Patent highlights December 2016–January 2017

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

First draft submitted: 19 February 2017; Accepted for publication: 1 March 2017; Published online: 9 May 2017

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WO/2016/188827

3-(6-chloro-3-oxo-3,4-dihydro-(2H)-1,4-benzoxazin-4-yl) propanoic acid derivatives and their use as KMO inhibitors

Bouillot AMJ, Denis A, Liddle J, Mirguet O, Walker AL

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MeSH keywords: kynurenine 3-monooxygenase • multiple organ failure • nerve degeneration • systemic inflammatory response syndrome

KMO is a flavin adenine dinucleotide outer mitochondrial membrane mono-oxygenase that oxidizes L-kynurenine to 3-hydroxykynurenine as part of the major route of catabolism of tryptophan, ultimately leading to the formation of quinolinic acid, an N-methyl-D-aspartate receptor agonist and potential neurotoxin [1]. Several small molecule KMO inhibitors have been investigated in models of Huntington's disease [2]. Increased kynurenine levels have also been associated with the development of sepsis following trauma [3], and with multiple organ failure secondary to acute pancreatitis [4]. GlaxoSmithKline now presents 6-chlorobenzoxazine compounds (and in the associated disclosure WO/2016/188828, 5-chlorobenzothiazoles) that are loosely based on the lead compound GSK180 (3-(5,6-dichloro-2-oxo-1,3-benzoxazol-3-yl)propanoic acid) which,

with an pIC_{50} of 8.2 against human KMO, is already highly active *in vitro* [4]. Presumably (no detailed data are disclosed) the improvements are not so much in activity (their mean pIC_{50} is said to be at least 7.5) but are in other pharmacological properties. More KMO inhibitors have been claimed by CHDI, Inc. (WO/2013/016488 being the last in a series of disclosures), Newron Pharmaceuticals SpA (EP-1475385, EP-1424333) and The J David Gladstone Institutes (WO/2008/022281, WO/2008/022286).

Published: 1 December 2016

WO/2016/189091

Methods and pharmaceutical compositions (NTSR1 inhibitors) for the treatment of hepatocellular carcinomas

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MeSH keywords: gastrointestinal hormones • hepatocellular carcinomas • neurotensin • NT1-R protein

The tridecapeptide neurotensin is best known for its actions in the CNS, but in the periphery, it acts as a hormone: after fatty meals it is released by the endocrine cells of the intestinal mucosa into the portal vein, stimulating pancreatic and biliary secretions, inhibiting small bowel and gastric motility and facilitating fatty acids

translocation [5]. Constant overstimulation of its high-affinity receptor, NTSR1, causes overexpression and activation of EGFRs, rendering tumors more aggressive [6]; this has made the neurotensin system a potential target in cancer therapy [7]. Little is known concerning its role in the healthy liver, where neurotensin expression is repressed in adult age and only very low levels of NTSR1 can be found. Only in some fibrolamellar hepatocellular carcinomas (a rare subtype) it was reported to be re-expressed, in correlation with the response to chemotherapy, and the stage of the patients [8]. The inventors have obtained different data showing that the pattern in normal hepatocellular carcinoma resembles quite closely what has been reported for breast, colon, lung and brain tumors: patients showed NTSR1 labeling on 40/72 (56%) of their tumors where the staining was clonal, and 47/73 (64%) expressed neurotensin. The typical effect on tumor progression through EGFR expression was also seen, in xenografted mice as well as in patients. Patients with moderate or low mRNA expression for both ligand and receptor had a significantly better overall survival ($p = 0.0005$ in the log rank test); their 5-year survival was 53.8%, as opposed to 18.1% in patients with high expression (median survival, 80.7 vs 25.1 months). Also as in other solid tumors, the induced EGFR expression restored responsiveness to the receptor tyrosine kinase, sorafenib and erlotinib; whether that would outweigh the increased tumor aggressiveness remains an open question. Claims are directed toward antibodies and siRNAs targeting the components of the neurotensin system.

