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From *in silico* Demystification of GPCR Structure to the Design of New GPCR Ligands: The Human A_3 Adenosine Receptor as a Key Study.

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Abstract

G protein-coupled receptors (GPCRs) form a large protein family that plays an important role in many physiological and pathophysiological processes. Since the sequencing of the human genome has revealed several hundred new members of this receptor family, many new opportunities for developing novel therapeutics have emerged. The increasing knowledge of GPCRs (biological target space) and their ligands (chemical ligand space) enables novel drug design strategies to accelerate the finding and optimization of GPCR leads. The crystal structure of the recently published GPCR extend and support homology modeling studies and structure-based drug design approaches. On the other hand, the classical ligand-based design approaches (for example, virtual screening, pharmacophore modeling, quantitative structure-activity relationship (QSAR)) are still powerful methods for lead finding and optimization. In addition, the cross-target analysis of GPCR ligands has revealed more and more common structural motifs and three dimensional pharmacophores. Such GPCR privileged structural motifs have been successfully used by many pharmaceutical companies to design and synthesize combinatorial libraries, which are subsequently tested against novel GPCR targets for lead finding. In the near future structural biology and chemogenomics might allow the mapping of the ligand binding to the receptor. The linking of chemical and biological spaces will aid in generating lead-finding libraries, which are tailor-made for their respective receptor.

As we will summarize, the development of agonists and antagonists for the human A_3 adenosine receptors has so far been directed by traditional medicinal chemistry. The availability of crystallographic information promises to facilitate understanding of the drug-receptor interaction leading to the rational design of a potentially therapeutically important class of drugs.