Patent Highlights December 2018–January 2019

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

WO/2018/219847

Coactivators of MOP & NOP receptors in the treatment of addiction to drugs and/or psychostimulants

Inventors: Ciccocioppo R

Assignee: Università Degli Studi di Camerino, Camerino (Italy)

The nociceptin (previously, orphanin FQ) receptor is the fourth member of the opioid receptor superfamily. Nociceptin inhibits the expression of cocaine-induced conditioned place preference in the rat [1], but is without effect on place preference in cocaine-naïve rats even at high intracerebroventricular doses. Grünenthal's cebranopadol (GRT-6005), an almost full high-affinity agonist at both nociceptin and μ -opioid receptors [2], was equivalent to morphine in a Phase III clinical trial of patients with cancer-related pain. The discriminative stimulus exerted by its μ -receptor agonism seems to be reduced by its nociceptin receptor agonism [3]. Considering all the above, nociceptin receptor agonists should be devoid of abuse liability not only as analgesics but also as therapeutics for stimulant addiction. Indeed, rat experiments showed that cebranopadol (25 or 50 μ g/kg p.o.) significantly reduced cocaine self-administration, without development of tolerance, under fixed and progressive ratio schedules of reinforcements indicating reduced motivation for cocaine following drug treatment. Neither the nociceptin receptor blocker SB-612111 nor naltrexone alone were able to antagonize cebranopadol-induced reduction of cocaine self-administration; however, they did so completely when coadministered. Cebranopadol also attenuated yohimbine- and cue-induced reinstatement of heroin seeking, a finding that has been, in part, addressed by Grünenthal's WO/2016/116280. Note that similar effects have recently been reported for a pure nociceptin agonist, AT-312 (Astraea Therapeutics LLC) [4].

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MeSH keywords: analgesics, opioid/cebranopadol/substance-related disorders

WO/2018/222665

Methods & compositions for preventing or treating inflammatory diseases

Inventors: Barbut D, Stolzenberg E, Zasloff M

Assignee: Enterin Laboratories, Inc., Merion, PA (USA)

Alpha-synuclein is abundant in the human brain; and although synuclein aggregation pathology is also present in both sporadic and familial cases of Alzheimer's disease, it is usually considered only for its role in neurodegenerative synucleinopathies – primarily, Parkinson's disease, dementia with Lewy bodies (of which it is primary structural component), and multiple system atrophy. Smaller amounts of α -synuclein are found in myocardial and gastrointestinal muscles, skin, lungs, liver, kidney and joint synovial membranes. The present invention is based on the finding that α -synuclein is a potent chemoattractant for peripheral leukocytes involved in the inflammatory response (monocytes, neutrophils, natural killer (NK) cells, granulocytes and macrophages) that have surface expression of CD11b, an integrin family member that pairs with CD18 to form the CR3 heterodimer. This is in direct analogy to what is seen in the brain and microglia [5]. Inflammation in peripheral tissues containing α -synuclein

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can be reduced by either lowering its local concentrations, or by interrupting its signaling to CD11b, which is directly involved in cellular adhesion, although migration can only take place in the presence of the CD18 subunit. Inhibition of α -synuclein expression or secretion can be achieved by squalamine (a potent antiangiogen that had been investigated for cancer) or other aminosterols, or by miR-34b and miR-34c [6]; its binding can be blocked by suitable antibodies that block interaction sites on α -synuclein or CD11b. To determine if α -synuclein expression in the enteric nervous system is associated with infection and/or inflammation, biopsies taken over a 9-year period from children who underwent endoscopy for upper GI tract distress were analyzed. (A pediatric population was chosen to exclude cases of 'preclinical Parkinson's disease'). Most of the 42 patients exhibited pathological evidence of acute and/or chronic mucosal inflammation; α -synuclein was expressed in 19/23 (83%) of duodenal biopsies with confirmed *H. pylori* gastritis or esophageal candidiasis. For the peer review companion papers, see Perni *et al.* [7,8].