Published: 1 December 2017

WO/2016/196117

Small molecule analogs of the NEMO binding peptide

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MeSH keywords: Duchenne muscular dystrophy

- NEMO protein, human • I-kappa B kinase
- NF-kappa B • sepsis

Activation of the transcription factor NF- κ B via the canonical pathway is mediated by the upstream I κ B kinase (IKK), a heterotrimer consisting of two catalytic subunits, IKK α and IKK β , and a regulatory subunit, IKK γ or NEMO (NF- κ B essential modulator) [9]. An 11-amino acid peptide (TALDWSWLQTE), comprising the binding domain between the β and γ

subunits, can block the interaction between the α and β subunits and hence, the chronic overactivation of NF- κ B that is observed in many aging-related diseases [10]. This invention, which claims priority to a US Provisional Application dating back to 2007, represents another attempt to develop small molecule inhibitors that have the same inhibitory activity, efforts that are also underway elsewhere [11,12] and have created NF- κ B inhibitors, such as BAY11-7082, MG132, PG201 and MLN0415; all of which are lacking in one or the other of their pharmaceutical properties. The inventors generated a pharmacophore model and used it to screen the ZINC 8.0 database (~900,000 compounds). 2(2-Fluoroanilino)nicotin-(2-amino-2-keto-ethyl) ester reduced activation of NF- κ B by TNF- α in 293-NF- κ B-luciferase reporter cells at low micromolar concentrations. In the next round, 15 structural analogs with a similarity score >90% were identified, and ultimately two minimally differing nonesters, SR12460 and SR12454 (IC_{50} values for TNF- α driven NF- κ B activation, 11.2 and 20.2 μ M, respectively) were found to be stable *in vivo* and exhibited potent therapeutic effects in murine models of endotoxemia and Duchenne muscular dystrophy.

Published: 8 December 2016

WO/2016/196281

MTAP inhibitors for the treatment of sickle cell disease

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MeSH keywords: hemodynamics

- methylthioadenosine phosphorylase • sickle-cell anemias

Approximately a third of adult sickle-cell disease patients do not respond to the only broadly approved (but side-effect burdened) drug, hydroxyurea. Due to the importance of inflammatory cascades in the vaso-occlusive crises that characterize the disease, anti-inflammatory therapies (in seeming paradox, even compounds releasing carbon monoxide at subtoxic levels) are being actively pursued to treat these symptoms of the disease [13]. 5'-Methylthioadenosine, a nucleoside with immunomodulatory potential [14,15] that is generated from S-adenosylmethionine and is present in all mammalian tissues, was without clear effect in the Berkeley (BERK) mouse model of sickle-cell disease when delivered in single intraperitoneal doses. The inventors attributed that to its rapid clearance, and proposed enabling its sustained *in vivo* accumulation (up to 100 $\times$ in plasma for

>24 h) by blocking its catabolic phosphorylase (MTAP). A single dose (15 mg/kg ip.) of the MTAP inhibitor, methylthio-DADMe-immucillin-A, a transition-state substrate analog originally developed to inhibit polyamine synthesis for cancer therapy [16], dramatically decreased the number of rolling leukocytes, mitigated vascular endothelial activation and protected against hemolysis in BERK mice, resulting in improved hemodynamics. During steady state, treatment did not change red blood cell count, hemoglobin levels and hematocrit. The inventors are the founder and the senior scientist, respectively, of the New York City company, Nanometics LLC (meanwhile renamed PHD Biosciences) which is referred to in the invention, and to which the application was originally assigned.

Published: 8 December 2016

WO/2016/200827

p62-ZZ chemical inhibitor

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MeSH keywords: multiple myeloma
• sequestosome-1 protein • zinc fingers

The p62 protein (also known as sequestosome-1; SQSTM1/p62) takes part in selective autophagy; specifically, in dismantling cytoplasmic aggregates that are observed in neurodegenerative diseases and cancers [17]. Moreover, regulation of the NF-κB pathway by p62 modulates the osteoclastogenesis pathway, making it important in multiple myeloma and osteolytic bone metastases [18]. The p62 ZZ zinc finger domain is implicated in these mechanisms, as it binds to RIP1, which contains a death domain that interacts with the TNF receptor, which can then activate NF-κB and p38 MAPK signaling [19]. The novel p62 ZZ inhibitors that are presented here inhibit growth of the MM1S multiple myeloma cell line at concentrations of approximately 2 μM, without toxicity to normal stromal cells. Efficacy and tolerability of N-(3,4-bis((4-fluorobenzyl)oxy)benzyl)-1-cyclohexylmethanamine (XIELP1-106) was evaluated in the treatment of subcutaneous RPMI-8226 human multiple myeloma xenograft model. Treatment with XIELP1-106 (60 mg/kg, ip., q3d × 4 weeks) reduced tumor volume by 23% (p = 0.001) and prevented animal death throughout the 60-day study, while the median survival time of the vehicle treated mice was 42 days. These might be the first small molecule inhibitors for this target. For the companion peer review paper, see Teramachi *et al.* [20]. Also see

Curelab Oncology, Inc.'s WO/2015/100446 claiming p62/SQSTM1 encoding nucleic acids.

