Patent highlights, August–September 2019

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A snapshot of recent noteworthy developments in the patent literature of relevance to pharmaceutical and medical research and development.

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WO/2019/144842

Thiazole-5-formic acid derivative, preparation method therefor and use thereof

Inventors: Wang H, Sun M

Assignee: Xiangbei Welman Pharmaceutical Co. Ltd (Guangzhou, China)

Two main classes of drugs are available to lower blood uric acid levels: inhibitors of urate tubular reabsorption (probenecid, benzbromarone) that increase discharge of uric acid from the kidney; and xanthine oxidase inhibitors (allopurinol, febuxostat) that reduce uric acid synthesis. Febuxostat, discovered at Tejin, is highly efficient but used to be recommended only as a second-line drug, although the newest meta-analysis of clinical trials seems to show less cardiac-related mortality and adverse skin reactions compared with allopurinol [1]. A group from Hamdard University (New Delhi) has published their febuxostat analogs that could be superior in terms of safety and/or efficacy [2,3] but other xanthine oxidase inhibitor candidates have been built on different templates. The Chinese inventors have kept to the 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-1,3-thiazole scaffold, and derivatized mainly at febuxostat's carboxyl group. In a rat model of hyperuricemia based on administration of uric acid and oteracil (an orotate phosphoribosyltransferase inhibitor) some compounds showed superiority over febuxostat at oral doses of 10 mg/kg qd.

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MeSH keywords: febuxostat • gout • xanthine oxidase

WO/2019/148132

Gcn2 Inhibitors and uses thereof

Inventors: Bayly A, Bleich M, Charrier J-D et al.

Assignee: Merck Patent GmbH (Darmstadt, Germany); Vertex Pharmaceuticals, Inc. (MA, USA)

Gcn2 is an ubiquitously expressed eukaryotic eIF2 α kinase that is activated by amino acid deficiency via direct binding of the cognate transfer RNAs. The resulting phosphorylation of eIF2 α initiates protein translation, which causes a reduction in the translation of most mRNAs leading to reduced global utilization of amino acids. Many additional roles have been identified in long-term memory formation, immune system regulation and cancer [4] (amino acid depletion is a potent immune evasion mechanism of the tumor microenvironment). Antitumor agents, optionally in combination with anti-CTLA4 or anti-PD1/PD-L1 checkpoint-blocking antibodies, are what the inventors primarily seem to have in mind. Hundreds of compounds – mostly imidazo[1,2-*b*]pyridazin-3-ylpyridines – have been characterized chemically and their K_i or IC₅₀ values for Gcn2 determined; virtually all are in the nanomolar range. An *in vitro* assay was established to monitor IL-2 levels secreted by human T cells in response to the Gcn2 inhibitors and showed mostly nanomolar to micromolar EC₅₀ values for the 15 compounds subjected to this test. Considering that the Gcn2 nutritional amino acid sensing might be a major coordinator for maintaining the redox balance and cellular homeostasis in healthy ageing [5] such inhibitors might attract more interest in the future. Also see the companion disclosure WO/2019/148136.

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MeSH keywords: amino acids • EIF2AK4 protein, human • neoplasms

WO/2019/150309

Modulators of Gpr68 and uses thereof for treating and preventing diseases

Inventors: Hammack S, Laffitte B, Patapoutian A, Xu J

Assignee: The inventors, represented by Novartis AG (Basel, Switzerland)

Gpr68 is a proton-sensing orphan receptor that responds to extracellular acidity and regulates a variety of cellular functions. It is highly upregulated in numerous types of cancer, and appears to maintain acidosis in the tumor microenvironment [6]. This document provides methods of modulating flow-mediated dilation response, flow-mediated outward remodeling or of reducing systemic vascular resistance of small-diameter arteries by modulators of a *GPR68* gene product. The inventors focused on membrane-integrated proteins as the most probable candidates for novel mechanosensors. They constructed a limited library of 21925 unique siRNAs against 2765 unique genes encoding proteins with two or more predicted transmembrane domains (a characteristic trait shared by ion channels and GPCRs). The primary screen in a shear stress assay using transfected MDA-MB-231 human breast cancer cells yielded 56 hits, for which 26 potential genes were reconfirmed in a secondary screen. *GPR68* was the only one to show significantly reduced calcium transients caused by disturbed shear stress upon knockdown. Further focused research provided evidence for a necessary and sufficient role of Gpr68 in the shear stress-induced release of calcium from stores, showing this orphan receptor to be a mechanotransducing flow sensor in the arteriolar endothelium that is required for laminar shear stress responses of mouse primary microvascular endothelial cells. This suggests therapeutic possibilities for various angiopathies and heart failure. No specific compounds are claimed. For the peer review companion paper, see Xu *et al.* [7].

