Published in final edited form as:

Curr Opin Chem Biol. 2010 August ; 14(4): 437–439. doi:10.1016/j.cbpa.2010.06.178.

Critical challenges and emerging paradigms in drug discovery

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The drug discovery enterprise has for several years been going through a period in which the productivity of current approaches has been questioned. We have become much better at finding drug-like compounds that bind to and modulate a particular molecular target, but have been less successful in translating this capability into beneficial effects on complex diseases in diverse patient populations. The reviews in this issue address some of the underlying causes of this angst, for example: how to rationally anticipate how inhibitory activity will translate into pharmacological activity; whether to aim to inhibit one or multiple targets; how to combat the emergence of drug resistance; and how to harness the potential of protein engineering to develop biopharmaceuticals with novel activities.

Any attempt to capture a forward-looking perspective on the field of drug discovery is necessarily somewhat subjective, and cannot hope to be comprehensive. In putting together this special issue on 'Next Generation Therapeutics' we have addressed this challenge by assembling a diverse set of articles, contributed by leading scientists from both the academic and the industrial research communities. Some of these reviews address areas of rapid change or important emerging paradigms in drug discovery, while others highlight recent progress and future prospects in challenging areas such as neglected disease research and drug resistance that are certain to be the focus of intense effort in the coming years. In doing so we have included articles that address important issues in both small-molecule (synthetic organic) and biopharmaceutical (protein drug) research.

The development of drugs for neglected diseases that affect millions of people continues to be an important area of research. Paul O'Neill discusses an important area of antimalarial drug research, the inhibitors of the cytochrome *bc1* complex of the parasite's mitochondria. Atovaquone is an antimalarial drug that binds to this electron transfer complex. Resistance to atovaquone developed rapidly after it was introduced into the field. Thus, new analogs in this series are being developed which can hopefully be combined with other antimalarial agents in drug combinations that may suppress the onset of resistance.

Drugs to combat another parasitic disease, leishmaniasis, are also needed because of limitations of current drugs including toxicity and drug resistance. Karl Werbovets reviews many of the new compounds in development over the past few years as anti-leishmanial agents. Some of these agents are novel and some are novel formulations of existing drugs.

With their worldwide emergence, multi-drug resistant and extensively drug resistant strains of *Mycobacterium tuberculosis*, the causative agent of tuberculosis, are serious concerns. John Blanchard reviews the most promising drug candidates that are currently in late stage development. Also reviewed is information about the mechanism of action of these drug candidates.

In seeking to optimize the biological potency of drug candidates, drug discoverers traditionally focused on increasing the binding affinity between the inhibitor and its target. However, in recent years the idea has emerged that the kinetic lifetime of the inhibited complex might in some circumstances be a more predictive and relevant *in vitro* measure of activity. This change in thinking has begun to affect how compounds are assessed during the lead optimization process, and which compounds are chosen for advancement. Hau Lu and Peter Tonge review recent literature and current thinking on the importance of drug–target residence time in the discovery of current and future pharmaceuticals.

Many in the pharmaceutical industry have traditionally been wary of compounds that interact covalently with their target, a bias that is somewhat at odds with the large number of successful drugs that function by a covalent mechanism. Russell Petter and coauthors review recent examples of the development of covalent kinase inhibitors, the evidence supporting their efficacy and safety *in vivo*, and their potential applications against targets that have developed resistance mutations. They particularly focus on ‘targeted covalent inhibitors’ — i.e. inhibitors that are designed in a structure-based manner to covalently label a nucleophilic residue that is not directly involved in the target enzyme's catalytic function.

It has become apparent in recent years that a significant number of proteins exist in a native state that lacks stable secondary and tertiary structure. For these so-called intrinsically disordered (ID) proteins — which include important signaling molecules and other potential drug targets — folding into a compact, well-defined structure is coupled to binding to their natural ligand. The extent to which ID proteins can be targeted by small-molecule inhibitors has been an open question, however. The article by Steve Metallo reviews recent literature showing that it is possible to achieve potent, selective small-molecule inhibitors against ID protein targets, and discusses some of the issues involved in identifying and optimizing such compounds.

The accumulation of knowledge about intracellular signaling processes over many years has led to a sustained interest in signaling proteins as drug targets. An important challenge in this field is that the complex and often nonlinear functional interactions that characterize signaling networks make it difficult to predict the biological consequences of therapeutic intervention at a particular point. The field of pathway pharmacology has emerged to address how the activity of particular steps and processes relate to the overall function of the system in the context of dynamic signaling networks. Bart Hendricks reviews recent literature in this area, addressing methods to gather the complex, pathway-level datasets required to inform such work, and the model-based analysis and interpretation of the resulting data to generate useful insights for drug discovery.

