

Ian M. Bell

“The Discovery of Orally Bioavailable CGRP Receptor Antagonists: From Concept to Clinical Efficacy”

Abstract: G-protein-coupled receptors (GPCRs) have been the focus of many successful drug discovery programs and are the targets of about one third of all marketed pharmaceuticals. However, the identification of orally bioavailable drugs that target Family B GPCRs, for which the endogenous ligands are large peptides, has proved to be challenging. The calcitonin gene-related peptide (CGRP) receptor is a multimeric protein containing the calcitonin receptor-like receptor, a Family B GPCR. The natural ligand is the 37-amino-acid CGRP, a neuromodulator which is believed to play a key role in migraine pathogenesis. Clinical evidence for the utility of CGRP receptor antagonists for the acute treatment of migraine was initially provided with intravenously-administered olcegepant. Our program to develop orally bioavailable CGRP receptor antagonists began with a benzodiazepine-containing HTS lead of micromolar potency and high molecular weight. Initial optimization of this benzodiazepine led to the identification of the advanced clinical compound telcagepant. A complementary approach to the evolution of the HTS lead provided a structurally diverse back-up compound, MK-3207. The discovery of these clinical compounds will be discussed, with an emphasis on the key challenges facing the drug discovery program and the solutions we identified.

Dr. Bell was educated at Cambridge University and received an M.A. in Natural Sciences and a Ph.D. in Organic Chemistry. Following postdoctoral work at the Scripps Research Institute, working in the lab of Donald Hilvert, he joined Merck Research Laboratories in 1994. He is currently a Senior Investigator in the Medicinal Chemistry Department at West Point. He has worked on a number of programs in the areas of oncology and neuroscience, most recently on CGRP receptor antagonists.