Published: 8 August 2019

MeSH keywords: GPR68 protein, human • mechanical signal transduction • vascular endothelium

WO/2019/152680

Methods and compositions for treating cancer using Chrna6 inhibitors

Inventors: Kahvejian A, Mata-Fink J, Hurov JB, Shu CJ, Fankhauser MA, Stanley JA

Assignee: Flagship Pioneering Innovations V, Inc. (MA, USA)

Nicotinic acetylcholine receptors (nAChRs) are not limited to the CNS and peripheral nervous system and synaptic transmission; they are widely expressed in various organs, and are key players in cancer development [8] where a pronounced acetylcholine-based metabolic-signaling system is often essential [9]. Interest has focused mostly on $\alpha 7$ and $\alpha 9$ nAChR subtypes while investigations of the $\alpha 6$ subtype have been mostly limited to neurology and psychiatry, including alcohol addiction [10,11]. That it is expressed in immune cells along with many other subtypes has been known [12], but it was up to the inventors to demonstrate that it is highly and specifically expressed by human Treg cells. Inhibition of $\alpha 6$ nAChRs leads to an increase in IFN- γ expressing CD8⁺ T cells, which explains the repressive effect of inhibitors on cancer: overexpression of $\alpha 6$ nAChRs negatively correlates with survival of cancer patients. The few known $\alpha 6$ small-molecule antagonists with subtype selectivity include CHEMBL3104238 and CHEMBL3107687. All other conceivable agent types that could inhibit $\alpha 6$ nAChRs or reduce their expression (antibodies and other binding polypeptides, interfering RNAs) are also claimed. At 3 nM, a conotoxin led to a trend of increasing interferon-expressing CD8⁺ T cells, suggesting that blockade of $\alpha 6$ nAChRs by this compound impairs the ability of Tregs to suppress CD8⁺ activity. On an indirect note, these findings could also add more support to the observation that smoking is particularly detrimental for cancer patients.

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MeSH keywords: neoplasms • nicotinic receptor alpha6 • regulatory T cells

WO/2019/157495

Methods for preventing and/or treating bone loss conditions by modulating irisin

Inventors: Spiegelman BM, Kim H, Rosen C, Bonewald L

Assignee: Dana Faber Cancer Institute, Inc. (MA, USA); Indiana University (IN, USA); Maine Medical Center Research Institute (ME, USA)

Clinical evidence for the effect of endurance training on bone strength in elderly persons is controversial; however, it is known that physical activity stimulates the production of several hormone-like molecules from skeletal muscle and their release into the bloodstream. One of these myokines is irisin, the secreted form of the glycosylated type I membrane protein FNDC5. Irisin increases the differentiation of bone marrow stromal cells into mature

osteoblasts [13] and has also been shown to play a role in the control of bone mass with positive effects on cortical mineral density and geometry *in vivo* [14]. The present invention is based on the discovery of an opposite effect: irisin activates osteocytes to produce bone-mobilizing hormones that diminish bone mineral content, especially sclerostin. Extensive experiments with the MLO-Y4 osteocyte cell line demonstrated that the effect is mediated by αV integrin, which is thereby identified as an irisin receptor at concentrations that correspond well with the irisin blood levels in healthy humans (3–5 ng/ml). *FND5* knockout mice completely resist osteoporosis after ovariectomy. The same route is responsible for thermogenesis in adipose tissue cells induced by irisin. Consequently, αV integrin blockers of any type might be candidates for the treatment of conditions associated with low bone strength, and potentially also for lipolysis disorders (not claimed). For the peer review companion paper, see Kim *et al.* [15]. Also note that there is substantial evidence for cross-talk between αV integrins and TGF- β during pathological epithelial-to-mesenchymal transition, and that anti-integrin therapeutics are considered potential treatments for TGF- β -related disorders [16].

