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What would be the observable consequences if phospholipid bilayer diffusion of drugs into cells is negligible?
Douglas B. Kell

Abstract
For drug transport across (i.e., through) an intact biological membrane, two main routes are possible: drugs may cross (i) through the phospholipid bilayer portion of the membrane, and/or (ii) via proteinaceous pores or transporters. Perhaps surprisingly, there is in fact no direct scientific evidence that the first of these takes place at any significant rate because, in the experiments performed to date, it has neither been varied as an independent variable nor measured directly as a dependent variable. Using a standard hypothetico-deductive framework, I assess the intellectual and observable consequences of assuming that, for drugs, phospholipid bilayer diffusion is negligible – ‘PBIN’ – (i.e., may be neglected, relative to transporter-mediated transmembrane fluxes). Predictions and postdictions of the PBIN hypothesis are not refuted by available experimental evidence.

Amphetamines, new psychoactive drugs and the monoamine transporter cycle
Harald H. Sitte, Michael Freissmuth

Abstract
In monoaminergic neurons, the vesicular transporters and the plasma membrane transporters operate in a relay. Amphetamine and its congeners target this relay to elicit their actions: most amphetamines are substrates, which pervert the relay to elicit efflux of monoamines into the synaptic cleft. However, some amphetamines act as transporter inhibitors. Both compound classes elicit profound psychostimulant effects, which render them liable to recreational abuse. Currently, a surge of new psychoactive substances occurs on a global scale. Chemists bypass drug bans by ingenuous structural variations, resulting in a rich pharmacology. A credible transport model must account for their distinct mode of action and link this to subtle differences in activity and undesired, potentially deleterious effects.

What would be the observable consequences if phospholipid bilayer diffusion of drugs into cells is negligible?
Douglas B. Kell

Abstract
For drug transport across (i.e., through) an intact biological membrane, two main routes are possible: drugs may cross (i) through the phospholipid bilayer portion of the membrane, and/or (ii) via proteinaceous pores or transporters. Perhaps surprisingly, there is in fact no direct scientific evidence that the first of these takes place at any significant rate because, in the experiments performed to date, it has neither been varied as an independent variable nor measured directly as a dependent variable. Using a standard hypothetico-deductive framework, I assess the intellectual and observable consequences of assuming that, for drugs, phospholipid bilayer diffusion is negligible – ‘PBIN’ – (i.e., may be neglected, relative to transporter-mediated transmembrane fluxes). Predictions and postdictions of the PBIN hypothesis are not refuted by available experimental evidence.
**Volume 36, Issue 2, February 2015**

**Ata collection as a barrier to personalized medicine**
David Zakim, Matthias Schwab

**Abstract**

Basic life science research holds the promise of personalizing medical care. However, translation steps from the laboratory to the bedside are not trivial. Results from clinical research are difficult to replicate in part because study cohorts are poorly defined phenotypically. Here, we discuss how computer technology can improve the collection of clinical data to enable translation of insights from basic science to validated clinical guidelines.

**Supersaturation is a major driving force for protein aggregation in neurodegenerative diseases**

Prajwal Ciryam, Rishika Kundra, Richard I. Morimoto, Christopher M. Dobson, Michele Vendruscolo

**Abstract**

The solubility of proteins is an essential requirement for their function. Nevertheless, these ubiquitous molecules can undergo aberrant aggregation when the protein homeostasis system becomes impaired. Here we ask: what are the driving forces for protein aggregation in the cellular environment? Emerging evidence suggests that this phenomenon arises at least in part because the native states of many proteins are inherently metastable when their cellular concentrations exceed their critical values. Such ‘supersaturated’ proteins, which form a ‘metastable subproteome’, are strongly driven towards aggregation, and are over-represented in specific biochemical pathways associated with neurodegenerative conditions. These observations suggest that effective therapeutic approaches designed to combat neurodegenerative diseases could be aimed at enhancing the ability of the cell to maintain the homeostasis of the metastable subproteome.

**Three-finger snake neurotoxins and Ly6 proteins targeting nicotinic acetylcholine receptors: pharmacological tools and endogenous modulators**

Victor I. Tsetlin

**Abstract**

Snake venom neurotoxins and lymphocyte antigen 6 (Ly6) proteins, most of the latter being membrane tethered by a glycosylphosphatidylinositol (GPI) anchor, have a variety of biological activities, but their three-finger (3F) folding combines them in one Ly6/neurotoxin family. Subsets of two groups, represented by α-neurotoxins and Lynx1, respectively, interact with nicotinic acetylcholine receptors (nAChR) and, hence, are of therapeutic interest for the treatment of neurodegenerative diseases, pain, and cancer. Information on the mechanisms of action and 3D structure of the binding sites, which is required for drug design, is available from the 3D structure of α-neurotoxin complexes with nAChR models. Here, I compare the structural and functional features of α-neurotoxins versus Lynx1 and its homologs to get a clearer picture of Lynx1–nAChR interactions that is necessary for fundamental science and practical applications.

**Current treatment strategies for inhibiting mTOR in cancer**

Francesca Chiarini, Camilla Evangelisti, James A. McCubrey, Alberto M. Martelli

**Abstract**

Mammalian target of rapamycin (mTOR) is a Ser/Thr kinase that regulates a wide range of functions, including cell growth, proliferation, survival, autophagy, metabolism, and cytoskeletal organization. mTOR activity is dysregulated in several human disorders, including cancer. The crucial role of mTOR in cancer cell biology has stimulated interest in mTOR inhibitors, placing mTOR on the radar of the pharmaceutical industry. Several mTOR inhibitors have already undergone clinical trials for treating tumors, without great success, although mTOR inhibitors are approved for the treatment of some types of cancer, including advanced renal cell carcinoma. However, the role of mTOR inhibitors in cancer treatment continues to evolve as new compounds are continuously being disclosed. Here we review the three classes of mTOR inhibitors currently available for treating cancer patients. Moreover, we highlight efforts to identify markers of resistance and sensitivity to mTOR inhibition that could prove useful in the emerging field of personalized medicine.
The GPCR heterotetramer: challenging classical pharmacology

Review Article

Author: Sergi Ferré

Abstract

Two concepts are gaining increasing acceptance in G protein-coupled receptor (GPCR) pharmacology: (i) pre-coupling of GPCRs with their preferred signaling molecules, and (ii) GPCR oligomerization. This is begging for the introduction of new models such as GPCR oligomer-containing signaling complexes with GPCR homodimers as functional building blocks. This model favors the formation of GPCR heterotetramers – heteromers of homodimers coupled to their cognate G protein. The GPCR heterotetramer offers an optimal framework for a canonical antagonistic interaction between activated Gs and Gi proteins, which can simultaneously bind to their respective preferred receptors and to adenylyl cyclase (AC) catalytic units. This review addresses the current evidence for pre-coupling of the various specific components that provide the very elaborate signaling machinery exemplified by the Gs–Gi–AC-coupled GPCR heterotetramer.

The 12/15-lipoxygenase as an emerging therapeutic target for Alzheimer's disease

Yash B. Joshi, Phillip F. Giannopoulos, Domenico Praticò

Abstract

Alzheimer's disease (AD) is a chronic neurodegenerative condition characterized by progressive memory loss. Mutations in genes involved in the production of amyloid-β (Aβ) are linked to the early-onset variant of AD. However, the most common form, sporadic AD, is considered to be the result of an interaction between environmental risk factors and various genes. Among them, recent work has highlighted the potential role that the 12/15-lipoxygenase (12/15LO) pathway may play in AD pathogenesis. 12/15LO is widely distributed in the central nervous system, and its levels are upregulated in patients with AD or mild cognitive impairments. Studies using animal models have implicated 12/15LO in the molecular pathology of AD, including the metabolism of Aβ and tau, synaptic integrity, and cognitive functions. We provide an overview of this pathway and its relevance to AD pathogenesis, discuss the mechanism(s) involved, and provide an assessment of how targeting 12/15LO could lead to novel AD therapeutics.

