Patent highlights April–May 2018

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

WO/2018/058246

Treatment of inflammatory bowel disease with nucleoside triphosphate diphosphohydrolase, P2Y2 antagonist &/or P2Y6 antagonist

Inventors: Sévigny J, Salem M

Assignee: Université Laval, Québec (Canada)

Inflammatory bowel diseases seem to be triggered by an intestinal epithelial dysfunction, probably in response to danger signals that might only suggest the presence of pathogens but nevertheless amplify and sustain the release of proinflammatory cytokines. There is considerable evidence that activation of purinergic receptors by nucleotides such as ATP and UTP, constitutes at least part of these signals and not only in the intestinal tract [1,2]. This signaling is terminated by nucleoside triphosphate diphosphohydrolases (e.g., NTPDase-1, CD39). NTPDases are expressed by immunosuppressive supTh17 T-helper cells [3]. The inventors have demonstrated that NTPDase-8 is expressed on epithelial cells at the apical surface of the mouse and human colon. Although its gross effect on nucleotide hydrolysis in the entire intestine is minimal, its precise localization makes it a most important regulator of intestinal inflammation. Degradation of nucleotides by apyrase, selective blockade of P2Y6 receptors by MRS 2578 or knockout of the P2Y2 receptor protects mice against dextran sodium sulfate-induced colitis and decreases epithelial permeability and chemokine secretion. Selective P2Y2 and P2Y6 ligands have been described [4] but antagonists are rare.

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MeSH Keywords: adenosine triphosphatases/colitis, purinergic P2, ulcerative/receptors.

WO/2018/059263

Bismuth (III) compounds & methods thereof

Inventors: Sun H, Kao RYT, Wang R, Lai TP, Zhang H, Li H

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

Infections by multidrug-resistant bacterial strains producing metallo- β -lactamases (MDLs; as opposed to classical serine β -lactamases) are resistant to nearly all β -lactam antibiotics, including the carbapenems [5]. The present disclosure approaches the problem with the simple Bi(III) salts that are used in *Helicobacter pylori* eradication protocols (where they interfere with bacterial iron metabolism [6]) to treat gastritis and duodenal ulcers. The bismuth compounds displace two Zn(II) ions with one Bi(III) ion. As the inventors demonstrated with x-ray crystallography, this metal exchange triggers the release of the Zn(II) cofactors, which irreversibly inhibits the MDL enzyme. The bismuth compounds are combined with broad-spectrum β -lactam antibiotics (e.g., carbapenems) to which sensitivity is now restored even in previously multiresistant *Enterobacteriaceae* and *Klebsiella* strains expressing the particularly difficult New Delhi metallo- β -lactamases [7]. In a murine peritonitis model, co-administration of colloidal bismuth subcitrate and meropenem postponed death and raised the 20-h survival rate to 50%, compared with 25% with meropenem alone. For the peer review companion paper see Sun *et al.* [8] The search for MDL inhibitors has produced other interesting results; for example, the antihypertensive angiotensin-converting enzyme inhibitor captopril proved to be a useful lead compound [9].

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MeSH Keywords: β -lactamase NDM-1/ β -lactam resistance/bismuth subcitrate

**newlands
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WO/2018/067638**HMGB1 protein inhibitors***Inventors: Kovacs B, Shabbahrami K, Nicola G**Assignee: Afecta Pharmaceuticals, Inc., Irvine, CA (USA)*

HMGB1, also known as amphoterin, is a member of a family of the high-mobility group DNA-binding proteins, expressed at high levels in the nucleus of almost all cells. Originally believed to be a nonhistone nuclear protein that bends DNA [10], it is now known that HMGB1 is also secreted as a prototypical alarmin that activates innate immunity and mediates T cell-dendritic cell interaction [11,12]. The receptors RAGE, TLR2 and TLR4 are its primary targets; secretion of the proinflammatory cytokines IL-1 β , IL-6 and IL-17 and TNF- α is the result. Many approaches to inhibit HMGB1 have been investigated [13], and some anti-inflammatory agents, including salicylate (see WO/2016/133792) and glycyrrhizin [14] (a component of licorice) have been found to bind to it. Among the inventors' inhibitors, N-[2-(diethylamino)ethyl-3-(4-methoxyphenoxy)propanamide seemed to be the most effective when tested on freshly isolated peripheral blood mononuclear cells or CD14⁺ monocytes from healthy volunteers treated with human recombinant HMGB1 protein; it reduced the expression of various inflammatory cytokines and other genes known to be upregulated by HMGB1 by almost 90%.

