Oxagen's GPCR Programme

Programme Objective

- Identification of G-protein coupled receptors involved in inflammatory disease by genetic association studies

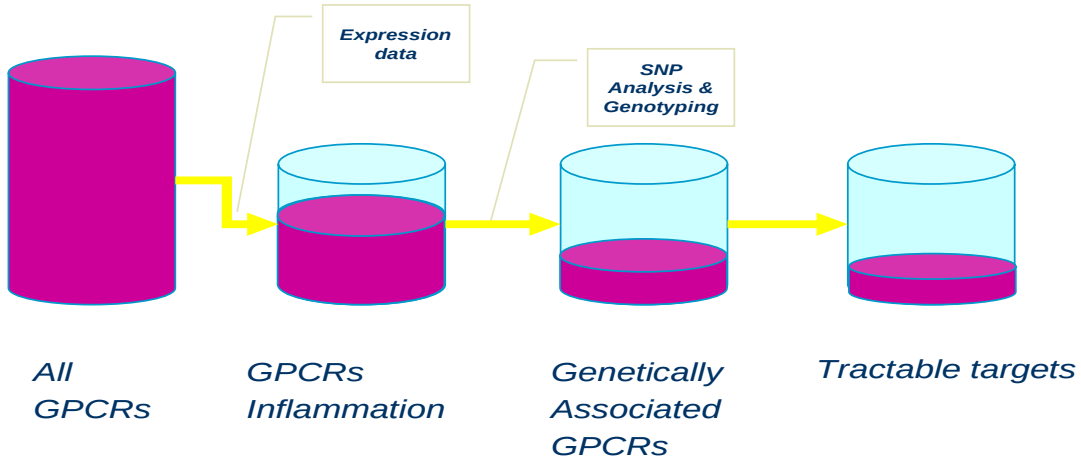
Background

G- protein-coupled receptors are not only highly tractable drug targets but also attractive candidates for genetic association studies because they are more polymorphic than most other classes of gene and these polymorphisms frequently lead to functional changes in the levels of expression or biological activity that can predispose to common diseases. A large-scale study to identify functional variants in G-protein-coupled receptors associated with inflammatory diseases has highlighted a spectrum of novel biological insights that range from identifying the involvement of orphan receptors in certain diseases through to highlighting new therapeutic indications for existing drugs.

Technology

The diagram below shows the overall process used by Oxagen. Approximately 200 GPCRs were selected for study based on their expression pattern across inflammatory cells and tissues. Variants in these genes in populations were then identified and the relative frequency of these variants or SNPs (single nucleotide polymorphisms) were determined across DNAs from populations with a range of inflammatory diseases and compared to populations of control subjects having no disease. Following complex statistical analysis over or under - abundance of particular variants in certain disease populations implicates the genes in question in the disease process.

Target Selection Process



This process of selection and genotyping has led to the output summarised below.

Output from GPCR Programme

	Orphan (11receptors)	Liganded (29 receptors)	Drugged * (20 receptors)
Autoimmune	4	11	7
RA	0	2	0
IBD	2	7	4
Psoriasis	5	3	4
Asthma	1	7	9

66 associations with 60 GPCRs in 5 diseases

The numbers in the table refer to the number of target GPCRs with genetic associations to a particular disease, for example there are 4 orphan receptors, 11 receptors with known ligands and 7 receptors against which drug like molecules (or even marketed drugs) are available in the public domain with associations in autoimmune disease.