Novel therapeutic targets in rheumatoid arthritis

Marije I. Koenders, Wim B. van den Berg

Abstract

Rheumatoid arthritis (RA) is an autoimmune disease that leads to inflammation and destruction of synovial joints. Despite the broad spectrum of antirheumatic drugs, this heterogeneous disease is still not well controlled in up to 30% of patients. Here, we discuss two pathways that are regarded as interesting novel therapeutic targets in the field of rheumatology: the Janus kinase (JAK) pathway and the T helper-17 (Th17) pathway [including interleukin (IL)-17, IL-21, IL-22, and granulocyte-macrophage colony-stimulating factor (GM-CSF)]. We also review the therapy potential of biologicals and small-molecule inhibitors blocking these pathways. Advances in combination therapy in addition to progress in biomarker screening will help us to further achieve effective and personalized healthcare for patients with RA.

α2-Adrenoceptors in the treatment of major neuropsychiatric disorders

Salomon Z. Langer

Abstract

Presynaptic autoreceptors mediate a retrograde transfer of information by a negative feedback mechanism mediated by the transmitter of the neuron, and fulfill an autoregulatory function in neurotransmission in the peripheral and central nervous system (CNS). Starting with norepinephrine (NE), it was later reported that an autoreceptor-mediated negative feedback mechanism exists for other neurotransmitters, including dopamine (DA), serotonin, acetylcholine, histamine, GABA, and glutamate. This feedback mechanism regulates calcium-dependent transmitter release and synthesis through terminal presynaptic autoreceptors, while the firing rate of the neuron is regulated through somatodendritic autoreceptors.
The future of EPAC-targeted therapies: agonism versus antagonism
Euan Parnell, Timothy M. Palmer, Stephen J. Yarwood

Abstract
Pharmaceutical manipulation of cAMP levels exerts beneficial effects through the regulation of the exchange protein activated by cAMP (EPAC) and protein kinase A (PKA) signalling routes. Recent attention has turned to the specific regulation of EPAC isoforms (EPAC1 and EPAC2) as a more targeted approach to cAMP-based therapies. For example, EPAC2-selective agonists could promote insulin secretion from pancreatic β cells, whereas EPAC1-selective agonists may be useful in the treatment of vascular inflammation. By contrast, EPAC1 and EPAC2 antagonists could both be useful in the treatment of heart failure. Here we discuss whether the best way forward is to design EPAC-selective agonists or antagonists and the current strategies being used to develop isoform-selective, small-molecule regulators of EPAC1 and EPAC2 activity.

Towards tissue-specific pharmacology: insights from the calcium-sensing receptor as a paradigm for GPCR (patho)physiological bias
Katie Leach, Arthur D. Conigrave, Patrick M. Sexton, Arthur Christopoulos

Abstract
The calcium-sensing receptor (CaSR) is a widely expressed G protein-coupled receptor (GPCR) that mediates numerous tissue-specific functions. Its multiple ligands and diverse roles attest to the need for exquisite control over the signaling pathways that mediate its effects. ‘Biased signaling’ is the phenomenon by which distinct ligands stabilize preferred receptor signaling states. The CaSR is subject to biased signaling in response to its endogenous ligands. Interestingly, the ‘natural’ bias of the CaSR is altered in disease states, and small molecule drugs engender biased allosteric modulation of downstream signaling pathways. Thus, biased signaling from the CaSR also has important implications pathophysiologically and therapeutically. As outlined in this review, this novel paradigm extends to other GPCRs, making the CaSR a model for studies of ligand-biased signaling and for understanding how it may be used to foster selective drug activity in different tissues.

Epigenetic-related therapeutic challenges in cardiovascular disease
Concetta Schiano, Maria Teresa Vietri, Vincenzo Grimaldi, Antonietta Picascia, Maria Rosaria De Pascale, Claudio Napoli

Abstract
Progress in human genetic and genomic research has led to the identification of genetic variants associated with specific cardiovascular diseases (CVDs), but the pathogenic mechanisms remain unclear. Recent studies have analyzed the involvement of epigenetic mechanisms such as DNA methylation and histone modifications in the development and progression of CVD. Preliminary work has investigated the correlations between DNA methylation, histone modifications, and RNA-based mechanisms with CVDs including atherosclerosis, heart failure (HF), myocardial infarction (MI), and cardiac hypertrophy. Remarkably, both in utero programming and postnatal hypercholesterolemia may affect the epigenetic signature in the human cardiovascular system, thereby providing novel early epigenetic-related pharmacological insights. Interestingly, some dietary compounds, including polyphenols, cocoa, and folic acid, can modulate DNA methylation status, whereas statins may promote epigenetic-based control in CVD prevention through histone modifications. We review recent findings on the epigenetic control of cardiovascular system and new challenges for therapeutic strategies in CVDs.
Nanomedicine to overcome radioresistance in glioblastoma stem-like cells and surviving clones
Delphine Séhédic, Annabelle Cikankowitz, François Hindré, François Davodeau, Emmanuel Garcion

Abstract
Radiotherapy is one of the standard treatments for glioblastoma, but its effectiveness often encounters the phenomenon of radioresistance. This resistance was recently attributed to distinct cell contingents known as glioblastoma stem-like cells (GSCs) and dominant clones. It is characterized in particular by the activation of signaling pathways and DNA repair mechanisms. Recent advances in the field of nanomedicine offer new possibilities for radiosensitizing these cell populations. Several strategies have been developed in this direction, the first consisting of encapsulating a contrast agent or synthesizing metal-based nanocarriers to concentrate the dose gradient at the level of the target tissue. In the second strategy the physicochemical properties of the vectors are used to encapsulate a wide range of pharmacological agents which act in synergy with the ionizing radiation to destroy the cancerous cells. This review reports on the various molecular anomalies present in GSCs and the predominant role of nanomedicines in the development of radiosensitization strategies.

Quantifying the impact of transporters on cellular drug permeability
Pär Matsson, Luca A. Fenu, Patrik Lundquist, Jacek R. Wiśniewski, Manfred Kansy, Per Artursson

Abstract
The conventional model of drug permeability has recently been challenged. An alternative model proposes that transporter-mediated flux is the sole mechanism of cellular drug permeation, instead of existing in parallel with passive transmembrane diffusion. We examined a central assumption of this alternative hypothesis; namely, that transporters can give rise to experimental observations that would typically be explained with passive transmembrane diffusion. Using systems-biology simulations based on available transporter kinetics and proteomic expression data, we found that such observations are possible in the absence of transmembrane diffusion, but only under very specific conditions that rarely or never occur for known human drug transporters.

Featuring the nucleosome surface as a therapeutic target
Isabel Torres Gomes da Silva, Paulo Sergio Lopes de Oliveira, Guilherme Martins Santos

Abstract
Chromatin is the major regulator of gene expression and genome maintenance. Proteins that bind the nucleosome, the repetitive unit of chromatin, and the histone H4 tail are critical to establishing chromatin architecture and phenotypic outcomes. Intriguingly, nucleosome-binding proteins (NBPs) and the H4 tail peptide compete for the same binding site at an acidic region on the nucleosome surface. Although the essential facts about the nucleosome were revealed 17 years ago, new insights into its atomic structure and molecular mechanisms are still emerging. Several complex nucleosome:NBP structures were recently revealed, characterizing the NBP-binding sites on the nucleosome surface. Here we discuss the potential of the nucleosome surface as a therapeutic target and the impact and development of exogenous nucleosome-binding molecules (eNBMs).

Menstruation pulls the trigger for inflammation and pain in endometriosis
Alexis Laux-Biehlmann, Thomas d’Hooghe, Thomas M. Zollner

Abstract
Endometriosis is a chronic, hormone-dependent, inflammatory disease, characterized by the presence and growth of endometrial tissue outside the uterine cavity. It affects 5–10% of the female population of reproductive age and is frequently associated with moderate to severe pain, subfertility, and a marked reduction in health-related quality of life. Here, we propose a new pathophysiological concept of endometriosis, summarizing recent findings in one unifying picture. We propose menstruating tissue as the trigger for inflammatory pain in endometriosis through the activation of innate immune cells and peripheral nerve endings. We speculate how innovative treatment modalities beyond hormonal treatment will improve patients’ lives.

