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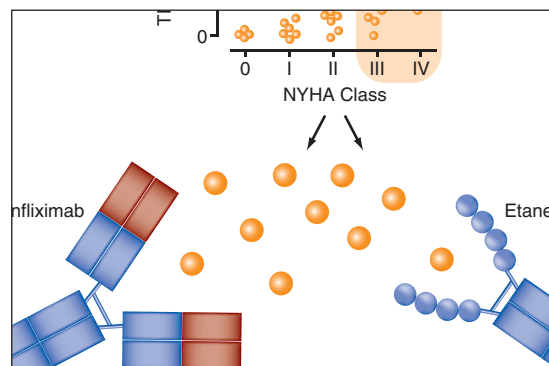
pharmacological perspectives from biology, chemistry and genomics

VIEWPOINTS

79 TNF α : A Tipping Point in Cardiovascular Health

Drugs that target tumor necrosis factor- α (TNF α) have paved new avenues for treating chronic inflammatory diseases such as rheumatoid arthritis. Anti-TNF α drugs have also been evaluated in the treatment heart failure and other cardiovascular events that are caused or accompanied by high circulating concentrations of TNF α . Surprisingly, however, anti-TNF α therapies cause both beneficial and detrimental cardiovascular effects. Here, we suggest that the disappointing cardiovascular outcome of pharmacological interventions with TNF α -targeted drugs could be reconciled with the Janus-like behavior of TNF α , a molecule that conveys both negative and positive stimuli to the heart.

Fabio Cacciapaglia, Pierantonio Menna, Luca Navarini, Antonella Afeltra, Emanuela Salvatorelli, and Giorgio Minotti

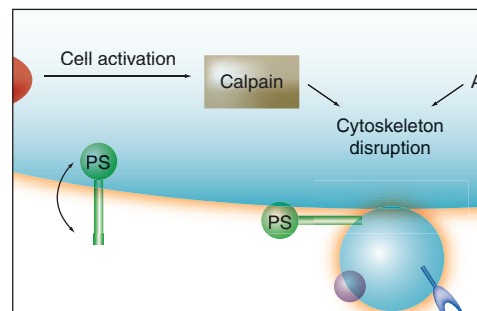


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Cardiovascular preconditioning requires a game of Hi-Lo

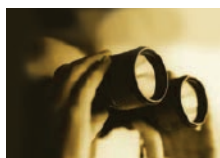
88 Intercellular Signaling: Appreciating the Role of Microvesicular Transport

Microvesicles, which may include microparticles (MPs) and exosomes, are released from a wide variety of cells and have emerged as novel actors of cell-cell communication. Although the pathways governing the formation and release of MPs are different from those of exosomes, the mechanisms by which they transfer biological information to recipient cells are very similar. Recent studies have found that microvesicles are critical modulators of vascular cell functions, inflammation, and immunity. We summarize current research into the cellular and molecular mechanisms involved in the transfer of biological messages by microvesicles.

Simon Tual-Chalot, Daniela Leonetti, Ramarosan Andriantsitohaina, and M. Carmen Martinez



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Big effects in small packages

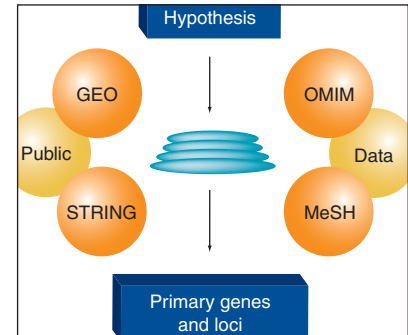


VIEWPOINTS, continued

95 Using Sophisticated Tools to Dig for Disease Genes

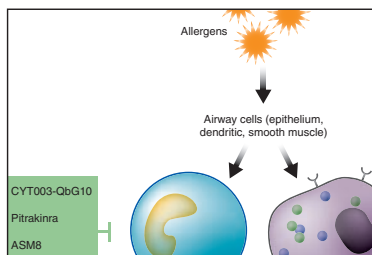
Scientists have discovered basic mechanisms of mammalian development and disease through studying diverse animal models and human Mendelian disorders. The recently constructed database of Genotypes and Phenotypes (dbGAP) has made available to the scientific community extensive human genetic data from large, well-characterized phenotypes. Here we discuss how, in our view, the availability of dbGAP data has changed the traditional scientific approach to the identification of the genetic contributors to human disease and traits. Further, dbGAP has created new opportunities to discover genes important for mammalian development and disease traits through the targeted analysis of coding variants and the application of pathway-based approaches.

