Preface

With almost 600 reviews, transient receptor potential (TRP) channels arguably represent today’s most extensively reviewed pharmacological targets. The literature on TRP channels is vast and still growing: It has exploded from a mere 21 papers in 1995 to over 2,000 in the past 2 years. Yet, even the most studied TRP channels like TRPV1 continue to surprise: as Bernd Nilius points it out in his Introduction, “We are still at the beginning of the beginning.”

Over the past decade, both gain- and loss-of-function mutations in TRP channels (so-called TRP channelopathies) have been identified in human disease states ranging from focal segmental glomerulosclerosis (TRPC6) and familial episodic pain syndrome (TRPA1) through brachyolmia and hereditary arthropathy of hand and feet (TRPV4) to mucolipidosis type-4 (TRPML1) and amyotrophic lateral sclerosis and parkinsonism/dementia complex (TRPM7). These findings imply a therapeutic potential for drugs targeting TRP channels in a wide variety of diseases, many with no existing satisfactory treatment options. Indeed, a number of potent, small molecule TRPV1, TRPV3, and TRPA1 antagonists have already entered clinical trials, and many more are in preclinical development.

The TRP superfamily of ion channels in humans is a diverse family of 28 cation channels with varied physiological functions. Their name stems from their similarity on the sequence level to the original *trp* gene from *Drosophila* which, when mutated, resulted in a transient receptor potential in the presence of continued exposure to light. Overall, few generalizations can be made about TRP channels. Most family members share a low level of structural similarity, but some channels are very highly homologous to each other (e.g., TRPC3 and TRPC7; TRPV5 and TRPV6). Many TRP channels form functional channels as homotetramers, though heteromultimerization is not uncommon. The latter phenomenon may have important implications for drug discovery.

Consistent with their diverse structure, TRP channels also serve diverse functions including afferent sensory functions (mechanical, chemical, thermal, noxious, etc.) as well as efferent mechanisms (of growth control, cellular differentiation, vasoregulation, mediator release, etc.). While most family members are cation channels with limited selectivity for calcium, both calcium- (TRPV5 and TRPV6) and sodium-selective (TRPM4 and TRPM5) family members exist. In addition, some TRP channels transport noncanonical cations such as iron (TRPML1), magnesium (TRPV6), or zinc (TRPA1).

Of the 28 TRP channels discovered until today, seven sense hot or warm temperatures (TRPV1 to TRPV4, TRPM2, TRPM4, and TRPM5), whereas two (TRPA1 and TRPM8) are activated by cold. Together, these channels, referred to as “ thermoTRPs,” cover a wide temperature range with extremes that fall between 10°C (TRPA1) and 53°C (TRPV2). The temperature sensor is believed to be associated with the C terminus. In support of this model, swapping the C-terminal domain of TRPV1 with that of TRPM8 was shown to change the temperature sensitivity of TRPV1 from hot to cold.

Animal data and human genetic studies have shown that TRP channel dysfunction (“TRP channelopathy”) can cause various pathological conditions. In fact, the TRML
(mucolipin) and TRPP (polycystin) families were named after the human diseases they are associated with (mucolipidosis and polycystic kidney disease, respectively). The founding member of the M (melastatin) family, TRPM1, was identified via comparative analysis of genes that distinguish benign nevi and malignant melanoma. The A (ankyrin) family has only one known member (TRPA1), and its name refers to the unusually high number of ankyrin repeats at the N terminus of the channel protein. Mammalian TRP channels that are most similar to those in *Drosophila* are referred to as canonical (TRPC). Last, the V (vanilloid) family came into existence by expression cloning of the capsaicin receptor TRPV1.

The aim of these volumes is ambitious: They open with a series of “state-of-the-art” minireviews on the most interesting TRP channels (from TRPA1 to TRPV4), followed by a collection of cookbook-like protocol chapters describing various methodologies (ranging from capsaicin inhalation test in humans through rodent models of anxiety to stroke, cancer, diabetes, and experimental colitis models) relevant to TRP channel research. Pain models (TRPs = “Targets for Relief of Pain”) were previously detailed in our *Analgesia: Methods and Protocols* volume in the *Methods in Molecular Biology* series. Here, we focus on non-pain models in keeping with the alternative interpretation of TRPs: “Truly Remarkable Proteins.”

It is our hope that this book will be useful for graduate students in academic laboratories as well as for scientists developing new drugs at Pharma and clinicians interested in novel drugs in the pipeline.

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