Angiotensins as therapeutic targets beyond heart disease
Danielle Gomes Passos-Silva, Enrique Brandan, Robson Augusto Souza Santos

Abstract
The renin–angiotensin system (RAS) plays a pivotal role in cardiovascular and hydro-electrolyte homeostasis. Blockade of the RAS as a therapeutic strategy for treating hypertension and related cardiovascular diseases is well established. However, actions of the RAS go far beyond the targets initially described. In this regard, the recent identification of novel components of the RAS, including angiotensin-(1–7) [Ang-(1–7)], Ang-(1–9), and alamandine, have opened new possibilities for interfering with the development and manifestations of cardiovascular and non-cardiovascular diseases. In this article, we briefly review novel targets for angiotensins and its therapeutic implications in diverse areas, including cancer, inflammation, and glaucoma.
Endocannabinoid signaling at the periphery: 50 years after THC
Mauro Maccarrone, Itai Bab, Tamás Bíró, Guy A. Cabral, Sudhansu K. Dey, Vincenzo Di Marzo, Justin C. Konje, George Kunos, Raphael Mechoulam, Pal Pacher, Keith A. Sharkey, Andreas Zimmer

Abstract
In 1964, the psychoactive ingredient of Cannabis sativa, Δ⁹-tetrahydrocannabinol (THC), was isolated. Nearly 30 years later the endogenous counterparts of THC, collectively termed endocannabinoids (eCBs), were discovered: N-arachidonylethanolamine (anandamide) (AEA) in 1992 and 2-arachidonoylglycerol (2-AG) in 1995. Since then, considerable research has shed light on the impact of eCBs on human health and disease, identifying an ensemble of proteins that bind, synthesize, and degrade them and that together form the eCB system (ECS). eCBs control basic biological processes including cell choice between survival and death and progenitor/stem cell proliferation and differentiation. Unsurprisingly, in the past two decades eCBs have been recognized as key mediators of several aspects of human pathophysiology and thus have emerged to be among the most widespread and versatile signaling molecules ever discovered. Here some of the pioneers of this research field review the state of the art of critical eCB functions in peripheral organs. Our community effort is aimed at establishing consensus views on the relevance of the peripheral ECS for human health and disease pathogenesis, as well as highlighting emerging challenges and therapeutic hopes.

Amyloid biomarkers in Alzheimer's disease
Kaj Blennow, Niklas Mattsson, Michael Schöll, Oskar Hansson, Henrik Zetterberg

Abstract
Aggregation of amyloid-β (Aβ) into oligomers, fibrils, and plaques is central in the molecular pathogenesis of Alzheimer's disease (AD), and is the main focus of AD drug development. Biomarkers to monitor Aβ metabolism and aggregation directly in patients are important for further detailed study of the involvement of Aβ in disease pathogenesis and to monitor the biochemical effect of drugs targeting Aβ in clinical trials. Furthermore, if anti-Aβ disease-modifying drugs prove to be effective clinically, amyloid biomarkers will be of special value in the clinic to identify patients with brain amyloid deposition at risk for progression to AD dementia, to enable initiation of treatment before neurodegeneration is too severe, and to monitor drug effects on Aβ metabolism or pathology to guide dosage. Two types of amyloid biomarker have been developed: Aβ-binding ligands for use in positron emission tomography (PET) and assays to measure Aβ42 in cerebrospinal fluid (CSF). In this review, we present the rationales behind these biomarkers and compare their ability to measure Aβ plaque load in the brain. We also review possible shortcomings and the need of standardization of both biomarkers, as well as their implementation in the clinic.
Improving transparency of clinical trials
Rafael Dal-Ré

Abstract
Recent data reveal that subtle selective publication affects critical aspects of trial reporting, in some cases altering the interpretation of results. Timely prospective registration could help deter selective reporting and clinical trial stakeholders from government authorities to journal editors should work together to foster prospective registration of trials.

Anthracyclines/trastuzumab: new aspects of cardiotoxicity and molecular mechanisms
Luc Rochette, Charles Guenancia, Aurélie GudjonciK, Olivier Hachet, Marianne Zeller, Yves Cottin, Catherine Vergely

Abstract
Anticancer drugs continue to cause significant reductions in left ventricular ejection fraction resulting in congestive heart failure. The best-known cardiotoxic agents are anthracyclines (ANTHs) such as doxorubicin (DOX). For several decades cardiotoxicity was almost exclusively associated with ANTHs, for which cumulative dose-related cardiac damage was the use-limiting step. Human epidermal growth factor (EGF) receptor 2 (HER2; ErbB2) has been identified as an important target for breast cancer. Trastuzumab (TRZ), a humanized anti-HER2 monoclonal antibody, is currently recommended as first-line treatment for patients with metastatic HER2+ tumors. The use of TRZ may be limited by the development of drug intolerance, such as cardiac dysfunction. Cardiotoxicity has been attributed to free-iron-based, radical-induced oxidative stress. Many approaches have been promoted to minimize these serious side effects, but they are still clinically problematic. A new approach to personalized medicine for cancer that involves molecular screening for clinically relevant genomic alterations and genotype-targeted treatments is emerging.

The emerging molecular machinery and therapeutic targets of metastasis
Yutong Sun, Li Ma

Abstract
Metastasis is a 100-year-old research topic. Technological advances during the past few decades have led to significant progress in our understanding of metastatic disease. However, metastasis remains the leading cause of cancer-related mortalities. The lack of appropriate clinical trials for metastasis preventive drugs and incomplete understanding of the molecular machinery are major obstacles in metastasis prevention and treatment. Numerous processes, factors, and signaling pathways are involved in regulating metastasis. Here we discuss recent progress in metastasis research, including epithelial–mesenchymal plasticity, cancer stem cells, emerging molecular determinants and therapeutic targets, and the link between metastasis and therapy resistance.

New therapeutic targets for cancer bone metastasis
Jing Y. Krzeszinski, Yihong Wan

Abstract
Bone metastases are dejected consequences of many types of tumors including breast, prostate, lung, kidney, and thyroid cancers. This complicated process begins with the successful tumor cell epithelial–mesenchymal transition, escape from the original site, and penetration into the circulation. The homing of tumor cells to the bone depends on both tumor-intrinsic traits and various molecules supplied by the bone metastatic niche. The colonization and growth of cancer cells in the osseous environment, which awaken their dormancy to form micro- and macro-metastasis, involve an intricate interaction between the circulating tumor cells and local bone cells including osteoclasts, osteoblasts, adipocytes, and macrophages. We discuss the most recent advances in the identification of new molecules and novel mechanisms during each step of bone metastasis that may serve as promising therapeutic targets.
Hypoxia-inducible factors in cancer stem cells and inflammation
Gong Peng, Yang Liu

Abstract
Hypoxia-inducible factors (HIF) mediate metabolic switches in cells in hypoxic environments, including those in both normal and malignant tissues with limited supplies of oxygen. Paradoxically, recent studies have shown that cancer stem cells (CSCs) and activated immune effector cells exhibit high HIF activity in normoxic environments and that HIF activity is critical in the maintenance of CSCs as well as the differentiation and function of inflammatory cells. Given that inflammation and CSCs are two major barriers to effective cancer therapy, targeting HIF may provide a new approach to developing such treatments.

Towards universal therapeutics for memory disorders
Miao-Kun Sun, Thomas J. Nelson, Daniel L. Alkon

Abstract
Evidence is accumulating that many memory disorders, including those due to neurodegenerative diseases, traumatic brain injury (TBI), vascular disease, or abnormal brain development, share common features of memory-related pathology. Structural and functional deficits of synapses are at the core of the underlying pathophysiology, constituting a critical point of convergence in memory disorders. Memory therapeutics that target synaptic loss and dysfunction – that is, to slow, halt, or reverse progression of the disorders at the level of synapses, via synaptogenic molecular cascades such as those of protein kinase C (PKC) and brain-derived neurotrophic factor (BDNF) – possess universal therapeutic value for many forms of memory disorder. They may be useful either as standalone interventions for patients with memory disorders or as adjuncts to drugs that target the underlying pathology.

