Patent Highlights February–March 2018

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

First draft submitted: 27 April 2018; Accepted for publication: 1 May 2018; Published online: 8 June 2018

WO/2018/019681

Purine and 3-deazapurine analogues as choline kinase inhibitors

Inventors: Casale E, Corti E, Gnocchi P et al.

Assignee: Nerviano Medical Sciences s.r.l., Nerviano, Italy

Choline kinase is ubiquitously distributed in eukaryotes and catalyzes the first phosphorylation step of the Kennedy pathway for the *de novo* synthesis of phosphatidylcholine, the most abundant phospholipid in mammalian cellular membranes [1]. Fast-growing tissues, including tumors, have a high demand for this enzyme. Of the three isoforms (α 1, α 1, β), expression of the α forms correlates with aggressiveness of many solid tumors, including pancreatic cancer [2] and T-cell lymphoma [3]. Choline kinase α inhibitors can inhibit tumor growth [4], and in fibroblast-like synoviocytes cultured from rheumatoid arthritis patients they suppress cell migration and resistance to apoptosis features that contribute to cartilage destruction [5]. The inventors present *in vitro* data for many new inhibitors that are up to 100-fold selective against the β isoform (IC₅₀ values in the mid-nanomolar range for α and in the low micromolar range for β), which is important because the fact that genetic choline kinase β deficiency causes muscular dystrophy suggests that its inhibition might lead to muscle and bone problems [6].

Published: 1 February 2018

MeSH keywords: choline kinase • neoplasms

WO/2018/020418

Treatment and prevention of sleep disorders

Inventors: Harris SC, Kapil RP, Kyle DJ, Whiteside G

Assignee: Purdue Pharma L.P., Stamford, CT, USA

Older insomnia drugs are barbiturate or benzodiazepine GABA-A receptor agonists that potentiate the sedative effects of GABA by increasing the duration or frequency of neuronal chloride channel opening. Newer drugs such as ramelteon act on melatonin receptors in the suprachiasmatic nucleus or are orexin receptor antagonists (suvorexant). The inventors have turned their attention to an alternative target, the ORL-1 opioid-like receptor for which the peptide nociceptin (orphanin FQ) is the endogenous ligand. Agonists and antagonists are both believed to have significant therapeutic potential [7]. That ORL-1 small molecule agonists (Ro 65–6570 and Org 26383) have hypnotic effects that are not reversed by the classical opioid antagonist, naloxone was first reported in 2007 [8]. Such agents are also anxiolytic [9], a function in which they cooperate with orexin [10]. The preferred ORL-1 agonists of the invention contain two-bridged carbocycles and two stereocenters; an almost complete set of preclinical data on acute efficacy and safety in rodents is disclosed. The inventors claim that these compounds should be particularly useful in sleeping disorders related to alcohol abuse. In this context, it is of interest that E Lilly is investigating an ORL-1 antagonist (LY-2940094) as a treatment for alcohol dependence; the agent was moderately effective in a Phase II clinical study but predictably, side effects included insomnia and anxiety [11].

Published: 1 February 2018

MeSH keywords: alcoholism • ORL1 receptor • sleep initiation and maintenance disorders

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WO/2018/027169

Use of ADAMTS13 for treating, ameliorating and/or preventing vaso-occlusive crisis in sickle cell disease, acute lung injury and/or acute respiratory distress syndrome

Inventors: Ewenstein B, Goldstein B, Majer B, Rossato P, Scheifflinger F, Turecek M

Assignee: Baxalta, Inc., Bannockburn, IL, USA; Baxalta GmbH, Zug, Switzerland

In March 2017, Shire, Plc announced that the USFDA had granted Fast Track designation for SHP655 (a recombinantly produced version of the disintegrin and metalloprotease with a thrombospondin motif, ADAMTS13) for the treatment of acute episodes of hereditary thrombotic thrombocytopenic purpura in patients with a constitutional deficiency of ADAMTS13 (which cleaves the von Willebrand factor). The original designation of SHP655 was BAX930; Baxalta had conducted the Phase I study [12] before its 2016 merger with Shire that created a company with a strong focus on rare and neglected diseases. Shire is now looking for larger markets for rADAMTS13: sickle cell disease, where extracellular hemoglobin liberated by intravascular hemolysis blocks von Willebrand factor cleavage by binding to the ADAMTS13 proteolytic site [13]; and certain acute respiratory distress conditions associated with microvascular coagulopathy, which would conceivably involve what is observed in malaria [14] or in pulmonary aspergillosis [15]. Presented data show that SHP655 completely protected SCD mice against death from vaso-occlusive crisis precipitated by hypoxia/reoxygenation (0 vs 83.3% mortality in vehicle-treated animals).

