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Omics: Informed drug and biomarker discovery

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Abstract
OMICS encompasses several disciplines in which high- dimensional data are generated from molecules such as DNAs (genomics), RNAs (transcriptomics), proteins as DNAs (genomics), RNAs (proteomics), or metabolites (metabolomics). In recent years, the use of high-throughput omics technologies has led to the rapid discovery of many candidate biomarkers. However, very few tumor biomarker tests have passed the high bars for routine clinical application. Due to uncertainty in growth curves of pharmaceutical industry in spite of significant increases in investment and technological knowhow, gaps are ascertained in the future drug markets due to dwindling discovery pipelines and increasing regulatory control. The cumulative duration of discovery from concept to commercialization is unacceptably lengthy, and adds to the deepening crisis. Existing animal models predicting clinical translations are simplistic, highly reductionist and, therefore, not always fit for purpose. Thus, the coming of age of Omics-based applications makes available a formidable technological resource to further expand our knowledge of the complexities of human disease. The standardization, analysis and comprehensive collation of the "data-heavy" outputs of these sciences are indeed challenging. A renewed focus on increasing reproducibility by understanding inherent biological, methodological, technical and analytical variables is crucial if reliable and useful inferences with potential for translation are to be achieved. Herein, we discuss the potential implications of recent Omics-based advances for the drug development process. This review focuses on omics based study in drug discovery process.

Keywords: drug discovery; omics; genomics; proteomics; metabolomics

Introduction
Omic technologies which are also referred as high-dimensional biology are used for the detection of genes (genomics), mRNA (transcriptomics), proteins (proteomics) and metabolites (metabolomics) in specific biological samples in non-targeted and non-biased manner. These are also referred as high-dimensional biology and the integration of these techniques is called systems biology. The basic aspect of these approaches is that a complex system can be understood more thoroughly if considered as a whole. Systems biology and omics experiments differ from traditional studies where systems biology experiments are hypothesis-generating, using holistic approaches where no hypothesis is known or prescribed but all data are acquired and analyzed to define a hypothesis that can be further tested. The individual Omics disciplines i.e. genomics, transcriptomics, proteomics and metabolomics have the singular advantage of being complimentary for cross validation, and together could potentially enable a much-needed systems biology perspective of the perturbations underlying disease processes. If current adverse trends are to be reversed, it is imperative that a shift in the R & D focus from speed to quality is achieved.

Methods
The review contains published articles and grey literature within the last ten years (2008-2017) on studies and reviews highlighting importance of omics for drug discovery and pharmacological screening of drugs. The present review have included published articles as well as grey literature from online resources: PUBMED, PLOS ONE, Google Scholar, Science Direct, Shodhganga and Institutional repositories.
Inclusion Criteria: The literature included reviews and original articles on omics which were published /dated within last ten years. Literature included following keywords in single or in combination of the following keywords drug discovery; omics; genomics; proteomics; metabolomics.

Drug Development Pathways

The drug development pathway for a small molecule entails an exhaustive process which includes basic research, target identification and validation, lead generation and optimization, pre-clinical testing, phased-clinical trials in humans and regulatory approval by the FDA. The process of drug development begins with the identification of a novel target (protein, DNA, RNA, metabolite, etc.) followed by its subsequent validation to confirm a therapeutic effect. This involves assay development or optimization (biochemical, cell-based, cytotoxicity, etc.), whereby an objective methodology is derived to capture the intended interaction between a library of compounds and the specific target. Confirmed "hits" from high-throughput screens are then organised by chemical type to identify "leads" or chemical scaffolds which could be further refined by medicinal chemistry informed by structure-activity relationships (SAR), to optimize physicochemical and pharmacological properties for enhanced potency and selectivity.

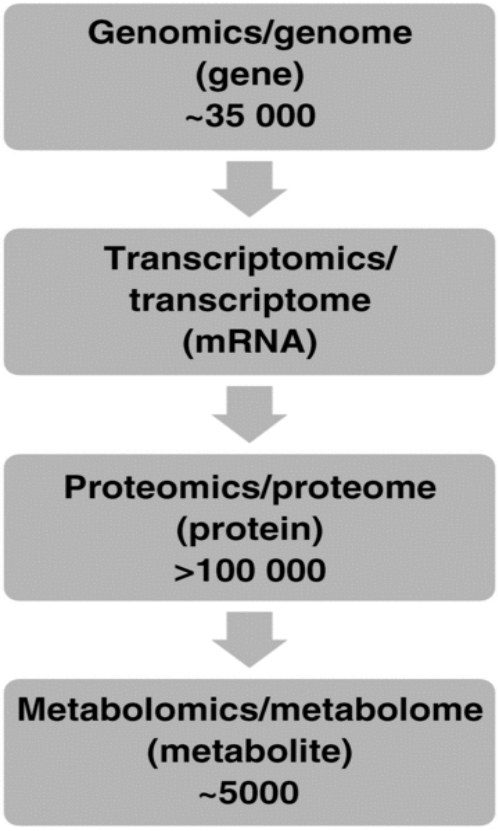


Fig 1: 'Omic' technologies: genomics, transcriptomics, proteomics and metabolomics

