Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

ELSEVIER

Pharmaceutical biotechnology

Editorial overview

Brian Metcalf* and Rino Rappuoli†

Current Opinion in Biotechnology 2003, **14**:618–620

0958-1669/$ – see front matter
© 2003 Elsevier Ltd. All rights reserved.

DOI 10.1016/j.copbio.2003.10.008

Brian Metcalf

*Incyte Corporation Experimental Station, E336 Route 141 & Henry Clay Road Wilmington, DE 19880, USA
e-mail: bmetcalf@incyte.com

Brian Metcalf is currently Executive Vice President and Head, Drug Discovery at Incyte Corporation. Before joining Incyte in 2002, he was Chief Scientific Officer, Kosan Biosciences. He previously spent 17 years with SmithKline and French and later with SmithKline Beecham. At the time he left SB, he was Senior Vice President, Discovery Chemistry and Platform Technologies. Before joining SK&F he held research positions at Merrell Dow in Strasbourg, France and in Cincinnati, Ohio. His initial training was in chemistry with a PhD from the University of Western Australia and postdoctoral studies at University College London and at Stanford.

Rino Rappuoli

†Chiron Corporation, Via Fiorentina 1, 53100 Siena, Italy
e-mail: rino_rappuoli@chiron.it

The main theme of Rino Rappuoli's research has been bacterial pathogenesis. Understanding the molecular mechanisms by which pathogens cause disease was used as a means for the rational design of innovative tools to prevent infection. Research activities have centred on a variety of pathogens. He is co-founder of the field of cellular microbiology, a discipline that has merged cell biology and microbiology, and developed the first recombinant bacterial vaccine (against pertussis) and a conjugate vaccine against meningococcus C. Both products have been approved for human use. Currently, he is involved in the development of a vaccine against group B meningococcus using a genome-based approach, termed reverse vaccinology.

In a world facing an increase of antibiotic-resistant bacterial strains, the emergence of new viruses and viral strains, increased incidence of cancer and chronic diseases, and the threat of bioterrorism, there is a great need for new and safer remedies for disease diagnosis, prevention and cure. Fortunately, the incredible technological progress that started with recombinant DNA and which was recently boosted by the new field of genomics, provides a large variety of potential new solutions. In this section on pharmaceutical biotechnology, a series of reviews, linked by virtue of their analyses of the impact of various biotechnologies on drug discovery and diagnostics, provide an overview of how these new technologies might help us to overcome resistance to antibiotics, allow us to detect novel viruses, enable target validation in transgenic animals and promote the development of new approaches to drug delivery.

Barrett and Barrett present a cogent plea for increased support for new antibacterial research based on the frightening worldwide emergence of resistance to all classes of antibacterials. This dire situation is set against the scene of big pharma concurrently retreating from this field of drug discovery. Several philosophical points arise in the consideration of directions for new research. The sequencing of bacterial genomes offers an exciting intellectual landscape, as it is possible through scanning pertinent bacterial genomes to identify conserved genes that offer broad-spectrum targets. Using knockout studies, it is also possible to establish if targets are essential or not, and even to assign essentiality in an *in vivo* situation, as opposed to *in vitro*. Pragmatically, however, success so far has been limited. If these new genes are viable targets, why have they not been discovered as the target of novel antibacterials identified by whole-cell screening over many decades? Perhaps we need to learn how to manage these new classes of targets. Certainly, inhibitors or antagonists of these new targets can be discovered by screening against the expressed and isolated protein (or RNA) target, but often such hits do not exhibit antibacterial activity. In these cases, such compounds presumably do not enter, or are exported from, bacterial cells. The chemical effort to take a compound that does not enter bacterial cells and to convert it to one that does, while still retaining activity against the target, should not be underestimated. Therefore, there is a dilemma facing the research manager — success would bring 'sure thing' major payoffs, but the current issues and previous history make re-entering this field of drug discovery a high-risk endeavor. This is a terrible pity given the emerging nature of the crisis.

'Novel biologically active natural and unnatural products' by Myles describes advances in the 14-membered macrolide antibiotic field, where resistance issues have forced drug discovery scientists to manipulate the naturally occurring polyketides extensively so that a new class, the ketolides, has been discovered with increased potency against resistant strains.