Published: 15 December 2016

WO/2016/201373

Diaryl and arylheteroaryl urea derivatives useful for the prophylaxis and treatment of REM sleep disorders

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MeSH keywords: nelotanserin • REM sleep
parasomnias • serotonin 5-HT₂ receptor antagonists

The inventors have found that compounds acting as inverse agonists at 5-HT_{2A} serotonin receptors (nelotanserin, pimavanserin, pruvanserin, eplivanserin, volinanserin, glemanserin, ketanserin, ritanserin, clozapine), and also potentially novel ones which are very closely related to nelotanserin, such as 1-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-4-methoxyphenyl]-3-(2,4-difluorophenyl)urea, can treat REM sleep disorders. This is not really surprising, as it has been reported for Arena Pharmaceuticals' nelotanserin and primary insomnia in 2008 [21], for Axovant's own pimavanserin and sleep maintenance in 2011 [22], and considering that Eli Lilly's pruvanserin had been in clinical development for insomnia; indeed the entire drug class is well known for its potential to treat insomnia [23], and antipsychotics with strong activity of this type have a tradition of being misused to keep unruly dementia patients pacified during the night. However, the invention's limitation to parasomnias that involve loss of motor and speech inhibition during rapid eye movement sleep phases, often a prodromal or comorbid symptom in neurodegenerative diseases [24,25], justifies novelty claims; even more so as no specifically approved drugs exist (clonazepam, which is extensively used off-label, will potentiate cognitive impairment). A protocol for a Phase II, double-blind, 28-day cross-over study of nelotanserin versus placebo in REM behavior disorder patients with Lewy body dementia is presented; this is study NCT02708186 which commenced patient enrolment in March 2016 and has a planned completion date in June 2017. NCT02871427, which also includes patients with night-time visual hallucinations, should conclude in July 2018.

Published: 15 December 2016

WO/2016/204884

FGF receptor ligands for treating diabetes and obesity

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MeSH keywords: diabetes mellitus • fibroblast growth factors • klotho protein

Some of the many FGFs that are known do not only have cytokine-like actions, they can also act as hormones [26]. Two of the three endocrine FGFs (FGF19 and FGF21) can prevent or ameliorate diet-induced obesity, improve glucose homeostasis and reduce hepatosteatosis [27]. The inventor's team had shown earlier [28] that FGF19, while also affecting peripheral organs and tissues, acts on the CNS through melanocortin to achieve these antidiabetic and metabolic effects, activating ERK1/2 in hypothalamic AGRP/NPY neurons while reducing FOS, and preventing the induction of AGRP and NPY mRNA in mice fasted overnight; which effectively makes FGF19 a partial leptin mimetic. Studies in mice that had either of the two hypothalamic FGF receptors genetically ablated had shown that both receptors mediate metabolic actions. Pharmacological blockade of hypothalamic ERK1/2 phosphorylation prevented the glucose lowering effect of FGF19 but mice with no FGF receptor 2 expressed in hypothalamic AGRP neurons showed lower weight gain after 3 months on a high fat diet, although the *a priori* prediction would have suggested a worsened metabolic state in the absence of FGFR2. These conflicting data are reconciled in a model of antagonism between FGF ligands at FGF receptor homo- and heterodimers. FGF8 (a FGF19/21 antagonist) binds to a groove that is conserved between the FGF receptors and also binds Klotho and β Klotho, co-receptors for FGF receptors that avidly bind FGF19 and FGF21 [29]. A 13-amino acid peptide (PNFTQH-VREQLV), injected intraparenchymally into the mediobasal hypothalamus of 8-month-old outbred mice that were fasted overnight and then subjected to an oral glucose tolerance test, produced improved glucose tolerance (median area under the curve, 33.5 ng-min/dl as opposed to 43.7 ng-min/dl in controls). The brain FGF system is a highly complex, and often quite confusing, field [30] where research and development are still in their early days.

