Public-Private Partnership in precompetitive Research

a European perspective

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Targeted therapy represents 57% of the cost of anticancer drugs (public hospital sector)
Translational research needs high quality specimens

Patients \[\rightarrow\] Annotated biological samples \[\rightarrow\] -Omics HTS

Basic sciences \[\leftarrow\]

Model systems

Bioinformatics Data bases

Knowledge \[\rightarrow\] Biomarkers Drug targets \[\rightarrow\] Personalized medicine
### Table 2 Cancer biomarkers that are currently in clinical use.

<table>
<thead>
<tr>
<th>Tumor marker</th>
<th>Cancer type</th>
<th>Year of discovery and reference</th>
<th>Application based on ASCO and/or NACB recommendations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-fetoprotein</td>
<td>Germ-cell hepatoma</td>
<td>1963(^5)</td>
<td>Diagnosis&lt;br&gt;Differential diagnosis of NSGCT&lt;br&gt;Staging&lt;br&gt;Detecting recurrence&lt;br&gt;Monitoring therapy</td>
<td>80</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Medullary thyroid carcinoma</td>
<td>1970s(^6)</td>
<td>Diagnosis&lt;br&gt;Monitoring therapy</td>
<td>82</td>
</tr>
<tr>
<td>CA125</td>
<td>Ovarian</td>
<td>1981(^7)</td>
<td>Prognosis&lt;br&gt;Detecting recurrence&lt;br&gt;Monitoring therapy</td>
<td>80</td>
</tr>
<tr>
<td>CA15-3</td>
<td>Breast</td>
<td>1984–5(^8),(^9)</td>
<td>Monitoring therapy</td>
<td>77</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>Pancreatic</td>
<td>1979(^8)</td>
<td>Monitoring therapy</td>
<td>86</td>
</tr>
<tr>
<td>Carcinoembryonic antigen</td>
<td>Colon</td>
<td>1966(^6)</td>
<td>Monitoring therapy&lt;br&gt;Prognosis&lt;br&gt;Detecting recurrence&lt;br&gt;Screening for hepatic metastases</td>
<td>77,80</td>
</tr>
<tr>
<td>ER and PgR</td>
<td>Breast</td>
<td>1970s(^6)</td>
<td>Select patients for endocrine therapy</td>
<td>77</td>
</tr>
<tr>
<td>HER2</td>
<td>Breast</td>
<td>1985–6(^8),(^9)</td>
<td>Select patients for trastuzumab therapy</td>
<td>77</td>
</tr>
<tr>
<td>Human chorionic gonadotropin-β</td>
<td>Testicular</td>
<td>1938(^8)</td>
<td>Diagnosis&lt;br&gt;Staging&lt;br&gt;Detecting recurrence&lt;br&gt;Monitoring therapy</td>
<td>80</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>Germ cell</td>
<td>1954(^9)</td>
<td>Diagnosis&lt;br&gt;Prognosis&lt;br&gt;Detecting recurrence&lt;br&gt;Monitoring therapy</td>
<td>80</td>
</tr>
<tr>
<td>Prostate-specific antigen</td>
<td>Prostate</td>
<td>1979(^2)</td>
<td>Screening (with DRE)&lt;br&gt;Diagnosis (with DRE)</td>
<td>80</td>
</tr>
<tr>
<td>Thyroglobulin</td>
<td>Thyroid</td>
<td>1956(^2)</td>
<td>Monitoring</td>
<td>82</td>
</tr>
</tbody>
</table>

Abbreviations: DRE, digital rectal examination; ER, estrogen receptor; NACB, National Academy of Clinical Biochemistry; NSGCT, nonseminomatous germ cell tumor; PgR, progesterone receptor.

*Nat Clin Pract Oncol* doi:10.1038/nкопnc1187
Trends of Journal Publication on Biomarkers and FDA Approval of Biomarkers

Triangles (green) represent the number of FDA-approved markers per year (data from FDA and Nat Rev Can 2005). Red squares and circles indicate publications under the Medline medical subject heading biomarker.
<table>
<thead>
<tr>
<th>BCR-ABL translocation:</th>
<th>Chronic Myeloid Leukemia/ Acute Lymphoblastic Leukemia</th>
<th>Imatinib prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- BCR-ABL detection</td>
<td></td>
<td>1- Imatinib prescription</td>
</tr>
<tr>
<td>2- BCR-ABL quantification</td>
<td></td>
<td>2- Monitoring of minimal residual disease</td>
</tr>
<tr>
<td>3- ABL mutation</td>
<td></td>
<td>3- Resistance to Imatinib</td>
</tr>
<tr>
<td>KIT and PDGFRA mutations</td>
<td>GIST</td>
<td>Imatinib prescription</td>
</tr>
<tr>
<td>HER2 amplification</td>
<td>Breast and gastric cancers</td>
<td>Trastuzumab prescription</td>
</tr>
<tr>
<td>KRAS mutations</td>
<td>Colorectal cancer</td>
<td>Panitumumab and cetuximab prescription</td>
</tr>
<tr>
<td>EGFR mutations</td>
<td>Lung cancer</td>
<td>Gefitinib and erlotinib prescription</td>
</tr>
<tr>
<td>EML4-ALK translocations</td>
<td>Lung cancer</td>
<td>Crizotinib prescription</td>
</tr>
<tr>
<td>BRAF mutation V600E</td>
<td>Melanoma</td>
<td>Vemurafenib prescription</td>
</tr>
</tbody>
</table>