Published: 15 August 2019

MeSH keywords: *FND5* protein, human • integrin αV • osteoporosis • SOST protein, human

WO/2019/160840

Paraspeckle component 1 (Pspc1) promoting epithelial-mesenchymal transition, stemness and metastasis as an anticancer agent

Inventors: Jou Y-S, Lang Y-D, Yeh H-W

Assignee: Academia Sinica (Taipei City, Taiwan)

Paraspeckles – subnuclear RNA-protein structures that are built around a specific long noncoding RNA – are involved in the control of gene expression [17,18]. The inventors have discovered that a paraspeckle component protein, Pspc1 is no less than a master activator of prometastatic switches. It is a phosphorylation-dependent substrate of the nuclear and tumor-suppressive tyrosine kinase Ptk6, phosphorylation of Pspc1 leading to suppression of epithelial-to-mesenchymal transition, expression of cancer stem cell properties and metastasis. A 131 amino acid residue Pspc1 C-terminal fragment (which inhibits both Pspc1 and nuclear, but not cytoplasmic, Ptk6 through its unique proline-rich interacting domain) was identified as a potential therapeutic for suppressing tumorigenesis in an orthotopic model of hepatocellular carcinoma. Drug development would require targeting to the nucleus; experimental methods are known but still far from pharmaceutical routine. For the peer review companion paper, see Yeh *et al.* [19,20].

Published: 22 August 2019

MeSH keywords: neoplasm metastasis • PSPC1 protein, human • PTK6 protein, human • RNA-binding proteins

WO/2019/162945

Methods for treating memory impairment and cognitive dysfunction

Inventor: Kaphzan H

Assignee: Carmel Haifa University Economic Corporation Ltd (Haifa, Israel)

Angelman syndrome is a rare genetic neurodevelopmental disorder that is attributable to deletion or lack of function of a part of chromosome 15 that contains the *UBE3A* gene coding for a ubiquitin-protein ligase. The multiple and pervasive symptoms include severe intellectual deficits [21]. In a mouse model of Angelman syndrome, hippocampal CA1 and CA3 pyramidal cells exhibit increased expression of the $\alpha 1$ subunit of Na/K-ATPase. Behavioral and electrophysiological abnormalities are rescued if this overexpression is prevented by genetic interventions [22]. The inventor now extends these findings to memory impairment and other cognitive dysfunctions, in Angelman syndrome but also in other neurological disorders. That the Na/K-ATPase electrogenic pump is one of the fundamental mechanisms supporting learning has been known since before the millennium [23] but memory disorders are almost always associated with its inhibition (e.g., in Alzheimer's disease). Instead, the inventor shows that in the case of Angelman syndrome an Na/K-ATPase inhibitor, marinobufagenin (an endogenous cardiotonic steroid) is beneficial by reducing the effects of overexpression of the pump's alpha subunit. Other digitalis-like inhibitors are also claimed and might also be effective. For the peer review companion paper, see Rayi *et al.* [24].

Published: 29 August 2019

MeSH keywords: Angelman syndrome • ATP1A1 protein, human • cognitive dysfunction • rare diseases

WO/2019/165284**Methods of treating nonalcoholic steatohepatitis and compositions therefore***Inventor: Barnea ER**Assignee: BioIncept LLC (NY, USA)*

The recent definition of nonalcoholic fatty liver disease (NAFLD; believed to affect 25–30% of the adult population in Europe and North America), and its progressed form nonalcoholic steatohepatitis as distinct medical conditions has triggered an avalanche of research and many suggestions for drug targets and potential therapeutic agents. Preimplantation Factor (PIF), as claimed here, is a novel addition to the growing armamentarium, and not as unlikely as it might seem considering the primary role of this embryo-secreted peptide in reproduction: PIF has extensive immunoregulatory properties [25], and a synthetic version was in clinical trials (by the assignee) for autoimmune hepatitis [26]. Data from this Phase I study (NCT02239562) are heavily cited in this application, which notes that the similarities between autoimmune hepatitis and NAFLD are substantial [27]. The inventor provides extensive cell culture and animal model data to this effect. In the hypercholesterolemic *APOE* knockout mouse model of liver steatosis, synthetic PIF reduces inflammatory CD4⁺ cells, which are drivers of fibrosis, while not affecting NKT cells. It also protects normal mice against cytomegalovirus infection, which is a risk factor for NAFLD. The patent document outlines a protocol for a Phase II clinical study in autoimmune hepatitis (NCT03593460) that was supposed to commence in 2019 but has been withdrawn.

