Emerging molecular targets

High-throughput screening and combinatorial chemistry are dramatically changing drug discovery. At the *First Annual Conference of the Society for Biomolecular Screening*, held last November in Philadelphia, some companies reported that they are now screening 100,000 or more compounds every 6 months, and others revealed plans to screen 50,000 compounds per month. At such rates, a target may be active in a screening program for less than 6 months before it is replaced, and the limiting factor for the screening laboratory may soon be the number of molecular targets available. Because of such developments, an entirely new paradigm for the selection of molecular targets for drug discovery is evolving.

Traditionally, targets have been selected by focusing on enzymes, receptors or proteins that have been carefully characterized and directly associated with a particular therapeutic area. In the past, targets were sought with high specificity for cell- or tissue-type, and for which proof-of-principle studies clearly demonstrated that the action of a bioactive molecule could elicit a therapeutic effect. These criteria evolved for programs in which a target might be screened for several years before a lead or even a bioactive compound was found. Scientists and management needed to be almost completely certain of the validity of the target before investing the resources required by the screening program. With the rapid screening rates now available, it may become common practice to screen many targets for which there is less certainty of a therapeutic outcome; once a bioactive compound is discovered, it could then be used as the critical tool to determine the therapeutic potential of the target.

Human Genome Sciences, Inc. (HGS; Rockville, MD, USA) in collaboration with SmithKline Beecham Pharmaceuticals (King of Prussia, PA, USA) is taking this approach. They have pioneered the high-throughput sequencing of human cDNA obtained from tissue- and cell-specific mRNA. Scientists at HGS have identified and sequenced tissue-specific genes, genes that are expressed only during disease states, and genes that are activated during specific stages of development. By comparing the sequences of such genes with those that code for known proteins, they have identified novel protein kinases, growth factor receptors, proteases involved in osteoporosis, novel G protein-coupled receptors, new adhesion proteins and 7 trans-membrane receptors. Such proteins are likely to be important drug targets, but would not have been incorporated into screening programs in the past without more information on their physiological roles. However, these targets are now being screened at SmithKline Beecham's laboratories, and, according to disclosure by the company at a recent analysis meeting, a number of new lead compounds for osteoporosis, atherosclerosis, inflammation and cancer have been identified. According to W.A. Haseltine, HGS Chairman and CEO, between 60 and 70 new drug targets have been identified from the sequencing data.

The screening laboratory will play an increasingly important role in basic research and in decision-making about which targets are selected for further research, and this exciting new paradigm for drug discovery will require a new mindset for the discovery scientist.

Tim *and* Per *genes*

Circadian rhythms appear to be regulated by the accumulation and interaction of the protein products of the *Tim* and *Per* genes. These recent findings, reported in a series of three papers by Young, M.W. and coworkers, were based upon studies of the fruit fly *Drosophila* [*Science* (1995) 270, 805–808, 808–810, 811–815]. These findings may have direct application to humans, and the Tim and Per proteins may be interesting new targets for the discovery of drugs that alter human circadian rhythms. According to the authors, such drugs might be useful in regulating sleep/wake cycles, body temperature, mental alertness, pain sensitivity and hormone production.

The accumulation of the Tim and Per RNAs and proteins in fruit fly brain cells appears to be a controlling factor for the body clock cycle. From about noon, there is a gradual coordinated accumulation of the Tim and Per RNAs over several hours, with peak accumulation around dusk. The Tim and Per proteins bind to one another and accumulate in the nuclei of the brain cells where they turn off additional production of the Tim and Per mRNAs, with maximum accumulation of the Tim and Per proteins occurring just before dawn.

Thus, compounds that interfere with the production of Tim and Per mRNA production or the interaction of the Tim and Per protein binding, which is reported to be weak, may prove to be effective in altering circadian rhythms.

I-κB and NF-κB

Glucocortoids are widely used anti-inflammatory agents, but their use is limited because of severe side-effects, including diabetes, blood disorders, cataracts, glaucoma and hypertension. Recent reports from Baldwin, A.S., Jr. [*Science* (1995) 270, 283–286] and from Karin, M. [*Science* (1995) 270, 287–290] suggest that glucocorticoids exert their anti-inflammatory actions by inducing the synthesis of the protein I-κB.

I-κB forms a complex with, and inhibits the action of, the transcription factor NF-κB. The latter promotes the transcription of numerous mediators of inflammation and lymphokine genes, including IL-2. Thus, by stimulating the synthesis of I-κB, glucocorticoids block the transcription of NF-κB-dependent inflammatory proteins. If more selective compounds can now be discovered that inhibit NF-κB or promote the synthesis of I-κB, then the immune suppressant properties of the glucocorticoids may be achieved without the side-effects.

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Monitor: March issue

The human genome holds the key to the development of new therapeutic strategies for traditionally recalcitrant chronic diseases and to the molecular mechanisms involved in drug disposition, metabolism and toxicity. In the *Monitor Profiles* section of the March issue of *Drug Discovery Today*, Dr David Bailey and Dr Martin Mackay of the Discovery Biology Division of Pfizer Central Research, UK, explore the genome revolution and its impact on drug discovery and development.