Ohtani, T. and co-workers provides a useful insight into this field[1] and describes the various approaches to inhibiting the activation of this pathway, including interfering with the formation of the IL-6/IL-6Rα/gp130 complex. The review includes coverage of neutralizing protein-based approaches, cytokine therapy and development of artificial cytokines based on the 'receptor conversion model'. The paper concludes by discussing the central role of STAT3 in pathogenesis and the importance of controlling STAT3 through future therapies focusing on the induction of negative regulatory molecules and the use of chimeric antibodies.

1 Ohtani, T. *et al.* (2000) gp130 mediates signalling as a therapeutic target. *Emerg. Ther. Targets* 4, 459–479

Insulin kinase receptor

Type II diabetes mellitus is characterized by a lack of response to insulin. The study of the mechanism of insulin action has led to the identification of the insulin receptor as a tyrosine kinase. A recent review describes the modulation and therapeutic implications of this insulin receptor kinase[2].

In summary, binding of insulin results in rapid activation of the insulin receptor kinase leading to the autophosphorylation of a receptor tyrosine residue and the potential to phosphorylate other cellular substrates. The activation of insulin receptor kinase by peroxovanadium compounds in the absence of insulin, leading to the full activation of the insulin cascade, together with studies on mutant insulin receptor kinases indicate that the insulin receptor kinase function is both necessary and sufficient for insulin signalling. Following activation, the insulin receptor kinase is rapidly internalized within the endosomal apparatus of the cell where it is capable of maintaining insulin signalling; the modulation of insulin receptor kinase within the endosome therefore represents a means of import to modulate insulin signalling. In fact, in recent years several endosomal processes have been shown to regulate insulin receptor kinase activity including a specific insulin protease (endosomal acidic insulinase) and an insulin receptor kinase-associated phosphotyrosine phosphatase that dephosphorylates and inactivates the insulin receptor kinase. Because both endosomal acidic insulinase and the insulin receptor kinase-associated phosphotyrosine phosphatase limit the duration and extent of insulin activity, inhibitors of these enzymes might be suitable therapeutic targets for the future development of agents for the treatment of insulin resistance.

2 Posner, B.I. (2000) The insulin receptor kinase: modulation and therapeutic implications. *Emerg. Ther. Targets* 4, 541–549

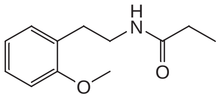
Andrew Lloyd

Combinatorial chemistry

Melatoninergic ligands

Melatonin (*N*-acetyl-5-methoxytryptamine) is the vertebrate pineal gland hormone secreted during darkness, which regulates the circadian rhythm in a large number of animals and in humans. Melatonin can be used to control diseases associated with circadian rhythm disorder and also alleviates jet-lag, regulates delayed-sleep-phase syndrome and induces sleep. Conversely, it has been implicated in seasonal and winter depression and has also been reported to have anti-proliferative effects on mammary cell lines. It has been demonstrated that several of the effects of melatonin are mediated through G-protein-coupled receptors, and coupling to one of the G_i family of G proteins appears to be the common signalling pathway for the receptors characterized to date. Cloning studies reveal two recombinant mammalian melatonin receptors termed mt_1 and MT_2. The design and preparation of molecules selective for these receptors are important steps for their pharmacological characterization. A solid-phase mix and split approach was used to identify compounds that are capable of mimicking or antagonizing the response to melatonin[1].

A library of 108 compounds in mixtures of 12 was prepared on a Merrifield-based solid-phase resin and, following iterative re-synthesis of individual compounds from active mixtures, one of the most potent and selective compounds identified was (**i**), which had a K_i value of 6.56 nM (human MT_2) and was 12-fold selective over human mt_1 (K_i = 81.2 nM). This library has enabled the exploration of affinities of the phenylalkylamido derivatives, exemplified by (**i**), for the human melatoninergic receptors mt_1 and MT_2. Several structural features have been determined that lead to high potency, such as the favoured propyl side-chain seen in (**i**).