**Targeted therapy represents 57% of the cost of anticancer drugs (public hospital sector)**

- **Bovacizumab**: 19.3%
- **Rituximab**: 16.8%
- **Docetaxel**: 11.5%
- **Trastuzumab**: 12.8%
- **Pemetrexed**: 8.1%
- **Cetuximab**: 6.7%
- **Bortezomib**: 5.5%
- **Irinotecan**: 4.8%
- **Others**: 9.1%

Source: ATIH-PMSI MCO base 2009
F. Calvo, INCa
THE STEPS OF BIOMARKER DISCOVERY AND VALIDATION

Opportunity evaluation → Discovery & Technical feasibility → Lead generation → Lead confirmation → Marker validation in a clinical setting → Marker validated (on 1 platform)

Basic research
Research infrastructures
Competitive career tracks

Clinical studies
Sample availability and quality
Quality insurance
Information management
• A shift from a single biomarker to multiparametric biomarkers
  ➢ new technologies
  ➢ IT: metadata integration, bioinformatics, systems biology etc.
  ➢ Validation: genetic background, environmental contexts (life style), ethics etc.

• Precompetitive public-private partnerships

• Sharing of intellectual property rights

• Implementation of new knowledge and processes in clinical practices

A novel model, based on data integration and validation
Early phases of innovation: proof of concept

Education, training

Centres of excellence, innovation clusters, infrastructures
Public Private cooperation

Is required to integrate:

• Capital
• Knowledge
• Expertise
• Techniques

A shift of paradigm to achieve new products and new processes.
Criteria for success

- A novel paradigm for public-private partnerships
  - moving to collaboration instead of « isolation »
  - refining the intellectual property bases

- Access to biological samples and data, with standardized procedures

- Academic environment: project-driven

European Infrastructures (ESFRI roadmap)
BBMRI, ECRIN linked to national infrastructures

- Pharma-Diagnostics companies win-win interactions

- Simplified discussions with regulatory agencies
Examples of biobanking networks

**Transient biobanking networks**

- **International Cancer Genome Consortium**
  - To describe genomic, transcriptomic and epigenomic changes in 50 different tumor types and/or subtypes

- **Human Genome Project**
  - To specify a reference sequence (~10 libraries)

- **1000 Genomes Project**
  - To describe sequence variation

- **International Human Epigenome Consortium**
  - To describe >1000 epigenomes

- **Wellcome Trust Case Control Consortium**
  - To discover common SNPs in common disease

- **IMI U-biopred**
  - To discover omic biomarkers in asthma

- **Japan Biobank**
  - To accrue rapidly 300,000 samples for genetics and pharmacogenetics in 50+ diseases

**Network infrastructures**

- **BBMRI : Biobank and BioMolecular resources Research Infrastructure**
  - To link national biobanking initiatives

- **UK DNA Banking Network**
  - To add scientific value to MRC genetic collections

- **German biobanking platform**
  - To link national centres of excellence

- **French biobanques Infrastructure**
  - To link all biological resource centres

- **Spanish Biobanks infrastructure**
  - To link all biological resource centres

- **BBMRI.se (Sweden)**
  - National large-scale biobanking facility

- **String of Pearls Initiative**
  - To accrue samples in 9 diseases from 8 NL hospitals
European Research Council.
7th Framework Program: Networks: public-private
Access for Industry

Common good (donations)
- Medical data
- Biological samples
- Knowledge

Public (not-for-profit)

Industry
- Diagnostics
- Drugs

Private (for-profit)

?
Expert Centres: Win-Win for Public and Private Sectors

**Common good**
- Medical data
- Biological samples
- Knowledge
- Public (not-for-profit)

**Expertise**
- Data

**Primary data generation**
- Public – Private pre-competitive (not-for-profit)

**Industry**
- Diagnostics
- Drugs
- Private (for-profit)

**Standardisation of data generation**
- Basis for data sharing
- Better usage of finite resources
- Collaborative research to improve innovation
A change of scale in the infectious disease field

• The BIOASTER Technology Research Institute will be structured around main R&D programs and technological platforms
  
  • 3 « product » oriented research programs aiming at designing new marketable products. Design of these products will rely partly on technologies developed in the technological platforms
  
  • 5 technological platforms, featuring structural equipment on which “technology-oriented” collaborative R&D projects will be conducted and services will be offered by SMEs
Back up
R&D in the bioindustry needs Biobanking infrastructures

Old linear R&D model

New in-life testing

From: “Pharma 2020: The vision”
What Drives Successful Diagnostic Test (DX) Development?