Interestingly, genetic engineering of the biosynthetic machinery of erythromycin A production has recently allowed modification of the central polyketide scaffold, as distinct from previous efforts which manipulated the appending sugar residues. The review continues by looking at semisynthetic taxols, leading to orally absorbed analogs, and the epothilones, which have a taxol-like mechanism but have activity against some taxol-resistant tumors. A further class of microtubule stabilizers is represented by discodermolide, which, although having a similar mechanism of action to the taxols and epothilones, has been reported to be synergistic with taxol in some tumor cell lines. This article illustrates that production of these complex structures relies on a combination of fermentation and semisynthetic procedures. For some compounds such as discodermolide, the only practical source is total synthesis, it being too difficult to isolate enough material from the discodermia sponge species for *in vivo* studies. It appears that future advances in this field might be dependent on the availability of fermentation procedures to produce fragments of the final material, which can be modified by semisynthesis and then chemically linked. Current technology, which allows manipulation of polyketide gene clusters to make unnatural natural products, might prove an excellent approach, as appropriate fragments could be designed with subsequent synthetic studies and medicinal chemistry structure–activity relationships in mind.

Moving from antibacterials to antivirals, Molla and Kohlbrenner review the dramatic progress that has been made in the HIV field with approved drugs now available from four mechanistic classes. Such is the resistance emergence of HIV that combinations of three (or more) drugs are now being used to slow the onset of resistance. Nevertheless, in the short time it has taken from the discovery that HIV is causative for AIDS to the approval of these drugs, the availability of these drugs is a triumph for workers in the field. The rapid emergence of resistance, however, ensures that research must continue with new mechanisms of drug action, possibly involving the host cell. Not noted in the review, but newsworthy nevertheless, is the gesture of western pharmaceutical companies to make available at low, or no cost, treatment regimens to the developing countries.

It has proven more difficult to develop drugs against hepatitis C virus (HCV), however, because the inability to replicate this virus in culture has limited the screening of antiviral compounds. Recently, the availability of a cell screening assay has given a new boost to this field. Current discovery paradigms reflect those targets found successful for HIV — a protease and a polymerase. For HCV, however, screening against these targets has not been as successful as for HIV and therapy still relies on augmenting host defenses via interferon, which despite its limitations has proven to be the dominant medical treatment.

Although drugs against HIV are a continuing success story, and new approaches to HCV treatment are emerging, the review by Osterhaus and colleagues is a chilling reminder that new viral infections are constantly appearing, as evidenced by the severe acute respiratory syndrome (SARS) outbreak in the fall of 2002. Impressively, the virus was identified and its genome sequenced in a rare display of international cooperation. Notably, however, its natural reservoir is still not identified and hence the epidemic could re-emerge. This is really the theme of this review — that the natural reservoirs of a number of deadly viruses, such as SARS-associated coronavirus and Ebola, are yet to be identified, and of course antiviral therapy is not even on the horizon.

Hegde, White and Debouck review the interplay of transciptomics and proteomics. The key issues revolve around the conclusions one can draw from these different technologies and how one uses the conclusions. The authors point out that different conclusions will be reached using the two technologies, as mRNA levels cannot be consistently relied upon to predict protein abundance, mainly owing to mRNA splicing and/or post-translational modifications. Thus, using high-throughput transcriptional profiling technology is fraught with danger if the conclusions are used in target identification (i.e. the linkage of a specific gene to being causative for disease). By contrast, the multigenic signatures obtained from these analyses will be invaluable in diagnosis and in following a pharmacodynamic response in animal models or in the clinic.

While the relative merits of proteomics and transcriptomics technologies as they relate to target validation will continue to be explored and argued, there is no doubt as to the impact of transgenic animals, as they allow the direct effect of the absence (or overexpression) of a gene of interest to be studied. Critical here, but less well recognized, is that many of these knockout or knockin animal models will have no phenotype until challenged. Brodmerkel and Vaddi describe a number of situations where key mediators in models of human disease have been uncovered. These demonstrations set the scene for small-molecule drug discovery or antibody development.

In keeping with the general theme of all these reviews, that of the impact of biotechnology on drug discovery, the article by Pedraz and colleagues addresses the impact of biotechnology on drug delivery. The authors make the point that the financial impact of drug delivery systems is certainly impressive, although it is not clear exactly where that impact is (one suspects that smoking cessation treatments make an important contribution). As noted by the

authors, ''an adequate peptide and protein drug delivery system has not yet been attained'', although reference is made to advances in the oral delivery of insulin and the resultant control of fasted blood glucose levels. An enticing view of the future is the encapsulation of live cells that secrete protein agents such as ciliary neurotrophic factor, although currently these studies are still at the animal level.