Published: 8 February 2018

MeSH keywords: ADAMTS13 protein • sickle cell anemia • von Willebrand factor

WO/2018/027175

Use of Swell1 inhibitors and modulators to treat Type 2 diabetes and obesity

Inventors: Sah R

Assignee: University of Iowa Research Foundation, Iowa City, IA, USA

Volume-regulated anion channels control cell volume by opening upon cell swelling, but they also transport drugs or their metabolites, and have roles in extracellular signal transduction. VRACs are heteromers of the pannexin homologous protein LRRC8A (also named Swell1) with other LRRC8 members [16,17]. Using shRNA and CRISPR/cas9-mediated *SWELL1* silencing while exploring the swell-activated ion channel signaling in patch-clamped adipocytes, the inventors discovered that Swell1 loss of function disrupts insulin-PI3K-AKT2 signaling *in vitro* and *in vivo*. The selective Swell1 inhibitor DCPIB (4-[(2-butyl-6,7-dichloro-2-cyclopentyl-2,3-dihydro-1-oxo-1H-inden-5-yl)oxy]butanoic acid) induced a compensatory increase in adipocyte Swell1 protein expression. Adipose-targeted *SWELL1* knock-out (Adipo KO) mice have increased insulin resistance. When administered to mice raised on a high-fat diet, DCPIB normalized glucose tolerance associated with obesity. In the model presented here, Swell1 senses adipocyte volumetric expansion and acts as a feed-forward amplifier to further promote adipocyte expansion, energy storage and enhance insulin sensitivity during times of caloric excess. For the peer review companion papers, see Zhang *et al.* [18] and Xie *et al.* [19].

Published: 8 February 2018

MeSH keywords: adipocytes • insulin resistance • LRRC8 protein, human

WO/2018/029660

Methods of treating diseases associated with repeat instability

Inventors: Pearson CE, Nakamori M, Nakatani K

Assignee: The Hospital for Sick Children, Toronto, Ontario, Canada; Osaka University, Osaka, Japan

Ongoing gene-specific CAG/CTG trinucleotide repeat expansions are responsible for at least 16 of the >40 neurodegenerative diseases caused by unstable repeats, including Huntington's disease and myotonic dystrophy. This invention presents a simple solution for the instability that this introduces into the patients' DNA: naphthyridine-benzoazaquinolone. This hybrid molecule was first described in 2004 as a strong stabilizer of guanine-adenine mismatches in duplex DNA [20] and was reported as a ligand for the CAG-CAG triad shortly thereafter [21]. It binds hairpins comprising ten CAG repeats with high affinity and increases their melting temperature by >30°C [22]. In the inventors' work described here, naphthyridine-benzoazaquinolone did not block complementary strand hybridization, but did bind specifically to 'slipped-out' strands containing a CAG20 (but not a CTG20) repeat, suggesting that the compound is specific for tracts that are actively unstable, and will not affect physiological repeats or sequences during recombination of single-stranded DNA. Its *in vivo* effects were investigated in Huntington's

disease R6/2 transgenic mice, which contain a 150–160 CAG triplet repeat, focusing upon the striatum. Repeated intrastriatal injections over a 4-week period actually achieved a measurable shortening of the repeats (~0.5 repeats lost/week), limited to the injection site and without altering brain morphology. This seems to be a novelty: other compounds can reduce genome instability and slow the repeat expansion dynamics but do not achieve contractions. For the peer review companion paper, see Li *et al.* [23].

Published: 15 February 2018

MeSH keywords: genomic instability • Huntington disease • trinucleotide repeat expansion

WO/2018/031579

Momelotinib for treating of ACVR1-mediated diseases

Inventors: Whitney JA, Warr MR, Koh B, Theurl I

Assignee: Gilead Sciences, Inc., Foster City, CA, USA

Constitutive gain-of-function mutations in *ACVR1*, the gene coding for activin A receptor type-1, a kinase from the BMP receptor family, have been identified in fibrodysplasia ossificans progressiva, an extremely rare disorder of connective tissue ossification in characteristic anatomic patterns. A selective ALK2 inhibitor (LDN-212854) that inhibits BMP signaling is effective in a mouse model [24,25] but there is no effective prevention or treatment for the human condition yet. Similar mutations are present in diffuse-intrinsic pontine gliomas [26], unresectable and highly aggressive pediatric brain cancers for which only radiotherapy provides palliative benefits. Gilead is trying a new angle with its JAK2 inhibitor, momelotinib (originally developed by an Australian company, Cytopia [Richmond, Victoria], then by Canada's YM Bioscience [ON, Canada] which was taken over by Gilead in 2013) which was not superior to its rival ruxolitinib in two Phase III myelofibrosis trials. No data are presented and no mechanistic explanation is given. The scientific basis can be tracked to a 2017 paper [27] reporting that momelotinib treatment can normalize hemoglobin and red blood cell numbers in a rat model of chronic anemia, driven by direct inhibition of ACVR1/ALK2. The patent examiner has cited this reference as critically damaging novelty and inventiveness, which seems unfounded given the application's August 2016 priority date.

