The explosion of biomedical data such as in genomics, structural biology and pharmacology can provide new opportunities to improve our understanding of human physiology and disease. G protein-coupled receptors (GPCRs) mediate a vast variety of critical biological processes and provide an ideal case study on the focused integration of these amounts of data with innovative computational tools to gain novel insights into receptor biology. My dissertation focuses on how to harness the biodata revolution i) to identify new trends in GPCR drug discovery, ii) to investigate how subtle genetic variations can imbalance GPCR signalling, iii) to discover novel human signalling systems and iv) to understand the determinants of selectivity between receptors and their signalling partners.

In manuscript 1, we reported a recent analysis of all GPCR drugs and agents in clinical trials, which revealed current trends across drug targets, molecule types and therapeutic indications. The field is readily exploring previously untargeted receptors such as peptide and protein GPCRs and is investigating new types of agents such as monoclonal antibodies, recombinant proteins and allosteric modulators. The advent of GPCR structures are starting to impact drug discovery and new opportunities are emerging for GPCR targeted agents in oncology and metabolic diseases.

In manuscript 2, we examined the prevalence and spectrum of GPCR genetic variants from ~60,000 individuals and presented evidence for variants of two receptors on their putative impact on drug response. The potential economic burden on the society for not accounting for drug target induced side-effects has been discussed.

In manuscript 3, we investigated the human peptide signalling system and universal characteristics of peptide ligands and their cognate receptors. With these insights, we select putative peptide binding receptors among class A orphan GPCRs and design a library of potentially new endogenous peptide ligands. We identified multiple new receptor-ligand pairs in a multifaceted screening approach, with 26 new ligands paired with 5 receptors among additional indicative pairings for 5 receptors.

In manuscript 4, we laid the foundation for understanding the molecular basis of coupling selectivity within individual receptors and G proteins. Universally conserved patterns of amino acids in the G proteins are recognised by individual receptors differently through distinct residues - like non-identical cuts in keys (receptors) opening the same lock (G proteins).

In summary, this thesis provides new perspectives in the field of computational receptor biology and highlights the value of data integration from public databases alongside key experiments, allowing for new ways to make use of the unexplored wealth of biological data.