Published: 6 December 2018

MeSH Keywords: alpha-synuclein/CD11b antigen/CD18 antigens/cholestanols/squalamine

WO/2018/223969

Application of *N*-benzyl tryptanthrin derivative as tryptophan dioxygenase inhibitor

Inventors: Yang Q

Assignee: Fudan University, Shanghai (China)

Tryptophan 2,3-dioxygenase (TDO) is one of the enzymes that catalyze the first- and rate-limiting step in tryptophan catabolism to *N*-formylkynurenine [9] (the others are IDO1 and IDO2). While the IDOs are extrahepatic, TDO is mainly expressed in the liver. It is upregulated in many cancers and is associated with tumor immune escape, increasing the level of regulatory T cells in the body and subsequently inducing immune tolerance. However, there are few studies on the use of TDO inhibitors in oncology, and even less in major depression [10] and multiple sclerosis [11], where it is also supposed to play a role. The only reasonably selective inhibitor (vs the IDOs) known from the literature is (E)-3-[2-(4'-pyridyl)-vinyl]-1*H*-indole (540C91) [12], while the most recently reported diaryl hydroxylamines [13] are nonselective. The inhibitors disclosed here, such as 8-(4-phenyl-1*H*-1,2,3-triazole-1-methylene)-2-methyltryptamine, also belong in the nonselective class, with micromolar IC₅₀ values. Achieving selectivity for TDO versus the IDOs is difficult because the heme-containing active centers of TDO and IDO1 are highly similar, although the overall aminoacid sequence of these enzymes differ substantially.

Published: 13 December 2018

MeSH keywords: depression/multiple sclerosis/neoplasms/tryptophan oxygenase/quinazolines

WO/2018/225018

Novel substituted sulfoximine compounds

Inventors: Sharma R, Iyer P, Agarwal S

Assignee: Cadila Healthcare Ltd, Ahmedabad (India)

The nucleotide-binding oligomerization domain (NOD)-like receptor family protein NLRP3 is an intracellular signaling molecule that senses many pathogens, as well as environmental and host-derived factors; it is a crucial element of the inflammasome, which activates proinflammatory interleukins via caspase-1 [14]. Current treatments for NLRP3-related conditions include biologic agents that target IL-1, such as the recombinant IL-1 receptor antagonist anakinra, the neutralizing IL-1 β antibody canakinumab and the IL-1 trap rilonacept. Small-molecule inhibitors could provide a cheaper and more convenient alternative for treating severe inflammatory diseases [15]. While the University of Queensland had disclosed sulfonylureas as NLRP3 inhibitors in WO/2016/131098, Cadila is now following-up with phenyl sulfonimideamides, which carry a hexahydro-*s*-indacene substituent. The most active ones, such as *N*'-cyano-*N*-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)pyridine-3-sulfonimidamide, have low-nanomolar IC₅₀ values in lipopolysaccharide-primed THP1 monocytes. *In vivo* experiments with IL-1 β assays in serum of lipopolysaccharide-treated mice are mentioned without presenting results.

Published: 13 December 2018

MeSH keywords: inflammasomes/NLRP3 protein/septic shock

WO/2018/232150**Methods of treating RBP4-related diseases with triazolopyridines***Inventors: Lin Y-HT, Wang C-CI*