Published: 15 February 2018

MeSH keywords: activin receptors, type I • Janus Kinase 2 • momelotinib • myositis ossificans

WO/2018/034883

Condensed thiophene derivatives useful as NaPi-IIb inhibitors

Inventors: Coates DA, Fales KR, Peterson JA *et al.*

Assignee: Eli Lilly & Co., Indianapolis, IN, USA

In end-stage renal disease, hyperphosphatemia precipitates secondary hyperparathyroidism, which causes bone lesions, calcification of the large vessels and cardiac dysfunction; however, even small increases in serum phosphate levels, within the normal or near-normal range, may correlate with increased morbidity and mortality. Current treatments employ phosphate adsorbents of various types [28] to reduce the amount of inorganic phosphate available for absorption from the GI tract by the NaPi-IIb transporter (also known as Slc34a2). A more pharmacological approach is to inhibit the transporter itself, which is accomplished by the tetrahydrobenzothiophene compounds of the invention. Mice orally dosed with 4-[2-[2,6-difluoro-4-[[3-[[4-(4-hydroxybutylcarbamoyl)-2,2-dimethyl-piperazin-1-yl]methyl]benzoyl]amino]-4,5,6,7-tetrahydrobenzothiophene-3-carbonyl]amino]phenyl]ethyl]benzoic acid and radioactive phosphate after a 16-h fasting period show 69–76% inhibition of phosphate uptake and its increased fecal excretion. While this is impressive, it remains to be determined if the effect could be compensated by enhanced renal reabsorption (achieved through Slc34a1 and Slc34a3 which are mainly expressed in the kidney), as has been observed in *SLC34A2* knockout mice [29]. It should be noted that the NaPi-IIb transporter seems to have conflicting roles in tumor biology: while being associated with unfavorable prognosis in colorectal cancer [30], it is reported as a favorable prognostic marker in lung adenocarcinoma [31].

Published: 22 February 2018

MeSH keywords: chronic kidney failure • sodium-phosphate cotransporter proteins, Type IIb

WO/2018/035410

Compositions and methods of treatment using expanded-size DNA analogs

Inventors: Pomerantz RT, Kool ET

Assignee: Temple University of the Commonwealth System of Higher Education, Philadelphia, PA, USA; The Board of Trustees of the Leland Stanford Jr. University, Stanford, CA, USA

Unnatural nucleotides have recently attracted much interest because they could offer ways to expand the genetic code, offering entirely new perspectives for synthetic biology [32]. Size-expanded deoxyribonucleotides, which include a benzene ring within the base moiety of each canonical nucleoside can be stably inserted as genetic information in bacteria through several rounds of replication [33]. Although these artificial building blocks significantly expand the width of the helix, they retain canonical base-pairing interactions and exhibit stronger base-stacking interactions, increasing the thermostability of the resulting xDNA compared with canonical DNA. Certain translesion DNA polymerases (in particular, Pol θ) can effectively utilize size-expanded nucleotides as substrates. It is precisely this high mismatch and gap extension tolerance of Pol θ that contributes to its role in cancer, and suggest it as a drug target for tumors with deficient homologous recombination, such as breast and ovarian cancers possessing BRCA mutations [34,35]. However, there are currently no reported inhibitors of this polymerase. The inventors have designed xDNA deoxyribonucleoside monophosphate analogs that contain a benzene ring within the base moiety of each nucleoside, are selectively and efficiently incorporated by Pol θ (especially, if they are based on purines), with steady-state kinetics surprisingly similar to those seen with natural nucleotides, but inhibit its DNA synthesis activity. They uniquely exhibit this novel function compared with all other human polymerases from the X, B, A and Y families. Concentrations of 5–50 μ M are effective *in vitro*. In contrast to replicative polymerases, Pol θ incorporates dxGMP even when an equimolar amount of dGTP is present in the reaction, suggesting that analogs of dxGMP might be developed as selective inhibitors of Pol θ .