[Ref: The Obstetrician & Gynaecologist, Vol 13 (3) pages 189-195, 18 Jul 2011]

Preliminary lead generation and optimization is entirely an *in vitro* process, whereby selected leads are then progressed through a series of complex surrogate assays to evaluate efficacious bio-pharmacological traits, class/compound-specific toxicological properties and favourable absorption, distribution, metabolism, and excretion (ADME) properties. It is in these early stages of testing that most compounds fail. Further lead validation is through efficacy, ADME and toxicology testing in animal models. A drawback of this *in vivo* process is that the current short-term testing protocol employed primarily defines the toxicological profile rather than therapeutic efficacy. During this stage of the development process, scale-up methodologies for the use of the selected lead in clinical trials are tested. The clinical trial process itself can commence only after FDA approval of an Investigational New Drug (IND) application which details pre-clinical results, proposed mode of drug action, potential side effects and manufacturing information. The Phased clinical trials (I, II and III) are overseen by a clinical research team in close communication with the FDA, with Phase I focussing on drug safety, Phase II on effectively, and Phase III on confirming the findings on a larger population cohort. A successful outcome in the clinical trials will lead to the submission of a New Drug Application for further scrutiny and approval by the FDA and other regulatory bodies.

Challenges to drug discovery

The most important step in the drug discovery process is the identification of a lead molecule which potently modulates the chosen target to produce a desirable pharmacological outcome which translates predictably to the human host. The success of this process is reliant on two factors: firstly, access to robust, scientific literature permitting the acquisition of available knowledge on the biological processes underlying health and disease; secondly, the availability of appropriate pre-clinical tests and model systems that permit the verification of safe, efficacious and translatable pharmacokinetic and pharmacodynamic (PK/PD) relationships. Although animal models have indeed proved predictive in many instances, inadequate testing for congruence with human disease has led to costly translational failures, and remains a deficit in the pre-clinical developmental phase. The extensive study by Seok *et al.*, (2013) [10] exemplifies this challenge in their report on the failure of mouse models in human inflammatory disease.

Models that can accurately mimic human disease and reliably characterize the longitudinal behaviour of clinical endpoints are urgently needed to minimize attrition and associated risk in the next phase of clinical development. Appropriate biomarkers which represent these endpoints and which enable better clinical phenotyping as well as patient stratification will be useful tools to validate pre-clinical assumptions more predictably. Patient heterogeneity is a crucial factor contributing to failure at the clinical trial phase. Omics technolology can potentially offer new ways to stratify patients and enable the clustering of more homogeneous cohorts. This clearly must go beyond merely the simplistic identification of a gene polymorphism in association with a disease trait, and entail rather a more complex mapping of the wider association between genotype and associated phenotypes.

Recent times have witnessed a relentless focus on improving speed and efficacy of the drug development processes (e.g., first to market) in the hope of attaining fast financial returns. The reality, however, is a sharp decline in productivity with failure to recover returns on investment. Such initiatives, while important, have taken the focus off the quality of science, a critical starting point of the process. The driving impetus towards profitability and early returns has resulted in an over-reliance on high-throughput technical advances, before such technologies were allowed a maturation phase. The long-term returns and sustainability of the industry are more likely to be secured through initiatives focusing on the quality of the science underpinning the process, rather than on merely the speed and efficiency of the process. Earlier (Pre-IND) engagement with regulatory bodies may significantly reduce the delays that occur at this stage of the process by enabling better communication and clarity on the process.

Justifiably, the industry has attempted to put in place wider measures to curb or cope with the spiraling declines in R&D productivity. In the last decade there has been a significant increase in the outsourcing of drug discovery activities to low-cost locations like India and China where rapid expansion have occurred in the investment on academic and government-funded research sectors to maximize opportunities, particularly for diseases relevant to each country. There is a significant likelihood that viable leads are disregarded very early in the process, purely on the basis of thresholds dictated by systems that are far from optimal in terms of fit for purpose.