Assignee: Belite Bio, Inc., Cayman Islands

Retinol-binding protein 4 (RBP4), the sole retinol transporter in blood, is secreted from adipocytes and liver. Serum RBP4 levels correlate tightly with insulin resistance, cardiovascular disease and other metabolic syndrome factors [16]. It is considered as a potential biomarker for early management of Type II diabetes [17]. In nonalcoholic fatty liver disease or steatohepatitis, its secretion is disturbed along with the vitamin A metabolism [18]. However, pathological causation is not clearly evident in these conditions as far as the literature is concerned: during a high-fat diet challenge in mice, elevated levels of RBP4 in the circulation fail to aggravate the worsening of systemic parameters of glucose and energy homeostasis [19], although it promotes insulin-induced aortic smooth muscle cells [20]. Nevertheless, the inventors have created phenylpiperidine-substituted triazolopyridines such as 3-(4-(2-trifluoromethyl)phenyl)piperidine-1-carbonyl-[1,2,4]triazolo(4,3-a)pyridine-6-carbonitrile, which administered p.o. at 25 or 50 mg/kg in a mouse model of nonalcoholic steatohepatitis, reduced RBP4 expression and improved plasma insulin levels and glucose tolerance relative to controls. Outlines of planned clinical Phase I and II trials are also presented.

Published: 20 December 2018

MeSH keywords: diabetes mellitus/nonalcoholic fatty liver disease/retinol-binding proteins, plasma

WO/2018/228934**Heteroaromatic compounds as vanin inhibitors***Inventors: Bosanac T, Burke MJ, Cook BN, Disalvo DT, Kirrane TM, Sen Y*

Assignee: Boehringer Ingelheim International GmbH, Ingelheim (Germany)

Vanin enzymes are extracellular pantetheinases that catalyze the cleavage of pantethine and pantetheine into pantothenic acid (vitamin B5, a precursor to coenzyme A) and cystamine and cysteamine, respectively [21]. Expression of vanin-1 is upregulated in response to free fatty acids, PPAR activation or oxidative stress. Homozygous *VNN1* knockout mice lack the cysteamine/cystamine redox system, and also show immunological alterations [22]; they are also partially protected against colitis induced by chemicals or *Schistosoma* infection [23]. The situation in humans should be similar: vanin-1 is upregulated in epithelial biopsies from patients with inflammatory bowel diseases, and individuals with a gain-of-function polymorphism in the *VNN1* regulatory region have increased susceptibility to such diseases [24]. In systemic sclerosis, elevated vanin-1 levels in skin and blood correlate with disease severity [25] (claimed in WO/2017/097838); other associations include nephropathy, diabetes, atherosclerosis and hepatic disease. Pfizer had been first to disclose vanin-1 inhibitors in WO/2016/193844 and had followed-up with pyrimidine carboxamides in WO/2018/011681 for the treatment of Crohn's disease and ulcerative colitis. The compounds disclosed here are also carboxamides, preferably with pyridooxazines and pyrrolidines as substituents. IC₅₀ values are in the low-nanomolar range for recombinant vanin-1 and roughly an order of magnitude higher in a whole human blood assay. Treatment claims are for a very broad range of diseases.

Published: 20 December 2018

MeSH keywords: connective tissue diseases/inflammatory bowel diseases/vanin 1 protein, human

WO/2018/236899**Treating disease & promoting weight loss by inhibiting the TMA/FMO3/TMAO pathway***Inventors: Hazen SL, Brown JM*

Assignee: The Cleveland Clinic Foundation, Cleveland, Ohio (USA)

Trimethylamine N-oxide is generated from trimethylamine (produced from dietary nutrients such as choline, lecithin and carnitine by gut microbial lyases) by hepatic flavin-containing monooxygenases (primarily FMO3) [26]; this is the TMA/FMO3/TMAO pathway. TMAO is associated with microbial dysbiosis and its dysregulation is being studied for its linkage with cardiovascular and neurological disorders, renal diseases and cancer [27]. TMAO being a potent atherogen, the link of FMO3 with cholesterol is particularly strong [28,29]. Applications to achieve weight loss in obesity, as claimed here, do not seem to have been reported so far. Plasma TMAO levels in mice and FMO3 mRNA expression in men demonstrated positive correlations with obesity. The complex therapy can consist of elements including: 3,3-dimethyl-1-butanol or a derivative; acetylsalicylic acid or a derivative, optionally