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MeSH Keywords: HMGB1 protein/interleukins

WO/2018/070510**Myogenesis-inducing agent***Inventors: Hohjoh H, Fukuoka M**Assignee: National Center of Neurology and Psychiatry, Tokyo (Japan)*

During a comprehensive characterization of microRNA species in murine blood, the inventors have found that expression of miR-199a-3p is low in aged mice compared with young ones. This microRNA is well known, mainly for its role as a tumor suppressor [15] but also as a regulator of adipocyte differentiation [16] and cardiomyocyte survival and as a contributor to the functional benefits of carvedilol therapy [17]. That it can act as a muscle cell differentiation promotor, as the inventors now claim, is not surprising, considering a 2013 paper from a Chinese group that reported its strong expression in skeletal muscle and its induction during C2C12 myoblast differentiation [18]; however, the inventors are correct in stating that no report on the utility of miR-199a-3p in muscular dystrophy, muscle damage or age-related atrophy has been published. Mouse data to this effect are presented, also in aged mice. In the mdx mouse model of muscular dystrophy, it reduced creatine kinase levels in plasma. miR-199a-3p seems to act by suppressing the expression of *LIN28B* and *SUZ12*, the two recently reported oncogenes.

Published: 19 April 2018

MeSH Keywords: miR-199a, human/muscular atrophy/muscular dystrophies

WO/2018/071531**HPPK inhibitors useful as antibacterial agents***Inventors: Ji X, Genbin S, Shaw GX**Assignee: The United States of America, as represented by the Secretary, Department of Health and Human Services, Bethesda, MD (USA)*

This disclosure provides linked purine–pterin compounds that are novel inhibitors of HPPK, a kinase responsible for an essential step in the biosynthesis of folic acid. While this is an essential B-group vitamin, often given in fortified food, the microbial folate pathway is an ideal target for developing antibacterial agents. While some dihydrofolate reductase inhibitors (e.g., iclaprim) have been developed as antibiotics, HPPK inhibitors (none of which has yet entered clinical use) target the second essential enzyme in the pathway which catalyses the transfer of pyrophosphate from ATP to 6-hydroxymethyl-7,8-dihydropterin to form the diphosphate [19]. The inventors, who had created the original series of bisubstrate analog inhibitors by linking 6-hydroxymethylpterin to adenosine [20,21] have continued their structure-based approach. They have developed 6-Hydroxymethyl-7,8-dihydropterin pyrophosphokinase (HPPK) inhibitors with significantly improved potency, primarily by varying the linker moiety between the purine (still adenosine) and the pyridine in such a way that that it mimics the transition

state of pyrophosphoryl transfer. In many cases, the crystal structure of the inhibitor in complex with *Escherichia coli* HPPK was determined. The two best compounds have K_d values in the high nanomolar range.

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MeSH Keywords: antibacterial agents/diphosphotransferases

WO/2018/073474

Allosteric TAO inhibitors as antiparasitical & antifungal agents

Inventors: Dardonville C, De Koning HP, Ebiloma GU

Assignee: Consejo Superior de Investigaciones Científicas (CSIC), Madrid (Spain); The University Court of the University of Glasgow, Glasgow (UK)

Trypanosoma mastigotes (the form of the parasite present in the mammalian bloodstream) depend on the host glycolysis system for NADH generation. A cytochrome-independent and cyanide-insensitive terminal oxidase of their mitochondrial electron transport chain, the alternative trypanosome oxidase (TAO) [22,23] oxidizes the NADH that accumulates during glycolysis. TAO is unique to trypanosomes, differs substantially from mammalian terminal oxidases and therefore is an ideal drug target because it does not occur in mammals; however, it was not before 2013 that the structure of TAO in complex with derivatives of ascofuranone (one of its prototypical inhibitors) was reported [24]. The compounds of this patent application are also loosely based on ascofuranone. They exhibit IC_{50} values in the nanomolar range against recombinant TAO and *in vivo* EC_{50} values against cultured *T. brucei* in the 3.8–49 μ M range, up to ten-times more potent than salicylhydroxamic acid (another widely used trypanocidal TAO inhibitor) in this assay. These compounds are equally active on resistant strain B48 and do not exhibit cross resistance with other trypanocidal drugs such as pentamidine and diminacene. Structure–activity data show an enhancing effect of an aliphatic chain longer than four carbon atoms on the trypanocide activity. TAO is a member of the larger group of alternative oxidases [25]. Other pathogenic parasites, such as *Cryptosporidium parvum* or fungi, such as *Candida albicans*, have related alternative oxidases that are also essential for them. The TAO inhibitors disclosed here may be useful for the treatment of candidiasis.