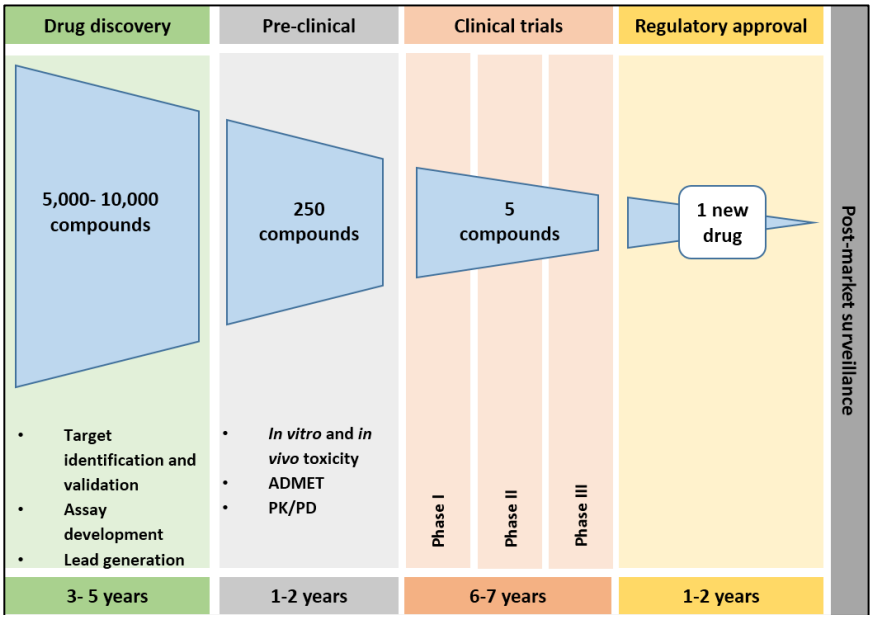


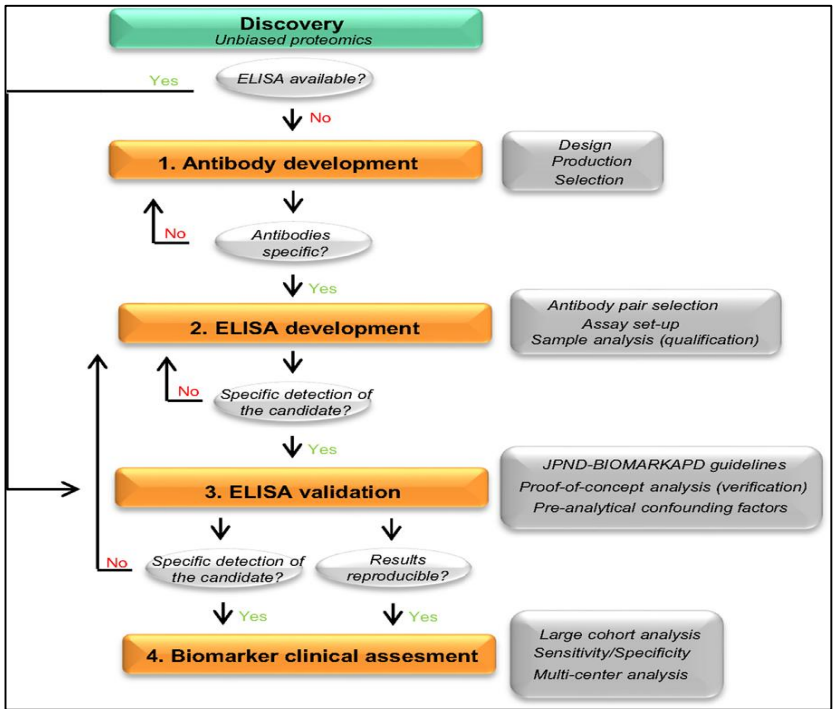
Fig 2: Drug discovery and development timeline.
[Adapted from http://cmidd.northwestern.edu/files/2015/10/Drug_RD_Brochure-12e7vs6.pdf; http://www.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf]

Biomarker development

The process of biomarker development comprises four main steps: discovery, analytical validation, evaluation of clinical utility, and clinical use.

Discovery

In the discovery phase, the analysis of biospecimens leads to candidate biomarkers. Biospecimens may derive from cell lines, animal models, biopsies from existing cohorts, samples from patients enrolled in ongoing clinical trials, or archived samples from finished prospective studies or biobanks. Besides the identification of candidate biomarkers, this step may provide potential therapeutic tar- gets and knowledge on the molecular mechanisms by which candidate biomarkers contribute to the pathological state.



[Reference: www.frontiersin.org]

Fig 3: The biomarker development process.