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MeSH keywords: clinical trial • nonalcoholic fatty liver disease • synthetic preimplantation factor

WO/2019/169001**Chromene derivatives as inhibitors of TCR-Nck interaction***Inventors: Castro J, Gegete Mateos A, Machin PL, Vandeusen CL**Assignee: Artax Biopharma, Inc. (MA, USA)*

Upon activation, the T-cell receptor (TCR) undergoes a conformational change and recruits cytosolic proteins to form the TCR signalosome [28]. This complex includes a protein comprising the noncatalytic region of a tyrosine kinase (Nck) whose SH3 domain binds to the proline-rich sequence motif in the CD3ε subunit of the T-cell receptor, stabilizing its conformational change and thereby ensuring effective transmission of the activation signal [29]. This makes Nck a promising target for immunomodulatory therapies, especially for autoimmune diseases. Prompted by the 4-(4-fluorophenyl)chromenes disclosed as inhibitors of TCR–Nck interaction by the Spanish National Research Council in WO/2012/042078, the inventors continued derivatization of this template. Compounds were tested for Nck–SH3/TCR–CD3ε competitive interaction by an interferometric optical detection method; for inhibition of CD3-mediated phosphorylation of ZAP70 (a step that destabilizes the signalosome [30]) in a Jurkat cell-based homogeneous time-resolved fluorescence assay; and for metabolic stability in a microsomal assay. 3-((4-(4-Fluorophenyl)-3-(pyrrolidin-1-ylmethyl)-2H-chromen-6-yl)oxy)-N-hydroxypropanimidamide is an example of compounds that achieved a more than 50% maximum inhibition in the ZAP70 phosphorylation assay.

Published: 6 September 2019

MeSH keywords: autoimmune diseases • benzopyrans • Nck protein • T-cell receptor

WO/2019/169112**Inhibition of Olig2 activity***Inventors: Beaton G, Mchardy SF, Lopez A Jr, Campos B, Wang H-YL**Assignee: Curtana Pharmaceuticals, Inc. (TX, USA)*

Because of the high resistance of their stem cells to radiation and cytotoxic drugs, gliomas continue to be among the most significant challenges in oncology. Available therapeutic methods prolong life only for months on average, usually at the price of very significant deterioration in the quality of life. One promising target is Olig2, a basic helix-loop-helix transcription factor. It is highly expressed in all diffuse gliomas, and is found in virtually all glioblastoma multiforme cells positive for the CD133 stem cell marker but is absent from normal brain and non-malignant tissues outside the CNS [31,32]. The nitrogen-rich compounds described herein (e.g., 1-(4-amino-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea) are among the first small-molecule expression inhibitors of Olig2. Their template might be covered by one or more of the pharmacophores published in 2017 by a large US cancer collaboration and the San Diego Supercomputer Center [33]. Various cell culture and animal model experiments are

described but no data are presented. Protocol outlines of Phase I/II clinical studies in patients with medulloblastoma, recurrent Rb-positive glioblastoma or recurrent malignant astrocytoma are also disclosed.

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MeSH keywords: glioma • neoplastic stem cells • oligodendrocyte transcription factor 2 • phenylurea compounds

WO/2019/170904

Piperidines or piperidones substituted with urea and phenyl

Inventors: Jakob F, Merla B, Rider D, Dunkern T, Wagener M

Assignee: Grünenthal GmbH (Aachen, Germany)

The widely expressed G-protein-coupled lipoxin A4 receptor (FPR2) mediates calcium mobilization not only in response to its cognate agonist and its analogs but also binds various other ligands such as serum amyloid A, bacterial products, neuropeptides and even HIV and influenza virus envelope proteins [34]. In addition to anti-inflammatory and proresolution effects of FPR2 ligands, lipoxin A4 has been shown to directly alleviate hyperalgesia and bone-cancer pain in animal models. For this document, which carries on from the urea- and phenyl-substituted cyclic amines or lactames disclosed in WO/2018/054549, Grünenthal has synthesized and tested (in a FLIPR assay using CHO cells recombinantly expressing FPR2 or FPR1) about 130 compounds, some of which have FPR2 IC₅₀ values in the picomolar range. All of these also bind to FPR1 to a degree, but selectivity for FPR2 is mostly high. Such agents could find their first applications in asthma [35] and chronic obstructive pulmonary disease (COPD) [36], where reduced lipoxin levels are commonly observed.