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MeSH Keywords: antifungal agents/oxidoreductases/trypanocidal agents/trypanosomiasis

WO/2018/081085

Methods of diagnosis & treatment of Alzheimer's disease

Inventors: Zhan X, Stamova B, Sharp F

Assignee: The Regents of the University of California, Oakland, CA (USA)

This patent application explores and exploits the theory that Alzheimer's disease could, at least in part, have an etiology of bacterial infection. Prion-like 'corruptive protein-templating' from sources outside the central nervous system, including even intestinal bacteria, has been considered as a potential element in the pathogenic cascade [26,27]. Indeed, recent evidence indicates that A β functions, if perhaps only in one of several roles, as a member of a class of an innate immune defense molecules that utilizes fibrillation to protect the host from a wide range of infectious agents [28]. It has long been known that lipopolysaccharide (LPS) from Gram-negative bacteria binds soluble amyloid and that injection of LPS followed by ischemia-hypoxia produces plaque-like aggregates of β -amyloid in rat brains [29]. The inventors present data showing that *E. coli* K99 was detected in grey matter in nine out of 13 Alzheimer patients compared with one out of ten control cases and in white matter in ten out of 13 Alzheimer cases versus four out of ten control cases. Results for LPS were ambiguous: it was detected by immunofluorescence in neurons, oligodendrocytes and microglia from all 11 tested Alzheimer brains and all of seven control brains, but its levels were higher in patients. The inventors propose using antibiotics useful to treat a gram-negative bacterial infection, TLR4 antagonists and/or antibodies that specifically bind to an immunogenic antigen of a Gram-negative bacterium, all delivered through the blood–brain barrier, as a therapy or preventive measure for Alzheimer's disease. Notably, many of the old tricyclic antidepressants could be used as TLR4 antagonists.

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MeSH Keywords: Alzheimer disease/*Escherichia coli*/lipopolysaccharides

WO/2018/083157**Substituted pyrido[3,4-*b*]indoles for the treatment of cartilage disorders***Inventors: Gretzke D, Ritzeler O, Heinelt U, Wehner V, Schmidt F*

Assignee: Sanofi SA, Paris (France)

8-Aryl-substituted and 8-heteroaryl-substituted β -carboline derivatives that stimulate chondrogenesis and cartilage matrix synthesis have been designed with a perspective toward their development for osteoarthritis. A total of 296 compounds have been characterized; the best ones have submicromolar EC₅₀ values for the induction of type II collagen protein as a marker of chondrocytic differentiation in the murine ATDC5 cell line [30] (e.g., 120 nM for 8-(4-methoxy-phenyl)-1-methyl-9H-pyrido[3,4-*b*]indole-6-carbonitrile). They are also said to be strong inducers of SOX-5, SOX-6 and SOX-9, which are central transcription factors in the chondrogenic differentiation pathway [31], but no supporting data are presented. Especially data on SOX-9 would be interesting; its gene promoter is methylated, and protein expression is decreased, in osteoarthritis [32].

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MeSH Keywords: carboline/osteoarthritis/SOX transcription factors

WO/2018/085491**5-HT_{1F} receptor agonists & mitochondrial biogenesis***Inventors: Lindsey CC, Beeson CC, Schnellmann RG*

Assignee: MUSC Foundation for Research Development, Charleston, SC (USA); US Department of Veterans Affairs, Washington, DC (USA)

Despite the advances in therapeutic techniques, the mortality and morbidity of patients with acute kidney injury remain high. In mouse models of this condition, mitochondrial proteins and molecules in the mitochondrial biogenesis signaling pathways are decreased within 24 h and do not recover over 6 days. 5-HT_{1F} receptor agonists, which are usually discussed only in the context of migraine, are also expressed in renal proximal tubule cells and might offer a perspective. Two 5-HT_{1F} agonists, LY-334370 and LY-344864, have already shown promise [33], in addition to a pan-5-HT₂ receptor agonist that can be expected to cause more side effects [34]. The two compounds from Eli Lilly had been active in the nanomolar range, but the inventors pushed the EC₅₀ values for *in vitro* mitochondrial biogenesis dose responses in cultured rabbit proximal tubules down to 20 pM for several compounds (e.g., 7-methoxy-*N*-(2-methoxyethyl)-4-oxo-4H-pyrido[1,2- α]pyrimidine-3-carboxamide). The uncoupled mitochondrial respiration rate was used as a surrogate measure. The effect was also demonstrated in fully differentiated podocytes, which also express the 5-HT_{1F} receptor. For the peer review companion paper see Gibbs *et al.* [35]

Published: 11 May 2018

MeSH Keywords: acute kidney injury/serotonin 1F receptor

WO/2018/086530**Sulfonamide compound as cccDNA inhibitor***Inventors: Fu Z, Zhang Y, Luo M, Chen S, Li J, Xu H, Yang L, Zhang X*

Assignee: Chia Tai Tianqing Pharmaceutical Group Co. Ltd, Lianyungang, Jiangsu (China)

