The *Discussion Forum* provides a medium for airing your views on any issues related to the pharmaceutical industry and obtaining feedback and discussion on these views from others in the field. You can discuss issues that get you hot under the collar, practical problems at the bench, recently published literature, or just something bizarre or humorous that you wish to share. Publication of letters in this section is subject to editorial discretion and company-promotional letters will be rejected immediately. Furthermore, the views provided are those of the authors and are not intended to represent the views of the companies they work for. Moreover, these views do not reflect those of Elsevier, *Drug Discovery Today* or its editorial team. Please submit all letters to Steve Carney, Editor, *Drug Discovery Today*, e-mail: S.Carney@elsevier.com

Trends in the development of therapeutic anti-cytokine antibodies

In a recent issue of *Drug Discovery Today,* Zagury and Gallo provided an excellent review [1] that focused on the use of therapeutic anti-cytokine monoclonal antibodies (mAbs). I would like to supply further information about this topic. The Tufts Center for the Study of Drug Development (http://csdd.tufts.edu/), founded in 1976, collects clinical development and regulatory review data for a variety of investigational and approved therapeutics, including mAb, recombinant protein and small molecule products. The data are used in our studies of the development of innovative therapeutics by the pharmaceutical and biotechnology industry, and the approval for marketing of these products [2].

As of January 2004, our databases contained records for 311 therapeutic mAbs that entered clinical study sponsored by commercial firms during 1980 through 2003, including 30 anti-cytokine mAbs. These 30 mAbs were designed to target the following cytokines: interferon (IFN)-γ, interleukins 4, 5, 6, 8, 10, 12, 15 and 18, transforming growth factors β1 and 2, tumor necrosis factor (TNF)-α, and vascular endothelial growth factor (VEGF). Of the anti-cytokine mAbs, 16 products are treatments for autoimmune diseases (e.g. rheumatoid arthritis, Crohn's disease, psoriasis, systemic lupus erythematosus, multiple sclerosis, allergic rhinitis or asthma). These 16 mAbs target IFN-γ, interleukins 4, 5, 8, 10, 12, 15, 18 and TNF-α. Most (62%) of the products are still in clinical study, although two anti-TNF mAbs, infliximab and adalimumab, are approved in the USA. Therefore, the autoimmune anti-cytokine mAbs have a calculated approval success rate of 33%. In comparison, the cohort of all mAbs studied as treatments for autoimmune diseases (55 products) has an 18% approval success rate, and the cohort of anti-cytokine mAbs studied in any therapeutic category has a 20% approval success rate.

Regarding mAb immunogenicity, humanized and human mAbs (which are designed to elicit little or no immune response from patients) have entered clinical study in increasing numbers over the past decade. For example, nearly 60 humanized mAbs were first administered to humans from 1995–2000, although fewer than 20 human mAbs entered clinical studies in the same period. The number of human mAbs in studies is now beginning to grow – at least 25 human mAbs started human testing between 2001 and 2003. Of the 13 products approved in the USA from 1995–2003, two are murine, three are chimeric, seven are humanized, and one is human. The approved human mAb, adalimumab, is produced in a mammalian cell expression system.

Expansion of the current pipeline to include more studies of both passive and active immunotherapy, especially in light of the role of cytokines in immunological disorders and cancer [3], could benefit patients with chronic and serious diseases in the future. In the near term, patients can benefit from the anti-cytokine mAbs marketed now, and will soon benefit from the launch of the humanized anti-VEGF mAb, bevacizumab, in the USA.

References

1 Zagury, D. and Gallo, R.C. (2004) Anti-cytokine Ab immune therapy: present status and perspectives. *Drug Discov. Today* 9, 72–81
2 Reichert, J.M. (2003) Trends in development and approval times for new therapeutics in the United States. *Nat. Rev. Drug Discov.* 2, 695–702
3 Dranoff, G. (2004) Cytokines in cancer pathogenesis and cancer therapy. *Nat. Rev. Drug Discov.* 3, 11–22

Janice M. Reichert
Tufts Center for the Study of Drug Development
192 South Street, Suite 550
Boston, MA 02111, USA

Target driven chemistry in drug discovery

An increasing number of research groups in industry and academia are exploring target-driven chemistry as a tool to identify new small molecule inhibitors. Complementary to the traditional tools of drug discovery, such as HTS and structure based design, this approach aims to reduce the number of inactive compounds synthesized and screened in the discovery process, as well as to compensate for the lack of precision in the predictive ability of computational chemistry.

