, no complete matches for the 18 patients with a PFS ratio >=1.3 were noted.

The Bisgrove study and others like it prove that it is possible to perform molecular profiling on patients’ tumours from many centres with excellent quality control.
A practical example: over 12,000 patients analysed!

Target Now® Overview

A combination of the most clinically relevant technologies

**Analysis**

**IHC**
- Multiple profiles depending on tumor type with a total of over 30 different “protein targets”
- Additional 22 IHC validated

**Microarray**
- Looking at the over- or under-expression of RNA in a whole genome microarray for both fresh frozen and FFPE tissues
- Summarizing ~80 of the most significant or resistant targets

**FISH**
- Identifying gene copy number alterations in tumor tissue (EGFR, HER2, TOP2A, cMYC)

**Mutational Analysis**
- Identifying gene mutations in tumor tissue (e.g. KRAS, BRAF, EGFR, c-Kit, PIK3CA etc.)

**Output**

Unique molecular “blueprint” of patient tumor
- Gene Expression
- Quantitative Protein Expression
- Mutational Analysis
- Gene Copy Number Aberrations

Literature-based prioritized ranking of drug targets in tumor and their associated therapies

Information on therapies that might not otherwise have been considered based on the lineage of the tumor
Target Now ® Summary of Agents

Clinical History and Prior Therapies

Clinical History: Per the submitted patient history, the patient is a 69-year-old female with a history of metastatic colon cancer. She underwent a right hemicolectomy in November 2007. The patient has received the following therapeutic agents/regimens: FOLFOX (12/07 - 05/08); 5-FU plus leucovorin (started 06/08); irinotecan (03/09 - 04/09); and capecitabine (05/09 - 08/09).

<table>
<thead>
<tr>
<th>Patient Information</th>
<th>Specimen Information</th>
<th>Ordered By</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Patient</strong></td>
<td><strong>Primary Tumor Site</strong>: Colon: Cecum</td>
<td><strong>Test Ordering Physician</strong></td>
</tr>
<tr>
<td>Case Number: MP-TN10-00000</td>
<td><strong>Specimen Site</strong>: Colon: Cecum</td>
<td>The Cancer Center</td>
</tr>
<tr>
<td>Date Of Birth: 09/05/1940</td>
<td><strong>Specimen Collected</strong>: 11/16/2007</td>
<td>1234 Main Street</td>
</tr>
<tr>
<td>Sex: Female</td>
<td><strong>Specimen Received</strong>: 1/30/2010</td>
<td>Dallas, TX 12345</td>
</tr>
<tr>
<td>SSN: XXX-XX-XXXX</td>
<td><strong>Date Reported</strong>: 2/8/2010</td>
<td>123-456-7890</td>
</tr>
</tbody>
</table>

Target Now Summary

<table>
<thead>
<tr>
<th>Agents Associated With Clinical Benefit</th>
<th>Agents Associated With Lack of Clinical Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>irinotecan</td>
<td>cetuximab, panitumumab</td>
</tr>
<tr>
<td>nab-paclitaxel</td>
<td>trastuzumab</td>
</tr>
<tr>
<td>doxorubicin, liposomal-doxorubicin, epirubicin</td>
<td>temozolomide</td>
</tr>
<tr>
<td>octreotide</td>
<td>gemcitabine</td>
</tr>
<tr>
<td>asparaginase, pegaspargase</td>
<td>cisplatin, carboplatin, oxaliplatin</td>
</tr>
<tr>
<td>sunitinib, sorafenib</td>
<td>erlotinib, gefitinib</td>
</tr>
<tr>
<td>azacitidine, decitabine</td>
<td>lapatinib</td>
</tr>
</tbody>
</table>
## Target Now® Details Agents Associated with Clinical Benefit

The role of Target Now is to identify biomarkers and therapies associated with clinical benefit or lack of clinical benefit for cancer patients. The selection of any, all or none of the matched agents resides with the discretion of the treating physician. If a patient's tumor has previously progressed on an agent identified as associated with clinical benefit on this report, the patient should not be re-treated with this agent.

<table>
<thead>
<tr>
<th>Agents Associated With CLINICAL BENEFIT</th>
<th>Summary Statement</th>
<th>Lineage of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>irinotecan</td>
<td>High expression of TOPO1 has been associated with benefit from irinotecan.</td>
<td>CRC</td>
</tr>
<tr>
<td>nab-paclitaxel</td>
<td>High expression of SPARC has been associated with benefit from nab-Paclitaxel.</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>doxorubicin, liposomal doxorubicin, epirubicin</td>
<td>High expression of TOPO2A has been associated with benefit from anthracycline-based therapy.</td>
<td></td>
</tr>
<tr>
<td>octreotide</td>
<td>High expression of SSTR2 and SSTR5 has been associated with benefit from somatostatin analogs.</td>
<td></td>
</tr>
<tr>
<td>asparaginase, pegasparagase</td>
<td>Low expression of ASNS has been associated with benefit from asparaginase or pegasparagase.</td>
<td></td>
</tr>
<tr>
<td>sunitinib, sorafenib</td>
<td>Over expression of c-Kit by DNA microarray has been associated with benefit from multi-targeted kinase inhibitors.</td>
<td></td>
</tr>
<tr>
<td>azacitidine, decitabine</td>
<td>High expression of DNMT3A has been associated with benefit from DNA methyltransferase inhibitors.</td>
<td></td>
</tr>
</tbody>
</table>
Large Number of Compounds Available
To whom do we give which drug and in what combination?

- Total number of oncology drugs approved in US is around 300\(^1\)
- Number of new cancer medicines and vaccines being tested in the US is 861 (either in clinical trials or awaiting approval by the FDA)\(^2\)
- How can we best decide which is the best combination for efficacy and for which patients?

- **New thinking is required!!!**

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\(^1\) Source: NCI, \(^2\) Source: cancernetwork.com '09
How can we encourage new ways of demonstrating clinical efficacy for personalized and therefore rare therapeutic regimes?

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How can we better show the effectiveness of therapies in real life rather than just clinical trials?
Challenge

How can we encourage and validate new ways of redefining disease from blood samples?

How can we create a market in Europe to reward public and private investment in key areas of precision Diagnostics required for Personalised Medicine?
Personalized Medicine Requires A MAJOR Change in Perspective on the part of all stakeholders almost simultaneously!

- Re-classification of diseases at the molecular level
- Major innovation in how we demonstrate clinical efficacy
- Move on from companion diagnostics for each therapy to definition of the right therapeutic combination for each patient.
- Change in the way patient information is generated/used to accelerate innovation in medicine.
- Encourage novel partnerships and collaborations
Key stakeholders in Health

Patients
Doctors
Health care providers/payers
Regulators
Basic (biomedical) Researchers and funders
Private Sector

How do we best support the extensive dialog between the key stakeholders required to implement personalized medicine effectively in Europe?