Published: 22 February 2018

MeSH keywords: DNA polymerase θ • neoplasms • nucleic acid synthesis inhibitors

WO/2018/037593

Therapeutic agent for primary biliary cholangitis

Inventors: Nakamura M, Kojima S, Tanigawa R

Assignee: Kowa Co., Ltd., Aichi, Japan

Primary biliary cholangitis (PBC) is a chronic progressive liver disease, resulting in chronic cholestasis with fibrotic destruction of hepatic parenchymal cells, and can eventually progress to cirrhosis. It is presumed to be of autoimmune origin with genetic predisposition [36] and can progress without clinical symptoms for a long time. Although it is a rare disease, PBC is a leading cause of liver transplantation in adult women. Obeticholic acid (Intercept Pharmaceuticals' [NY, USA] Ocaliva[®]), a potent and selective agonist of the farnesoid X receptor, was approved as a treatment in 2016, an improvement over the older ursodeoxycholic acid but with pruritus as a major side effect. Kowa presents an alternative: (R)-2-[3-[[N-(benzoxazol-2-yl)-N-3-(4-methoxyphenoxy)propyl]aminomethyl]phenoxy]butyric acid, a compound which is identifiable as pemafibrate (K-877), a selective PPAR α modulator [37] approved for hyperlipidemia in Japan and in Phase III trials for dyslipidemia in the USA and Europe [38]. Data from PBC patients in these trials show reductions in alkaline phosphatase and bilirubin serum levels. Meanwhile, Kowa's development pipeline shows pemafibrate as being in Phase I trials for PBC. It is also under investigation as a treatment for nonalcoholic steatohepatitis [39].

Published: 1 March 2018

MeSH keywords: biliary cirrhosis, primary • pemafibrate • peroxisome proliferator-activated receptor α

WO/2018/038684

Macrophage stimulating protein receptor (or RON – recepteur d'origine nantais) antibodies and use thereof

Inventors: Lane D, Koh XY, Hwang L-A

Assignee: Agency for Science, Technology and Research, Singapore

RON, a tyrosine kinase receptor from the MET proto-oncogene family, is aberrantly expressed in human tumors and promotes cancer cell invasion [40]. The α chain of its endogenous ligand, the serum macrophage-stimulating protein (a member of the plasminogen-related growth factor family) mediates receptor dimerization, followed by

autophosphorylation of tyrosines in the cytoplasmic receptor kinase domains [41]. RON has been suggested as a novel target for HIF-1 α [42], and seems to have crosstalk with androgen receptor signaling in castration-resistant prostate carcinoma: expression of androgen receptors on PC-3 cells leads to activation of RON only under conditions of androgen deprivation [43]. Despite the interesting therapeutic implications, and the increasing numbers of papers on RON/MSP, there are very few good and relatively selective small molecule inhibitors, such as BMS-777607 which significantly reduce glomerular hypertrophy, capillary dilation and congestion and endothelial injury in the Townes sickle cell disease mouse model [44]. The inventors have generated monoclonal antibodies that bind to human and murine RON and can undergo receptor-mediated endocytosis. The therapeutic effect of multiple 15 mg/kg doses of two antibodies on nude mice bearing human cell line HT29-luc derived tumors was investigated. At day 21, animals treated with mAbs 7G8 or 6D4 showed 76 and 50% tumor growth inhibition.

Published: 1 March 2018

MeSH keywords: neoplasms • RON protein

WO/2018/041812

Compounds for the treatment of intractable epilepsy and DOORS syndrome

Inventors: Verstrecken P, Lüthy K, Versées W, Fischer B, Paesmans J

Assignee: VIB VZW, Gent, Belgium

TBC1D24 encodes a unique protein with an N-terminal TBC (Tre2/Bub2/Cdc16) domain linked to a TLDC (TBC/LysM) domain [45]. The protein binds Arf6, a Ras-related family of small GTPases that regulates dendritic branching, spine formation and axonal extension [46]. *TBC1D24*-related disorders comprise a continuum of features that were originally described as distinct, recognized phenotypes of seizure-associated genetic conditions: DOOR syndrome (deafness, onychodystrophy, osteodystrophy, mental retardation and seizures); familial-infantile myoclonic epilepsy; progressive myoclonus epilepsy; early-infantile epileptic encephalopathy 16; and others. There is no distinct correlation with mutation type or location yet, but patterns are emerging [47,48]. The inventors report the crystal structure of the TBC domain of the *Drosophila* homolog protein, Skywalker, which revealed an unusual cationic pocket that is highly conserved among TBC1D24 orthologs but is absent in other known TBC domains. The most prevalent and severe forms of TBC1D24-induced neurological disease are caused by mutations that map to this pocket, which allows the TBC domain to bind directly to membranes containing phosphoinositides phosphorylated in the four and five position. Inhibitors of synaptojanin-1 and other phosphoinositide phosphatases could be therapeutic; alkyl phospholipids are suggested as candidate compounds. Miltefosine (a WHO Essential Medicine used for leishmaniasis), and the cytotoxic drugs perifosine, edelfosine, and erufosine were all able to rescue fruit flies with Skywalker cationic pocket mutations when provided with food. Erufosine should be of particular interest because it crosses the human blood–brain barrier. For the peer review companion paper, see Fischer *et al.* [49].