delivered directly to the colon or cecum; an FMO3 inhibitor (tenofovir, methimazole or an antibody); a gut TMA lyase inhibitor (e.g., iodomethyl choline); fecal microbiota transplantation; a probiotic, prebiotic or broad-spectrum antibiotic that reduces TMA production in the gut; an antiplatelet agent; a TMA and/or TMAO sequestering agent; a compound comprising at least one of: ethanol amines, trimethylsilylethanol, phosphocholine and P,P,P-trimethyl ethanolphosphine; and an inhibitor of TMA-induced trace amine-associated receptor 5 activation. In 6-week-old male C57BL6/J mice maintained on either 60% high-fat diet with 0.06% (w/w) TMA lyase inhibitor iodomethyl choline for 20 weeks, weight gain was significantly reduced versus high-fat controls; this was replicated in leptin-deficient ob/ob mice on standard chow with or without iodomethyl choline. For closely related work from the inventors concerning platelet responsiveness, see Zhu *et al.* [30].

Published: 27 December 2018

MeSH keywords: flavin-containing monooxygenase/methylamines/obesity

WO/2019/002548

Treating migraine by agonizing TREK1, TREK2 or heteromers including them

Inventors: Sandoz G, Royal P, Baron A, Lesage F, Verkest C

Assignees: Institut National de la Santé et de la Recherche Médicale (INSERM), Paris (France); Centre National de la Recherche Scientifique (CNRS), Paris (France); Université Nice Sophia Antipolis, Nice (France)

The prevailing theory of migraine pathophysiology claims that it is, at least in part, due to neuronal ion channel dysfunction. TWIK-related spinal cord potassium channel (TRESK), a two-pore-domains potassium (K2P) channel, has been linked to inherited migraine with aura [31,32]. In humans, two types of loss-of-function mutations of TRESK are known: TRESK-MT, a 2-bp frameshift mutation in the *KCNK18* gene, which causes premature truncation of TRESK [33], and TRESK-C110R, a missense variant. Although both mutants result in a strong reduction of the TRESK current, only TRESK-MT produces an increase in trigeminal neuron excitability and is associated with aura migraine. The inventors have found that the MT mutation puts an alternative start codon in frame, which leads to the translation of a second TRESK fragment. Surprisingly, the gene products, termed MT1 and MT2, have different dominant negative effects: Only MT1 targets TRESK directly while MT2 acts on TREK1 and TREK2, members of another subfamily of K2P channels that heteromerize with TRESK physically and functionally. Overexpression of normal TRESK subunits in cultured mouse trigeminal neurons reduces their excitability [34], suggesting that TRESK channel openers could treat migraine. The preferred small-molecule agonists are ML67 and its congeners, particularly ML67-33 (2,7-dichloro-9,9-dimethyl-10-[2-(1H-tetrazol-5-yl)-ethyl]-9,10-dihydro-acridine [35]). For the peer review companion paper, see Royal *et al.* [36].

Published: 3 January 2019

MeSH keywords: migraine with aura/potassium channels/TRESK protein, human

WO/2019/007362

Methods for treating inflammation & related diseases & disorders by inhibiting alpha protein kinase 1

Inventors: Xu T, Li TR, Xu C, Pan J, Liu D, Pan Y

Assignee: Shanghai Yao Yuan Biotechnology Co. Ltd., Shanghai (China)

Alpha kinases, of which six subtypes are currently known, represent a novel protein kinase superfamily, displaying little sequence similarity to conventional protein kinases. ALPK1 phosphorylates myosin and plays an essential role in the exocytic transport to the apical plasma membrane [37]. Genetic association studies suggest that some of its rarer polymorphisms might increase the risk for gout in hyperuricemia [38], but most importantly there are close and confirmed ties to innate immunity [39] and cancer. The balance between ALPK1 and testosterone might play a role in testosterone-mediated inhibition of proinflammatory cytokines [40]. In this patent application, the focus is on inflammatory bowel disease (where ALPK1 involvement via IL-12 had been reported by a different group [41] 1 year after the priority date of this patent document), radiation-induced inflammation, arthritis and obesity; animal model data are presented for all of these. The preferred small-molecule ALPK1 inhibitor is 1-benzyl-3-cetyl-2-methylimidazolium (NH125; a compound originally reported as a potent antibacterial [42]); however, the biological data presented in the application were obtained with ALPK1 knockout mice.