Arginase: an old enzyme with new tricks
Ruth B. Caldwell, Haroldo A. Toque, S. Priya Narayanan, R. William Caldwell

Abstract
Arginase has roots in early life-forms. It converts L-arginine to urea and ornithine. The former provides protection against NH₃; the latter serves to stimulate cell growth and other physiological functions. Excessive arginase activity in mammals has been associated with cardiovascular and nervous system dysfunction and disease. Two relevant aspects of this elevated activity may be involved in these disease states. First, excessive arginase activity reduces the supply of L-arginine needed by nitric oxide (NO) synthase to produce NO. Second, excessive production of ornithine leads to vascular structural problems and neural toxicity. Recent research has identified inflammatory agents and reactive oxygen species (ROS) as drivers of this pathologic elevation of arginase activity and expression. We review the involvement of arginase in cardiovascular and nervous system dysfunction, and discuss potential therapeutic interventions targeting excess arginase.

Targeting SREBPs for treatment of the metabolic syndrome
Selma M. Soyal, Charity Nofziger, Silvia Dossena, Markus Paulmichl, Wolfgang Patsch

Abstract
Over the past few decades, mortality resulting from cardiovascular disease (CVD) steadily decreased in western countries; however, in recent years, the decline has become offset by the increase in obesity. Obesity is strongly associated with the metabolic syndrome and its atherogenic dyslipidemia resulting from insulin resistance. While lifestyle treatment would be effective, drugs targeting individual risk factors are often required. Such treatment may result in polypharmacy. Novel approaches are directed towards the treatment of several risk factors with one drug. Studies in animal models and humans suggest a central role for sterol regulatory-element binding proteins (SREBPs) in the pathophysiology of the metabolic syndrome. Four recent studies targeting the maturation or transcriptional activities of SREBPs provide proof of concept for the efficacy of SREBP inhibition in this syndrome.
Volume 36, Issue 7, July 2015

**IVIg for relapsing–remitting multiple sclerosis: promises and uncertainties**  
Jagadeesh Bayry, Hans-Peter Hartung, Sriti V. Kaveri

**Abstract**
Despite promising clinical trials, intravenous immunoglobulin (IVIg) therapy in relapsing–remitting multiple sclerosis (MS) has met with uncertainties that might be attributed to small patient cohorts, heterogeneity in the patients, dose of IVIg, or the duration and window of treatment.

**FDA-approved small-molecule kinase inhibitors**  
Peng Wu, Thomas E. Nielsen, Mads H. Clausen

**Abstract**
Kinases have emerged as one of the most intensively pursued targets in current pharmacological research, especially for cancer, due to their critical roles in cellular signaling. To date, the US FDA has approved 28 small-molecule kinase inhibitors, half of which were approved in the past 3 years. While the clinical data of these approved molecules are widely presented and structure–activity relationship (SAR) has been reported for individual molecules, an updated review that analyzes all approved molecules and summarizes current achievements and trends in the field has yet to be found. Here we present all approved small-molecule kinase inhibitors with an emphasis on binding mechanism and structural features, summarize current challenges, and discuss future directions in this field.

**A new model of reverse cholesterol transport: enTICEing strategies to stimulate intestinal cholesterol excretion**  
Ryan E. Temel, J. Mark Brown

**Abstract**
Cardiovascular disease (CVD) remains the largest cause of mortality in most developed countries. Although recent failed clinical trials and Mendelian randomization studies have called into question the high-density lipoprotein (HDL) hypothesis, it remains well accepted that stimulating the process of reverse cholesterol transport (RCT) can prevent or even regress atherosclerosis. The prevailing model for RCT is that cholesterol from the artery wall must be delivered to the liver where it is secreted into bile before leaving the body through fecal excretion. However, many studies have demonstrated that RCT can proceed through a non-biliary pathway known as transintestinal cholesterol excretion (TICE). The goal of this review is to discuss the current state of knowledge of the TICE pathway, with emphasis on points of therapeutic intervention.

**Designing selective inhibitors for calcium-dependent protein kinases in apicomplexans**  
Raymond Hui, Majida El Bakkouri, L. David Sibley

**Abstract**
Apicomplexan parasites cause some of the most severe human diseases, including malaria (caused by *Plasmodium*), toxoplasmosis, and cryptosporidiosis. Treatments are limited by the lack of effective drugs and development of resistance to available agents. By exploiting novel features of protein kinases in these parasites, it may be possible to develop new treatments. We summarize here recent advances in identifying small molecule inhibitors against a novel family of plant-like, calcium-dependent kinases that are uniquely expanded in apicomplexan parasites. Analysis of the 3D structure, activation mechanism, and sensitivity to small molecules had identified several attractive chemical scaffolds that are potent and selective inhibitors of these parasite kinases. Further optimization of these leads may yield promising new drugs for treatment of these parasitic infections.
Adipokines in health and disease
Mathias Fasshauer, Matthias Blüher

Abstract
Obesity increases the risk for metabolic, cardiovascular, chronic inflammatory, and several malignant diseases and, therefore, may contribute to shortened lifespan. Adipokines are peptides that signal the functional status of adipose tissue to targets in the brain, liver, pancreas, immune system, vasculature, muscle, and other tissues. Secretion of adipokines, including leptin, adiponectin, fibroblast growth factor 21 (FGF21), retinol-binding protein 4 (RBP4), dipeptidyl peptidase 4 (DPP-4), bone morphogenetic protein (BMP)-4, BMP-7, vaspin, apelin, and progranulin, is altered in adipose tissue dysfunction and may contribute to a spectrum of obesity-associated diseases. Adipokines are promising candidates both for novel pharmacological treatment strategies and as diagnostic tools, provided that we can develop a better understanding of the function and molecular targets of the more recently discovered adipokines.

Inflammatory reaction after traumatic brain injury: therapeutic potential of targeting cell–cell communication by chemokines
Stefka Gyoneva, Richard M. Ransohoff

Abstract
Traumatic brain injury (TBI) affects millions of people worldwide every year. The primary impact initiates the secretion of pro- and anti-inflammatory factors, subsequent recruitment of peripheral immune cells, and activation of brain-resident microglia and astrocytes. Chemokines are major mediators of peripheral blood cell recruitment to damaged tissue, including the TBI brain. Here we review the involvement of specific chemokine pathways in TBI pathology and attempts to modulate these pathways for therapeutic purposes. We focus on chemokine (C-C motif) ligand 2/chemokine (C-C motif) receptor 2 (CCL2/CCR2) and chemokine (C-X-C motif) ligand 12/chemokine (C-X-C motif) receptor 4 (CXCL12/CXCR4). Recent microarray and multiplex expression profiling have also implicated CXCL10 and CCL5 in TBI pathology. Chemokine (C-X3-C motif) ligand 1/chemokine (C-X3-C motif) receptor 1 (CX3CL1/CX3CR1) signaling in the context of TBI is also discussed. Current literature suggests that modulating chemokine signaling, especially CCL2/CCR2, may be beneficial in TBI treatment.

HDAC8: a multifaceted target for therapeutic interventions
Alokta Chakrabarti, Ina Oehme, Olaf Witt, Guilherme Oliveira, Wolfgang Sippl, Christophe Romier, Raymond J. Pierce, Manfred Jung

Abstract
Histone deacetylase 8 (HDAC8) is a class I histone deacetylase implicated as a therapeutic target in various diseases, including cancer, X-linked intellectual disability, and parasitic infections. It is a structurally well-characterized enzyme that also deacetylates nonhistone proteins. In cancer, HDAC8 is a major ‘epigenetic player’ that is linked to deregulated expression or interaction with transcription factors critical to tumorigenesis. In the parasite Schistosoma mansoni and in viral infections, HDAC8 is a novel target to subdue infection. The current challenge remains in the development of potent selective inhibitors that would specifically target HDAC8 with fewer adverse effects compared with pan-HDAC inhibitors. Here, we review HDAC8 as a drug target and discuss inhibitors with respect to their structural features and therapeutic interventions.

