



## **Genomics Tools: From Research and Development to the Clinic**

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In June 2009, Cambridge Healthtech Institute held a summit at the Fairmont Hotel, San Francisco with the aim of examining the current and future roles of genomics and related 'omics' technologies in drug development. I was invited to speak about the role of new technologies is the development of new medicines and discuss the role which omics based technologies are beginning to play in the estimation of long term and repeated dose drug toxicity. During this event, a number of topics were addressed.

The overall message conveyed at this meeting was that personalized medicine is big business. Here, I will briefly describe what I consider to be the highlights of this event.

I was most excited by John Eberhardt III's discussion of how biomarkers can influence decision-making within the clinic. John described DecisionQ Corp's work with the US Department of Defence where clinical information, and soon omics derived biomarkers, is being used to build profiles of soldiers wounded in active service. This kind of multivariant mapping has resulted in around 70 biomarkers being characterized. Each model takes around 19 months to develop and around 24 months to access. The end result is a tool that can not only help to identify the type of sutures, post-operative care and which patients will heal, but also play a role in deciding whether enlisted soldiers will be suitable for the front line or not, depending on the probability that they will heal well should they be injured. John was very much of the inclination that statistics do not make a good biomarker. A good biomarker would be one which, all facts considered and weighed, demonstrates a pattern consistent with a particular outcome. In John's wound healing model, for instance, interleukin 6 levels are impaired in patients with impaired healing.

Biomarkers assist with patient selection for one in four cancer therapeutics with most biomarkers confirming the status of a drug target, rather than how its function might be modulated. In this sense, biomarker qualification requires a sophisticated appraisal of data from a variety of sources, including, but not limited to protein, metabolic and gene analysis. Anahita Bhatena (Abbott) examined the role of pharmacogenetics in drug development. She explained that whilst pharmacogenetics opened up, albeit limited, opportunities for personalized and tailor made management, the cost and success of pharmacogenetic analysis varies significantly depending on whether a disease is monogenic or not. Furthermore, although the interplay between genetic make up and environmental factors in determining drug disposition and pharmacokinetics is relatively

easy to see during phase I/II clinical studies, how genetics affects efficacy and safety often requires large cohort clinical studies. The Abbott approach involves a small panel of *in vitro* studies to determine the influence of polymorphisms on drug metabolism and transport. More detailed analysis of genetic linkage to drug metabolism and disposition is a theme that is carried over through Phase I and II trials and any new observations are again confirmed using *in vitro* tests. The information from all these studies is then collated to build pharmacokinetic models to inform lead optimization and development. Hence, biomarkers are co-developed alongside the therapeutic to assist with labeling and enrichment to suit specific patient groups.

Daniel Burns (Duke University) pointed out that personalized medicine is not a new concept. X-Rays, for instance, are a form of personalized medicine. However, since it is becoming increasingly difficult to develop safer and more effective medicines whilst the number of 'easy' targets is dwindling and less information is available about some of the newer targets, pharmaceutical companies are investing heavily in personalized medicine. He also pointed out that, at present, the time to registration remains at around 12-15 years and that *in vitro* tests have not improved this situation, albeit many improve mechanistic understanding. Pharmaceutical companies are more inclined to contract out phase I and II studies. However, pharmacogenetic studies are often run in-house as bridging studies as to improve the output from small cohort clinical studies. While it is clear that copy number as well as polymorphisms is important, the 1000 genomes project launched last year (<http://www.1000genomes.org/page.php>) is likely to vastly improve understanding of the consequences of human genetic variation. Perhaps this will also help to overhaul the way in which species differences are viewed and help to ensure that animal models are only used if they are capable of providing information that can be used to estimate drug targeting, disposition, safety or efficacy representative of specific patient populations.

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