Published: 22 December 2016

WO/2016/207785

NADPH oxidase 4 inhibitors

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MeSH keywords: fibrosis • NADPH oxidase 4 protein, human

Endothelial cells, vascular smooth muscle cells and adventitial fibroblasts express multiple isoforms (the Nox family) of NADPH oxidase, a multicomponent enzyme that catalyzes the generation of superoxide from oxygen and NADP⁺. Nox4 is one of the four isoforms that generate reactive oxygen species in all cell types of the vascular system (but also in hepatic and brain cells, hematopoietic stem cells, osteoclasts and keratinocytes) and are counterbalanced by dismutase enzymes [31]. Nox4 acts as an oxygen sensor, and its induction in ischemia has been associated with various diseases and/or disorders. While Nox4 is required for maintenance of the differentiated vascular smooth muscle cell phenotype [32], it may also play a critical profibrotic role in heart failure [33] and in idiopathic pulmonary fibrosis [34]. The invention relates to 2,5-disubstituted benzoxazole and benzothiazole Nox4 inhibitors that were tested in an assay based on human embryonic kidney cells overexpressing a tet receptor and transfected with a Nox4-expressing tet-on vector. Selectivity toward other Nox isoforms is not reported; that would have been of particular interest since the most widely reported small molecule Nox inhibitor, GKT137831 (Genkyotex S.A., Geneva; in Phase II for fibrotic disorders), also inhibits Nox1 [35]. This is a new field for Actelion, which is to be acquired by Johnson & Johnson, but its discovery and early-stage clinical development will be spun off into a small innovation-driven company.

Published: 29 December 2016

WO/2016/210272

Composition for modulating an XBP1 pathway in a keratinocyte and methods of use

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MeSH keywords: keratinocytes • skin • transcription factors • XBP1 protein, human

The transcription factor XBP1 promotes the production and secretion of proteins under conditions of endoplasmic reticulum stress, contributing to the unfolded

protein response [36]. Most XBP1-related work has focused on autophagy in cancer and neurodegenerative diseases. In the skin, which contains an extensive array of immunologically responsive cell types that contribute to both innate and adaptive immunity, XBP1 induces terminal differentiation of epidermal cells under conditions of calcium depletion [37]. The inventors have found that transient overexpression of XBP1 creates a keratinocyte that is itself an immune modulator, capable of acting as an adjuvant in dermal vaccination. Data are provided demonstrating that recombinantly expressing XBP1 in skin cells results in significantly increased durable antigen-specific and systemic IFN- γ and Granzyme B-expressing CD8⁺ T-cell immune responses to a codelivered transgenic antigen, and also promoted accumulation of systemic memory and resident CD8⁺ T cells in the skin at the immunization site. Experiments in B6 mice and with human skin epidermal and dermal explants demonstrate that a proinflammatory cutaneous microenvironment is created, as evidenced by increased expression of cytokines and chemokines, and infiltration of lymphocytes and antigen presenting cells. Convincing data are presented from B6 mice that were immunized against B16-OVA (a poorly immunogenic murine melanoma cell line) according to the invention and challenged with the cells 5 months later.

Published: 29 December 2016

WO/2017/004359

GLS1 inhibitors for treating disease

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MeSH keywords: glutaminase • neoplasms

Glutaminase, a mitochondrial enzyme, converts glutamine to glutamate, providing a source of nitrogen for amino acid and nucleotide synthesis, and a carbon skeleton to fuel the citric acid cycle. Kidney-type glutaminase (GLS1 or KGA; which, belying its name, can be found throughout the body) is frequently found overexpressed in cancer cells, and is attracting increasing attention as a drug target [38,39]. Bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulfide has served as a lead structure for the development of GLS1 inhibitors [40], and several Phase I studies have been conducted with CB-839 (Calithera Biosciences, Inc., CA, USA) [41]. The trisubstituted thiadiazol-2-yl (or 1,3,4-thiadiazole-2-acetamide or -carboxamide) moiety is also present in the compounds of this invention. Their inhibitory activity against GLS1 is presented in three categories of which only the first (IC₅₀ <100 nM) seems to equal

known GLS1 inhibitors. However, *in vitro* activity is only one element in drug discovery and this seems to be the first time that the University of Texas has ventured into GLS1 inhibitor patenting. For work from Cornell University and Ithaca College with different chemical structures, see WO/2016/090350.

Published: 5 January 2017

WO/2017/006270

Deoxyuridine triphosphatase inhibitors

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MeSH keywords: antineoplastic agent resistance
• dUTP pyrophosphatase • neoplasms