Published: 12 September 2019

MeSH keywords: asthma • chronic obstructive pulmonary disease • FPR2 protein, human

WO/2019/174277

Phosphoethanolamine transferase inhibitors

Inventors: Chen S, Chan K-F

Assignee: The Hong Kong Polytechnic University (Hong Kong, China)

Carbapenem-resistant Enterobacteriaceae are among the latest antibiotic-resistant strains that have emerged; blood-stream infections currently carry a 50% mortality rate [37]. Only polymyxins, peptide antibiotics that had been essentially discontinued from clinical use because of their nephrotoxic and neurotoxic side effects, are effective as a last resort [38]. However, a new colistin (polymyxin E) resistance plasmid encoding the Mcr-1 protein (a phosphoethanolamine transferase that structurally modifies lipid A) has been spreading to carbapenem-resistant Enterobacteriaceae, creating an ‘ultimate superbug’ that is currently untreatable while also pointing to a new drug target [39]. The inventors claim remedies that are well known in the antimicrobial field: salts of cetylpyridinium (commonly used antiseptic components of mouthwashes and other over-the-counter [OTC] products) and domiphen, another quaternary ammonium antiseptic sometimes used in cosmetics. At first sight, this is not a great surprise: such compounds are cationic detergents that can attack virtually all single-cell membranes. But the inventors show that cetyltrimethylammonium bromide and domiphen bind directly to a hydrophobic pocket in the transmembrane domain of Mcr-1 and reduce its enzymatic activity at concentrations around 80 µM. A synergistic antimicrobial effect of colistin and cetylpyridinium chloride/domiphen bromide on Mcr-1-producing bacteria was observed. In addition, the effect of colistin on Mcr-negative colistin-sensitive bacteria was potentiated, suggesting an ability to also inhibit other phosphoethanolamine transferases, such as EptA, that are involved in lipid A biosynthesis.

Published: 19 September 2019

MeSH keywords: carbapenem-resistant Enterobacteriaceae • cetylpyridinium • domiphen • MCR-1 protein, *E. coli* • quaternary ammonium compounds

WO/2019/182191

Pharmaceutical composition for prevention or treatment of neurodegenerative disease and comprising Cox2-acetylating agent as active ingredient

Inventors: Bae J-S, Jin HK, Lee JY

Assignee: Kyungpook National University Industry-Academic Cooperation (Daegu, South Korea)

Although no large double-blind trial investigating cyclooxygenase inhibitors for the treatment or prevention of Alzheimer’s disease has produced robust and reproducible positive results, there is no dispute that neuroinflammation

has a crucial role here, as in other neurodegenerative diseases. The inventors turned to sphingosine kinase-1 (SphK1) and demonstrated that its expression and activity are reduced in neurons (but not in microglia and astrocytes) of the murine APP/PS1-double transgenic model of Alzheimer's disease, while levels of the SphK2 isoenzyme are normal in all brain cell types. Engineering APP/PS1 mice to additionally express neuronal SphK1 reduced their increased β -amyloid production at 9 months age and also reduced their cerebral amyloid angiopathy. Having excluded the A β -generating enzyme Bace-1 and proteins related to endocytosis and autophagy as mediators for this effect, the inventors focused on pro- and anti-inflammatory markers and found them decreased and increased, respectively. The presence of the so-called specialized proresolving lipid mediators [40] (such as lipoxin A4 and resolvins D1 and D2), which are produced by lipoxygenase and COX-2, among the restored anti-inflammatory mediators suggested that modulation of the acetylation of the COX-2 active center by SphK1 could play a role: acetylsalicylic acid achieves this, blocking biosynthesis of prostaglandins but not of specialized proresolving mediators [41]. Indeed, the Inventors were also able to show that SphK1 is an acetyl-CoA dependent acetyltransferase of COX2. For the peer review companion paper, see Lee *et al.* [42]. Also see WO/2019/182370 and '371.