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A proposal for an ‘equal peer-review’ statement  
Khaled Moustafa

**Abstract**
To make the peer-review process as objective as possible, I suggest the introduction of an ‘equal peer-review’ statement that preserves author anonymity across the board, thus removing any potential bias related to nominal or institutional ‘prestige’; this would guarantee an equal peer-review process for all authors and grant applicants.

Halal pharmaceutical industry: opportunities and challenges  
Mohd Nor Norazmi, Li Sze Lim

**Abstract**
The expanding global Muslim population has increased the demand for halal pharmaceuticals. However, there are several challenges for this emerging niche industry, foremost of which is the need to establish a proper, well-regulated, and harmonized accreditation and halal management system.

Assay strategies for identification of therapeutic leads that target protein trafficking  
P. Michael Conn, Timothy P. Spicer, Louis Scampavia, Jo Ann Janovick

**Abstract**
Receptors, enzymes, and ion channels are traditional targets of therapeutic development. A common strategy is to target these proteins with agents that either activate or suppress their activity with ligands or substrates that occupy orthosteric sites or have allosteric interactions. An alternative approach involves regulation of protein trafficking. In principle, this approach enables ‘rescue’ of misfolded and misrouted mutant proteins to restore function, ‘shipwrecking’ of undesirable proteins by targeting them for destruction, and regulation of levels of partially expressed wild type (WT) proteins at their functional sites of action. Here, we present drug discovery strategies that identify ‘pharmacoperones’, which are small molecules that serve as molecular templates and cause otherwise misfolded mutant proteins to fold and route correctly.

Exploring the potential of adjunct therapy in tuberculosis  
Geetha Vani Rayasam, Tanjore S Balganesh

**Abstract**
A critical unmet need for treatment of drug-resistant tuberculosis (TB) is to find novel therapies that are efficacious, safe, and shorten the duration of treatment. Drug discovery approaches for TB primarily target essential genes of the pathogen Mycobacterium tuberculosis (Mtb) but novel strategies such as host-directed therapies and nonmicrobicidal targets are necessary to bring about a paradigm shift in treatment. Drugs targeting the host pathways and nonmicrobicidal proteins can be used only in conjunction with existing drugs as adjunct therapies. Significantly, host-directed adjunct therapies have the potential to decrease duration of treatment, as they are less prone to drug resistance, target the immune responses, and act via novel mechanism of action. Recent advances in targeting host–pathogen interactions have implicated pathways such as eicosanoid regulation and angiogenesis. Furthermore, several approved drugs such as metformin and verapamil have been identified that appear suitable for repurposing for the treatment of TB. These findings and the challenges in the area of host- and/or pathogen-directed adjunct therapies and their implications for TB therapy are discussed.
Looking below the surface of nicotinic acetylcholine receptors
Clare Stokes, Millet Treinin, Roger L. Papke

Abstract
The amino acid sequences of nicotinic acetylcholine receptors (nAChRs) from diverse species can be compared across extracellular, transmembrane, and intracellular domains. The intracellular domains are most divergent among subtypes, yet relatively consistent among species. The diversity indicates that each nAChR subtype has a unique language for communication with its host cell. The conservation across species also suggests that the intracellular domains have defining functional roles for each subtype. Secondary structure prediction indicates two relatively conserved alpha helices within the intracellular domains of all nAChRs. Among all subtypes, the intracellular domain of α7 nAChR is one of the most well conserved, and α7 nAChRs have effects in non-neuronal cells independent of generating ion currents, making it likely that the α7 intracellular domain directly mediates signal transduction. There are potential phosphorylation and protein-binding sites in the α7 intracellular domain, which are conserved and may be the basis for α7-mediated signal transduction.

Nitric oxide in liver diseases
Yasuko Iwakiri, Moon Young Kim

Abstract
Nitric oxide (NO) and its derivatives play important roles in the physiology and pathophysiology of the liver. Despite its diverse and complicated roles, certain patterns of the effect of NO on the pathogenesis and progression of liver diseases are observed. In general, NO derived from endothelial NO synthase (eNOS) in liver sinusoidal endothelial cells (LSECs) is protective against disease development, while inducible NOS (iNOS)-derived NO contributes to pathological processes. This review addresses the roles of NO in the development of various liver diseases with a focus on recently published articles. We present here two recent advances in understanding NO-mediated signaling – nitrated fatty acids (NO2-FAs) and Sguanylation – and conclude with suggestions for future directions in NO-related studies on the liver.

Cell encapsulation: technical and clinical advances
Gorka Orive, Edorta Santos, Denis Poncelet, Rosa María Hernández, José Luis Pedraz, Lars U. Wahlberg, Paul De Vos, Dwaine Emerich

Abstract
Treating many chronic diseases will require a tight, minute-to-minute regulation of therapeutic molecules that is currently not achievable with most pharmaceutical therapies. For these diseases, implantable living cellular systems may be able to provide unlimited drug delivery, enabling seamless matching of treatment duration with disease longevity. Cell encapsulation is an advanced technology that achieves this goal and represents a viable therapeutic option. The advanced state of the field has allowed researchers to inch forward into therapeutic domains previously untouchable because of the myriad disparate fields that intersect biomaterials and cells. Here, we discuss the next generation of clinical trials and potential approaches, ‘smart’ and responsive encapsulation systems, sophisticated and multifunctional devices, and novel imaging tools, together with the future challenges in the field.

Targeting GLI factors to inhibit the Hedgehog pathway
Paola Infante, Romina Alfonsi, Bruno Botta, Mattia Mori, Lucia Di Marcotullio

Abstract
Hedgehog (Hh) signaling has emerged in recent years as an attractive target for anticancer therapy because its aberrant activation is implicated in several cancers. Major progress has been made in the development of SMOOTHENED (SMO) antagonists, although they have shown several limitations due to downstream SMO pathway activation or the occurrence of drug-resistant SMO mutations. Recently, particular interest has been elicited by the identification of molecules able to hit glioma-associated oncogene (GLI) factors, the final effectors of the Hh pathway, which provide a valid tool to overcome anti-SMO resistance. Here, we review results achieved in developing GLI antagonists, explaining their mechanisms of action and highlighting their therapeutic potential. We also underline the relevance of structural details in their discovery and optimization.
Apelin, Elabela/Toddler, and biased agonists as novel therapeutic agents in the cardiovascular system
Peiran Yang, Janet J. Maguire, Anthony P. Davenport

Abstract
Apelin and its G protein-coupled receptor (GPCR) have emerged as a key signalling pathway in the cardiovascular system. The peptide is a potent inotropic agent and vasodilator. Remarkably, a peptide, Elabela/Toddler, that has little sequence similarity to apelin, has been proposed as a second endogenous apelin receptor ligand and is encoded by a gene from a region of the genome previously classified as ‘non-coding’. Apelin is downregulated in pulmonary arterial hypertension and heart failure. To replace the missing endogenous peptide, ‘biased’ apelin agonists have been designed that preferentially activate G protein pathways, resulting in reduced β-arrestin recruitment and receptor internalisation, with the additional benefit of attenuating detrimental β-arrestin signalling. Proof-of-concept studies support the clinical potential for apelin receptor biased agonists.

