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192 Overcoming Neuropathic Pain: A New Lead in Pain Management

Voltage-gated sodium channels in nociceptive neurons are attractive targets for novel pain therapeutics. Although drugs that target voltage-gated sodium channels have proven value as pain therapeutics, the drugs that are currently available are non-specific sodium channel inhibitors, which limit their usefulness. Recently, a selective small-molecule inhibitor of Na\(_{\text{v}}\)1.8, a voltage-gated sodium channel isoform that participates in peripheral pain mechanisms, has been developed. This exciting new compound shows efficacy in several animal models of pain and is anticipated to be only the first of many new isoform-specific sodium channel blockers.

Anthony M. Rush and Theodore R. Cummins

195 Outflanking the Side Effects of COX-2 Inhibitors

Non-steroidal anti-inflammatory drugs (NSAIDs) are inhibitors of the cyclo-oxygenase (COX)-1 and -2 activities of prostaglandin G/H synthase-1 and -2, respectively. They have been extensively used in the treatment of prostaglandin E\(_2\)-mediated chronic inflammatory diseases. Selective COX-2 inhibitors (coxibs), which were developed to provide an alternative with reduced gastrointestinal risk for the traditional NSAIDs, have been associated with an increased incidence of major adverse cardiovascular events. Could the targeting of microsomal prostaglandin E\(_2\) synthase (mPGES-1) lead to novel anti-inflammatory drugs with possibly reduced risks of gastrointestinal and cardiovascular side effects?

Leo Timmers, Gerard Pasterkamp, and Dominique P.V. de Kleijn

199 Anti-Oncomirs: First Steps in Exploiting Natural Inhibitors of Oncogene Expression

MicroRNAs (miRNAs or mirs) are small, non-coding RNAs that bind specific mRNAs and decrease their translation or increase their degradation. miRNAs may modulate the formation and maintenance of tumors by regulating oncogene and tumor suppressor expression. For example, overexpression of a subset of miRNAs has been inversely correlated with certain tumor phenotypes, suggesting a role in tumor suppression. Pairs of oncogenes and the corresponding miRNAs that attenuate their expression have been recently identified. These miRNAs, or “anti-oncomirs,” can act as natural inhibitors of oncogene function, indicating the possibility that they might be developed as novel therapeutics.

Andrei Goga and Christopher Benz
203  **Boot cAMP for Trypanosomes: Exploiting the Differences between Human and Parasite Enzymes**

Trypanosomatid parasites cause numerous human diseases, including African sleeping sickness and Chagas disease, affecting millions of people worldwide. There are few effective therapeutic options presently available to treat these diseases, and new anti-trypanosomal drugs are urgently needed. The adenosine 3',5'-monophosphate (cAMP) signaling pathway in these parasites appears to be an attractive target for new therapeutics, as the enzymes that create and destroy cAMP are regulated differently from their mammalian counterparts. This review briefly summarizes the current knowledge of cAMP signaling in trypanosomes and highlights studies of enzymes in the cAMP signaling pathway that are crucial for the survival of the parasite and are, therefore, good targets for new anti-trypanosomal drugs.

*Sunil Laxman and Joseph A. Beavo*

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216  **Controlled Delivery of Synergistic Drug Ratios to Tissue Targets In Vivo**

Cancer chemotherapy treatments typically employ drug combinations in which the dose of each agent is pushed to the brink of unacceptable toxicity; however, emerging evidence indicates that this approach may not be providing optimal efficacy due to the manner in which drugs interact. Specifically, whereas certain ratios of combined drugs can be synergistic, other ratios of the same agents may be antagonistic, implying that the most efficacious combinations may be those that utilize certain agents at reduced doses. Advances in nano-scale drug delivery vehicles now enable the translation of in vitro information on synergistic drug ratios into improved anticancer combination therapies in which the desired drug ratio can be controlled and maintained following administration in vivo, so that synergistic effects can be exploited. This “ratiometric” approach to combination chemotherapy opens new opportunities to enhance the combinatorial effectiveness of existing and future therapeutic agents across a spectrum of human diseases.

*Lawrence D. Mayer and Andrew S. Janoff*