This issue is dedicated to the founder and driving force behind Cellular Signalling Journal, Miles D. Houslay (MDH), who recently retired as Editor in Chief. MDH built Cellular Signalling from the ground upwards to appeal to a general readership that thrived on mechanistic insights into signal transduction and to celebrate his achievements I have commissioned a special issue that celebrates his excellence in the cell signalling arena. The contribution of MDH to the cyclic AMP signaling field is evidenced by his international reputation stemming from over 150 publications in this area. In particular, MDH has become a world leader on the enzyme family phosphodiesterase 4 (PDE4s) and his highly cited papers on "PDE4ology"contain some noteworthy "firsts". MDH was first to discover that members of the PDE4 family can be localized via their unique N-terminal region [1], first to silence PDE4s with siRNA [2], first to construct a dominant negative PDE4 [3], first to displace endogenous, targeted pools of PDE4 with peptides [4] and first to define a function for a single PDE4 isoform [5]. MDH has also been a leader in the characterization of many PDE4 isoforms that are too many to mention here[6]. Taken together these breakthroughs hatched the idea that although PDE4 isoforms may be expressed at a low level, their activity and positioning in cells underpinned the distinct physiological consequences of individual receptor activation [7]. The concept of highly cAMP compartmentalized signaling orchestrated by tethered phosphodiesterases has been adopted by other groups around the world (including my own) and has been supported by data gathered using modern techniques that allow visualization of cAMP gradients [8]. MDH has also been an influential force in the development of novel concepts concerning the pharmacology of PDE4s, publishing many original papers and seminal reviews that have inspired the next generation of cAMP signallers [9, 10]. Indeed, MDH has advised large pharma on the development of PDE4 inhibitors and this has recently bourne fruit with the recent approval of Apremilast, a PDE4 inhibitor that presents a new mechanism of action for the treatment of psoriasis [11].

To honour his contribution, I have asked friends, collegues and collaborators of MDH to submit articles toward this special issue of Cellular Signalling. The manuscripts I received in response, are a mixture of novel, primary research articles and enlightening reviews, which are apt as they broadly cover the areas in which MDH has built his reputation. The review contributed by my lab discusses the importance of the intra-cellular targetting of a single PDE4 isoform (PDE4D5) by virtue of its unique N-terminal region. From my contribution it is clear that RACK1 and βarrestin are the best characterized scaffolds for PDE4D5, so it is appropriate that this issue also contains a paper from the Bolger lab, who discovered the association between RACK1 and PDE4D5 in collaboration with MDH [12]. Graeme Bolger and collegues outline a previously undiscovered function of PDE4 isoform scaffolding, reporting that the sequestration of PDE4D5 by either RACK1 or βarrestin inhibits dimerization of the PDE. They conclude that it is likely that the monomeric form of the PDE4D5 enzyme, which is favoured by βarrestin for delivery to the β-adrenergic receptor, undertakes hydrolysis of cAMP to promote receptor desensitization. In the same vein, Enno Klussmann has provided a topical review on the protein-protein interactions of PDE4 enzymes. He outlines the critical influence of MDH in raising awareness of the importance of PDE4 anchoring in the cell to the tailoring of cAMP-specific

responses. Key to this was the introduction of peptide mapping which allowed delineation of PDE4 interaction sites and discovery of cell-permeable peptide disruptors that could displace targeted PDE4s in order to tease out their function.

In conjunction with the spatial positioning of PDE4s, another feature of this enzyme family that influences its unique ability to shape cAMP gradient in space and time is the many phosphorylation events that confer fine control of PDE4 activity and cross-talk with other signaling systems. This issue contains a comprehensive and informative review by The Conti lab that highlights the importance of the post translational modification of PDE4s in feedback regulation. The pioneering contribution of the Houslay lab in investigating activating phosphorylations by PKA within the URC1 region of long-form PDE4s and the discovery of inhibitory phosphorylation by ERK Mapkinase at the C-terminal end of the catalytic unit of PDE4s is acknowledged.

The ubiquitous nature of cAMP signaling and the role of targeted PDE4 in shaping receptor specificity of function has resulted in the identification of this enzyme family as a key player in a diverse variety of cells, tissue types and major organs. One setting where the Houslay lab has made an important contribution to the role of PDE4s is in cardiac signaling. To celebrate this, we have primary research papers from the groups of Manuela Zaccolo, John D. Scott and Donald Maurice. The first (Zaccolo) investigates the mechanism behind the disruption of compartmentalized cAMP signaling observed in a cellular model of cardiac hypertrophy. In a novel twist, it appears that PDEs and PKA enzymes change their cellular location and the resulting lack of connectivity contributes to the development of cardiac remodeling. The second report by the Scott lab investigates the functional significance of a protein complex containing the PKA anchoring protein AKAP150 and the phosphatase activated by calcium ions, calcineurin. As this phosphatase is responsible for the activation of the transcription factor NFAT, which in turn leads to the silencing of potassium gated channels following myocardial infarction (MI), the sequestration of the phosphatase by AKAP150 to the sarcolemma represents a signal transduction node that could be targeted to lessen the chances of lethal arrhythmia following MI. Following on in the cardio-vascular theme, the third paper by Don Maurice and team, long term collaborators of MDH, have added a report that describes a novel role for PDE4 in modulating the responses of vascular endothelial cells under laminar flow conditions. When shear stress is high, PDE4D activity increases and this in turn promotes morphological and gene expression changes, which help the cells adapt to the flow environment.

With increasing understanding of the role that PDE4s have in diseases that are a product of aberrant cAMP signalling, in depth knowledge about the regulation, activity and pharmacology of PDE4 make MDH an attractive target as a collaborator for large Pharma. This issue carries contributions from Pete Schafer from Celgene (a company that has recently put a novel PDE4 inhibitor, Apremilast, on the market) and Nick Brandon from Astra Zeneca (formerly with Wyeth and Pfizer) that extole and build on seminal contributions by MDH. In his review, Nick Brandon has outlined the importance of MDH's input in identifying

a complex between PDE4 and DISC1, a signaling scaffold protein that has been identified as a risk factor for psychiatric disease. That heightened cAMP can cause disruption of DISC1-PDE4 complex and also that DISC1 binding to PDE inhibits the enzyme suggest the complex could be exploited for novel therapeutic approaches. On a different note, Pete Schafer presents novel experimental data on the anti-inflammatory mechanism of action of the PDE4-specific inhibitor Apremilast, which can proceed via a protein complex involving PDE4 and CD271. The paper shows the effectiveness of Apremilast in preventing the migration and differentiation of fibroblasts, actions that underpin is effectiveness against psoriasis. Finally, and continuing the PDE inhibition theme, we have an original research article from the Beavo lab investigating the synergism between concomitant inhibition of PDE4 and PDE8 in testicular Leydig cells. Compelling phosphoproteomics data suggests that PDEs from both families work together to orchestrate steroidogenesis via many cell signaling pathways to ensure timely testosterone secretion following exposure to luteinizing hormone.

In conclusion, this special issue of Cellular Signalling aims to review emerging concepts and report on novel, topical research developments within the cAMP field. All of the contributers have been influenced in different ways by MDH and I hope that this issue is a fitting tribute

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