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Evidence is steadily accumulating that a large number of diseases in which historical therapies have made no significant impact in outcome are suddenly for the first time effectively treated to yield outcomes unimaginable with prior therapies. Because of the complexities of signaling mechanisms and variation in these mechanisms between disease processes, thorough and standardized testing of efficacy and toxicity in each predicted therapeutic indication remains mandatory. This is particularly true for tumor necrosis factor-alpha (TNFα)-targeting therapies, which may have a role in palliation of symptoms of a much more diverse array of diseases than perhaps previously foreseen, but can occasionally trigger very significant adverse effects due to complexity of signaling down-stream of TNFα.

The diversity of biological signaling mechanisms targeted by available therapeutics is still a small fraction of potential therapeutic targets. Increasing accuracy in definition of targets and effects and a remarkable variety of approaches taken to identify and target the key factors in the pathogenesis of disease will bring increasingly effective novel targeted drugs for individual diseases. The review by deLara and Noble (2007) of an intriguing hypothesis for the pathogenesis of asthma points out how evidence from varied disciplines has converged. The 'hygiene hypothesis' of asthma, supported by a wealth of epidemiological studies, suggests that the dramatic increase in incidence of asthma is related to reduced antigen exposures in childhood due to improved hygiene. Elucidation of the differential response in the Th1/Th2 immune response pathways in response to microbial pathogens, and crucial corroborating evidence from genetic studies of hereditary asthma, has led to a plausible mechanistic explanation for the epidemiological observation. These observations are crucial for rational targeting of asthma as well as atopic disorders in general.

Though monoclonal antibodies remain formidable therapeutics as evidenced by papers in this issue reviewing their use in treatment of colon cancer, ankylosing spondylitis, and psoriasis, the most coveted prizes remain the small molecules with favorable pharmacological properties that affects these pathways specifically, having only the desired effect and little or no untoward effects. Towards such a goal of rational drug-design, imagine a single chemical scaffold useful as a backbone of multiple drugs to specifically target several different signaling pathways. Isatin, an endogenous MAO inhibitor seems to fit this description. Isatin analogs appear to naturally target multiple enzymatic pathways involved in inflammatory and degenerative disorders. Much work still lies ahead in development of this therapeutic to the exquisitely refined drug-design which led to the development of nilotinib, a clearly improved drug for targeting the best defined target, Bcr-Abl. In contrast to the specificity of Bcr-Abl signaling, NFκB, an important down-stream element of TNFα signaling, remains a very complex centerpiece linked to innumerable events that can lead to different outcomes depending on context.

At the other end of the spectrum is a highly logical, direct, and empiric approach to therapy without particular regard to a particular protein target, but nevertheless targeted anatomically and physiologically to deliver an anticancer immune adjuvant effect. The novel approach that has actually been translated into human clinical trial is the use of vaccination site-draining lymph node as an immune adjuvant. Although still

quite preliminary because of the small number of patients, the findings of response and stable disease in advanced cases are of major interest.

## References

de Lara C, Noble A. 2007. Dishing the dirt on asthma: what we can learn from poor hygiene. *Biologics Target Ther*, 1:139–50.