Personal Medicine

Biomarker research is fundamental to the delivery of targeted therapeutics. An industry shift towards a more collaborative approach to patient-derived data has potential to secure results in developing successful bespoke cancer treatments

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Despite some remarkable instances of new treatments impacting disease, the biopharmaceutical industry has suffered substantial setbacks in the last decade. Even with the commitment of considerable financial resources and scientific acumen, many current clinical programmes are halted in Phase 2, with a lack of efficacy as the culprit (1,2). This trend is particularly worrisome in light of the current and upcoming patent cliffs – an issue of concern to many in the pharmaceutical community.

Within this trend, F Prinz *et al* noted: "This indicates the limitations of the predictivity of disease models and also that the validity of the targets being investigated is frequently questionable, which is a crucial issue to address if success rates in clinical trials are to be improved"(2). From the drug discovery side of the business, we must then consider what pre-clinical activities can help to mitigate this trend, and how do we identify the disease models that enable us to draw the right conclusions that will reflect desired clinical outcomes?

In this context, biomarker research, and its potential in personalising future therapies, looks promising. Biomarkers play a vital role in the development and delivery of targeted therapeutics within the pharmaceutical industry at large, and they factor into the field of cancer genomics in a particularly meaningful way.

Genetic Biomarkers

The genetic biomarkers of cancer, those genes and their by-products that are aberrant have a salient impact on the course of disease, as well as potential responses to treatment. Knowing that the same cancers behave differently in certain populations, and therefore react non-uniformly to treatment regimens, cancer genomics can utilise the potential of targeted therapies to address the mercurial nature of this disease. Indeed, with the possibility of cancer genomic biomarkers to both classify and modify the disease, they have the ability to transform targeted treatments into truly personalised medicine, by factoring in the characteristics of the patient's cancer into the selection of treatment compound(s). These patient-centric, genetically defined indications will help to determine the therapeutic regimen with the greatest potential for successfully addressing cancer on a per patient basis.

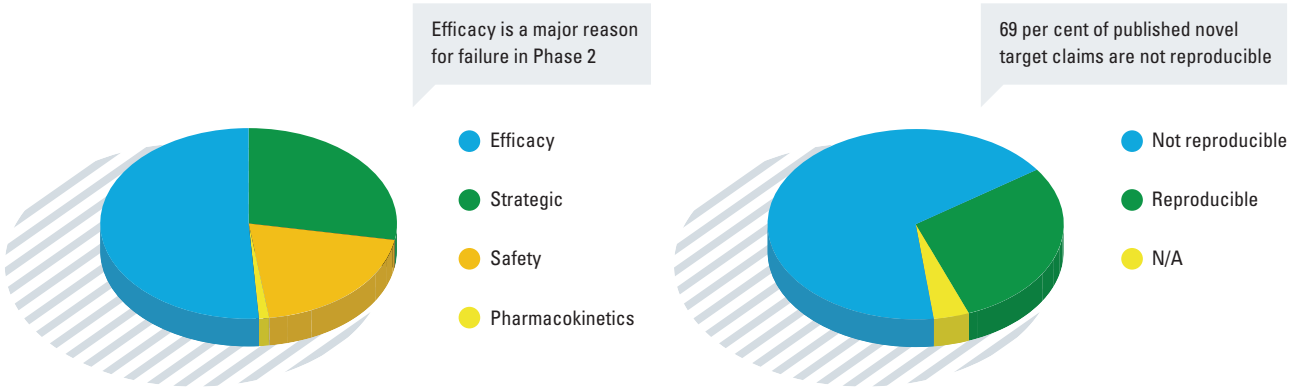
Biomarkers and targeted therapeutics not only provide the foundation for this transformational treatment approach, but they are also a mechanism in our arsenal to overcome significant obstacles that impede clinical progress. The challenge lies in identifying how to target these aberrations, and how to model their genomic biomarkers reliably and efficiently across a broad range of cancers to determine the appropriate context, or patient population, in which to target them.

Understanding Cancer Genomes

We have unprecedented knowledge of the cancer genome and the technology available to drive progress. Cancer genomic discovery programmes, in both academic and corporate environments, are helping to identify and predict which genomic biomarkers are vulnerable to, or associated with responses to, specific targeted therapeutics. Our understanding of the role that genomic alterations play in cancer is at an all-time high, due in part to several successes in developing novel cancer therapeutics in genetically defined populations. Furthermore, data shared worldwide in collaborative open access sources, including The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC), have been crucial in propelling industry knowledge of cancer genomics. So far, these public projects alone are making tremendous progress in the comprehensive characterisation of the genomes of more than 50 cancers (3,4).

