Trends, Challenges and Opportunities of Biomarkers in Translational Medicine

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Biomarkers have received much attention in the past decade and are still a buzzword in the biomedical field today. However, the focus has changed from the discovery of novel biomarkers to their applications in human medicine where their main promise resides in two application areas. In translational medicine, knowledge from preclinical models is translated to clinical practice using biomarkers that can reflect various aspects of a biological system including molecular pathways and intercellular signaling. Such studies are expected to greatly increase the knowledge of the mechanisms of human disease and pathophysiology, leading to a better diagnosis and more effective clinical treatment. In personalized medicine, biomarkers are used to profile patients and to define which treatment should be given to which patient at what time and at what dose. Such stratification biomarkers are expected to strongly increase the chance of a successful clinical treatment by selecting patients that are most likely to respond to a drug and/or to deselect patients that are predicted to exhibit adverse effects.

Current activities in both of these areas of biomarker research are aimed to strongly improve management of disease. However, ultimately their potential is to change disease management into health management,
other words, keeping healthy people healthy rather than curing diseased patients. Key drivers for such change would be tools (read biomarkers) that allow earlier detection of disease, better molecular classification of disease, improved personalized treatment, and improved monitoring of any effects of treatment.

It is safe to say biomarkers have not yet reached that status in all therapeutic areas. However, there are many shining examples where hard work has resulted in good clinical utility of biomarkers. To name a few: the use of validated genetic markers to predict the clinical response and side effects to marketed drugs (see www.fda.gov), the use of various non-invasive imaging modalities to map drug exposure and subsequent changes of metabolic activity in Alzheimer's disease (see Perrin et al, Nature 2009), and the use of gene expression to elucidate the molecular origin of metastases to better define the subsequent clinical treatment (see www.agendia.com).

Despite these successful examples, it was generally anticipated 10 years ago that progress in translational and personalized medicine would be more advanced than it is today. Particularly, it was anticipated that with the availability of the human genome sequence each person would have his/her genome on a chip to enable a physician to determine the best personalized care. However, exemplified by the cases described above, the maturation of a biomarker to a clinically usable test has shown to require a thorough and long-lasting research and development process.

To understand this apparent limited progress and to benefit from the lessons learned, it is interesting to reflect on the trends, challenges and opportunities regarding biomarkers in translational medicine.

**Trends:**

Perhaps the most pronounced change in biomarker research has been in the workplace of biomedical scientists. For both standardized and specialized activities, it was found to be more cost/resource/time-effective to outsource such tasks to dedicated service providers that perform high quality contract research as their core business. As a direct consequence, many activities within companies and universities are currently being outsourced, creating an interdependent functional network. Moreover, in line with the globalization of our society, the scope of this functional network has changed from a local to a global nature. Distance is no longer a key factor in selecting external expertise to support a project, but rather the quality, speed and costs of the external partners. Many scientists nowadays have developed global connections and routinely send samples across continents for analysis.

In addition, the marketplace has also globalized. Whereas earlier most, if not all of the commercial and research focus of pharmaceutical and diagnostic industries was on Western markets in Europe and USA, recently this shifted to the emerging markets, spearheaded by Brazil, Russia, India and China. However, distinct differences have been found in response to drugs originally developed for the Western markets but also in the pathophysiology and clinical features of diseases. Without doubt, the different genetic backgrounds, dietary preferences and lifestyle of populations across the globe contribute to this, but clearly more research is needed to investigate this. Supported by their increased economic power, the emerging countries currently invest heavily in biomarker research, aiming to improve existing therapeutic
treatments and generate more personalized drugs for their markets.

There have also been interesting trends regarding the nature of the biomarkers themselves. Parallel to identifying more candidate biomarkers, there is an increased desire to valorize biomarkers and develop them from basic research tools into robust diagnostic tests that can be applied for clinical decision making. Translational medicine needs such validated biomarkers, as only then one can prove equivalency of biological responses across models and humans. Recent research has yielded many translational biomarkers (DNA, RNA, protein, metabolite, and imaging) in different stages of validity that are being applied to provide data supporting translational and personalized medicine. An other interesting trend is to combine quantitative biomarker data and clinical read-outs to provide a more detailed characterization of a disease state. This enables clinicians not only to diagnose diseases but also to specify the subtype or causal origin of the pathophysiology, potentially leading to a more tailored treatment.

