

Preface

Since the first description of adenosine receptors 30 years ago, based on the valuable scientific discoveries and contributions by individuals working in the field of adenosine receptor (AR) research around the world elucidating AR molecular structure, pharmacology, and function, and the intensive efforts in chemistry to identify selective ligands for ARs, molecules that target all four AR subtypes, A₁, A_{2A}, A_{2B}, and A₃ARs have advanced to clinical trials with a recent FDA approval and an NDA submission. As contributing authors to this volume of the Handbook of Experimental Pharmacology (HEP), “Adenosine Receptors in Health and Disease”, these scientists describe the impact of their discoveries and contributions, as well as those by others, on defining the role of ARs in a number of different diseases and the advancement of this field of science and medicine. Since the inception of this area of basic science research, it has truly been an incredible experience for all of us in academia and the pharmaceutical industry to participate in and observe this captivating and fast-moving field advance from the bench to the clinic.

In the A₁AR area, A₁AR agonists have been tested in humans for the following conditions: atrial arrhythmias (Tecadenoson, Selodenoson and PJ-875); Type II diabetes (GR79236, ARA, and CVT-3619); and angina (BAY-68-4986). New partial A₁AR agonists are in development, including CVT-3619, that have the potential to provide enhanced insulin sensitivity without cardiovascular side effects and tachyphylaxis. Based on the diuretic/natriuretic and renoprotective effects of A₁ARs in the kidney, A₁AR antagonists are currently in late-stage clinical development, including KW3902 (rolofylline, Phase III), BG9928 (Adentri[®], Phase III), and SLV320 (Phase II), for acute decompensated heart failure (ADHF) with renal impairment. All three have high affinity for the human A₁AR subtype and demonstrate diuretic and renal protective effects in humans with ADHF with renal impairment. Moreover, to date, two PET ligands have been successfully tested in humans for the visualization of A₁ARs in the brain, [¹⁸F]CPFPX and [¹¹C]MPDX. The use of these PET imaging agents may provide valuable insights into sleep disorders and neurodegenerative disorders, e.g. Alzheimer’s Disease (AD).

In the A_{2A}AR area, A_{2A}AR agonists are currently in clinical trials, with one recent FDA approval and one NDA submission for the following indications: myocardial perfusion imaging (recently FDA approved LexiscanTM, regadenoson, CVT-3146; CorVue, binodenoson, MRE-0470, WRC-0470, NDA submission; apadenoson, ATL-146e), and wound healing (sonedenoson, MRE 0094). A_{2A}AR antagonists have been tested in clinical trials for Parkinson's Disease (PD), including istradefylline, KW 6002; BIIB014, V2006; and SCH 58261. Moreover, two A_{2A}AR PET ligands have been successfully tested in humans for the visualization of A_{2A}ARs in the brain, [¹¹C]TMSX and [¹¹C]KW-6002. The use of these PET imaging agents may provide valuable insights into PD, psychiatric diseases, and perhaps drug addiction.

In the A_{2B}AR area, a mixed A_{2B}/A₃AR antagonist, QAF 805, was tested in humans with asthma and an A_{2B}AR antagonist, CVT 6883, is in clinical development for asthma and currently is in Phase I clinical trials.

In the A₃AR area, A₃AR agonists are in clinical trials for the following indications: rheumatoid arthritis, dry eye syndrome, psoriasis (CF 101), and liver cancer, hepatitis, and liver regeneration (CF 102).

A number of other molecules that target AR subtypes and that are at various stages of preclinical development appear to be promising drug candidates for asthma, inflammation, sepsis, ischemia-reperfusion organ injury, fibrosis, ADHF with renal impairment, PD, AD, cancer, diabetes, obesity, glaucoma, and as coronary vasodilators for myocardial imaging. Moreover, based on the growing scientific evidence supporting the role of ARs in other neurodegenerative diseases and drug abuse and addiction, it is expected that AR-based drug candidates will enter clinical trials to target these diseases. We look forward with anticipation to the advancement of these promising drug candidates towards the clinic and their approval. We expect they will significantly alter the life styles and outcomes of patients with these diseases.

It has been our pleasure to work closely with the world-renowned AR scientists who contributed to this volume of the HEP. We are extremely grateful for their invaluable contributions to this area of science and medicine, which will be realized for generations to come. In this volume of the HEP, all of us have tried to present chapters with up-to-date information about the role of ARs in health and disease and the importance of ARs as drug targets for a number of different diseases. It was our intention to present this information in such a way that those who are not as closely associated with this area of science and medicine and with different interests and backgrounds can understand and appreciate its significance. We are especially indebted to Springer for providing us the opportunity to contribute this volume of the HEP and to Susanne Dathe for her support and successfully managing this project.

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