The process of transforming these insights into personalised medicine begins and ends with patient-derived data. With thousands of cancer genomes characterised, researchers can identify potential targets based on features of actual cancer patient samples. This information can then be applied to the

Figure 1: Clinical failures and validity of targets (1,2)



identification and development of novel drug discovery approaches directly linked to biomarkers. This approach will facilitate appropriate patient selection, aiding the efficiency of future clinical development. In particular, researchers can:

- Utilise genomic information from actual cancer samples to identify or engineer models representative of certain targets that are aberrant in human cancer samples
- Derive models from patient samples with specific genomic characteristics to further characterise tumors, and test their hypotheses at the preclinical stage

As a result, those experiments that graduate to the clinic will be more likely to avoid efficacy-related failure. This reverse translational approach addresses Prinz *et al's* issue of questionable target and unreliable model predictivity in the clinic. More importantly, it also enables discovery efforts to reflect appropriately the diversity of human cancer; it is not a one-size-fits-all disease, thus there will not be a single treatment solution.

One key preclinical question in the pre-genomics era was: 'In what patient populations will my drug work as it enters the clinic?' While still important, this issue must now be expanded to: 'What preclinical models best reflect the patient population that the potential therapy will address?' From this perspective, it is crucial for discovery programmes to give the clinical stage members of our industry access to a broad array of reliable preclinical models that reflect the diversity of human cancer.

Asking Questions

We have extraordinary insights in disease biology, coupled with considerable financial and resource investments, yet fewer and fewer effective therapies result – why is this?

In a recent analysis, Jack Scannell *et al* coined the expression 'Eroom's Law', which is the opposite of Moore's Law. It found that more money and time dedicated to R&D may not result in a commensurate increase of effective therapies (1,5).

We have an unprecedented understanding of the genomic landscape of cancers, and the intellectual, technical and logistical resources in place to generate significant results in this arena. What else, then, is required to accelerate the translation of genomics insights into efficacious personalised cancer treatments?

Firstly, we can prioritise the focus of preclinical genomic activity. Scientists are currently working to mine the large cache of publicly available cancer genomics data to identify new or credential existing therapeutic targets. However, the development of targeted therapies requires target validation – that is, to demonstrate systematically that a gene hypothesised as a cancer driver indeed plays a pivotal role in cancer cell growth and survival. Target credentialing demands high-quality preclinical studies conducted with models that are representative of patients' disease(s) and cancer genome.

Secondly, we can analyse potential explanations for the Eroom's Law phenomenon, from the invalidity of targets pursued in the clinic, to chronic duplication of efforts across the industry. The former issue, lack of valid novel targets, can be addressed in part by preclinical activities designed to increase the reliability of the targets in intended patient populations. For example, utilising the reverse translation research methodology described here, researchers could begin with a set of cancer cell lines that undergo biomarker profiling to determine which genetic aberration (gene mutation, amplification, or deletion) impacts the eventual expression of proteins and metabolites in cancer cells. The rich dataset generated from this analysis can be leveraged to select cell lines that best represent the genetic background of the targets for the validation process.

More significantly, investigators can also work with these cell lines on a macro scale to determine responses to various compounds – for example,

which biomarkers indicate a strong response, and which exhibit little-to-no response for a compound(s). Through a bioinformatics pipeline, researchers can associate responses or insensitivities to different biomarkers, ultimately yielding a powerful correlation of biomarkers and pharmacological response.

However, the challenge to making this methodology practical, and perhaps an underlying culprit of Eroom's Law, lies in large part with the cost-prohibitive nature of compiling and characterising cell lines or patient-derived models at a scale necessary to appropriately represent the diversity of the cancer genome. An industry shift towards more collaborative efforts could make a significant impact here, mitigating economic barriers that are currently interfering with the reliability of preclinical development.