Eric C. Wooten and Gordon S. Huggins



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Clues to disease and development

103 Asthma Therapeutics: Recent Strides, New Hurdles



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Asthmatic perspectives

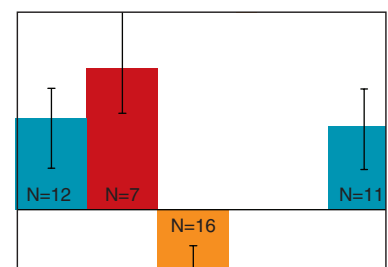
After years of disappointment, three recent phase 2 studies in asthma have brought positive results. The hurdles that asthma research has encountered are numerous: the heterogeneous nature of the disease; over-reliance on rodent models of allergy and inflammation; and the oversimplification of therapeutic complexities by depending on allergen challenge protocols to predict utility. These same hurdles may shed light on the three recent phase 2 results, which, although positive, indicate that traditional approaches to asthma therapeutics may be conceptually limited, resulting in drugs of relevance only for select subgroups of asthmatics.

Kevin Mullane

107 Drug Realities: Do Clinical Trials Comply?

The high failure rate of drugs in clinical trials, especially in the later stages of development, is a significant contributor to the costs and time associated with bringing new molecular entities to market. These costs, estimated to be in excess of \$1.5 billion when capitalized over the ten to fifteen years required to develop a new chemical entity, are one of the principal drivers responsible for the ongoing retrenchment of the pharmaceutical industry. Therapeutic areas such as psychiatry, now deemed very high risk, have been widely downsized, if not abandoned entirely, by the pharmaceutical industry. The extent to which patient noncompliance has marred clinical research has in some cases been underestimated, and one step to improving the design of clinical trials may lie in better attempts to analyze patient compliance during drug testing and clinical development.

Pál Czobor and Phil Skolnick



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Listening to clinical data

molecular interventions

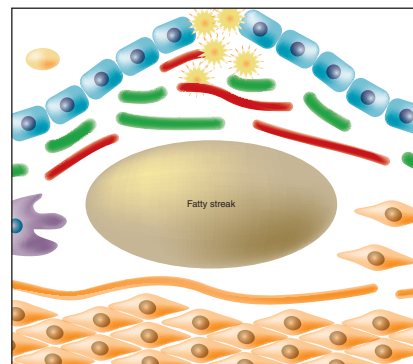
pharmacological perspectives from biology, chemistry and genomics

REVIEWS

111 Tapping a New Artery: Designing Better Anti-thrombotic Therapeutics

Cardiovascular disease and stroke are predominant causes of death in developed countries. Rupture of atherosclerotic plaque in an artery wall and the ensuing thrombotic events are the triggers for acute ischemic injury in these diseases. Platelet activation and aggregation play key roles in this process of atherothrombosis. Anti-platelet drugs thus provide the primary therapeutic strategy to combat these diseases. Although dual therapy with aspirin and clopidogrel is the current standard of care for most patients, it has significant limitations. Thus, there is an impetus to develop new anti-platelet drugs. One new drug that has received FDA approval recently, prasugrel, targets the platelet P2Y₁₂ receptor, as does clopidogrel. Several other new drugs show great promise in clinical trials and appear to be nearing approval. Some have traditional targets on the platelets; others, such as vorapaxar, terutroban, and sarpagrelate, generate more excitement as they are directed against novel targets.