1359-6446/04/$ – see front matter PII: S1359-6446(04)03025-9

One of the interesting new examples of target driven chemistry, *in situ* click chemistry, has been reviewed recently by Kolb and Sharpless [1]. To put this work in a broader perspective, it is fair to mention that many similar examples applying different chemical reactions have been reported recently to lead to the successful identification of new ligands for biological targets. The underlying chemical approaches can be loosely grouped into two major categories: the shift of chemical equilibrium by the target, and acceleration of preferred reactions in the presence of the target.

The first category is commonly referred to as dynamic combinatorial chemistry (DCC) and has been extensively reviewed [2]. The advantage of this equilibrium approach is that the target selects the best binding product of the reaction, which by definition is an active ligand. Among the problems that need to be addressed in DCC are the reversible linker groups in the ligands, which sometimes need to be replaced in the final drug candidates.

Target-accelerated, or kinetically controlled formation of active inhibitors has been based on multiple reactions, including nucleophilic substitutions [3,4], heterocycle formation [5] and alkene metathesis [6], among others. The *in situ* click chemistry stands apart as an orthogonal reaction, which is not affected by the functional groups present in the proteins and does not require complex catalysts. Target-accelerated approaches potentially allow for a broad choice of chemical reactions to combine building blocks. They also lead to stable products that with some luck could directly be used as drug leads. However, there are potential caveats in the reliance on the kinetic effects. In a catalytic process, the biological target selects the best binding transition state of the reaction, which does not necessarily correspond to the best binding product. It is therefore important to choose the reactions with product-like transition states, such as cycloaddition reactions, for the best desired effect. The formation of the triazole ring through *in situ* click chemistry is an example of such a reaction.

Another problem with the target-accelerated reactions is non-productive binding, an issue that is discussed extensively in classical textbooks [7]. The acceleration effect is primarily caused by the pre-assembly of building blocks on the target active site. However, the preassembled building blocks might have their reactive groups positioned at a large distance. In this case, potentially active binders will not be formed, resulting in false negatives in the screening process.

Despite these problems, the array of approaches to target driven chemistry is steadily shaping up as a new toolbox for drug discovery. By increasing the variety of chemical reactions that are compatible with the presence of the protein and broadening the range of conditions under which the protein targets retain their stability and binding properties, we will eventually be able to let the target pick its ligands from diverse sets of chemical building blocks.

References

1 Kolb, H.C. and Sharpless, K.B. (2003) The growing impact of click chemistry on drug discovery. *Drug Discov. Today* 8, 1128–1137

2 Ramstrom, O. and Lehn, J.M. (2002) Drug discovery by dynamic combinatorial libraries. *Nature Rev. Drug Discov.* 1, 26–36

3 Nguyen, R. and Huc, I. (2001) Using an enzyme's active site to template inhibitors. *Angew. Chem. Int. Ed.* 40, 1774–1776

4 Yu, Y.H. *et al.* (2002) Formation of a class of enzyme inhibitors (drugs), including a chiral compound, by using imprinted polymers or biomolecules as molecular-scale reaction vessels. *Angew. Chem. Int. Ed.* 41, 4459–4463

5 Lewis, W.G. *et al.* (2002) Click chemistry *in situ*: acetylcholinesterase as a reaction vessel for the selective assembly of a femtomolar inhibitor from an array of building blocks. *Angew. Chem. Int. Ed.* 41, 1053–1057

6 Nicolaou, K.C. *et al.* (2000) Target-accelerated combinatorial synthesis and discovery of highly potent antibiotics effective against vancomycin-resistant bacteria. *Angew. Chem. Int. Ed.* 39, 3823–3828

7 Jencks, W.P. (1969) *Catalysis in Chemistry and Enzymology*, McGrow Hill

Alexey V. Eliseev
Alantos Pharmaceuticals
790 Memorial Drive
Cambridge, MA 02139, USA