Published: 10 January 2019

MeSH keywords: ALPK1 protein, human/inflammatory bowel diseases

WO/2019/010583**Methods & uses related to Rett syndrome***Inventors: Justice M, Enikanolaiye A*

Assignee: The Hospital for Sick Children, Toronto (Canada)

Rett syndrome is an X-linked progressive neurodevelopmental disorder caused by mutations in *MECP2*, a gene coding for a methyl-CpG-binding protein [43,44] that acts as an epigenetically selective transcriptional repressor in brain neurons as they mature [45,46]. Most mutations disrupt the interaction of the MeCP2 protein with DNA or the SMRT corepressor complex. In at least 95% of all cases, the cause is a *de novo* mutation in the child. The inventors have discovered that activation of critical early response neuronal genes triggered by DNA double-strand breaks is attenuated in brain and liver of Mecp2/Y mice, while levels of the damage response exonuclease CtIP [47] are elevated – which, given the insufficiency of other elements required for DNA repair, contributes to genome destabilization. Provided data demonstrate that a nonsense codon mutation in CtIP improves longevity of Mecp2/Y mice. The obvious opportunity is to use antisense oligonucleotides or interfering RNAs directed against CtIP-coding nucleotides, or to design a CRISPR-Cas9 complex that modulates transcriptional activity of its gene. Also, since phosphorylation of CtIP is required for its activation an inhibitor of ribonucleotide reductase (trapiene, in clinical trials for cancers) can be used. The ATR kinase, which is responsible for the transduction of signals from the double-strand sensor complexes, is also a therapeutic target in this context; inhibitors (such as berzosertib and its analogs, effective at 30–60 mg/kg in the Mecp2/Y mouse model) are known as cancer cell sensitizers. Such pharmacologically induced reduction of CtIP level leads to reduction of Rett-like neurological symptoms in the mutant mice but had little effect on liver lipids.

Published: 17 January 2019

MeSH keywords: BCL11B protein, human/Rett syndrome/ribonucleotide reductases/thiosemicarbazones

WO/2019/012150**Selective organic cation transporter inhibitors for the treatment of depressive disorders***Inventors: Gautron S, Pietrancosta N, Acher F, Chausset-Boissaire L*

Assignees: Sorbonne Université, Paris (France); Centre National de la Recherche Scientifique (CNRS), Paris (France); Institut National de la Santé et de la Recherche Médicale (INSERM), Paris (France); Université Paris Descartes, Paris (France)

Organic cation transporters are important for many physiological functions and also for drug absorption and disposition; the International Transporter Consortium regularly issues recommendations on those that are important in drug development [48]. Subtypes OCT2 and OCT3 are expressed in the CNS where they modulate mood-related behavior and in particular, antidepressant efficacy [49,50]. The inventors selected disprocynium 24 (1,1'-diisopropyl-2,4'-cyanine, the most selective among the potent OCT inhibitor identified to date [51]; $K_i = 14$ nM for OCT3) as lead compound and attempted to design derivatives that lack its α -adrenoceptor-mediated hypotensive effects that were also seen with earlier analogs [52]. The best results in a battery of mouse models of chronic depression were obtained with (Z)-1-isopropyl-4-((1-isopropyl-6-methoxy-3,4-dihydroquinolin-2(1*H*)-ylidene)methyl)quinolin-1-ium iodide, which (given at 0.1–0.2 mg/kg per day) showed a faster onset of action on anhedonia and better action on anxiety than the selective serotonin reuptake inhibitor fluoxetine, with no anorectic effects after 3 weeks of treatment. In contrast, acute administration had only a moderate (but reproducible) antidepressant-like action on immobility time in the forced swim test, and no effect on locomotor activity or anxiety. For competing work using decynium-22 analogs, see Fraser-Spears *et al.* [53].