Jaehwa Choi and John C. Kermode

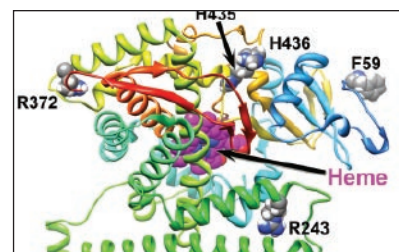


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Fighting plaque: New anti-thrombotics have "sharp teeth"

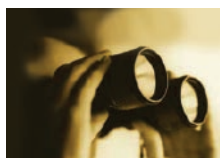
124 Finding Homes for Orphans, CYP by CYP

Genetic analyses have identified a wide spectrum of mutations in the *CYP4V2* gene from patients suffering from Bietti's crystalline corneoretinal dystrophy, and mutations in the *CYP4F22* gene have been linked to lamellar ichthyosis. These strong gene–disease associations will be better understood if we can elucidate the substrate specificity of the heretofore "orphan" P450s and unravel the biochemical pathways that go awry in disease states. The complex biotransformations that underlie eicosanoid signaling, however, pose great challenges for the enzymologist seeking to assign specific metabolic roles to these members of the CYP4 family. Inductive reasoning and modeling are crucial tools for designing the experiments that will define disease progression in terms of CYP function.

Edward J. Kelly, Mariko Nakano, Priyanka Rohatgi, Vladimir Yarov-Yarovoy, and Allan E. Rettie



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Modifying proteins and DNA to alter gene expression

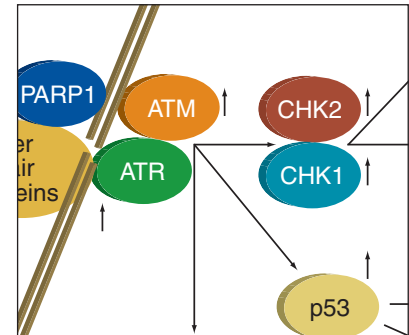


REVIEWS, continued

133 Checkpoint Kinase Inhibitors: Acting Far Past the Checkpoint

Cellular sensing of DNA damage, along with concomitant cell cycle arrest, is mediated by a great many proteins and enzymes. One focus of pharmaceutical development has been the inhibition of DNA damage signaling, and checkpoint kinases (Chks) in particular, as a means to sensitize proliferating tumor cells to chemotherapies that damage DNA. Although the clinical development of Chk inhibitors has overcome many initial obstacles, such drugs have nevertheless failed to show a high level of clinical activity when combined with DNA-damaging chemotherapeutic agents. One very likely reason is the induction of compensatory activities in response to the Chk inhibitor itself. A variety of experimental approaches indicate that the Chk inhibitors of interest influence basic signaling events that could not have been predicted. In this way, the clinical development of such inhibitors is tied to attempts to understand very broad connections among cell signaling pathways.

Paul Dent, Yong Tang, Adly Yacoub, Yun Dai, Paul B. Fisher, and Steven Grant

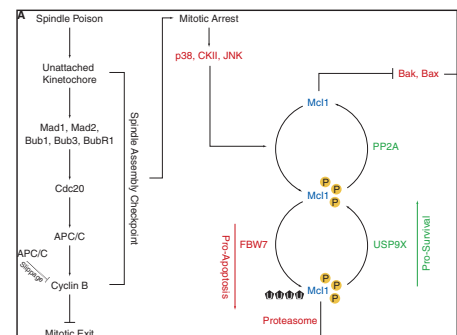


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Checking the checkpoints

141 Inhibiting the Spindle: Determining Life and Death in Prolonged Mitotic Arrest

Spindle poisons, such as paclitaxel and vinblastine, exert their potent anti-neoplastic effects through activation of the spindle assembly checkpoint, thereby arresting cells in mitosis. Unfortunately, only certain cancers are susceptible to these drugs, and many patients fail to respond to treatment. We review the pathways that are triggered by spindle poisons and highlight recent studies that describe the great variability of tumor cells in responding to these drugs. We also describe the recent identification of an apoptotic pathway that is activated by prolonged mitotic arrest. Emerging from these studies is not only a greater understanding of how these classic antimitotic agents bring about cell death, but also a wealth of potential new targets if anticancer therapeutics.

Daniel R. Matson and P. Todd Stukenberg



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"Ausweis, bitte!" Pausing at the checkpoint