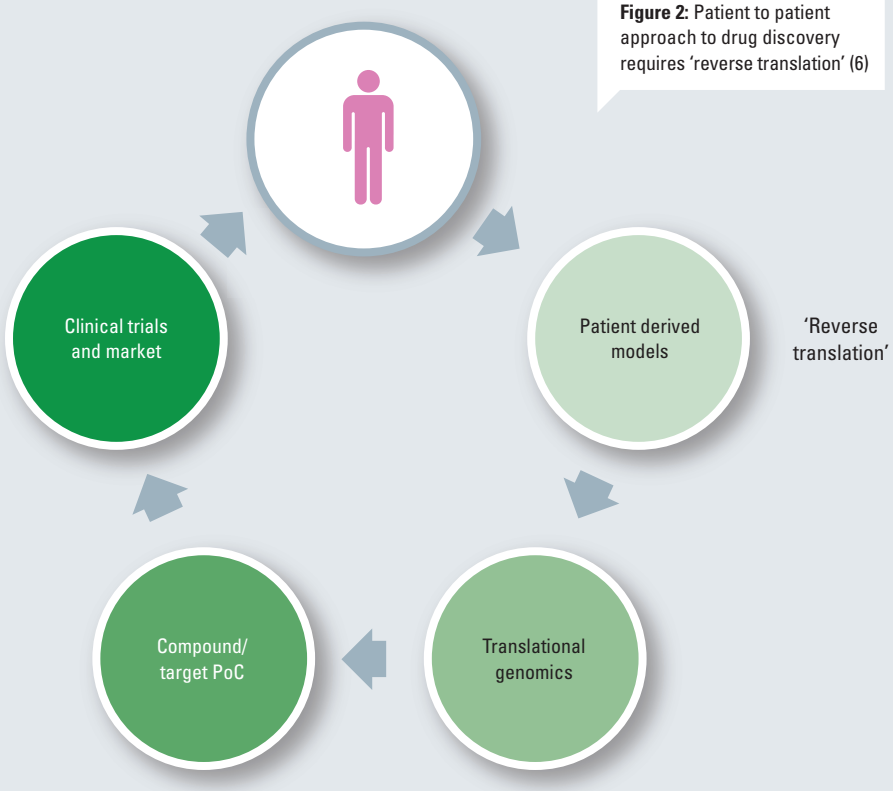


Figure 2: Patient to patient approach to drug discovery requires 'reverse translation' (6)

Sharing Data

To mitigate efficacy failures, overcome data volume obstacles and accelerate novel, efficacious genomic-related drug development we must share relevant preclinical data. While many reasons exist for the industry's diminishing returns, the enormous duplication of efforts in both academia and industry should be thoroughly examined as a way to improve the state of current oncology R&D. Unfortunately, there is no shortage of conditions that require treatment. As our research indicates, there is no panacea awaiting discovery, one which would be the answer to every patient, or every cancer. Genomics research shows us that all cancer patients are different and their disease states vary greatly, even within the same diagnosis.

With this almost limitless number of ways to address cancer, sharing preclinical data and experimental platforms presents tremendous opportunities to advance oncology discovery industry-wide. Open sharing of preclinical oncology discovery data, implemented through a network of institutes working symbiotically to address a wide range of cell lines and primary models and their associated biomarkers, targets, causes and vulnerabilities, could greatly facilitate the quest for novel cancer therapeutics. This alliance would provide the ability to compile thousands of models, characterised in-depth, for the cancer genome and related biomarkers. This information could be generated on uniform platforms and data-based for widespread industry use.

In genomic-powered oncology drug discovery, our entire scientific strategy has benefited significantly from massive public cancer genome mapping efforts. One can appreciate how the scientific engine empowered by institutes coming together to produce granular and practical insights can inspire us to consider other areas where the industry can share information,

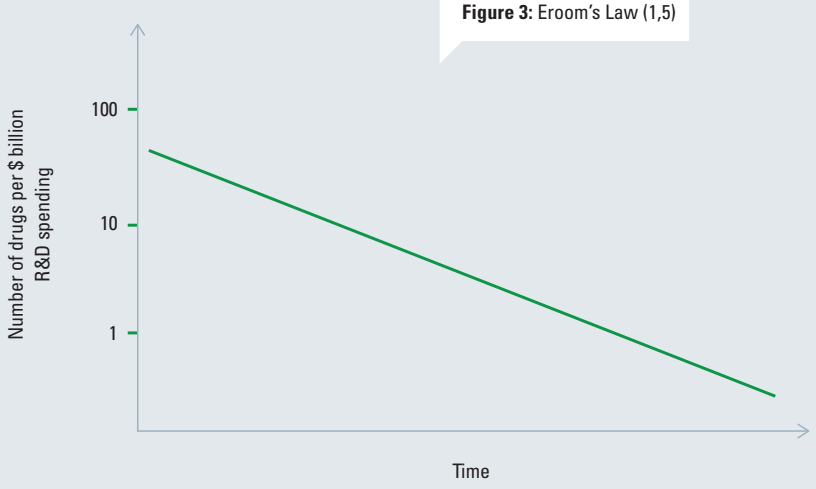


Figure 3: Eroom's Law (1,5)

and enable us to increase efficiency and accelerate discovery, in the hope of generating new medicines for patients with limited treatment options. Sharing preclinical models, including their genomic and biomarker profiles, is a natural extension of the TCGA and ICGC efforts and would be transformative for the drug discovery and development industry.

