Biomarkers in Personalized Medicine

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Biomarkers at the frontier of different knowledge

Diagnostic

“Drug Companion Test”

Basic Research & Life Sciences

Pharmaceutical

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12 mai 2011
The official NIH definition of a **biomarker** is:

"a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."

- a physical measurement
- a protein,
- RNA expression (gene arrays), DNA (SNPs),
- a metabolite
- a cell…
Companion biomarker:

- An *in vitro* diagnostic medical device required for the new approval of a therapeutic treatment, which serves to improve the risk/benefit profile of the treatment of a previously diagnosed condition through a classification of patients.
- It allows a « guided » drug prescription.
Key issues with new medicines today are:

Safety and efficacy

Main domains of application:
- Oncology
- Ilry complications of diabetes
- Cardiovascular diseases
- Neurodegenerative diseases
The Right Therapy for the Right Patient, at the Right Time

Best responders to therapy are identified using Personalized Medicine Tests and then given the targeted therapy at the right time to maximize efficacy and minimize adverse reaction.
A biomarker may be used to assess or detect:

- Diagnose a specific disease as early as possible – **diagnostic biomarker** (HCV RNA after infection; TnI post-AMI)

- Predict the risk of developing a disease – **susceptibility/risk biomarker** (BRCA1-breast cancer)

- Predict the evolution of a disease (indolent vs. aggressive) – **prognostic biomarker** (HER2-breast cancer) – but it can be **predictive** too.

- Predict the response and the toxicity to a given treatment – **predictive biomarker** (EGFR NSCLC/gefitinib)
Biomarker data useful to drug development, labels and patient care

• Reduce heterogeneity in the population by defining disease subsets and not clusters of symptoms
  • Herceptin® for metastatic breast cancer with HER2 overexpression

• Identify population subsets capable of responding to treatment
  • Tropism testing in HIV/AIDS before maraviroc (Selzentry®)

• Identify patients unlikely to benefit but subject to unnecessary adverse events
  • Panitumamab will not work in colorectal patients with mutated KRAS gene
  • Abacavir & allergic reaction in (HLA-B) patients with AIDS

• Find high risk patients to facilitate rapid and timely accrual of events or risk reduction for new drugs
  • Rosuvastatin prevents CV events when hs-CRP>3mg/dl
Overall survival curves of patients with a KRAS mutated and nonmutated tumor EGFR antagonists in metastatic colon cancer: cetuximab

Biomarker of response, identification of good responders

Lievre et al, Cancer Research 2006
Therapeutics

BM screening  Mechanistic & pathophysiological biomarkers  Explore concentration-response relationships  Pharmacogenomic biomarkers  Stratification biomarkers  Efficacy/toxicity/safety  Monitor treatment response

Basic Research  Prototype Design or Discovery  Preclinical development  Clinical phases I, II, III  FDA / EMA approval for launch

0  4 y  8 y  10 y

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Usefulness of BMs in Pharma

• Use biological information in order to:
  – Better understand the drug effects (POM, POC)
  – **Decrease devt time and devt costs**; Develop better drugs (more efficient and less risky)
  – **Decrease attrition rate** of drugs
  – Increase drug **efficacy**
  – Know earlier toxicity, adverse effects (POS)
  – Prescribe for each patient the best treatment (companion tests)
  – Optimize the treatment **costs**: use the expensive treatments for the patients who will benefit of it (companion tests)
Very few companion BMs are commercialized:
Attrition rate of BMs in pharma industry pipeline

30-60% BM used in development (pharma)

< 5% of BM commercialized with drugs

Most of the BMs are only developed for drug discovery phase
Latest date to begin a companion test program

Diagnostics

Therapeutics

Basic Research
Prototype Design or Discovery
Preclinical development
Marker Discovery
Marker Development
Clinical phases I, II, III
Regulatory
FDA / EMA approval
Marketed diagnostic kit

0 years
4 years
8 years
10 years

0 y
4 y
8 y
10 y

Marker discovery
Marker development
Clinical phases
Regulatory
FDA / EMA approval
Marketed diagnostic kit

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Technological challenges with BM
# Technologies to discover biomarkers

<table>
<thead>
<tr>
<th>Technologies</th>
<th>Types of technologies to get BMs</th>
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| Genomic & transcriptomic| - Genomic µarrays  
- mRNA profile analysis (Affym)  
- SNP (Affymetrix, Fluigent), sequencing  
- Epigenetic studies | |
| Proteomic               | - 2D Electrophoresis  
- Maldi TOF/Seldi TOF  
- MS analysis  
- Protein biochips  
- Imaging (MRI, PET..) | |
| Metabolomic             | NMR; Mass spec | |
| Circulating cells (cancer prognosis) | Cell detection (Fluigent); in vitro screening on cells, cell functional analysis; microvesicles investigation | |
| Antibodies              | Phage display, recombinant, HT Ab platforms | |
Various multiplex technologies