In the biomarker discovery space, new data-rich biomarker discovery technologies have emerged that are dramatically changing our knowledge of preclinical and human systems, information which is imperative to enable translational and personalized medicine. Particularly, next generation sequencing, whereby variants and regulation of DNA and RNA on nucleotide level are revealed, and mass spectrometry, whereby peptide, protein and metabolite isoforms are monitored to reflect acute perturbations of biological systems, have yielded a wealth of observations on variants in healthy and diseased states. This progress has dramatically changed the landscape of biomarker discovery and development and strongly increased the potential that biomarkers can have for human medicine.

Challenges:
Despite the progress that is made, several basic elements are not yet in place to permit biomarkers to reach their full potential in human medicine. First and foremost, there are still insufficient accepted robust biomarker tests that can be applied in the clinic. Human diseases are mostly complex in nature and it requires several biomarkers to mechanistically describe the imbalance in the metabolic equilibrium responsible for the disease and the effect of treatment. The number of published biomarkers with clear biological relevance needs to increase but, even more importantly, the clinical validation of such biomarkers needs to improve strongly. Without extensive validation, the outcome of a biomarker test cannot be used in important clinical decisions as done in
personalized medicine. Clinical biomarker validation should optimally be performed by applying standardized procedures and protocols to test independent clinical samples across multiple independent laboratories. However, in reality, this is rarely carried out. The commitment of biomarker researchers to engage in longlasting and expensive biomarker validation projects is limited which is partly due to the pressure to publish innovative findings in high impact journals and secure funding. Although clinical validation of biomarkers, including the development of quantitative biomarker assays with high accuracy, specificity and reproducibility is essential to enable translational and personalized medicine, it has limited news value and as such is less prone for publication. Also, despite constructive efforts by regional biobanks, there is a lack globally of (pre)clinical samples that are highly characterized, are properly stored, have associated phenotypical metadata and are being made available for multicenter biomarker validation. As a result of all this, researchers focus on objectives that are considered more innovative and achievable on short-term, which only rarely includes reporting of robust clinical biomarker validation.

A challenge in biomarker discovery is how to exploit the great potential of novel high-content technologies as mentioned above. Data analysis methods are still being optimized and knowledge on the biological interpretation of the newly identified variants is scarce. Moreover, there is often insufficient knowledge on variation in the biomarkers themselves across the various population groups in the world. A greater understanding of this natural variation is imperative prior to the use of such biomarkers to mechanistically characterize disease and treatment effects.

Opportunities: Embracing an optimistic view, I feel that each challenge is an opportunity for progress. The key to progress is funding which is strongly increasing for translational medicine globally. This, together with the downsizing of internal biomarker activities in larger companies, is a considerable stimulation of new economic business opportunities. Many specialized spin-off companies have been formed who, together with contract research organizations, vendors and central laboratories, are working together in collaborative spirit with larger companies and universities to drive pharmaceutical and diagnostic biomarker development. Importantly, this functional network now also includes the emerging markets and their populations, driving biomarker research across the globe.

An other opportunity lies in the nature of the funding of translational medicine. Funding agencies prefer to support multicenter consortia in public-private partnerships rather than single laboratories, bringing together basic and applied biomarker researchers and stimulating knowledge transfer and a focus towards applied biomarker research. Such collaborations have shown to lead to increased awareness of the value of cross-discipline biomarker research, improved data analysis workflows, and increased identification and development of biomarkers for specific diseases and mechanisms. In addition, there is now the opportunity to functionally link the multiple independent biorepositories across the globe through global networks and share access to unique clinical samples. Together, these initiatives will make robust biomarker assays and clinical samples available to a larger group of testing laboratories, thus increasing the quality of published validated biomarkers and their application in translational and personalized medicine.

Ultimately, this higher level of biomarker knowledge and tools will result in transformation of disease management into health management. At present, it may seem a utopia but with the impressive progress we have seen in recent years it may be sooner than expected.

About the Author

Alain van Gool was trained as a molecular and cellular biologist and specialized in translational biomarkers in pharmaceutical drug development. Since 1999, he has been working in pharmaceutical industry in the Netherlands and in Singapore (Organon 1999, Schering-Plough 2007, MSD 2009), focusing on translational and personalized medicine while working from research towards the clinic. Alain has been leading several technology-based laboratories, cross-functional biomarker expert teams, therapeutic project teams and external consortia with focus on the discovery, development and implementation of translational biomarkers in a variety of therapeutic areas including women’s health, oncology, inflammation and neuroscience. His technical expertise resides in molecular profiling (genetics, genomics, proteomics, metabolomics, bioinformatics). Alain holds a faculty position as visiting professor Molecular Profiling at the Radboud University Nijmegen in the Netherlands. He serves on several scientific advisory boards and has frequently been an invited speaker at translational medicine conferences.