Preface

The cyclic nucleotides, cAMP and cGMP perform ubiquitous signaling roles. In mammals, one or other or both are connected with the regulation of a panoply of key processes that include learning and memory, cell cycle control, differentiation, inflammation, cardiac functioning, smooth muscle relaxation/contraction, and visual signal transduction, to name but a few. As such, there has been much interest over the years in trying to identify, resolve, and comprehend the signaling systems associated with cAMP and cGMP in health and disease and to determine how this knowledge can be translated to generate novel means of therapeutic intervention.

Psychologically, most of us seem to be geared to a greater appreciation of the creation of objects and material rather than their destruction. Invariably, this translates into our collective approach to scientific problems. Certainly, in this regard, the G-protein-coupled receptor (GPCR)-stimulated generation of cAMP has attracted enormous attention over the past three decades. This interest has been translated into effective therapeutics that have exploited the diversity of receptor subtypes and their cell type-specific patterns of expression and been greatly facilitated as their binding site is exposed at the cell surface. More recently, enthusiasm for studying the enzymes that generate cGMP and mediate the cGMP-signaling pathway and its potential for drug targets have emerged. Efforts to target pharmacologically the enzymes that break down cyclic nucleotides, i.e., the cyclic nucleotide phosphodiesterases (PDEs) have more recently materialized, and some of the drugs produced in such programs have proven to be spectacularly successful in the clinic.

For many years, it has been an apparent conundrum that many organisms, including mammals together with lower organisms such as *Drosophila melanogaster* and *Caenhorhabidits elegans*, have stockpiled a mass of PDEs that catalyze the destruction of cAMP and cGMP. Work from many laboratories, including those contributing to this volume, has shed light on why nature has seen fit to not only conserve this diversity but also to elaborate on it throughout evolution. Thus, we see PDEs that have different affinities for cAMP and cGMP, such that low K_m enzymes can scavenge and ensure that signaling systems are truly switched off in resting cells, but then there are sets of PDEs with higher K_m values that "kick in" as cyclases are activated to produce more cAMP or cGMP in cells stimulated by various signals. PDEs also have regulatory features that (a) mediate negative

feedback pathways, which accelerate cyclic nucleotide hydrolysis; (b) provide for selective localization of particular PDE isoforms within a cell so as to confer precise regulatory control upon specific, spatially constrained cellular processes; and (c) provide for cross-talk with other signaling systems so as to integrate cellular responses. Some PDEs are activated through phosphorylation by cyclic nucleotide-regulated protein kinases and so provide a pivotal part of the cellular desensitization mechanism to the corresponding cyclic nucleotides.

Finally, over the last decade, we have seen the advent of genetically encoded sensors for both cAMP and cGMP. These have allowed for the visual appreciation of a phenomenon that has been inferred but, until this time, neither fully proven nor fully accepted, namely that both cAMP- and cGMP-signaling events are compartmentalized in cells. However, for this, you need the targeted, rather than the mass destruction of cyclic nucleotides, for such gradients to form in cells. Tethered subpopulations of cAMP and cGMP sensors subsequently interpret these PDE-shaped gradients. This new understanding offers a pivotal insight into the "why so many PDEs" conundrum. Thus, a large library of PDEs is available where individual isoforms are expressed on a cell type-specific basis. This allows targeting of particular PDEs to specific intracellular sites, membranes, and signaling complexes within cells so as to shape gradients and gate the activation of sensors around them. It is the diversity of PDEs, expressed on a cell type-specific basis with specific functional roles that offers potential for therapeutic exploitation.

The hope for the first PDE therapeutic was aimed at developing selective inhibitors of PDE3 for treatment of heart failure. The first clinical trials were performed with milrinone, which although enhancing cardiac function as hoped, was never mass-marketed as it gave rise to an increase in death rates due to arrhythmias. However, these unfortunate effects were most likely exacerbated by the fact that the patient cohort evaluated were end-stage patients; moreover, milrinone at higher concentrations can inhibit other PDEs. Nevertheless, milrinone is still used under hospital supervision and, furthermore, the highly specific and high affinity PDE3-selective inhibitor, cilostamide is approved for use in intermittent claudication and has no known arrhythmiogenic effect.

The concept that PDEs are promising drug targets has been spectacularly extended with selective inhibitors for the cGMP-hydrolysing PDE5. These compounds found a commercial niche for treating penile erectile dysfunction although the first of these compounds had ancestors that originated from programs designed to develop drugs for treatment of heart disease. Since then PDE5-selective inhibitors have progressed to being approved for treatment of pulmonary hypertension and, ironically, may progress back to a new found utility in the treatment of heart disease and other cardiovascular maladies. There has also been a huge effort by the pharmaceutical industry in developing selective inhibitors for members of the PDE4 family. Unfortunately in the race to do this, the generation of a multitude of such compounds ran well-ahead not only of our understanding of both the diversity of isoforms within the four genes PDE4 family, but also ahead of our understanding of their functional roles and structures. Undoubtedly, this has led to a lot of frustration over the years in appreciating which PDE4 isoform is the

"true target" in a particular tissue/cell type and how to deal with adverse side effects of such drugs, such as nausea. Nevertheless, we now have just seen approval for the first PDE4-selective inhibitor, which is being used as a therapeutic to treat chronic obstructive pulmonary disease (COPD). However, recent major advances in our understanding that particular PDE4 isoforms can perform specific functional roles through targeting to signaling complexes, plus new structural insights into how regulatory domains interact with catalytic units bodes well for subsequent generations of PDE4-selective inhibitors. These are likely to address additional therapeutic areas including cognition, psychosis, and cancer. In addition to this, a number of research programs are vigorously pursuing inhibitors of PDE10 for treatment of neuropsychological disorders.

This is then an exciting time for PDE research and development of drugs that target specific enzymes within the myriad of PDEs encoded by the human genome. Each PDE appears to have a specific functional role that affords novel opportunities for development of specific therapeutic interventions. The ability for genetic ablation of particular PDEs, coupled with siRNA-mediated knockdown of specific PDEs and the use of novel dominant negative approaches provide means of comprehending function and further defining potential targets. Furthermore, the huge increase in structural insight of catalytic and regulatory domains of PDEs has transformed our ability to optimize the design of specific inhibitors, and we look forward to the insights that will be derived from the resolution of more complex structures involving not only full-length PDEs, but also for PDEs in complex with specific partner proteins. The ability to assess changes in cAMP and cGMP around specific functional signaling modules will allow not only new biological insights but will also provide the potential for screening for new therapeutics.

Given the limitation in budget, we are inevitably constrained in what we can present. However, in the collection of articles in this volume, we hope to give you a taste of some of the exciting ideas and developments that are currently emerging in this dynamic and important field and how future therapeutic exploitation is currently shaping up. We hope that you enjoy and are inspired by reading them as much as we have been.

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