**Mechanism of Action of Broad-Spectrum Chemokine Inhibitors**

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**Inflammation**

- Inflammation is the body's response to harmful stimuli; however, inappropriate inflammation is a key component in many diseases, for example: asthma, hay fever, rheumatoid arthritis and cancer.
- Leukocytes are recruited to the affected area by chemokines. Therefore, chemokines are important pharmaceutical targets. There are over 50 different chemokines and 20 different chemokine receptors; consequently there is much redundancy in the chemokine system; therefore a Broad-Spectrum Chemokine Inhibitor – one which inhibits a number of different chemokines - is necessary.
- Peptide 3’ derived from chemokine MCP-1 was one of the first BSCI discovered; the critical motif for reactivity was found to be the tripeptide WVG, from this a molecule, FX97L, with a potency of 40 PM has been produced.1

**SOMATOSTATIN CRITICAL MOTIF**

- It has been discovered that BSCIs do not bind to chemokine receptors but to the sstr2 receptor for somatostatin.
- Somatostatin is a peptide of the nervous and endocrine system which regulates the secretion of growth hormone (GH).2 It previously has only weak association with the immune system, the tripeptide KWF was found to be crucial for GH regulation.
- This is a display of functional selectivity at the sstr2 receptor. Functional selectivity is the effect of one ligand having one agonism when bound to the receptor and another ligand having a different agonism at that same receptor.3
- BSCIs produce an anti-inflammatory affect when bound to sstr2 and somatostatin affects GH regulation when bound to sstr2.

**NR58-3.14.3 a cyclic peptide**

- NR58-3.14.3 is a 1 nM BSCI Critical motif for activity is WVG.4

**Current sstr2 ligands; all KWF analogues;**2

**The aim of my project is to synthesise a catalogue of structures starting off as GH regulators (KWF analogues) and moving along the scale to potential BSCIs (KWFQ analogues).**

**The Q mimic will be a lactam which retains the amide and has been found to be a successful pharmacological component.**

**These compounds will all be tested for their BSCI potency and GH inhibition.**

This will enable the structure activity relationship to be quantified and the Functional Selectivity balance to be determined.

**Synthetic targets: stepwise change of KWF and KWFQ analogues for structure activity relationship testing regarding BSCI and sstr2 inhibition ability.**

**Synthesis:**


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Thanks to Functional Therapeutics Ltd and Dr D. Grainger