DX regulatory approval drivers

1. Prototype
2. RUO/LDT

Analytical Validity → Clinical Validity

Scientific Hypothesis
Clinical Evidence
1. Training, test set
2. External validation-single site
3. External validation-multi-site

Clinical Validity → Clinical Utility

1. Demonstrate dx utility
2. Demonstrate therapeutic changes as SOC

DX reimbursement drivers

1. Demonstrate quality of life impact
2. Demonstrate cost reduction

For market success, developing a test represents a compelling investment for DX company...

...
**Expert Centers**

one of several patterns

- Provides efficient access to samples, data and expertise
- Mutual benefit from expertise and in-kind contributions
- Joint generation of pre-competitive data and knowledge
- Reduces requirements for sample shipment
- Gateway for global collaborations
1. **Screening**: e.g. mammography, fecal occult blood

2. **Diagnosis**: e.g. cardiac troponin

3. **Prognosis**: e.g. cytokeratins, estrogen receptors

4. **Prediction of response to treatment**: e.g. HER2

5. **Follow-up**: e.g. PSA
Biobanking infrastructure definition

– a **sustainable** network of biobanks and related facilities where each contributes a **specialism** (i.e. there is a division of labour) and which is capable of sharing data, samples and expertise between many users

– By contrast, consortia and collaborations constitute “transient networks”
Personalized Medicine
A novel model based on data integration and validation of biomarkers

- **New technologies**
genomics, metabolomics, imaging...

- **IT**
data bases, systems biology, bioinformatics...

- **Validation: clinical studies**
genetic background, environmental contexts (life style, nutrition...), assurance-quality, ethics etc..

- **Socio-economics aspects**
public health, cost benefit, reimbursement...
Personalized Medicine

A novel model based on data integration and validation of biomarkers

Various biological samples

Blood: plasma, serum
Tissue
Cells
Urine; Stools
Saliva
Exhaled breath
...

Various Tools

DNA
mRNA, miRNA
Metabolome
Proteome
Glycome
Microbiome
Imaging
Main challenges in biomarker discovery

Biological samples

Blood: plasma, serum
Tissue; Cells
Urine; Stools
Saliva; Exhaled breath...

Tools

DNA
mRNA, miRNA
Metabolome
Proteome
Glycome
Microbiome
Imaging
Personalised Medicine: Difficulties and challenges

A novel model, based on data integration and validation of biomarkers:

- **Technology:** genomics, proteomics, metabolomics, imaging etc..

- **Clinical studies**

  Different genetic background

  Different environmental contexts (life style, nutrition…)

  Clinical studies: quality, ethics etc..

- **Public health**

- **Economics:** Cost-benefit, reimbursement etc..
Personalised Medicine: Difficulties and challenges

A novel model, based on data integration and validation

- A change of paradigm:
  - Shift from unique to multiple, complex, biomarkers
    (multi-parameters = data intégration, bioinformatics, Computational biology, systems biology)

- Intellectual property?.

- Management and transfer of information: physicians, patients (cell phone, etc...).
"Biomarker research already has developed biological indicators that have had immense impact in prevention and treatment of disease... The identification of biomarkers is an essential element for the new era of predictive, preemptive, personalized medicine."

Elias Zerhouni, M.D., Director, National Institutes of Health
However

• The discovery of biomarkers is likely to be a gradual process, building on the collection of large data sets from preclinical studies and clinical trials.

• The scale of this endeavour is considerable. There is a complex set of barriers — logistical, scientific, regulatory and commercial — that impede progress,

• I argue for a collaborative, precompetitive public private partnership to foster biomarker discovery.
Criteria for success

- Access to biobanks infrastructures, clinical data, standardization (sampling procedures etc.)

A novel paradigm for industrial partners:
Moving to collaboration instead of «isolation»
Refining the intellectual property bases

- Academic environment: Project-driven

- Pharma-Diagnostics companies win-win interactions

- Simplified discussions with regulatory agencies
  Early discussions to define the requirements
  Reimbursements...

- Public-Private Partnerships:
  NCI biomarker network
  FDA
Steps of biomarker discovery and validation

- Discovery & Technical feasibility
- Lead generation
- Lead confirmation
- Marker validation in a clinical setting
- Marker validated (on 1 platform)

Clinical studies
Sample availability and quality
Quality insurance
Information management