

Chemistry tipping the biological seesaw

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Inflammation is the body's response to an injury, wound or infection with the aim being to destroy the foreign body and allow the healing process to begin. Inappropriate inflammation can be the cause or contribute to many diseases, for example hay fever, asthma, atherosclerosis and rheumatoid arthritis. The physical properties of inflammation are redness, heat, swelling and pain which are caused by the influx of leukocytes to the affected area. Chemokines are a type of signalling molecule which recruits leukocytes to the area of infection through the process of chemotaxis. Chemokines are therefore a suitable pharmaceutical target for anti-inflammatory agents.

Broad-Spectrum Chemokine Inhibitors (BSCIs) are a group of molecules which inhibit leukocyte migration caused by chemokines. There are over 50 different chemokines and 20 different chemokines receptors meaning the chemokine system is very complex. There is also much redundancy in the chemokine system consequently a broad-spectrum chemokine inhibitors which will affect a number of chemokines is important to have an effect on inflammation. The first BSCI was 'Peptide 3' which was a small peptide derived from the chemokine MCP-1. It was found that the critical motif for activity was the tripeptide WVG, tryptophan and valine represents a hydrophobic component next to an amide functionality of glutamine. A number of small molecules have been synthesised as potential drug candidates based on this structure. A caprolactam was used in place of the glutamine as it retains the amide functionality and has been shown to be a successful pharmaceutical component. The most successful BSCI so far is FX97L (**Figure 1**) with a potency of 40 pM.

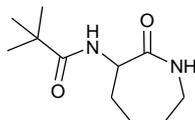


Figure 1: FX97L

It has been discovered that rather than binding to chemokines or chemokine receptors BSCIs work by binding to the $sstr_2$ receptor which usually binds the cyclic peptide somatostatin. Somatostatin is a peptide of the nervous and endocrine system, when bound to $sstr_2$ it is associated with growth hormone (GH) regulation. Small molecule $sstr_2$ ligands have previously been synthesised based on the tripeptide KWF which is thought to be the crucial motif for activity. Interestingly the amino acid that precedes the tryptophan in 'Peptide 3' is a lysine which makes the sequences in somatostatin and 'Peptide 3' quite similar.

This project involves synthesising a catalogue of molecules with structures similar to current $sstr_2$ ligands based on KWF, current BSCIs based on WFQ and hybrid molecules based on KWFQ. The balance of BSCI vs. GH regulating activity for these compounds will be tested in a range of *in vitro* and *in vivo* models testing leukocyte migration, anti-inflammatory activity, $sstr_2$ binding and GH regulation. This will enable us to determine the critical motifs for activity and give more information as to the binding at the $sstr_2$ receptor.