At present, hepatitis B virus infection can be controlled but not cured because current treatments only inhibit *de novo* virus production but fail to eliminate the viral covalently closed circular DNA (cccDNA) from nuclei of the infected hepatocytes, from which the latent virus can rebound. Hopes mostly rely on genetic therapies [36,37]. Very few small molecules are known that target cccDNA. Drexel University and the BS Blumberg Institute seem to have been the first to claim such agents, in WO/2013/130703 (claiming functionalized sulfonamides; [38]) and WO/2013/181584 (claiming macrocyclic ketones with an indole substituent). The present document loosely follows the '703 patent application, providing a series of sulfonamides which were tested in HepDES19 HepG2 cells derived from a cell line carrying the HBV genome; the cccDNA content was determined by quantitation of Southern blots. The mechanism is not discussed, but can be assumed to be the same as with the earlier sulfonamides, i.e., they might interfere primarily with the conversion of deproteinized relaxed circular DNA [39] into cccDNA instead of promoting the intracellular decay of cccDNA.

Published: 17 May 2018

MeSH Keywords: circular DNAs/hepatitis B, chronic

WO/2018/091598**Treatment of neurodegenerative diseases***Inventors: Guerreiro da Silva S, Michel PP*

Assignee: Institut du Cerveau et de la Moelle Epinière, Paris (France); Université Pierre et Marie Curie, Paris (France); Centre National de la Recherche Scientifique, Paris (France); Institut National de la Santé et de la Recherche Médicale, Paris (France)

Two-pore channels (TPCs) belong to the voltage-gated ion channel superfamily and are ubiquitously expressed. Mammalian TPC1 and TPC2 are localized at the endolysosomal membrane and have critical roles in regulating the physiological functions of these acidic organelles. The mechanism of TPC1 activation by voltage or phospholipids has just been reported [40]. TPC2 is required for intracellular Ca^{2+} signaling in response to nicotinic acid adenine dinucleotide phosphate (NAADP) or to mTOR inhibition by rapamycin; inactivation of mTOR may activate TPC2 and consequently lysosomal Ca^{2+} release [41]. The different gating and ion conducting properties of TPC1 and TPC2 suggest that these two ion channels may play complementary physiological roles as calcium release channels of the endolysosomal system [42]. In accordance with the presence of A β 42 and tau proteins found along clathrin endolysosomal internalization pathway, a mechanism based on abnormal lysosomal pH and TPC2-dependent cation homeostasis in Alzheimer's disease has been suggested [43]. Similar disruptions in lysosomal Ca^{2+} signaling might exist in Parkinson disease [44]. The inventors claim TPC1/2 agonists for the treatment of these (and additional) neurodegenerative diseases: NAADP, an NAADP lipophilic prodrug and a compound named trans-Ned-19 (structure provided).

Published: 24 May 2018

MeSH Keywords: Alzheimer disease/calcium channels/NAADP/TPC1 protein, human/Parkinson disease/TPC2 protein, human

WO/2018/095877**Indanylamino pyridyl cyclopropanecarboxylic acids, pharmaceutical compositions & uses thereof***Inventors: Eckhardt M, Peters S, Wagner H*

Assignee: Boehringer Ingelheim International GmbH, Ingelheim am Rhein (Germany)

The free fatty acid receptor (FFAR or FFA1) is a cell-surface G-protein coupled receptor that was first identified as an orphan receptor (GPR40). It is expressed in the insulin-secreting cells where its ligands augment the elevated plasma glucose-induced secretion of insulin [45]. In Phase III clinical trials, Takeda Pharmaceuticals' GPR40 agonist, fasiglifam (TAK-875) significantly improved hyperglycemia without hypoglycemia and weight gain but was discontinued because of unexpected liver toxicity [46]. More GPR40 modulators have been disclosed in WO/2004/041266 (Takeda Pharmaceutical Co., Ltd), WO/2007/033002 (Amgen, Inc.), and WO/2009/157418 (Daiichi Sankyo Co. Ltd), but in the present application Boehringer Ingelheim has improved on the compounds disclosed in its own application WO/2013/178575 in terms of potency, solubility and chemical stability at acidic pH. Chemically they resemble those from the '575 document closely, with most of the structure – in many cases, including the characteristic terminal carboxycyclopropyl group – preserved. (All known GPR40 agonists contain a pharmacophoric carboxylic acid group in their structure, allowing several polar interactions at the binding site of this receptor [47].) While diabetes clearly is the primary development target for free fatty acid receptor agonists, they might be useful in other therapeutic fields; for antagonists, suppression of inflammatory responses in periodontal diseases could be an example [48].

Published: 31 May 2018

MeSH Keywords: diabetes mellitus/FFAR1 protein, human

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