Published: 8 March 2018

MeSH keywords: digitorenocerebral syndrome • myoclonic epilepsies • TBC1D24 protein, human

WO/2018/053643

Compositions comprising SASP modulators and senescence attenuators as uses thereof for modulating cellular senescence

Inventors: Sapiéha P, Mallette FA, Oubaha M, Beaulieu N, Wilson A

Assignee: RSEM Limited Partnership, Montreal, QC, Canada

As terminally differentiated, postmitotic cells age they do not simply cease activity; they acquire characteristics of senescence, which can include the senescence-associated secretory phenotype (SASP). This is a dynamic, tightly regulated state where cells start secreting growth factors, proteases, cytokines, and other factors which can tip the balance to either an immunosuppressive/profibrotic environment or a proinflammatory/fibrotic state [50]. The inventors have focused on the role of SASP in the initiation of breakdown of vascular beds and subsequent retinal ganglion cell compromise in ischemic retinopathies. They claim to have identified an unexpected mechanism triggered by neurons in devascularized retinal zones where they enter the SASP state by activating the endoribonuclease activity of the endoplasmic reticulum stress effector inositol-requiring enzyme-1 α (IRE1 α , a serine/threonine protein kinase; not to be confused with the interferon-responsive element, a promoter-associated locus modulating gene expression). Factors produced through the SASP including semaphorin 3A propagate senescence across the ischemic retina to neurons, microglia and the overlying vasculature, contributing to destructive

preretinal angiogenesis. This is analogous to the paracrine senescence phenomena that promotes tumor initiation [51], yet another similarity between retinal neovascularization and cancer. Among the IRE1 α inhibitors suggested as potential therapeutic agents is MKC-3946, known to interfere with the unfolded protein response by inhibiting the Xbp1 pathway and inhibiting growth of multiple myeloma cells [52]. The same mechanism has been demonstrated in a *Drosophila* model of retinal degeneration [53]. Sema3a inhibitors can be antibodies, trap proteins or interfering RNAs.

Published: 29 March 2018

MeSH keywords: cellular senescence • ERN1 protein, human • retinal diseases • Semaphorin-3A

WO/2018/055235

Isioxazole-amides for treating cardiac diseases

Inventors: Kinnunen S, Tölli M, Välimäki M *et al.*

Assignee: University of Helsinki, Helsinki, Finland; University of Oulu, Oulu, Finland

The zinc finger transcription factor GATA4 has emerged as a key regulator of several cardiac genes, for example, those coding for natriuretic peptides and myosin chains. In the adult heart, GATA4 has a unique dual role, as a survival factor and as a mediator of the stretch-activated hypertrophic response under conditions of pressure overload and postischemic scarring. It is one of the cardiac-specific transcription factors that can convert mouse fibroblasts into cardiomyocyte-like cells, raising hope for direct cardiac reprogramming [54]. Pharmacological enhancement of this low-efficacy process could create new perspectives for the treatment of heart failure [55]. The isioxazole amides of the invention have been identified as targeting the interaction of GATA4 with its co-protein NKX2-5. This cardiac homeobox protein is essential for looping morphogenesis, lineage specification and maturation of ventricular cardiomyocytes. Co-immunoprecipitation and mobility shift assays were conducted to study protein–protein and protein–DNA interactions in the presence of the compounds. Those having the greatest effect were tested in neonatal rat cardiac myocyte cells to study their effect on basal and PE- and ET-1 – induced increase in cardiac gene expressions, and under mechanical stretching stress equivalent to that experienced in hypertonia. In a murine myocardial infarction model, N-[4-(diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide (30 mg/kg/d given in two daily ip. injections for four days) restituted about half of the infarction-induced decrease of cardiac contractility (as measured by ejection fraction and fractional shortening), as well as ANP and BNP expression. Relative fibrotic areas were not significantly reduced. For the peer review companion paper, see Kinnunen *et al.* [56] and Välimäki *et al.* [57].

Published: 29 March 2018

MeSH keywords: GATA4 transcription factor • heart failure • Homeobox Protein Nkx-2.5

Financial & competing interests disclosure

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.

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

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