Published: 26 September 2019

MeSH keywords: acetyltransferases • Alzheimer's disease • cyclooxygenase 2 • sphingosine kinase

WO/2019/182947

Arylnaphtalene compounds as vacuolar ATPase Inhibitors and the use thereof

Inventors: Davisson VJ, Lindstrom AR

Assignee: Purdue Research Foundation (IN, USA)

The Ebola epidemic continues its outbreaks in central and western Africa and while Marburg virus, another major hemorrhagic filovirus, has not caused epidemics of comparable size and severity it remains extant. Vaccines that could protect against both viruses are in development but there are no approved specific therapeutics. The multi-subunit enzyme vacuolar H⁺-ATPase (V-ATPase), whose role is to couple proton transport across cellular membranes with hydrolysis of ATP, is among those components of ESCRTs (Endosomal Sorting Complexes Required for Transport) that are subsumed by enveloped viruses (including Ebola and HIV) to facilitate their budding from the host cells [43]. The inventors focused on diphyllin, a naturally occurring arylnaphtalene V-ATPase inhibitor that has been investigated for osteoporosis [44], gastric cancer [45] and as an anti-influenza agent [46]. Candidate inhibitors were identified by an endosomal acidification assay in HEK293 cells using acridine orange fluorescence and cytotoxicity assays. Top candidates (primarily phenol ethers; imides were inactive and hydrazones were less active than diphyllin) were also tested in Marburg virus assays. For the peer review companion paper, see Lindstrom *et al.* [47].

Published: 26 September 2019

MeSH keywords: Ebolavirus • diphyllin • ESCRT complexes • Marburgvirus • proton-translocating ATPases

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References

1. Liu CW, Chang WC, Lee CC *et al.* The net clinical benefits of febuxostat versus allopurinol in patients with gout or asymptomatic hyperuricemia – a systematic review and meta-analysis. *Nutr. Metab. Cardiovasc. Dis.* 29(10), 1011–1022 (2019).
2. Ali MR, Kumar S, Afzal O, Shalmali N, Sharma M, Bawa S. Development of 2-(substituted benzylamino)-4-methyl-1,3-thiazole-5-carboxylic acid derivatives as xanthine oxidase inhibitors and free radical scavengers. *Chem. Biol. Drug Des.* 87(4), 508–516 (2016).
3. Ali MR, Kumar S, Afzal O *et al.* 2-Benzamido-4-methylthiazole-5-carboxylic acid derivatives as potential xanthine oxidase inhibitors and free radical scavengers. *Arch. Pharm. (Weinheim)* 350(2), e1600313 (2017).
4. Castilho BA, Shanmugam R, Silva RC, Ramesh R, Himme BM, Sattlegger E. Keeping the eIF2 alpha kinase Gcn2 in check. *Biochim. Biophys. Acta* 1843(9), 1948–1968 (2014).
5. Falcón P, Escandón M, Brito Á, Matus S. Nutrient sensing and redox balance: GCN2 as a new integrator in aging. *Oxid. Med. Cell Longev.* 2019, 5730532 (2019).