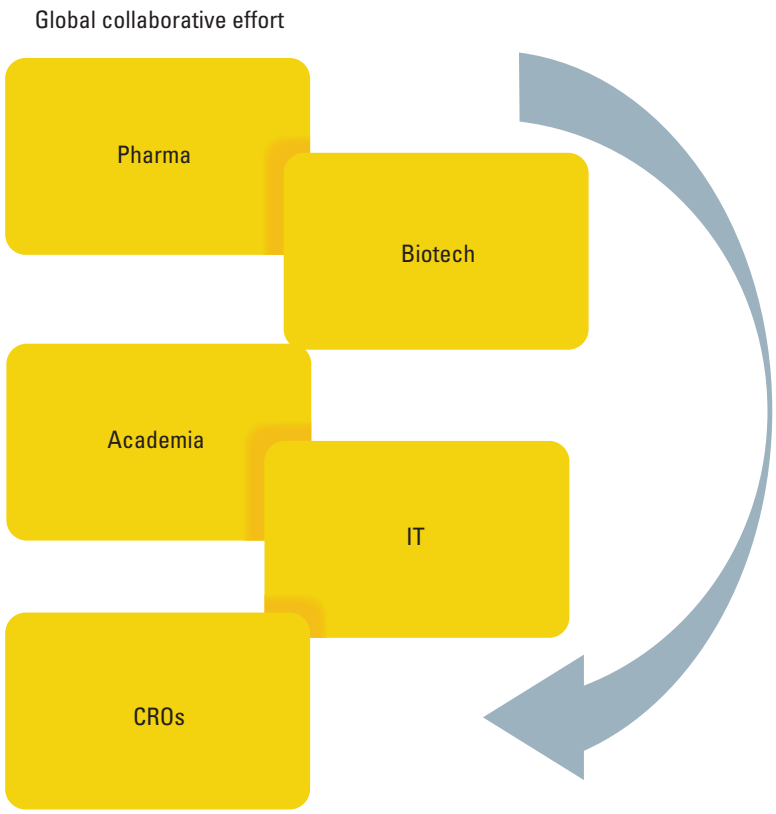
The diversity of the genetic basis of human cancer has left us with a monumental task; our greatest opportunity for success lies in acting collaboratively. With the volume of data and resource power required to analyse preclinical data effectively, sharing data facilitates a competitive advantage: the industry starting point will have less overlap, and will produce more insight on which to enable innovation. In addition, the data stemming from open collaborations at the preclinical stage is highly generalised and open to further proprietary development along the discovery process. Critically, in a budget-constrained environment, companies would save significant time, money and other resources early in the process by avoiding redundancy and leveraging basic industry tenets.

Although there are significant advantages, this type of cooperative network does not yet exist in the drug discovery industry. Facilitating this endeavour is not feasible for one company alone. Shifting our industry mindset to accept open collaborations, particularly in the preclinical stage, would be a major step towards improving clinical outcomes.

Conclusion

Biomarkers and their relationships to targeted therapeutics form the foundation for cancer genomics to deliver on the potential of truly personalised medicine. When early research data relevant to these concepts is openly shared across the industry, it creates an ecosystem by which companies can efficiently move their scientific programmes forward, increasing the industry's capacity to deliver personalised medicines to patients who today have limited treatment options. This transformation would give patients and the therapies the best opportunity for the most efficacious outcomes.

Figure 4: Open access collaboration (6)



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About the author

Markus Warmuth is President and CEO of H3 Biomedicine, a uniquely structured privately held oncology drug discovery enterprise based in Massachusetts. Prior to joining H3, he was Site Head of Oncology Drug Discovery for the Novartis Institute for Biomedical Research. Markus received his PhD in Medicine from the Ludwig-Maximilians University of Munich, Germany. He has also held positions with Clinical Cooperation Group Signalling at the German National Research Center of Environment and Health and the Genomics Institute of the Novartis Research Foundation in San Diego.