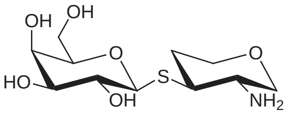


(i)

1 Langlois, M. *et al.* (2000) Synthesis of a small library of phenylalkylamide derivatives as melatoninergic ligands for human mt_1 and MT_2 receptors. *Bioorg. Med. Chem. Lett.* 8, 163–171

Inhibition of galactose-binding proteins

Despite a growing appreciation of the importance of complex carbohydrates in medicinally relevant receptor–ligand interactions, few carbohydrate-based drugs have reached the market. This is partly because of the polar and hydrolytically labile nature of carbohydrates, in addition to the fact that monovalent interactions between carbohydrates and proteins are often of low affinity. Nature usually uses polyvalency to ensure high affinity. A solution-phase parallel approach has been used to discover small molecules inhibiting β-galactosidase from *Escherichia coli*.[2] A library of 360 individual compounds was synthesized by alkylation of a galactopyranose ring followed by either reductive amination of a ketone functionality and acylation of the resultant amine, or reduction of the ketone to an alcohol. One of the most potent compounds prepared from this library was (**ii**), with a minimum inhibitory concentration of 76 μM for hemagglutination inhibition against *Abrus precatorius* toxin A.

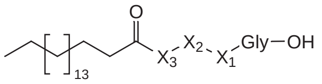


(ii)

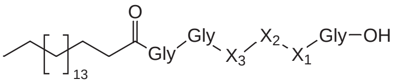
This type of approach could be useful in delivering small 'key sugar'-based 'carbohybrids' (pyranosides carrying structurally diverse aglycons), with high affinity for proteins, thereby efficiently inhibiting polyvalent carbohydrate–protein interactions. Such entities might prove to be attractive starting points for therapeutic development.

Combinatorial surface chemistry

Combinatorial chemistry and biological-based approaches have emerged as powerful aids for the discovery of novel pharmaceutical agents. However, nature itself is the best combinatorial chemist, in that four deoxyribonucleotides and 20 amino acids comprise the entire biological world, through the combination of these small molecular species. For example, a long polypeptide chain is a combination of different amino acids that fold into a three-dimensional protein structure, giving rise to an active site. This fundamental feature of proteins suggests a clue to the formation of their mimics. Substituting peptides for polar moieties of amphiphilic lipid molecules and compressing at the interface causes self-assembly of these functionalized lipids, to form protein-like supramolecular structures. Molecular recognition and binding events can then take place on these structures. A library of 250 compounds was synthesized as a mixture using the mix-and-split approach on Wang solid-phase resin[3]. This mixture was then used to determine the molecular recognition of a 10 mM concentration of D-maltose sub-phase, recognition being determined by the change in molecular area upon substrate binding.



X_1, X_2, X_3 = Gly, Glu, Tyr



(iii)

From this study, the most active mixture identified consisted of 54 components (**iii**) and indicated preferred groups necessary to bind maltose: polar (Glu) and aromatic (Tyr) amino acid groups, the structural elements in the binding site of maltose-binding protein. Thus, combinatorial surface chemistry could be used in the future for the design and creation of artificial proteins and enzymes, which might themselves have medicinal applications.

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[2] Hindsgaul, O. *et al.* (1999) Parallel solution synthesis of a 'carbohybrid' library designed to inhibit galactose-binding proteins. *Comb. Chem. High Throughput Screen.* 2, 335–352

[3] Leblanc, R.M. *et al.* (2000) Combinatorial surface chemistry – is it possible? *Angew. Chem. Int. Ed. Engl.* 39, 1854–1857

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Collaboration…

Epimmune (San Diego, CA, USA) has announced an expansion of their existing collaboration with the **Naval Medical Research Center** (NMRC, Forest Glen, MD, USA) to apply Immunosense technology to the identification of antigens from raw genomic data. This might be useful in the development of a vaccine against malaria. The NMRC, in partnership with **The Institute for Genomic Research** (TIGR, Rockville, MD, USA), comprises an international consortium of genomic research scientists and funding organizations, whose goal is to decipher the genetic code of the human malaria parasite, *Plasmodium falciparum*. Immunosense provides a way to rapidly identify antigens and epitopes within the primary DNA sequence of genes, by predicting which genomic sequences will code for antigens that might be recognized by cells of the immune system. Based on these predictions, biochemical and immunological assays are carried out to generate a database of potential therapeutic targets that could be developed as drugs or vaccines. To date, efforts to develop a vaccine against malaria have been hindered by the difficulty of provoking the highly complex immune response required to fight the disease. However, in addition to antigen fragments already identified for malaria, it is hoped that Immunosense will be an invaluable tool in the discovery of antigens that could enable novel vaccine development for tuberculosis, hepatitis, HIV and other infectious diseases. Furthermore, Epimmune is collaborating with the **Pharmacia Corporation** (Peapack, NJ, USA) to use this technology in the development of immune-stimulating drugs for the treatment of several types of cancer.