Polypharmacology — that is, drugs that work by targeting multiple different proteins — has emerged as an important theme, especially in kinase drug discovery. For most drugs that display polypharmacology this aspect of their behavior was not a designed property, however, and in many cases the therapeutic benefit associated with inhibiting secondary targets became recognized only at an advanced stage of development or indeed after marketing. An important challenge for drug discovery is to develop rational approaches for determining when polypharmacology is likely to be beneficial in treating a disease, and for discovering drugs that possess the desired selectivity profiles. In this issue Phillip Hajduk reviews the current status of approaches to quantifying and interpreting pharmacological relationships between potential drug targets, and to exploiting the resulting information to achieve a compound that will achieve the desired polypharmacological activity profile.

Gene expression is regulated in part by the covalent modification of DNA itself and of the histone proteins that bind to DNA and organize its structure. These so-called ‘epigenetic’

modifications are believed to be important in a variety of disease states, and thus the enzymes that catalyze these processes have emerged as important drug targets. Robert Copeland and coauthors summarize the different classes of epigenetic enzymes that have potential as drug targets, and review recent advances in the development of therapeutic inhibitors against them.

An alternative approach to modulating cellular signaling and function is to target cell surface receptors themselves rather than intracellular signaling processes. A number of recombinant protein drugs have been developed that target specific members of the large class of cytokine and growth factor receptors, including both agonists and antagonists of receptor function. There has so far been little success in developing small-molecule drugs that target these receptors, however. Gideon Schreiber and Mark Walter review the current status of our ability to develop protein and small-molecule drugs that modulate cytokine receptor signaling, in the context of our rapidly evolving understanding of the molecular mechanism by which receptors are activated by their natural ligands.

Approaches to discovering and developing protein drugs have evolved dramatically since the early days of the biotechnology industry. Early biopharmaceuticals were typically recombinant forms of human proteins, such as insulin, growth hormone or interferons, that were cloned and expressed with minimal variation from the naturally occurring amino acid sequence, or alternatively were mouse monoclonal antibodies that were rendered less immunogenic by expression as chimeras with human IgG with or without additional 'humanization' through point mutations. Justin Caravella and Alexey Lugovskoy review the very different situation that exists for the development of the biopharmaceuticals of tomorrow, which will reflect a sophisticated and rapidly evolving understanding of how proteins can be engineered to improve their properties as drugs or to introduce new functions.

There are now multiple antibody-based drugs on the market, many for the treatment of cancer. Stephen Alley reviews the exciting area of antibody–drug conjugates in which a cytotoxic drug is covalently attached to an engineered antibody that binds a protein that is enriched on the surface of cancer cells. There are many issues with these protein–drug conjugates that are being addressed including pharmacokinetics, stability of the drug–antibody linker, and selective release inside cells. Careful studies with appropriate labeled reagents are starting to shed some light on the mechanism of action of these complex therapeutics.

Ronald Kluger reviews recent developments in artificial oxygen-carrying factors that may be useful in emergency care blood replacement. These agents are needed in situations where human blood is not available because of storage or supply limitations (e.g. in military field situations). Reviewed are approaches based on appropriately chemically modified natural hemoglobins including hemoglobin–polymer covalent conjugates.

The articles that are briefly summarized above collectively review a range of issues that we believe are likely to be important in shaping the next generation of therapeutic agents. We thank the contributing authors for their hard work and the high quality of their contributions, and hope you will find these reviews as enjoyable and informative to read as we have done.

Biographies

Adrian Whitty received a BSc in chemistry from King's College London and a PhD in organic chemistry from the University of Illinois at Chicago. After postdoctoral work at Brandeis University with William P. Jencks he joined Biogen (now Biogen Idec) where he worked for 14 years. He joined the Boston University Chemistry Department in 2008. His

research group studies protein–protein and protein–ligand recognition, with an emphasis on how binding energy from these intermolecular interactions can be utilized to achieve biological function or inhibition. This research is applied in two distinct areas: developing a quantitative, mechanistic understanding of the activation and signaling of growth factor receptors; and advancing our ability to discover drugs that inhibit protein–protein interactions.

Michael H Gelb received a BS degree in chemistry and biochemistry from UC Davis and a PhD in biochemistry from Yale. He joined the UW 1985 and became professor of Chemistry and adjunct professor in Biochemistry in 1995. Gelb's awards include an Alfred P Sloan Fellowship, ICI Pharmaceuticals Award for Excellence in Chemistry, Pfizer Award in Enzyme Chemistry, Medicines for Malaria Venture Project of the Year, and an NIH MERIT Award. Gelb's research is in the area of Medicinal Enzymology. His laboratory works in three areas: understanding lipid mediator production related to inflammation; development of antiparasite drugs; newborn screening for inborn errors of metabolism.