Published: 17 January 2019

MeSH keywords: depressive disorder/disprocynium 24/organic cation transport proteins

WO/2019/016123**Targeting synaptogyrin-3 in tauopathy treatment***Inventors: Verstreken P, McInnes J, Zhou L*

Assignee: VIB VZW, Gent (Belgium); Katholieke Universiteit Leuven, K.U. Leuven R&D, Leuven (Belgium)

Synaptogyrins are tyrosine-phosphorylated proteins with two neuronal (synaptogyrins 1 and 3, which can be both expressed on the same synaptic vesicle) and one ubiquitous (cellugyrin) isoform [54]. Scientists working at Roche had previously claimed body fluid levels of synaptogyrins 1 and 3 or variants thereof as biomarkers for Alzheimer's disease (WO/2007/140975). However, no suggestion concerning a functional interaction with the six human tau protein

isoforms had been published until 2016 when Australian researchers tested proteins involved in presynaptic signal transduction, and found 2N tau-interacting proteins being specifically associated with neurological disease [55]. Using unbiased proteomic and genetic approaches, the inventors have found that synaptogyrin-3 mediates the association of N-tau with synaptic vesicles *in vitro* and *in vivo*. Reduction of *Drosophila* synaptogyrin or murine synaptogyrin-3 levels in neurons from fly and mouse models rescued tau-induced defects in vesicle mobility and neurotransmitter release, which are among the early presynaptic dysfunction in various tauopathies including Alzheimer's disease. At the time of filing (July 2017), they had not fully elucidated which part or structure in the tau N-terminus is required for binding to synaptogyrin-3. As a result, the document does not identify specific inhibitors, and makes it only a requirement that the N-terminal 112 amino acids of the human tau is an interaction partner. Peptide fragments derived from the N-terminus could provide suitable leads for the development of small-molecule synaptogyrin-3 inhibitors. For the peer review companion paper, see McInnes *et al.* [56].

Published: 24 January 2019

MeSH keywords: Alzheimer disease/synaptogyrins/tau proteins/tauopathies

WO/2019/022469

Use of NADPH or derivative thereof as β -lactamase inhibitor

Inventors: Cha SS, Na JH, Chung KM, Lee TH

Assignee: Industrial Cooperation Foundation Chonbuk National University, Jeonju-si (Korea); Ewha University – Industry Collaboration Foundation, Seoul (Korea)

This patent application, and its peer review companion paper [57] provide one of the exceedingly rare examples for a totally unexpected finding – in this case, the discovery that NADPH, the ubiquitous cofactor in so many enzymatic redox reactions, is an inhibitor of β -lactamases, and can therefore boost the activity of β -lactam antibiotics. In particular, this applies to the clinically relevant C-type β -lactases ACC-1 and AmpC EC2 (which is also competitively inhibited by citrate [58]). *In vitro*, NADPH restored the antibacterial activity of ceftazidime against a resistant *E. coli* strain producing AmpC BER (an S64A mutant). This was confirmed in a mouse model of peritoneal bacterial infection, although the doses were very high (670 mg/kg). 3-Acetylpyridine adenine dinucleotide is named as a potentially suitable NADP analog. Most recently, NADPH has offered other surprises: nocturin (a mitochondrial circadian clock phosphatase) and MESH1 (a cytoplasmic human homolog of the bacterial (p)ppGpp hydrolase SpoT) can use it as a substrate.

Published: 31 January 2019

MeSH keywords: antibiotic resistance/beta-lactamases/ceftazidime/NADP

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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