Volume 1 • Number 3 • 2007

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On the diversity of biological therapeutics

Increasingly precise definition of the molecular nature of disturbances in cellular homeostasis that characterize different disease is leading to an astounding array of novel and effective therapeutics. These are appearing at a rate unrivaled in history. Certainly, not all of these are simply the product of new development. For instance, the idea of enzyme replacement therapy has long roots, but advances in recombinant protein production and delivery techniques have led to successful implementation of enzyme replacement therapy; dosing is being optimized in clinical studies, and it appears that greater benefit will be realized with earlier therapy.

Certainly, enzyme inhibition is much simpler and more traditionally rooted in pharmacology. Remarkable success has been achieved using designer small molecule enzyme inhibitors. Increasingly refined small molecules such as imatinib, gefitinib, and tipifarnib, discussed in the present issue, are a testament to the significant of basic discoveries, the ingenuity of drug-designers, and hard work of translational researchers across pharma, academia, and communities.

Though dramatic progress has been made in the treatment of relatively uncommon disease with narrowly defined etiology, progress is less spectacular in development of targeted therapeutic for the more common disease, which have complex, multifactorial, and as yet incompletely defined mechanisms at the molecular level of pathophysiology. Modest improvements have been seen in solid-tumor therapeutic with wider implementation of biological therapeutics such as bevacizumab. The efficacy of targeted therapy for inflammatory disorders, such as rheumatoid arthritis and psoriasis, far exceeds the efficacy of targeted therapeutics for common solid malignancies. Perhaps this is because inflammatory disorders result form specific and relatively well characterized disturbances in immune effector cells, in the background of an essentially normal and functional genome and proteome. In contrast, genomic instability, and much more random and diverse array of defects that give rise to cancer are understandably more difficult even to fully characterize, much less target effectively with a single agent. Despite these limitations, solid tumor therapy has improved considerably, as evident in improving survival rates for disease in which conventional chemotherapy had only marginally affected overall survival.

The paradigms from the targeted therapy of rare and uncommon diseases with highly specific and effective agents can perhaps be applied to effective use of therapeutics for the more common solid malignancies. Increasingly precise definition of the significance of mutations in the EGF-receptor and tyrosine-kinases as well as other targets may soon allow widespread implementation of selectively targeting subgroups of common solid neoplasms. Such therapies have already caused *de-facto* reclassification of common neoplastic diseases into subcategories defined by mutations or protein-expression changes, and has already dramatically altered treatment paradigms, particularly in breast, colon and lung cancer. As with uncommon or rare neoplasms such as cutaneous T-cell lymphoma, chronic myelogenous leukemia or dermatofibrosarcoma protuberans, the subcategorized neoplasms of breast, lung or colon can also be exquisitely sensitive to specifically targeted therapies.

However, unlike inflammatory disorders, combination of targeted therapeutics will likely be necessary to achieve a similar level of efficacy in solid tumors. Unfortunately,

there are too may potential combinations, and pre-clinical algorithms for predicting the most efficacious combination are yet in their infancy. These efforts have been, and will likely continue to be led astray if methods of target identification and elucidation of signaling pathway connections rely too heavily on genomics, without necessary attention to the context of metabolic pathways, enzymes, and post-translational modifications, which can be defined by proteomics. Empiric combination therapies based on clinical observations of astute observers remains a welcome means of discovery of optimal combinations. In the present issue, the report of using gefitinib and radiation for carcinomatous encephalitis is intriguing in this respect, and suggest a clinically utilizable general radiosensitizing effect of gefitinib, if confirmed in larger controlled studies.

The idea of combining multiple targeted therapeutics to treat disorders of complex pathophysiology is extended to asthma by the though provoking article by Popescu (2007). Such therapeutics could promise the potential of a relatively long-term remission from asthma without even the need for rescue medications. The issues regarding systemic or local adverse reactions would be exponentially magnified by multi-targeting. Insufficient knowledge of the effects of such interventions on cellular metabolic pathways could potentially result in combinations that are inherently antagonistic. We need not look far to find examples where combining targeted biologicals has not improved efficacy. There are no clear-cut explanations to the observations regarding the relative failure of targeted therapeutics, other than the obvious complexity of disease pathology, or inaccurate models of signaling that have poorly defined connections to metabolic pathways or cellular processes. In the face of these obstacles, it is reassuring that discovery of novel therapeutic combinations could result from ingenious cross-disciplinary collaborations that are subject of several articles in the current issue.

References

Popescu FD, Popescu F. 2007. A review of antisense therapeutic interventions for molecular biological targets in asthma. *Biologics Target Ther*, 1:271–83.