The role of H₂S bioavailability in endothelial dysfunction
Rui Wang, Csaba Szabo, Fumito Ichinose, Asif Ahmed, Matthew Whiteman, Andreas Papapetropoulos

Abstract
Endothelial dysfunction (EDF) reflects pathophysiological changes in the phenotype and functions of endothelial cells that result from and/or contribute to a plethora of cardiovascular diseases. We review the role of hydrogen sulfide (H₂S) in the pathogenesis of EDF, one of the fastest advancing research topics. Conventionally treated as an environment pollutant, H₂S is also produced in endothelial cells and participates in the fine regulation of endothelial integrity and functions. Disturbed H₂S bioavailability has been suggested to be a novel indicator of EDF progress and prognosis. EDF manifests in different forms in multiple pathologies, but therapeutics aimed at remedying altered H₂S bioavailability may benefit all.

Peptidomics for the discovery and characterization of neuropeptides and hormones
Elena V. Romanova, Jonathan V. Sweedler

Abstract
The discovery of neuropeptides as signaling molecules with paracrine or hormonal regulatory functions has led to trailblazing advances in physiology and fostered the characterization of numerous neuropeptide-binding G protein-coupled receptors (GPCRs) as potential drug targets. The impact on human health has been tremendous: approximately 30% of commercial drugs act via the GPCR pathway. However, about 25% of the GPCRs encoded by the mammalian genome still lack their pharmacological identity. Searching for the orphan GPCR endogenous ligands that are likely to be neuropeptides has proved to be a formidable task. Here we describe the mass spectrometry (MS)-based technologies and experimental strategies that have been successful in achieving high-throughput characterization of endogenous peptides in nervous and endocrine systems.

New immunotherapies targeting the PD-1 pathway
Jordan M. Chinai, Murali Janakiram, Fuxiang Chen, Wantao Chen, Mark Kaplan, Xingxing Zang

Abstract
Ligands from the B7 family bind to receptors of the CD28 family, which regulate early T cell activation in lymphoid organs and control inflammation and autoimmunity in peripheral tissues. Programmed death-1 (PD-1), a member of the CD28 family, is an inhibitory receptor on T cells and is responsible for their dysfunction in infectious diseases and cancers. The complex mechanisms controlling the expression and signaling of PD-1 and programmed death ligand 1 (PD-L1) are emerging. Recently completed and ongoing clinical trials that target these molecules have shown remarkable success by generating durable clinical responses in some cancer patients. In chronic viral infections, preclinical data reveal that targeting PD-1 and its ligands can improve T cell responses and virus clearance. There is also promise in stimulating this pathway for the treatment of autoimmune and inflammatory disorders.
Functional studies cast light on receptor states
Frederick J. Ehlert

Abstract
Contemporary analysis of the functional responses of G-protein-coupled receptors (GPCRs) usually addresses drug–receptor interactions from the perspective of the average behavior of the receptor population. This behavior is characterized in terms of observed affinity and efficacy. Efficacy is a measure of how well a drug activates the receptor population and observed affinity a measure of how potently a drug occupies the receptor population. The latter is quantified in terms of the dissociation constant of the ligand–receptor complex. At a deeper level of analysis, drug–receptor interactions are described in terms of ligand affinity constants for active and inactive receptor states. Unlike observed affinity and efficacy, estimates of receptor state affinity constants are unperturbed by G proteins, guanine nucleotides, or other signaling proteins that interact with the receptor. Recent advances in the analysis of the functional responses of GPCRs have enabled the estimation of receptor state affinity constants. These constants provide a more fundamental measure of drug–receptor interactions and are useful in analyzing structure–activity relationships and in quantifying allosterism, biased signaling, and receptor-subtype selectivity.

Novel therapeutics in myocardial infarction: targeting microvascular dysfunction and reperfusion injury
Christopher B. Fordyce, Bernard J. Gersh, Gregg W. Stone, Christopher B. Granger

Abstract
Despite the large number of novel therapies under basic scientific investigation, the translation of cardioprotective strategies targeting reperfusion injury to improve patient outcomes following percutaneous coronary intervention (PCI) for myocardial infarction (MI) has been disappointing. The varying susceptibility of an individual to reperfusion injury, as well as the narrow window of opportunity in which to intervene, adds significant complexity. Here, we discuss the unmet need and challenges of translating cardioprotective strategies into clinical practice, review the pathophysiology of microvascular dysfunction and lethal reperfusion as they relate to promising novel therapeutics, and evaluate recent and ongoing clinical trials in the field.
Biologic Approaches to Treat Substance-Use Disorders
Phil Skolnick

Abstract
In contrast to traditional pharmacodynamic approaches to treat substance-use disorders (SUDs), the use of biologics (vaccines, monoclonal antibodies, and genetically modified enzymes) is based on a pharmacokinetic principle: reduce the amount of (and, ideally, eliminate) abused drug entering the central nervous system (CNS). Preclinical studies indicate that biologics are effective in both facilitating abstinence and preventing relapse to abused substances ranging from nicotine to heroin. While data are still emerging, the results from multiple clinical trials can best be described as mixed. Nonetheless, these clinical studies have already provided important insights using ‘first-generation’ tools that may inform the development of effective and commercially viable biologics to treat tobacco-, cocaine-, and methamphetamine-use disorders.

Gatekeepers Controlling GPCR Export and Function
Stéphane Doly, Stefano Marullo

Abstract
Regulated export of G protein-coupled receptors (GPCRs) from intracellular stores involves chaperones and escort proteins, which promote their progression to the cell surface, and gatekeepers, which retain them in intracellular compartments. Functional γ-aminobutyric acid (GABA)\textsubscript{B} receptors, the paradigm of this phenomenon, comprise GB1 and GB2 subunits forming a heterodimer. GB1 is retained in the endoplasmic reticulum (ER) in the absence of GB2. A specific ER-resident gatekeeper, prenylated Rab acceptor family 2 (PRAF2), is involved in GB1 retention and prevents its progression into the biosynthetic pathway. GB1 can be released from PRAF2 only on competitive interaction with GB2. PRAF2 is ubiquitous and belongs to a subgroup of the mammalian Ypt-interacting protein (Yip) family. Several other GPCRs are likely to be regulated by Yip proteins, which might be involved in the pathophysiology of human diseases that are associated with impaired receptor targeting to the cell surface.

Therapeutic Targeting of Siglecs using Antibody- and Glycan-Based Approaches
Takashi Angata, Corwin M. Nycholat, Matthew S. Macauley

Abstract
The sialic acid-binding immunoglobulin-like lectins (Siglecs) are a family of immunomodulatory receptors whose functions are regulated by their glycan ligands. Siglecs are attractive therapeutic targets because of their cell type-specific expression pattern, endocytic properties, high expression on certain lymphomas/leukemias, and ability to modulate receptor signaling. Siglec-targeting approaches with therapeutic potential encompass antibody- and glycan-based strategies. Several antibody-based therapies are in clinical trials and continue to be developed for the treatment of lymphoma/leukemia and autoimmune disease, while the therapeutic potential of glycan-based strategies for cargo delivery and immunomodulation is a promising new approach. Here we review these strategies with special emphasis on emerging approaches and disease areas that may benefit from targeting the Siglec family.
Protein Tyrosine Phosphatases in Hypothalamic Insulin and Leptin Signaling
Zhong-Yin Zhang, Garron T. Dodd, Tony Tiganis

Abstract
The hypothalamus is critical to the coordination of energy balance and glucose homeostasis. It responds to peripheral factors, such as insulin and leptin, that convey to the brain the degree of adiposity and the metabolic status of the organism. The development of leptin and insulin resistance in hypothalamic neurons appears to have a key role in the exacerbation of diet-induced obesity. In rodents, this has been attributed partly to the increased expression of the tyrosine phosphatases Protein Tyrosine Phosphatase 1B (PTP1B) and T cell protein tyrosine phosphatase (TCPTP), which attenuate leptin and insulin signaling. Deficiencies in PTP1B and TCPTP in the brain, or specific neurons, promote insulin and leptin signaling and prevent diet-induced obesity, type 2 diabetes mellitus (T2DM), and fatty liver disease. Although targeting phosphatases and hypothalamic circuits remains challenging, recent advances indicate that such hurdles might be overcome. Here, we focus on the roles of PTP1B and TCPTP in insulin and leptin signaling and explore their potential as therapeutic targets.