The clinical efficacy of anticancer agents that target *de novo* thymidylate metabolism is often compromised by drug resistance: nearly half of the patients who are treated with the thymidylate synthase inhibitor, 5-fluorouracil or its prodrug, capecitabine, do not benefit. Overexpression of dUTPase, a gatekeeper pyrophosphatase which has a protective role under physiological conditions because it counters the cytotoxic effect of uracil misincorporation, is the main reason for such resistance. Reducing the expression of dUTPase increases genome stress in cancer [42], and partially blocking its activity should restore tumor sensitivity. TAS-114 (Taiho Pharmaceutical Co., Ltd, Tokyo; 3-ethyl-4-[4-[4-(1-methylpyrazol-4-yl)imidazol-1-yl]pyrazolo[3,4-b]pyridin-1-yl]benzamide), a dual dUTPase and dihydropyrimidine dehydrogenase inhibitor, had favorable safety and pharmacokinetics in a Phase I clinical trial (NCT02025803) [43], and is now in Phase II for non-small-cell lung cancer. No other candidates seem to have reached the clinical stage. The cyclopropylmethoxy phenylalkyl sulfonamides that are presented here carry on from the University of Southern California's WO/2014/107622 and WO/2010/025308. Colony-forming assays were performed to evaluate their effectiveness alone and in combination with fluorodeoxyuridine at reducing cancer cell viability in colorectal (HCT 116), breast (MCF-7) and non-small-cell lung (H1299, A549, H358 and H460) cell line models. Increasing concentrations of fluorodeoxyuridine between 0.5 and 2.5 μ M demonstrated dose-dependent decreases in colonies formed in all evaluated cell lines; beyond that statement, no biological data are disclosed. For additional dUTPase inhibitors claimed by the applicants, see WO/2017/006271, WO/2017/006282 and WO/2017/006283.

Published: 12 January 2017

WO/2017/011356

Methods and compositions to treat drug-induced diseases and conditions

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MeSH keywords: acetaminophen • DNAJC15 protein, human • hsp40 heat-shock proteins • liver failure

MCJ, a small (150 amino acids) DNA-methylation-controlled protein and a unique member of the DnaJC subfamily of co-chaperones, contains a J-domain located at the C-terminus, while its N-terminal region has no homology with any other known protein. In contrast to other members of the family which are soluble, MCJ also contains a transmembrane domain. It is a negative regulator of mitochondrial respiration [44], and regulates the mitochondrial metabolic status of macrophages and their response to inflammatory stimuli [45]. It might also be a therapeutic target to enhance CD8⁺ T-cell responses [46]. In the present, the inventors have found a new application: preventing drug-induced liver cirrhosis. MCJ knockout mice with bile duct ligation were protected against development of fibrosis, and similar observations were made in the mouse model of acetaminophen-induced liver fibrosis. Primary hepatocytes from wild-type mice were completely protected against toxic injury from 10 mM acetaminophen by shRNAs directed against MCJ-encoding nucleic acids. Such interfering RNAs strongly repressed MCJ expression in wild-type mice for at least 7 days, and protected mice even when injected with invivolectamine 24 h after an acetaminophen bolus. This is particularly important because currently, the only treatment for patients who are admitted into the intensive care unit with acute hepatic failure due to overdose of acetaminophen (the second leading cause of acute liver injury) is N-acetylcysteine, which is effective only when administered within 8 h after the toxic dose.

Published: 19 January 2017

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WO/2017/015271

Elucidation of novel 13-series resolvins that increase with atorvastatin and clear infections
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MeSH keywords: bacterial infections

- docosahexaenoic acids • omega-3 fatty acids
- statins

The inventors have characterized four new molecules that are resolvins – a functional class of metabolites of Ω -3 polyunsaturated fatty acids that are produced in neutrophil–endothelial cocultures upon infection, enhance phagocytic clearance of bacteria, promote neutrophil apoptosis, modulate neutrophil chemotaxis and reduce inflammation severity and mortality in mouse models [47,48]. Resolvins are also present in human and mouse tissues after sterile inflammation. The ‘13-series’ resolvins of the invention are derived from n-3 docosapentaenoic acid, and contain conjugated triene and diene double bonds with each carrying a 13-carbon position alcohol: 7,13,20-trihydroxy-docosapentaenoic acid; 7,8,13-trihydroxy-docosapentaenoic acid; 7,12,13-trihydroxy-docosapentaenoic acid; and 7,13-dihydroxy-docosapentaenoic acid. The inventors initially used LC–MS/MS-based lipid mediator metabolite lipidomics, and found what had to be expected – that the biosynthesis of the new resolvins during neutrophil–endothelial cell interactions was initiated by endothelial COX-2. In a murine *E. coli* infection model, atorvastatin provided an additive effect via S-nitrosylation of COX-2 (a well-known anti-inflammatory activity of statins [49]; COX-2 acetylation by aspirin has a similar effect), increasing survival by >60%. For the peer review companion paper, see Dalli *et al.* [50].

Published: 26 January 2017

Financial & competing interests disclosure

The author has 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.

No writing assistance was utilized in the production of this manuscript.

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