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Chemical Genetics and Chemical Genomics: High Throughput Profiling of Drugs, Therapeutic Genes and Disease Networks

Tae Kook Kim

Korea Advanced Institute of Science and Technology, Dept. of Biological Sciences, Lab. of Chemical Genomics and Medicinal Bio-Systemics; Harvard Medical School, Institute of Chemistry and Cell Biology-Initiative for Chemical Genomics, Dept. of Biological Chemistry and Molecular Pharmacology, Harvard Cancer Center

With advances in determining the entire DNA sequence of the human genome, it is now critical to systematically identify the function of a number of genes in the human genome. These biological problems, especially those in human diseases including cancer, should be addressed in human cells in which genetic approaches have been extremely difficult to implement. To overcome this, my efforts have focused on the development of a novel "chemical genetic/genomic approach" that uses small molecules to "probe and identify" the function of genes in specific biological process or pathway in human cells. Due to the close relationship of small molecules with drugs, these systematic and integrative studies will lead to the "medicinal bio-systemic approach" which is critical to "formulate and modulate" complex biological (especially disease) networks by small molecules (drugs) in human bio-systems.

"What is the best way to study complex biological networks in human cells (bio-systems)?" Biochemistry and genetics are both powerful approaches, but ideally we would like to study protein function in human cells under physiologically relevant contexts (i.e. their own cellular and molecular environments); many complex biological questions about development and disease (especially cancer) are best addressed in human cells. I have become acutely aware of the problems of conventional techniques as I gain more experience in working on human cells. I therefore became interested in the development of a novel chemical genetic/genomic approach that substitutes small molecules for genetic mutations, and uses these chemical tools to probe the function of specific pathways/processes in human cells (bio-systems).

This approach that has evolved at Harvard ICCB-ICG (Institute of Chemistry and Cell Biology-Initiative for Chemical Genomics) involves: (1) identifying small molecules that affect specific cellular pathways with unbiased phenotype-based screens; (2) characterizing their action mechanisms and identifying the proteins whose activity is affected by these chemical ligands; and (3) studying the biological consequences of inhibition or activation of the target protein using the

small molecules as a tool. These procedures yield information that is similar to what could be learned from cloning a mutant gene from a genetic screen and using a conditional allele to study the function of the protein that it encodes in the genetic approach. This chemical genetic approach has been extensively complemented by functional genomic approaches, which will provide the relevant and creative directions for efficient discovery of bio-active small molecules (drugs) and genes (therapeutic disease genes) in the chemical genomic approach.

These novel idea and unique approaches to solve complex human biological problems have been substantially supported and validated by pioneering chemical genetic/genomic studies at Harvard ICCB-ICG during the last 4-5 years. I as a founding faculty member of Harvard ICCB-ICG have: (1) performed a number of proof-of-concept experiments (e.g. specificity of small molecules) to validate a novel chemical genetic/genomic approach; (2) started to develop core chemical genetic/genomic technologies (e.g. autoscopic imaging); and (3) started to apply these approaches to the identification of small molecules and their target proteins that affect a chosen biological pathway in human cells. With validation of scientific platforms for chemical genetics/genomics, I would like to now focus on the development of highly integrative technological platforms for systematic chemical genomics in human disease networks. These will lead to the "medicinal bio-systemics" which is critical to identify and catalog therapeutic genes (i.e. targets of therapeutic small molecules) for specific disease pathways and networks, and to formulate disease networks and database in human bio-systems using systems biology. Ultimately, the goal of the projects is to control complex biological (especially disease) networks through the development of novel therapeutics. Importance of chemical genomics and medicinal bio-systemics has been highligted to perform basic and clinical research for drug discovery and development.

1. Convenience & real-time kinetic studies Cell permeable drugs are immediately applicale to most systems, including those where genetic approaches are difficult such as primary human cells. Once they are generally available, drugs can be used to rapidly assess the possible involvement of a protein in a biological process, without the time investment required for construction of genetic vectors. In addition, a cell permeable drug can affect a cell whthin seconds of addition, and its effect can be rapidly reversed by washing out. The only genetic approach with comparable kinetics is temperature sensitive (ts) mutations. Good ts mutations are extermely difficult to find in human cell systems, and temperature change produces physiological effects of its own. The kinetic advantage of drug-based approaches to pertubing protein function is especially important for mechanistic analysis of highly dynamic human systems.

2. Impact on human biology (1) Mouse system has been frequently used as a model

system of human. However, information from mice can be limited because of species-specificity. Thus, many complex questions about development & disease are best addressed in human cells, using chemical genomics. (2) Many complex pathways in human development & disease is specific to different molecular conetxts. For example, genetic manupulation of all involved genes in different cell types is impractical to analyze those functions. Small molecules can be used as unique tools to systematically analyze these processes in different cellular & molecular context. (3) Certain proteins in biological processes turned out to be essential for survival of cells. Small molecules can be used to study the function of essential proteins involved in these processes through conditional modulation; which is difficult with traditional genetic approaches.

3. Impact on therapeutics (1) Drugs discovered as tools for basic biologists could lead directly to therapeutics. For example, the inhibitor and activator of the tumor suppressor that my lab discovered is generating much interest in pharmaceutical companies as an anti-cancer lead. (2) Chemical genomic studies will provide the novel therapeutic targets in the pharmaceutical approach. For example, pharmaceutical approaches are typically biased toward finding compounds that interact with validated therapeutic targets: specific proteins with known functions. In contrast, the chemical genomic approach involves screening of small molecules that affect a particular pathway or phenotype, rather than a single protein. Thus, identification of targets of chemical modulators from these unbiased screens will lead to the discovery of novel regulatory proteins as novel therapeutic targets in the pharmaceutical approach. Indeed, one target protein identified from a modulatory small molecule of the tumor suppressor that my lab discovered is generating much interest in pharmaceutical companies as a novel anti-cancer therapeutic protein. (3) Several technological platforms in chemical genomics and medicinal bio-systemics will be incorporated into drug development processes in numerous pharmaceutical companies. For example, chemical genomic and medicinal bio-systemic approaches differ from conventional pharmaceutical approaches in many aspects including: (i) less steps in drug developments; (ii) more synergistic drug development processes; (iii) multiple drugs/therapeutic taregts profilings; (iv) functional assay/screening for efficient drug developments; (v) bottom-up/reversed drug development processes; and (vi) multi-dimensional drug/disease database. These "disruptive drug value chains" may contribute to reducing the high attrition rates of screened drug hits, which is the one of intrinsic big problems in the pharmaceutical approaches. Indeed, several core technologies developed at Harvard ICCB-ICG laid the foundation of several companies and alliance of companies in the United States.