Chemistry Tipping the Biological Seesaw

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During a biological inflammatory response, patrolling leukocytes (white blood cells) release chemokines - a type of peptide cytokine - to summon other leukocytes. Inhibition of this process could provide a mechanism for new anti-inflammatory drugs.

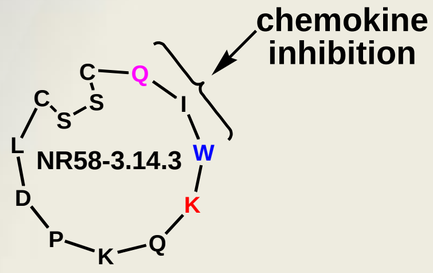
Traditionally inhibition has been sought by blocking chemokine receptors with antagonists, but we have found useful molecules by inhibiting functional cell migration – with great success.

*We would not have discovered **Broad-Spectrum Chemokine Inhibitors** (BSCIs) using a receptor antagonist approach as our functional screening approach has discovered a new biological target for anti-inflammatory drug design – the sstr$_2$ receptor.*

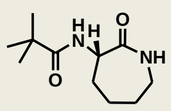
➢ Sometimes **inflammation** is inappropriate and can **exacerbate** certain **diseases** for example cancer, arthritis and asthma.

➢ Due to their role in initiating inflammation chemokines are therefore a good target for anti-inflammatory drugs – for example BSCIs.

➢ NR58-3.14.3 is a BSCI. It is a cyclic peptide with the critical motif being WIQ.



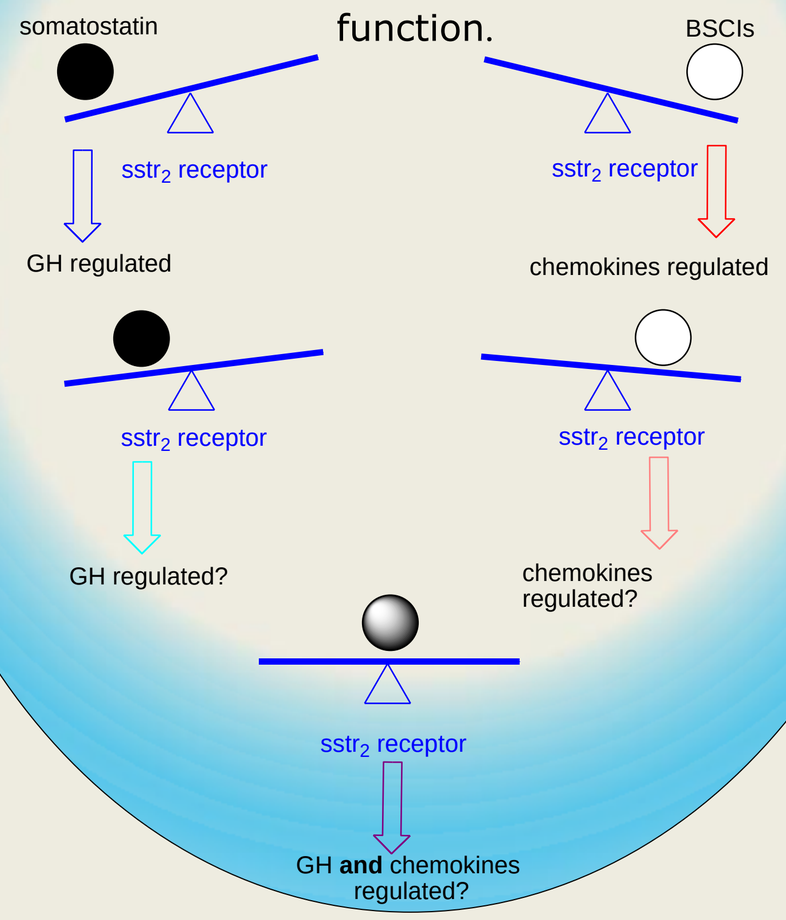
➢ FX97L is a 40 pM BSCI.[1] The Q motif is mimicked by a caprolactam which retains the amide and has been found to be a successful pharmacological component.



FX97L 40 pM BSCI

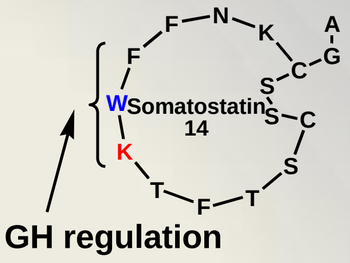
➢However, it has been discovered that BSCIs do not bind to chemokine receptors but to the **sstr$_2$** receptor for **somatostatin**.

The aim of my project is to synthesise a catalogue of molecules analogous to both somatostatin and BSCIs to investigate the important part of the molecules for tipping sstr$_2$ from GH to BSCI function.

