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Increasing clarity in the definition of cellular physiobiochemical mechanisms and the inter-relationships with regulatory molecules has put forth an increasingly refined framework for viewing and understanding potential therapeutic targets. The ability to synthesize and deliver as drugs, endogenous or exogenous proteins or nucleic acids in their native or altered state has also evolved along with this knowledge. Tools developed for modeling of proteins have also greatly accelerated the development of small molecule ligands developed as nominally specific drugs. Technology advancements have expanded our therapeutic armamentarium from sera to recombinant proteins, to intact cells. These novel therapeutic arts clearly did not exist in the days of old, thus deserves a name, perhaps biologics.

However, the term 'biologics' has already been taken many years earlier, and has been a staple of the pharmacological, medical and legal lexicon since. The legal definition of biologics originally included biological therapeutic substances with more obvious rationale (blood products, tissues, cells, vaccines) as well as novel targeted agents, but excludes small-molecule targeted agents which should be included under 'biologics'. Explosive growth of therapies derived on the basis of macromolecular and molecular understanding of the specific disease pathology will likely render this a moot point, because such therapies will surely dominate in number as compared with other therapies included under this rubric.

The more narrow interpretation of biologics would not include small molecule drugs, but because of the widespread use of in-silico drug-design, an increasing number of drugs are actually products of the art of biologics; certainly ACE-inhibitors, calcium channel inhibitors, H2-antagonists, proton-pump inhibitors, statins, β-lactam inhibitors, thrombin-inhibitors, and cyclo-oxygenase inhibitors represent the vast majority of all prescribed drugs. Present day versions of these classes of drugs are clearly and rationally designed utilizing the art of biologics. Since the number of drugs without clearly defined rationale in the framework of physiobiochemical pathways and regulatory molecules appears to be shrinking, it appears that the art of biologics has already permeated pharmacotherapy.

We ascribe the broader definition of biologics as the art of preparing, testing, and therapeutically perfecting the methods of clinical use of molecules of any size or origin, or cells to specifically target (activate, inactivate, or regulate) critical physiobiochemical mechanisms in order to gain therapeutic advantage. Because these mechanisms are interwoven for many clinically distinct diseases, dissemination of information across disciplines of medicine is imperative for development of optimal application in improving comfort and perhaps, an interdisciplinary sparks of imagination that will lead to new healing applications for myriad diseases.

The inaugural issue of *Biologics: Targets and Therapy* provides a glimpse into the state of the art and present clinical applicability of biologics in the fields of perinatology, transplant immunology, rheumatology, dermatology, and oncology. The diverse targets range from anatomical lesions in the brain to cell-surface epitopes, to intracellular kinases reflect an increasingly wide range of rationally designed pharmacological agents that as a whole have had a tremendous impact on suffering from disease conditions previously refractory to therapy, as well as on the natural history of disease, and the socioeconomic health of healthcare systems. Common themes encountered in papers describing therapeutic endeavors with biologics are uncertainties regarding definitions of the disease and

response criteria, dose and timing or therapy, adverse effects due to immune/inflammatory system interactions or imprecise targeting, potential for devastating unanticipated adverse events, and for some agents, striking efficacy unparalleled by any other previously existing therapy.

RSV pneumonia is recognized as risk factor for perinatal hospitalization for pulmonary ailments, particularly in the premature or otherwise ill infants. Palivizumab, an anti-RSV-G protein antibody confers a reduction in the frequency of repeat hospitalization in high-risk infants, whereas when given in the setting of active RSV-pneumonia, no benefit is seen. There is much debate regarding Palivizumab prophylaxis because of varying definitions of high-risk, yearly variation in severity of RSV infections, and perhaps geographically isolated genetic susceptibility factors. Certainly, administration after established RSV is not acutely beneficial, but passive immunity conferred by its administration appears beneficial in the majority of studies. These as well as studies of the TNFα-blocking drugs and kinase inhibitors emphasize the importance of carefully defining the disease populations under study and the outcome variables.

Because the targeting of TNFα at the cell surface is particularly convenient, and because this molecule controls a very large number of stress-response events, it is not at all surprising that agents targeting TNFα signaling are being applied clinically, and quite successfully, to a number of conditions including psoriasis, psoriatic-arthritis, ankylosing spondylitis, and inflammatory bowel disease. The large number of signaling pathways affected directly or indirectly by TNFα is also certainly responsible for the wide array of adverse effects. With improvement in definitions of pathways down-stream of TNFα, it is possible that additional or alternative interventions specifically attacking the target involved in pathogenesis, while sparing bystanders can develop. Careful documentation of adverse effects and circumstances, thus, can be very valuable future retrospective analyses seeking evidence for proposed pathways.

Whereas signaling pathways are generally well described in these papers, consistently absent are meaningful discussions of the effect of these signaling molecule in terms of biochemical effects. A much better understanding of the reasons for adverse effects, and rationale for reconsideration of targets and agents, and methods of optimization of biologics using concomitant small molecule therapy could develop when signaling is juxtaposed with biochemistry. An recent example relates to the role of lipid-hydroperoxide metabolism of the enzyme aldose reductase. Depletion or inhibition of aldose-reductase has now been shown in models of sepsis, shock, and malignancy to abrogate significant aspects of TNF-α-mediated signaling. These findings suggest that targeting down-stream of TNFα could give rise to a more specific or less toxic therapy.

As is unavoidable, once drugs originated through biologics become part of clinical practice within medical subspecialty, there is a tendency to expand application to related disorders not necessarily covered by initial indications. Such attempts are viewed with a jaundiced eye by third party payors, but in clinical trial settings, very meaningful results can be found.

Whereas dramatic and unquestionable effectiveness of many biologic therapies have been seen in all fields of medicine, it remains a therapeutic art in its infancy, not yet fully defined as to the scope of potential therapies to be included within it. Even the best established biologics, vaccines, have incompletely defined mechanisms, and application of novel paradigms exploiting recent findings regarding mechanisms of immunity and autoimmunity are on the horizon. In the present issue, Dr. Barabas' review puts forth a novel view of mechanisms leading to autoimmune phenomenon, and how a vaccine approach utilizing IgM-antigen complexes may be useful for treatment of autoimmune renal disease. The seemingly simple concept appears to have merit at least in animal models, and suggests a novel biologic approach to treatment of other autoimmune disorders. Stem cell therapies also hold enormous promise, and are certainly in the spotlight in the political arena. Though the present state of the art is still significantly distanced from clinical applicability, some promising developments combined with optimism regarding the development of targeted drugs to enhance engraftment and differentiation of stem cells are hopeful signs.

This inaugural issue puts forth the current state of the art and of opinion leaders from a small sampling of some of rationally derived therapeutic agents we refer to collectively as biologics, not necessarily because of their chemical composition, but because of their conception and development within the new art of biologics.

References

Barabas AZ, Cole CD, Barabas AD, et al. 2007. Preventive and therapeutic vaccination to combat an experimental autoimmune kidney disease. *Biologics: Targets & Therapy*, 1:59–68.