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Meetings of the minds: maximizing drug discovery

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By facilitated discussion with a series of experts, each with their own opinion as to the most important mechanisms operating in the disease, we gained further insights into the pathophysiology and where new approaches might have the greatest impact

"There are no such things as applied sciences, only applications of science."
Louis Pasteur
French biologist & bacteriologist (1822-1895)

Translating academic science into new therapies that treat the unmet medical need is the holy grail of applied biomedical sciences. The lines between basic scientific discovery, traditionally associated with academia, and directed inquiry, traditionally associated with pharmaceutical and biotechnology companies, are becoming increasingly blurred as the discovery of new therapies becomes more complex. Thus, strong partnerships between academic science and companies discovering new therapies are of crucial importance to bringing new therapies to suffering patients.

Understanding the etiology and progression of disease is crucial to the development of potential new therapies. Defining the pathophysiology and gaining a mechanistic understanding of disease processes drives the discovery of new targets for intervention, and offers the opportunity for disease modification beyond palliative care. Clinician-scientists are often in the best position to study these effects, as they are close observers of patients. They understand the natural course of disease and can define the medical needs not addressed by current therapies (unmet medical need). They also have direct access to human tissues including biopsies, blood and other tissues removed for medical purposes. These tissues provide an opportunity to study disease directly; however, there are challenges to studying human tissue in isolation. For example, disease is heterogeneous and tissue is often limited so that the number of studies and readouts are often restricted, making it hard to recognize subtle changes. In addition, tissue samples are obtained at a single time point, therefore, the dynamic course of disease is often difficult to assess and comparisons must be made across heterogeneous states. Furthermore, many patients will already be receiving therapy at the time of sampling, so distinguishing between treatment-mediated effects and the disease course may cloud interpretation. Thus, studying human disease is crucial for understanding pathophysiology; however, directed clinical investigations are often difficult as a result of these limitations.

Studying disease in animal models represents one approach to overcoming the limitations of analyzing isolated human tissue. These approaches in combination offer the best opportunity to establish and validate hypotheses associated with disease mechanisms and assessment of potential interventions. Animal models rarely recapitulate all aspects of the human disease, but individual models can be effectively

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used to dissect molecular mechanisms and gain understanding as to how these mechanisms impact disease in the context of a whole organism. These models can also be used to demonstrate the efficacy of a potential therapy in the context of a whole animal and thereby gain confidence that moving into clinical trials is warranted.

Bringing great minds together

"To be conscious that you are ignorant is a great step to knowledge."
Benjamin Disraeli
British politician (1804-1881)

The future of drug discovery requires the close collaboration of experts that represent three important disciplines. Clinicians bring an understanding of the unmet medical need and, thus, need to collaborate with basic scientists with a background in molecular, cellular and in vivo processes to inform the development and validation of model systems. Interaction of these experts with drug discovery scientists is crucial for translating that knowledge into new therapies. Many different approaches to fostering these initiatives have been considered and applied including conferences with open discussion forums, journal articles and expert meetings.

At Boehringer Ingelheim Pharmaceuticals (BI), we have taken one approach to bring together academic, medical and drug discovery expertise, with the goal of fostering innovation and driving drug discovery towards new approaches, new targets and improved success as we move programs into clinical trials. Many pharmaceutical and biotechnology companies organize expert meetings to review their portfolio and lend credibility to their selected targets, as well as to get expert opinion on how to advance those programs and on their likelihood of success. We felt that we needed to bring together diverse expertise that would provide a different perspective and give us new areas to explore, rather than confidence in work that was already in progress. Thus, we conducted 'disease pathogenesis' experts meetings.

Disease pathogenesis experts meetings bring together five or six experts who are focused on a disease of interest but who have distinct, yet complementary, backgrounds. Experts include clinician-scientists who understand disease pathogenesis and current therapies, and who are often involved in the conduct of relevant clinical trials. In addition, we invited one or two academic scientists who have a clear understanding of the mechanisms operating in these diseases and how animal models and cellular systems can be used to study the contribution of emerging information. These meetings were conceived and conducted as a partnership between medical and research colleagues at BI.

A meeting in action

The first disease pathogenesis experts meeting focused on rheumatoid arthritis (RA). The experts invited were from diverse areas and included an expert on the role of B cells in autoimmune disease, one with expertise in bone biology, another studying the role of synovial changes in RA, and an expert in immune cell trafficking. BI scientists all had expertise in drug discovery, in addition to expertise in specific relevant areas of biology. The meeting was co-chaired by a clinical expert from BI together with a research counterpart from the Department of Immunology and Inflammation. Preparation for the meeting included an extensive review of the literature and preparation of a series of questions to facilitate a directed discussion. Experts were asked to deliver a seminar on the first day, providing an overview of their area of expertise and how it had impacted

the study or treatment of RA. Although we asked for, and appreciated, ideas for new targets, we facilitated the discussion with an interest to debate the relative merits of individual approaches from a mechanistic point of view on the BI side, and then let the experts comment from their unique disease perspective as to the potential impact of our proposed approaches. We asked for their specific ideas on where the unmet medical need was not yet being exploited by our competitors. As this was some time ago, anti-TNF therapies had already been accepted, whereas ongoing Rituxan studies were highlighting the importance of B cells in the pathogenesis of RA. Approaches to understanding or regulating B cells were debated alongside those that might offer direct beneficial effects on bone. Approaches to synovial cells offered the opportunity to target components of the disease beyond the traditional anti-inflammatory methods that are directed towards cytokines and immune cells. By having a facilitated discussion with a series of RA and mechanistic experts, each with their own opinion as to the most important mechanisms operating in the disease, we gained further insights into the pathophysiology of RA and where new approaches might have the greatest impact. The experts felt that this was a valuable strategy and helped bring together scientists to debate ideas that may facilitate future therapies to treat RA. This information led us to new approaches and biological screens to identify new targets.

Obviously, the evidence required to assess whether these expert meetings will result in efficacious new therapies will take longer to obtain. However, this process has impacted drug discovery at BI and, more importantly, promoted a dialogue between disciplines and a willingness to work collaboratively in the best interest of patients.

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