 Cytometry Part A 69A:117–118 (2005)

Cytomics and Drug Discovery

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Received 10 March 2005; Revision Received 28 March 2005; Accepted 30 March 2005

Pharmaceutical companies try to develop new drugs that have a high success rate of reaching the market. However, current disease models lack a strong correlation to clinical reality, because of the underestimation of the complexity and variability of clinical disease processes. This leads to high attrition rates late in drug development and soaring costs. Improvement of disease models is an important issue to reduce the high attrition rates in drug development. Using cell-based disease models, which should take into account the molecular diversity of the human cytome, will improve the predictive value of drug discovery.

Key terms: drug discovery; disease models; cytomics; human cytome; molecular cell phenotype

Pharmaceutical and biotech companies try to develop new drugs that have a high chance of reaching the market and are able to fund their research. The current disease models used in drug discovery and preclinical development fail to predict failure in drug development (clinical phase I to III and IV) in 80–90% of all drugs entering clinical trials.

To improve their overall efficiency and profitability, companies try to bring down the high attrition rates of drug development. Improving disease models is an important issue to improve success rates in drug discovery and development. The cost to develop a single drug that reaches the market has increased tremendously in recent years.

It takes about 10 to 15 years and between US$ 500–800 million to bring a new drug to the market (1). In addition, only 3 out of 10 drugs generate enough profit to pay for the investment (2). This is mainly due to the high costs, low efficiency, and high attrition rate of the drug discovery and development process as a whole.

Coming out of drug discovery and preclinical development, drugs enter three phases of clinical trials, before they can be submitted for approval. Of all drugs that enter clinical trials, 38% fail to pass phase I. In phase II about 60% of the remaining drugs fail. In the final and most expensive stage, phase III, another 40% of the remaining candidates fail. Of those drugs that make it to be submitted to the FDA, 23% fail to be approved. This translates in a 10% overall success rate of drug molecules entering clinical trials (3). These attrition rates are much too high in the later stages of clinical development. Basically the currently used disease models show a correlation deficit to clinical reality, because of the underestimation of the complexity and variability of clinical disease processes in man (4).

FROM THE HUMAN GENOME TO THE CYTOME

The genome defines the genetic potential of an organism, but not entirely the spatial and temporal dynamics of cellular machinery in its response to environmental changes. From the genes to the entire cellular diversity (cytome) of an organism, multiple pathways build webs of complex molecular interactions. Predicting cellular dynamics from the genome upwards does not take into account influences and interaction from outside the genome itself.

Cytomes can be defined as cellular systems and the subsystems and functional components of the body. Cytomics is the study of the heterogeneity of cytomes, or more precisely, the study of molecular single cell phenotypes resulting from genotype and exposure in combination with exhaustive bioinformatics knowledge extraction (5). The regulation of cellular function in different cell types is a highly dynamic, spatially and temporally differentiated process.

Different cell types use regulatory mechanisms at multiple levels to adapt the common genetic blueprint of an organism to their own changing environment. A dynamic usage of its genetic potential allows a cell to perform short-term process regulation. The cellular proteins (proteome) evolve in a highly dynamic spatial and temporal environment (6). To understand the spatial (3D) and temporal (t) complexity in this 4D environment we need to

Part of this work was presented at the 10th Leipziger Workshop "Systems Biology and Clinical Cytomics," April 7–9, 2005, Leipzig, Germany.
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Published online 14 February 2006 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/cyto.a.20236

study a multithreaded, multidimensional and multiscale web of events.

THE CYTOME AND DRUG DISCOVERY

A disease and a drug interfere with multiple cellular function(s) and the impact on the cell differs depending on the cell type and its functional status (e.g. *differentiation,* cell cycle, diurnal oscillations). In recent years, cells have become increasingly studied as an instrument to treat complex diseases as in gene therapy and stem cells research. We need to improve our understanding of the dynamics of cellular *behavior* in order to improve our chances for success (7).

Screening of functional targets in drug discovery requires the appropriate intracellular environment to be present. The proper function of an intracellular protein depends on its processing and environment. Because of the heterogeneity of cell types and structural and functional differences between cells (e.g. hepatocytes, neural cell types, etc.) in a healthy and disease state, we need to take structural and functional heterogeneity into account (8). The primary cell type matters when studying disease processes as different cell types express different structures and functions in space and time. The phenotypic background in which a protein is expressed has to be taken into account when we want to study its function during drug discovery (9,10).

New developments in image-based and flow-based cytometry enable us to study cellular processes in great detail, so we can extract a multitude of structural and functional information from cells (11,12). Laser scanning (LSM) and wide-field microscopes (WFM) allow for studying molecular localization and dynamics in cells and tissues (13). Activity profiles of drugs can be studied in great detail by quantitative digital microscopy (14). In recent years, we have witnessed the development of large scale quantitative cellular research as in High Content Screening (15). Assembling a database of cellular processes by establishing a Human Cytome Project (HCP) would help us to improve our understanding of disease processes and their spatial and temporal dynamics at the cellular level (16,17). This would create a broad platform from which we could improve our basic understanding of cellular disease processes for drug discovery and development.

CONCLUDING REMARKS

To improve drug discovery and development, we should work towards a better quantitative understanding of the dynamics of cellular processes in multiple (primary) cell types. Using cell based disease models, which take into account the spatial and temporal molecular diversity of the human cytome, could help us to improve the predictive power of drug discovery. Improving our disease models by extracting more content from multiple (primary) cell types would allow us to bring down the attrition rates in drug development. Nature does not adapt or simplify itself to the level of our disease models, but we have to adapt our models to the complexity of nature.

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