6. Wiley SZ, Sriram K, Salmerón C, Insel PA. GPR68: an emerging drug target in cancer. *Int. J. Mol. Sci.* 20(3), pii:E559 (2019).
7. Xu J, Mathur J, Vessières E *et al.* GPR68 senses flow and is essential for vascular physiology. *Cell* 173(3), 762.e16–775.e16 (2018).
8. Chen J, Cheuk IWY, Shin VY, Kwong A. Acetylcholine receptors: key players in cancer development. *Surg. Oncol.* 4, 31, 46–53 (2019).
9. Friedman JR, Richbart SD, Merritt JC *et al.* Acetylcholine signaling system in progression of lung cancers. *Pharmacol. Ther.* 194, 222–254 (2019).
10. Gao F, Chen D, Ma X *et al.* Alpha6-containing nicotinic acetylcholine receptor is a highly sensitive target of alcohol. *Neuropharmacology* 149, 45–54 (2019).
11. Yang KC, Jin GZ, Wu J. Mysterious alpha6-containing nAChRs: function, pharmacology, and pathophysiology. *Acta Pharmacol. Sin.* 30(6), 740–751 (2009).
12. Fujii T, Mashimo M, Moriwaki Y *et al.* Expression and function of the cholinergic system in immune cells. *Front. Immunol.* 8, 1085 (2017).
13. Chen N, Li Q, Liu J, Jia S. Irisin, an exercise-induced myokine as a metabolic regulator: an updated narrative review. *Diabetes Metab. Res. Rev.* 32(1), 51–59 (2016).
14. Colaïanni G, Sanesi L, Storlino G, Brunetti G, Colucci S, Grano M. Irisin and bone: from preclinical studies to the evaluation of its circulating levels in different populations of human subjects. *Cells* 8(5), pii:E451 (2019).
15. Kim H, Wrann CD, Jedrychowski M *et al.* Irisin mediates effects on bone and fat via αv integrin receptors. *Cell* 178(2), 507–508 (2019).
16. Mamuya FA, Duncan MK. αv integrins and TGF- β -induced EMT: a circle of regulation. *J. Cell Mol. Med.* 16(3), 445–455 (2012).
17. Fox AH, Lamond AI. Paraspeckles. *Cold Spring Harb. Perspect. Biol.* 2(7), a000687 (2010).
18. Yamazaki T, Hirose T. The building process of the functional paraspeckle with long non-coding RNAs. *Front. Biosci. (Elite Ed.)* 7, 1–41 (2015).
19. Yeh HW, Hsu EC, Lee SS *et al.* PSPC1 mediates TGF- β 1 autocrine signalling and Smad2/3 target switching to promote EMT, stemness and metastasis. *Nat. Cell Biol.* 20(4), 479–491 (2018).
20. Yeh HW, Jou YS. PSC1 potentiates TGF- β -dependent metastatic dissemination. *Mol. Cell Oncol.* 5(4), e1472058 (2018).
21. Buiting K, Williams C, Horsthemke B. Angelman syndrome - insights into a rare neurogenetic disorder. *Nat. Rev. Neurol.* 12(10), 584–593 (2016).
22. Kaphzan H, Buffington SA, Ramaraj AB *et al.* Genetic reduction of the $\alpha 1$ subunit of Na/K-ATPase corrects multiple hippocampal phenotypes in Angelman syndrome. *Cell Rep.* 4(3), 405–412 (2013).
23. Brunelli M, Garcia-Gil M, Mozzachiodi R, Scuri R, Zaccardi ML. Neurobiological principles of learning and memory. *Arch. Ital. Biol.* 135(1), 15–36 (1997).
24. Rayi PR, Koyavski L, Chakraborty D, Bagrov A, Kaphzan H. $\alpha 1$ -Na/K-ATPase inhibition rescues aberrant dendritic calcium dynamics and memory deficits in the hippocampus of an Angelman syndrome mouse model. *Prog. Neurobiol.* doi:10.1016/j.pneurobio.2019.101676 (2019) (Epub ahead of print).
25. Barnea ER, Almogi-Hazan O, Or R *et al.* Immune regulatory and neuroprotective properties of preimplantation factor: from newborn to adult. *Pharmacol. Ther.* 156, 10–25 (2015).
26. O'Brien CB, Barnea ER, Martin P *et al.* Randomized, double-blind, placebo-controlled, single ascending dose trial of synthetic preimplantation factor in autoimmune hepatitis. *Hepatol. Commun.* 2(10), 1235–1246 (2018).
27. Tsuneyama K, Baba H, Kikuchi K *et al.* Autoimmune features in metabolic liver disease: a single-center experience and review of the literature. *Clin. Rev. Allergy Immunol.* 45(1), 143–148 (2013).
28. Werlen G, Palmer E. The T-cell receptor signalosome: a dynamic structure with expanding complexity. *Curr. Opin. Immunol.* 14(3), 299–305 (2002).
29. Paensuwan P, Hartl FA, Yousefi OS *et al.* Nck binds to the T cell antigen receptor using its SH3.1 and SH2 domains in a cooperative manner, promoting TCR functioning. *J. Immunol.* 196(1), 448–458 (2016).
30. Giardino Torchia ML, Dutta D, Mittelstadt PR *et al.* Intensity and duration of TCR signaling is limited by p38 phosphorylation of ZAP-70/T293 and destabilization of the signalosome. *Proc. Natl. Acad. Sci. USA* 115(9), 2174–2179 (2018).
31. Kosty J, Lu F, Kupp R, Mehta S, Lu QR. Harnessing OLIG2 function in tumorigenicity and plasticity to target malignant gliomas. *Cell Cycle* 16(18), 1654–1660 (2017).
32. Anderson JL, Muraleedharan R, Oatman N *et al.* The transcription factor Olig2 is important for the biology of diffuse intrinsic pontine gliomas. *Neuro. Oncol.* 19(8), 1068–1078 (2017).
33. Tsigelny IF, Mukthavaram R, Kouznetsova VL *et al.* Multiple spatially related pharmacophores define small molecule inhibitors of OLIG2 in glioblastoma. *Oncotarget* 8(14), 22370–22384 (2017).
34. He HQ, Ye RD. The formyl peptide receptors: diversity of ligands and mechanism for recognition. *Molecules* 22(3), pii:E455 (2017).
35. Planagumà A, Kazani S, Marigowda G *et al.* Airway lipoxin A4 generation and lipoxin A4 receptor expression are decreased in severe asthma. *Am. J. Respir. Crit. Care Med.* 178(6), 574–582 (2008).

