editorial

Alan P. Kozikowski

Allen B. Reitz

Filling the pipeline for neglected diseases: creation of a medicinal chemistry-centric international drug discovery institute [iDDi]

The pharmaceutical industry appears to be currently suffering from bipolar disorder. There has never been a better time to conduct biomedical research owing to new insight into the molecular basis of disease and greatly improved tools and processes available in drug discovery and development. However, the number of new molecular entities entering therapy per year has not increased over the past decade; therefore, the rate of expansion in the pharmaceutical industry that took place in the 1990s cannot be sustained.

Given this context, it is uplifting to consider that diseases that have traditionally been neglected, afflicting as much as one-sixth of the world's population, such as the helminth disorders, malaria and tuberculosis are now the focus of much more drug discovery research than ever before. A great deal of the increased funding in this area has come from the Bill and Melinda Gates Foundation. An excellent framework for this increased effort has been established as a scalable distributed network of research sites that, when taken together, provide all of the elements required for successful drug discovery including public private partnerships (PPPs) between government agencies, non-profit institutions, and industry. The Special Programme for Research and Training in Tropical Diseases (TDR) sponsored by the WHO, UNICEF, UNPD and the World Bank has established and championed this approach.

It is crucial that the drug discovery and development process for the neglected diseases apply modern methods of drug discovery including toxicology testing and critical review, in order to avoid costly mistakes and thus the squandering of limited resources. An important early discipline in the drug discovery process is Medicinal Chemistry (MC) that involves the chemical synthesis of compound libraries for biological testing, using computer-assisted and X-ray design strategies, and closely tracking early adsorption, distribution, metabolism and excretion (eAMDE) parameters, selectivity, and off-target toxic effects. MC often appears to be a black box in which an undefined level of pattern recognition and chemical intuition is required. Also, MC can be viewed as horribly inefficient, in that only 1 out of 8000–10,000 drug candidates prepared actually reaches the marketplace. Therefore, in a larger

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sense, the purpose of MC in drug discovery is only partly to prepare compounds for further characterization before acceptance into preclinical development. The full mission involves doing this in such a way that the compounds that are considered are those that have the greatest chance of success throughout the entire process leading to new medicines that can be prescribed to patients. In this sense, MC, when done properly, reduces the overall risk of failure as much as possible (derisking). The MC part of the discovery network for the neglected diseases is relatively underdeveloped, simply because earlier efforts focused on the production, distribution, and development of drugs available already or for new indications and screening of existing compound libraries. Also, MC is often challenging, difficult, and fraught with frustration and failure.

The newly formed International Drug Discovery Institute (www.i-ddi.org) has been established as a non-profit institute to augment MC in the public sector distributed research network for the neglected diseases in a dedicated, rapid-response manner. The iDDi is meant to tackle the MC problem and challenge directly. It has assembled a group of medicinal chemists with >500 years of medicinal chemistry knowledge, as well as a network of consultants willing to provide advice on drug design aimed at tuberculosis, malaria, dengue, helminth disorders, and related diseases. The iDDi seeks to collaborate with existing organizations in order to fill in the missing pieces of the scalable network that has already been established, and not to compete and lose momentum, enthusiasm, and resources. The iDDi is unique in being separate from any university and is entirely focused on the MC aspect of drug discovery with internal chemoinfomatic support while eADME analysis is largely outsourced. One of the benefits of a stand-alone non-profit model for the iDDi is that the technology transfer issues that often complicate interactions with universities and the private industry will be more standardized and hopefully easier to navigate. The potential collaborators for the iDDi include the TB Alliance, Medicines for Malaria Venture (MMV), Drugs for Neglected Diseases Initiative (DNDi), Swiss Tropical Institute, One World Health, and others. A stand-alone dedicated collaborator such as the iDDi for these testing and drug discovery laboratories is meant to improve the return on investment for the philanthropy that has been expended so far to fund them. Many of the key collaborators in the distributed neglected research endorse the iDDi concept because such a capability has the potential to respond more rapidly to shifting research priorities. Also, the iDDi can nurture and maintain an institutional memory of experience for these diseases, which can be lost in a distributed network that relies too heavily on one to two postdoctoral appointments each at distinct sites or contract research with groups that may lack a long-term or sustainable commitment to the area.

MC is a vibrant discipline that is done very differently today in industry than it was 10–20 years ago. Diversity in early library synthesis is often valued more than purity or structure confirmation, and there are many newer ways of thinking about compound library design that are improving research efficiency early on. The iDDi seeks to serve as a think-tank for MC as a discipline, using the neglected diseases as a rallying focus in order to minimize the secrecy that often shrouds the field. One of the key priorities for the iDDi is to provide subsidized training opportunities for medicinal chemists in developing countries, associated with an equipment-granting program if needed upon return to the home institution. In addition, the iDDi will provide typical postdoctoral research appointments and a visiting senior investigator and faculty visiting scholar program. Our goal is to create a state-of-the-art MC research capability in the public sector to discover new therapeutics to improve the public health, particularly for those who need it most throughout the world. The iDDi can respond to emerging needs on a real-time and rapid-response basis, without the need to wait for the next cycle of grant review or budget approval. The iDDi is meant to offer a sustainable research presence in which an institutional memory and expertise can develop, as surely there will be new challenges for the infectious and neglected diseases in the future, for no other reason than the drug resistance that emerges over time.

The iDDi is evaluating several different options to establish two sites, one in North America and one elsewhere. In this way, we seek to promote cross-training opportunities and insist on an international flavor to the research program right from the start. Currently, research showing promise for malaria (HDAC inhibitors) or tuberculosis screening are slated for the transfer to the iDDi. The intention of the iDDi is to become fully integrated into the TDR network of distributed research centers, rapidly supporting groups such as the MMV and DNDi. At full capacity, we anticipate 50–80 staff at each site with initial estimates of 10–15 by the end of 2008. These are ambitious goals, but required to address adequately the lack of dedicated MC support for the neglected diseases. Currently, 90% of medical funding is applied to only 10% of the world's population. Current estimates for the cost of discovering and developing one new drug are ca. $800 million. Even if this cost is much lower for new drugs in the area of the infectious, neglected diseases, the fact is that any successful effort is capital- and labor-intensive. The basic question is whether those who lack adequate medicine, simply because of where and when they were born, in which they played no role to select, deserve to have medicines discovered from the resource-intensive drug discovery research available to others. Those in the neglected disease area, including the generous donors and agencies that fund this work, say ''yes''. Most probably, research to discover new therapies for at least some of the neglected diseases will be as successful in the future as that for diseases, such as small pox and diphtheria, was in the past. The further question is how the larger human populations that result will live together peacefully in such a way that preserves life on earth for future generations of our and other species. The introduction into therapy of adequate medicine for the large numbers of people who suffer from the neglected diseases is fair and equitable and can be an example of how we can treat each other and the planet we live on in a better way than we have.

Alan P. Kozikowski
University of Illinois at Chicago, USA

Allen B. Reitz
International Drug Discovery Institute (iDDi), USA