Ideally, specimens must be collected from large prospective case-control studies involving a clearly defined set of patients in a specific clinical context and as complete as possible information on the clinical characteristics, inter- ventions and outcomes involved. Since it is not always possible to have such ideal conditions, which may also be costly and take a long time to achieve, many studies make use of archived specimens or biological models. At any rate, it is crucial to carefully define the inclusion criteria since poorly defined groups or heterogeneous samples may result in the development of signatures without therapeutic value. In this regard, it is worth mentioning that one of the main reasons why basic preclinical studies do not progress towards clinical applicability is that the samples used for biomarker discovery do not reflect the patient population in which those biomarkers are expected to be used. Another potential pitfall is sample heterogeneity that may result from deficiencies in the study design, such as non-matched confounding factors. Also, included in this category are poorly defined variables, such as the biospecimen source, the research question itself, target population, inclusion and exclusion criteria, and the endpoint of the study.

Sample handling is also an important aspect to be considered in studies aimed at biomarker discovery. It is necessary to follow standardized protocols during sample collection, storage, and processing, as well as to use validated and well calibrated analytical methods to achieve robust and reproducible analyses. A crucial aspect during the discovery phase is the confirmation of the findings using an independent sample set. As stated before, the high throughput nature of the omics technologies is particularly well suited for biomarker discovery since it allows a detailed molecular characterization of biospecimens. However, poor reproducibility and the high number of false positives makes it necessary to undertake both analytical and clinical validation so as to confirm or reject the suitability of a candidate biomarker in diagnosing or predicting the disease of interest.

Analytical validation

Once promising biomarkers have been identified, it is necessary to assess their usefulness with the sort of tools normally available to a clinical laboratory, such as FISH, RT-PCR, PCR, HPLC or some immunoaffinity based assay. Analytical validation of these tests must include dynamic range detection and reproducibility. If some of the complex omics technologies are to be used for routine clinical analysis, their technical reproducibility issues should also be addressed. The development of a combination of several types of molecules, as multilevel biomarkers, is an attractive option since the pathological state is determined by the complex interplay of various types of molecules, such as DNA, proteins, RNA and metabolites. However, analytical validation and determination of the statistical significance of such combinations require a higher number of studies than those necessary to develop a single-molecule biomarker. Currently, algorithms that integrate DNA methylation, copy number aberrations, point mutations and transcript levels in a multimodal signature are being developed, although there are some concerns about the size of the biopsy required to perform all the studies.

Evaluation of clinical utility

The confirmation of the ability of a candidate biomarker to diagnose or predict the clinical outcome can be done in prospective clinical trials in which the biomarker may direct patient management, in prospective/retrospective studies analyzing archived specimens, or using samples from a biobank. At this stage, the studies aimed at prognostic biomarker evaluation may not necessarily influence clinical decision making. However, to increase the clinical utility of these studies, it has been recommended that the studies in which a companion therapeutic agent is evaluated, omics-based biomarkers should also be included.

Clinical use

After the clinical usefulness has been demonstrated, the biomarker test must get regulatory approval, be commercialized, and incorporated into clinical practice guidelines.

Concluding remarks

The advent of the omics technologies has boosted the ability to characterize biospecimens at the molecular level. In the years to come, high-throughput analyses are expected to co-evolve with biomarker based precision medicine leading to better patient care. The complexity of the pathological state poses enormous challenges, and the various omics technologies still have technical issues like reproducibility and a high false positive rate. However, the joint effort of clinicians, researchers, bioinformaticians, and biostatisticians, in academia and industry will certainly make progress towards the development of sensitive and specific predictive, prognostic and diagnostic biomarkers.

The high-throughput nature of the omics technologies is enabling the fast discovery of candidate biomarkers with the results being described in a large number of preclinical reports. Much slower and time-consuming, large prospective well-designed studies will be essential for clinical validation. Arguably, the paradigm shift from a traditional “hypothesis-driven” research environment to one that is primarily “discovery-based” will fail to sit comfortably with many researchers. The integrative analysis of the large data sets churned out continues to prove a challenge, with advances in analytical methodology failing to keep abreast of technical advances. Nevertheless, for the first time ever, an integrated approach to modeling and defining the immense complexities of health and disease is emerging. Its implications are likely to transcend far beyond improving our mechanistic understanding of health and disease or drug and biomarker discovery. We are already seeing the heralding of the arrival of personalized medicine and a paradigm shift in the focus from disease to health. Clearly, the ultimate realization of such revolutionary visions and concepts will predictably entail many obstacles and hurdles from experimental, technical, analytical and financial viewpoints. The key to future drug discovery will reside in our ability to harness the powerful new technologies already at our disposal to integrate information from sequenced genomes, functional genomics, protein profiling, metabolomics and bioinformatics, in a manner that ensures a comprehensive systems-based analysis to further our understanding of the complexities of health and disease.

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