36. Bozinovski S, Anthony D, Vlahos R. Targeting pro-resolution pathways to combat chronic inflammation in COPD. *J. Thorac. Dis.* 6(11), 1548–1556 (2014).
37. Kelly AM, Mathema B, Larson EL. Carbapenem-resistant Enterobacteriaceae in the community: a scoping review. *Int. J. Antimicrob. Agents.* 50(2), 127–134 (2017).
38. Perez F, El Chakhtoura NG, Yasmin M, Bonomo RA. Polymyxins: to combine or not to combine? *Antibiotics (Basel)* 8(2), pii:E38 (2019).
39. Son SJ, Huang R, Squire CJ, Leung IKH. MCR-1: a promising target for structure-based design of inhibitors to tackle polymyxin resistance. *Drug Discov. Today* 24(1), 206–216 (2019).
40. Wei J, Gronert K. Eicosanoid and specialized proresolving mediator regulation of lymphoid cells. *Trends Biochem. Sci.* 44(3), 214–225 (2019).
41. Lucido MJ, Orlando BJ, Vecchio AJ, Malkowski MG. Crystal structure of aspirin-acetylated human cyclooxygenase-2: insight into the Formation of Products with Reversed Stereochemistry. *Biochemistry* 55(8), 1226–1238 (2016).
42. Lee JY, Han SH, Park MH *et al.* Neuronal SphK1 acetylates COX2 and contributes to pathogenesis in a model of Alzheimer's disease. *Nat. Commun.* 9(1), 1479 (2018).
43. Ahmed I, Akram Z, Iqbal HMN, Munn AL. The regulation of endosomal sorting complex required for transport and accessory proteins in multivesicular body sorting and enveloped viral budding - an overview. *Int. J. Biol. Macromol.* 127, 1–11 (2019).
44. Sørensen MG, Henriksen K, Neutsky-Wulff AV, Dziegiel MH, Karsdal MA. Diphyllin, a novel and naturally potent V-ATPase inhibitor, abrogates acidification of the osteoclastic resorption lacunae and bone resorption. *J. Bone Miner. Res.* 22(10), 1640–1648 (2007).
45. Shen W, Zou X, Chen M *et al.* Effects of diphyllin as a novel V-ATPase inhibitor on gastric adenocarcinoma. *Eur. J. Pharmacol.* 667(1-3), 330–338 (2011).
46. Chen HW, Cheng JX, Liu MT *et al.* Inhibitory and combinatorial effect of diphyllin, a v-ATPase blocker, on influenza viruses. *Antiviral Res.* 99(3), 371–382 (2013).
47. Lindstrom A, Anantpadma M, Baker L, Raghavendra NM, Davey R, Davisson VJ. Phenotypic prioritization of diphyllin derivatives that block filoviral cell entry by vacuolar (H⁺)-ATPase inhibition. *Chem. Med. Chem.* 13(24), 2664–2676 (2018).