- Luminex (multiplex profiling)
- MRM (multiple reaction monitoring) : quanti MS
- CBA (cytometric bead array) system - BD Biosciences
- Quansys Biosciences
- Meso Scale Discovery (electrochemiluminescence technology)
- Illumina (for proteins 48 plex), sequencing, genotyping
- Multiplexed PCR analysis
What do we miss? (technology)

3 important technological needs for identification of BMs:

• High throughput screening platforms to identify quicker and earlier biomarkers without labeling step (qMS);
• Quantitation & validation (/invalidation) techniques of candidate BMs in quicker and cheaper ways (Multiplex technologies) to address Rx (drug development, POM, POS, theranostic, risk stratification) and Dx (multifactorial complex pathologies) needs; Important decision based on those BMs
• Development of tools/methods for cell functional analysis
  
  – Development of analytical tools to discover small molecular markers to assess drug toxicity
  
  – Quicker methods for identification/diagnosis of severe pathological conditions (sepsis diagnostic, antibiotic resistance testing in emergency situation…)

What do we miss? (validation)

A critical step: validation of the clinical need

– Difficulty* of accessing cohorts (retro- and prospective) and appropriate bankings: **need for easier access to specimen repository and well characterized biobanks** (sample to storage).
– Lack of standardization in how specimens are collected.
– No biomarker **inventory** validated in Europe yet
– Need to develop European specific guidelines for biomarker qualification and clinical validation

* SMEs !
What do we miss? (data treatment)

- Large sample sizes required to validate **multiplex** tests are already generating massive data sets.
  - with whole-genome sequencing becoming generally used, data sets will only get bigger. Analyze through sophisticated mathematical, statistical and computational tools AND skills of specialists in bio-informatics & biostatistics.
  - For such large-scale projects, data must also be documented, stored and analyzed in **standardized** ways.
  - Compatibility of the formats used by industry and regulators to produce electronic patient health records.

- Generate pathophysiological knowledge by pathways analysis
Future steps to overcome those concerns
Recommendations for Biomarkers

• **Invent/create:**
  - Develop imaging technologies to understand toxicology mechanisms at the molecular, whole organ, and whole body level
  - Develop HT screening platforms
  - Establishment of web based knowledge centers (by categories: Disease/Technology/Cell-Tissue-Organ:/ Name of marker (protein, antibody, gene, etc.)); create a biomarker inventory validated (and challenged !) in Europe

• **Improve/develop:**
  - Include the devt of stratification BMs into the concept of disease prevention and drug development; to identify BM as early as possible in the workflow of drug discovery & devt (BM are different from assays !); new designs, new paradigms of development, new partnerships, new rules and authorization
  - WW (?) access to European repository biobanks through a portal; with epidemiologic/longitudinal disease cohorts
Recommendations for Biomarkers

• **Communicate:**
  - Improve linkage of biomarkers to clinical information (and patient information)
  - Coordination between disciplines & technologies: acceleration of partnerships between academic, medical research, clinicians, pharmas, diagnostic, biotech companies)

Translational medicine vision
In a glance

• Between Rx and Dx, challenges are often similar:
  – In the development process
  – To limit development costs and time to market
  – Access to cohorts, acceleration bioclinical studies valid°
  – Need of decisional algorithms and biomathematical data Mngt

• Although:
  – Different businesses, different timings, different ROI but real synergies
  – Goals sometimes different: candidate biomarkers to conduct « drug discovery », biomarkers predictive of adverse effects, biomarkers for theranostic versus use for diagnostic.
  – Hurrdles with regulatory, price and reimbursement of the Rx/Dx duo or the companion Dx
What do we hope?

- **Dx**: Better answer complex pathologies (ex: oncology, infectious diseases, neurodegenerative diseases, diabetes prediction, plaque rupture etc.) with a panel of BMs allowing better sensitivity and specificity of the clinical diagnostic.

- **Tx and companion test**: answer pharma’s needs
  - New « candidate BMs » to accompany the drug development (decrease attrition rate for Pharmas)
  - Registered companion tests by regulatory agencies with the drug (companion tests to select patients, drug follow up).

- An integrative medicine vision, integrating multi-technologies data (omics, phenotypings, imaging, in vivo functional studies), multi-disciplines, and some disease-specific centers of clinical excellence

- Address reimbursement and regulatory rules
“It’s far more important to know what person the disease has than what disease the person has.”

Hippocrates