Apolipoprotein C-III: From Pathophysiology to Pharmacology
Giuseppe Danilo Norata, Sotirios Tsimikas, Angela Pirillo, Alberico L. Catapano

Abstract
Apolipoprotein C-III (apoC-III) has a critical role in the metabolism of triglyceride (TG)-rich lipoproteins (TRLs). Animal models lacking the APOC3 gene exhibit reduced plasma TG levels, whereas the overexpression of APOC3 leads to increased TG levels. In humans, loss-of-function mutations in APOC3 are associated with reduced plasma TG levels and reduced risk for ischemic vascular disease and coronary heart disease. Several hypolipidemic agents have been shown to reduce apoC-III, including fibrates and statins, and antisense technology aimed at inhibiting APOC3 mRNA to decrease the production of apoC-III is currently in Phase III of clinical development. Here, we review the pathophysiological role of apoC-III in TG metabolism and the evidence supporting this apolipoprotein as an emerging target for hypertriglyceridemia (HTG) and associated cardiovascular disorders.

Ligands for the Nuclear Peroxisome Proliferator-Activated Receptor Gamma
Sascha Sauer

Abstract
Nuclear receptors are ligand-activated transcription factors, which represent a primary class of drug targets. The nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ) is a key player in various biological processes. PPARγ is widely known as the target protein of the thiazolidinediones for treating type 2 diabetes. Moreover, PPARγ ligands can induce anti-inflammatory and potentially additional beneficial effects. Recent mechanistic insights of PPARγ modulation give hope the next generation of efficient PPARγ-based drugs with fewer side effects can be developed. Furthermore, chemical approaches that make use of synergistic action of combinatorial ligands are promising alternatives for providing tailored medicine. Lessons learned from fine-tuning the action of PPARγ can provide avenues for efficient molecular intervention via many other nuclear receptors to combat common diseases.
Optimizing Clinical Research Participant Selection with Informatics
Chunhua Weng

Abstract
Clinical research participants are often not reflective of real-world patients due to overly restrictive eligibility criteria. Meanwhile, unselected participants introduce confounding factors and reduce research efficiency. Biomedical informatics, especially Big Data increasingly made available from electronic health records, offers promising aids to optimize research participant selection through data-driven transparency.

Fitting Transporter Activities to Cellular Drug Concentrations and Fluxes: Why the Bumblebee Can Fly
Pedro Mendes, Stephen G. Oliver, Douglas B. Kell

Abstract
A recent paper in this journal argued that reported expression levels, $k_{cat}$ and $K_m$ for drug transporters could be used to estimate the likelihood that drug fluxes through Caco-2 cells could be accounted for solely by protein transporters. It was in fact concluded that if five such transporters contributed ‘randomly’ they could account for the flux of the most permeable drug tested (verapamil) 35% of the time. However, the values of permeability cited for verapamil were unusually high; this and other drugs have much lower permeabilities. Even for the claimed permeabilities, we found that a single ‘random’ transporter could account for the flux 42% of the time, and that two transporters can achieve $10 \cdot 10^{-6}$ cm·s$^{-1}$ 90% of the time. Parameter optimisation methods show that even a single transporter can account for Caco-2 drug uptake of the most permeable drug. Overall, the proposal that ‘phospholipid bilayer diffusion (of drugs) is negligible’ is not disproved by the calculations of ‘likely’ transporter-based fluxes.

Lessons from Hot Spot Analysis for Fragment-Based Drug Discovery
David R. Hall, Dima Kozakov, Adrian Whitty, Sandor Vajda

Abstract
Analysis of binding energy hot spots at protein surfaces can provide crucial insights into the prospects for successful application of fragment-based drug discovery (FBDD), and whether a fragment hit can be advanced into a high-affinity, drug-like ligand. The key factor is the strength of the top ranking hot spot, and how well a given fragment complements it. We show that published data are sufficient to provide a sophisticated and quantitative understanding of how hot spots derive from a protein 3D structure, and how their strength, number, and spatial arrangement govern the potential for a surface site to bind to fragment-sized and larger ligands. This improved understanding provides important guidance for the effective application of FBDD in drug discovery.

Resolution Pharmacology: Opportunities for Therapeutic Innovation in Inflammation
Mauro Perretti, Xavier Leroy, Elliot J. Bland, Trinidad Montero-Melendez

Abstract
Current medicines for the clinical management of inflammatory diseases act by inhibiting specific enzymes or antagonising specific receptors or blocking their ligands. In the past decade, a new paradigm in our understanding of the inflammatory process has emerged with the appreciation of genetic, molecular, and cellular mechanisms that are engaged to actively resolve inflammation. The ‘resolution of acute inflammation’ is enabled by counter-regulatory checkpoints to terminate the inflammatory reaction, promoting healing and repair. It may be possible to harness this knowledge for innovative approaches to the treatment of inflammatory pathologies. Here we discuss current translational attempts to develop agonists at proresolving targets as a strategy to rectify chronic inflammatory status. We reason this new approach will lead to the identification of better drugs that will establish a new branch of pharmacology, ‘resolution pharmacology’.
Emerging Role of Sirtuin 2 in the Regulation of Mammalian Metabolism
Pedro Gomes, Tiago Fleming Outeiro, Cláudia Cavadas

Abstract
Sirtuins are an evolutionarily conserved family of NAD$^+$-dependent deacylases that display diversity in subcellular localization and function. SIRT2, the predominantly cytosolic sirtuin, is among the least understood of the seven mammalian sirtuin isoforms described (SIRT1–7). The purpose of this review is to summarize the most recent findings about the potential roles and effects of SIRT2 in mammalian metabolic homeostasis. We discuss the different functions and targets of SIRT2 in various physiological processes, including adipogenesis, fatty acid oxidation, gluconeogenesis, and insulin sensitivity. We also cover the role of SIRT2 in inflammation and oxidative stress due to the possible implications for metabolic disorders. Finally, we consider its potential as a therapeutic target for the prevention and treatment of type 2 diabetes.

L1-CAM and N-CAM: From Adhesion Proteins to Pharmacological Targets
Federico Colombo, Jacopo Meldolesi

Abstract
L1 cell adhesion molecule (L1-CAM) and neural cell adhesion molecule (N-CAM), key members of the immunoglobulin-like CAM (Ig-CAM) family, were first recognized to play critical roles in surface interactions of neurons, by binding with each other and with extracellular matrix (ECM) proteins. Subsequently, adhesion was recognized to include signaling due to both activation of β-integrin, with the generation of intracellular cascades, and integration with the surface cytoskeleton. The importance of the two Ig-CAMs was revealed by their activation of the tyrosine kinase receptors of fibroblast growth factor (FGF), epidermal growth factor (EGF), and nerve growth factor (NGF). Based on these complex signaling properties, L1-CAM and N-CAM have become of great potential pharmacological interest in neurons and cancers. Treatment of neurodegenerative disorders and cognitive deficits of neurons is aimed to increase the cell Ig-CAM tone, possibly provided by synthetic/mimetic peptides. In cancer cells, where Ig-CAMs are often overexpressed, the proteins are employed for prognosis. The approaches to therapy are based on protein downregulation, antibodies, and adoptive immunotherapy.

Pharmacological Modulation of the N-End Rule Pathway and Its Therapeutic Implications
Jung Hoon Lee, Yanxialei Jiang, Yong Tae Kwon, Min Jae Lee

Abstract
The N-end rule pathway is a proteolytic system in which single N-terminal amino acids of short-lived substrates determine their metabolic half-lives. Substrates of this pathway have been implicated in the pathogenesis of many diseases, including malignancies, neurodegeneration, and cardiovascular disorders. This review provides a comprehensive overview of current knowledge about the mechanism and functions of the N-end rule pathway. Pharmacological strategies for the modulation of target substrate degradation are also reviewed, with emphasis on their in vivo implications. Given the rapid advances in structural and biochemical understanding of the recognition components (N-recognins) of the N-end rule pathway, small-molecule inhibitors and activating ligands of N-recognins emerge as therapeutic agents with novel mechanisms of action.
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PML: The Dark Side of Immunotherapy in Multiple Sclerosis
Clemens Warnke, Tomas Olsson, Hans-Peter Hartung

Abstract
Progressive multifocal leukoencephalopathy (PML) is a threat to patients with multiple sclerosis (MS) who undergo treatment with drugs that interfere with normal immune physiology. Here, we summarize PML incidence in MS, risk factors, surveillance strategies, and case definitions to inform neurologists and other clinicians treating patients with immune-mediated diseases.