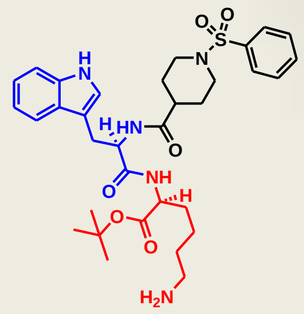


➢Somatostatin is a peptide involved in **growth hormone** (GH)regulation.[2]

➢ It is a cyclic peptide with the critical motif being KWF.[3]



➢ An example of an sstr$_2$ ligand based on the WKF motif.

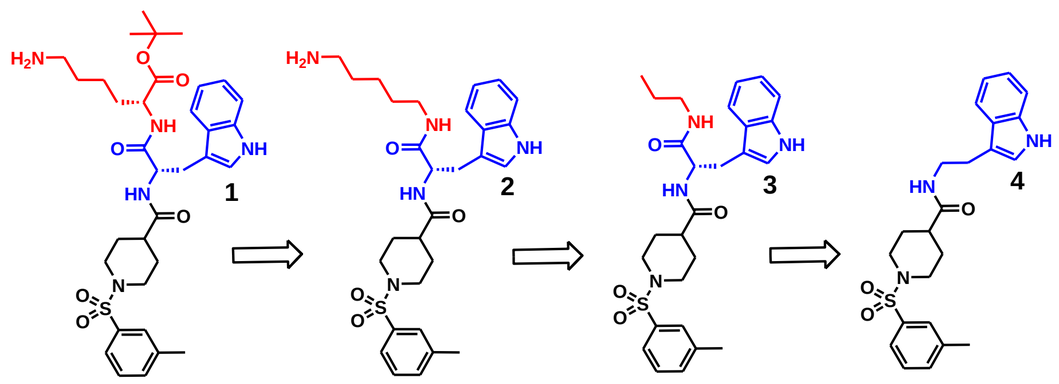


sstr$_2$ ligand based on WKF critical motif

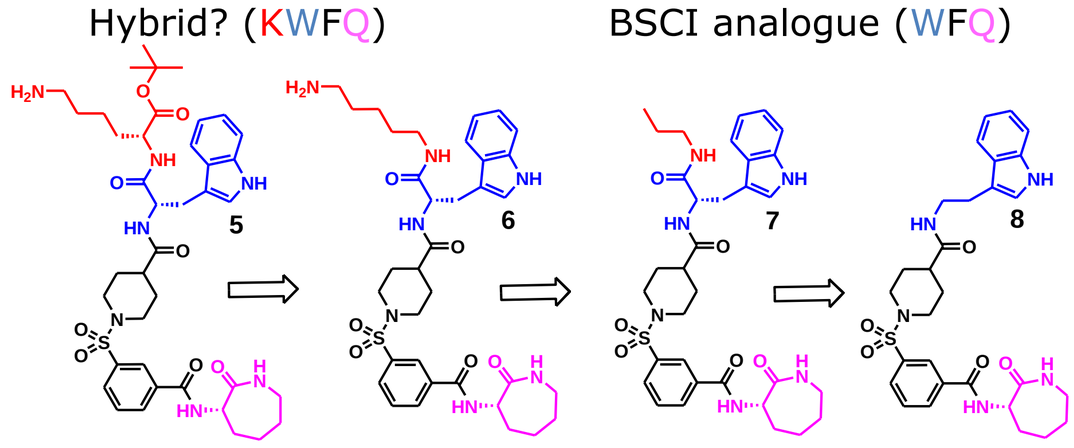
➢ **Functional selectivity** is the ability for a receptor to have different functions depending on the molecule to which it is bound.

➢The sstr$_2$ receptor therefore displays functional selectivity – when somatostatin is bound GH is affected but when BSCIs are bound chemokines are affected.[4]

Somatostatin analogue (KWF)



Hybrid? (KWFQ)



BSCI analogue (WFQ)

➢ Synthesis:

➢ Future Work – 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.

1. D. J. Fox, J. Reckless, H. Lingard, S. Warren and D. J. Grainger, *J. Med. Chem.*, *2009*, *52*, *3591-3595*.
2. B. A. Hay, B. M. Cole, F. DiCapua, G. W. Kirk, M. C. Murray, R. A. Nardone, D. J. Pelletier, A. P. Ricketts, A. S. Robertson and T. W. Siegel, *Bioorg. Med. Chem. Lett.*, 2001, 11, 2731-2734.
3. D. J. Fox, J. Reckless, S. M. Wilbert, I. Greig, S. Warren and D. J. Grainger, *J. Med. Chem.*, 2005, 48, 867-874.
4. A. Schonbrunn, *Mol. Cell. Endocrinol.*, 2008, 286, 35-39.

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