Polypharmacology Shakes Hands with Complex Aetiopathology
James S. Brodie, Vincenzo Di Marzo, Geoffrey W. Guy

Abstract
Chronic diseases are due to deviations of fundamental physiological systems, with different pathologies being characterised by similar malfunctioning biological networks. The ensuing compensatory mechanisms may weaken the body’s dynamic ability to respond to further insults and reduce the efficacy of conventional single target treatments. The multitarget, systemic, and prohomeostatic actions emerging for plant cannabinoids exemplify what might be needed for future medicines. Indeed, two combined cannabis extracts were approved as a single medicine (Sativex®), while pure cannabidiol, a multitarget cannabinoid, is emerging as a treatment for paediatric drug-resistant epilepsy. Using emerging cannabinoid medicines as an example, we revisit the concept of polypharmacology and describe a new empirical model, the ‘therapeutic handshake’, to predict efficacy/safety of compound combinations of either natural or synthetic origin.

Targeted Therapies for Triple-Negative Breast Cancer: Combating a Stubborn Disease
Murugan Kalimutho, Kate Parsons, Deepak Mittal, J. Alejandro López, Sriganesh Sripahari, Kum Kum Khanna

Abstract
Triple-negative breast cancers (TNBCs) constitute a heterogeneous subtype of breast cancers that have a poor clinical outcome. Although no approved targeted therapy is available for TNBCs, molecular-profiling efforts have revealed promising molecular targets, with several candidate compounds having now entered clinical trials for TNBC patients. However, initial results remain modest, thereby highlighting challenges potentially involving intra- and intertumoral heterogeneity and acquisition of therapy resistance. We present a comprehensive review on emerging targeted therapies for treating TNBCs, including the promising approach of immunotherapy and the prognostic value of tumor-infiltrating lymphocytes. We discuss the impact of pathway rewiring in the acquisition of drug resistance, and the prospect of employing combination therapy strategies to overcome challenges towards identifying clinically-viable targeted treatment options for TNBC.

TGR5 and Immunometabolism: Insights from Physiology and Pharmacology
Alessia Perino, Kristina Schoonjans

Abstract
In the past decade substantial progress has been made in understanding how the insurgence of chronic low-grade inflammation influences the physiology of several metabolic diseases. Tissue-resident immune cells have been identified as central players in these processes, linking inflammation to metabolism. The bile acid-responsive G-protein-coupled receptor TGR5 is expressed in monocytes and macrophages, and its activation mediates potent anti-inflammatory effects. Herein, we summarize recent advances in TGR5 research, focusing on the downstream effector pathways that are modulated by TGR5 activators, and on its therapeutic potential in inflammatory and metabolic diseases.
Recent Advances and New Strategies in Targeting Plk1 for Anticancer Therapy
Kyung S. Lee, Terrence R. Burke Jr, Jung-Eun Park, Jeong K. Bang, Eunhye Lee

Abstract
Polo-like kinase 1 (Plk1) plays key roles in regulating mitotic processes that are crucial for cellular proliferation. Overexpression of Plk1 is tightly associated with the development of particular cancers in humans, and a large body of evidence suggests that Plk1 is an attractive target for anticancer therapeutic development. Drugs targeting Plk1 can potentially be directed at two distinct sites: the N-terminal catalytic kinase domain (KD), which phosphorylates substrates, and the C-terminal polo-box domain (PBD) which is essential for protein–protein interactions. In this review we summarize recent advances and new challenges in the development of Plk1 inhibitors targeting these two domains. We also discuss novel strategies for designing and developing next-generation inhibitors to effectively treat Plk1-associated human disorders.

Advances in Computational Techniques to Study GPCR–Ligand Recognition
Antonella Ciancetta, Davide Sabbadin, Stephanie Federico, Giampiero Spalluto, Stefano Moro

Abstract
G-protein-coupled receptors (GPCRs) are among the most intensely investigated drug targets. The recent revolutions in protein engineering and molecular modeling algorithms have overturned the research paradigm in the GPCR field. While the numerous ligand-bound X-ray structures determined have provided invaluable insights into GPCR structure and function, the development of algorithms exploiting graphics processing units (GPUs) has made the simulation of GPCRs in explicit lipid–water environments feasible within reasonable computation times. In this review we present a survey of the recent advances in structure-based drug design approaches with a particular emphasis on the elucidation of the ligand recognition process in class A GPCRs by means of membrane molecular dynamics (MD) simulations.

NAMPT as a Therapeutic Target against Stroke
Pei Wang, Chao-Yu Miao

Abstract
Nicotinamide phosphoribosyltransferase (NAMPT), also an adipokine known as visfatin, acts via enzymatic activity to synthesize nicotinamide mononucleotide (NMN) and then to maintain homeostasis of nicotinamide adenine dinucleotide (NAD), which plays a dual role in energy metabolism and biological signaling. Of note, the NAMPT metabolic pathway connects NAD-dependent sirtuin (SIRT) signaling, constituting a strong intrinsic defense system against various stresses. Most recently, studies have demonstrated several mechanisms by which NAMPT might serve as a therapeutic target against ischemic stroke, including cerebroprotection in the acute phase as well as vascular repair and neurogenesis in the chronic phase. The molecular mechanisms underlying these benefits have been explored in vivo and in vitro for neural cells, endothelial progenitor cells, and neural stem cells. Therapeutic interventions using NMN, NAMPT activators, and ischemic conditioning are promising for stroke salvage and rehabilitation. This review discusses the current NAMPT data in the context of translational efforts for stroke treatment.
Exercise Pills: At the Starting Line
Shunchang Li, Ismail Laher

Abstract
Sedentary lifestyles, limited physical exercise, and prolonged inactivity undoubtedly increase chronic diseases, including obesity, type 2 diabetes, and cardiovascular diseases. It is widely acknowledged that exercise induces a number of physiological adaptations that have beneficial effects in the prevention and treatment of these chronic metabolic diseases. Unfortunately, exercise compliance is extremely low and often not possible. The development of exercise science and molecular techniques has increased our understanding of the molecular pathways responsive to exercise. Knowledge of these molecular targets has led to the development of chemical interventions that can mimic the beneficial effects of exercise without requiring actual muscle activity. This review focuses on the concept of ‘exercise pills’ and how they mimic the effects produced by physical exercise including oxidative fiber-type transformation, mitochondrial biogenesis, increased fat oxidation, angiogenesis, and improvement of exercise capacity. We also review candidate exercise pills, and contrast the beneficial effects and molecular mechanisms between physical exercise and exercise pills.

Katie Leach, Arthur D. Conigrave, Patrick M. Sexton, Arthur Christopoulos

Abstract
The calcium-sensing receptor (CaSR) is a widely expressed G protein-coupled receptor (GPCR) that mediates numerous tissue-specific functions. Its multiple ligands and diverse roles attest to the need for exquisite control over the signaling pathways that mediate its effects. ‘Biased signaling’ is the phenomenon by which distinct ligands stabilize preferred receptor signaling states. The CaSR is subject to biased signaling in response to its endogenous ligands. Interestingly, the ‘natural’ bias of the CaSR is altered in disease states, and small molecule drugs engender biased allosteric modulation of downstream signaling pathways. Thus, biased signaling from the CaSR also has important implications pathophysiological and therapeutically. As outlined in this review, this novel paradigm extends to other GPCRs, making the CaSR a model for studies of ligand-biased signaling and for understanding how it may be used to foster selective drug activity in different tissues.