Patent highlights December 2019–January 2020

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

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WO/2019/227198

Methods & compositions comprising tankyrase inhibitors for generating insulin producing cells

Inventors: MC Nostro, F Sarangi, R Korytnikov, E McGaugh, HC Poon

Assignee: University Health Network, Toronto (Canada)

Tankyrases are multifunctional poly (ADP-ribose) polymerases that regulate Wnt signaling, telomere maintenance and mitosis through PARsylation, in other words, transfer of an ADP-ribose from the cosubstrate NAD⁺ onto a target protein [1]. Many other proteins have tankyrase-binding motifs, and the functional significance of such interactions is only in the early stages of being uncovered; one example are proteins involved in miRNA processing [2]. Prior to this disclosure, the use of tankyrase-1 inhibitors, which are mostly seen as cancer drug candidates, has not been documented with respect to the differentiation of pancreatic progenitor cells, which have the potential to generate a high percentage of insulin-producing β -like cells. Contacting an endodermal cell population expressing the pancreatic endocrine transcription factor Pdx1 with an EGF and a tankyrase inhibitor that binds to the adenosine subsite of the enzyme (e.g., XAV939, IWR-1-endo, MN64, WIKI4, G007-LK, JW74 or JW55) induces the differentiation of at least a portion of the pancreatic progenitor population into additional expression of Nkx6.1, another transcription factor. Pdx1/Nkx6.1 double-positive progenitor cells can easily differentiate further into functional cells which, upon subcutaneous injection into immunocompromised mice, produce insulin and glucagon like β and α cells. When the EGF/tankyrase-treated cells were injected under the kidney capsules of streptozotocin-treated immunocompromised mice, normoglycemia was achieved without additional insulin. This could be an attractive novel way to generate cells for the treatment of diabetes. Note that systemic glucose homeostasis is also directly regulated by the PARsylation activity of tankyrase in adipocytes, mediated in part by adipocyte-secreted factors that modulate hepatic glucose production [3].

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MeSH keywords: diabetes mellitus • Pdx-1 protein, human • TNKS protein, human

WO/2019/229250

Inhibitors of N-acetylphosphatidylethanolamine phospholipase D

Inventors: ED Mock, Al Kotsogianni Tefisoglou, S Van Boeckel, M Van der Stelt

Assignee: Universiteit Leiden, Leiden (The Netherlands)

NAPE-PLD is a phospholipase that synthesizes N-acylethanolamines (NAEs; a family of signaling lipids) from N-acetylphosphatidylethanolamines. NAEs, which include, for example, the endocannabinoid anandamide and the satiety factor oleoylethanolamide, exert their effects through a multitude of G-protein coupled or nuclear receptors and ion channels. Selective NAPE-PLD inhibitors are of potential interest because they could modulate NAE signaling especially through CB₁, CB₂ or PPAR- α receptors or TRPV1 channels, giving them potential in neurodegenerative diseases, pain, psychiatry, cancer and obesity [4]. The first such inhibitor, the quinazoline sulfonamide ARN19874, was reported only 3 years ago by Italian researchers [5]. The novel inhibitors presented

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here are pyrimidine carboxamides. The pIC_{50} values obtained in an *in vitro* assay based on the membrane protein fraction of HEK293T cells transiently overexpressing NAPE-PLD are presented for 91 of the 205 compounds and were in the 5–7 range. It would be interesting to see how these compounds fare in combination with bile acids, for which NAPE-PLD has an allosteric binding site that can accelerate catalysis several fold [6,7]. Additional lipidomics assays are described but no results are presented. Given the novelty of this target these compounds should be very useful templates for lead optimization.

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MeSH keywords: lipidomics • NAPE-PLD protein, human

WO/2019/236625

Excitatory amino acid transporter-2 activators & methods of using thereof

Inventors: K Hodgetts, C-L Lin

Assignees: Ohio State Innovation Foundation (OH, USA); The Brigham & Women's Hospital, Inc. (MA, USA)

One potential approach for preventing glutamate neuronal excitotoxicity is to enhance its reuptake through its major synaptic transporter, excitatory amino acid transporter-2 (Eaat2). While it is not possible to increase its net transport performance, it is possible to increase its expression [8]. Two compounds from this application, 2-(2-[methylamino]ethyl)-6-(pyridine-2-yl)pyridazine-3(2H)-one and an N-methyl derivative, have been intensely characterized. The EC_{50} in primary murine astrocytes is 250 nM. For Eaat2 *in vivo* induction studies, wild-type C57BL/6 mice were treated orally with 10 mg/kg/day for up to 28 days, which increased expression up to 2.37-fold. In wild-type FVB/NJ mice, dose-dependent induction of Eaat2 expression was seen with single doses in the 1–40 mg/kg range, and as early as 4 h postdose. After 10 mg/kg/day for 7 days, their hippocampal slices showed electrophysiological evidence of increased synaptic plasticity. In rTg(tauP301L)4510 mice (a tauopathy model of Alzheimer's disease) who were fed the compound at 10 mg/kg/day for 2–8 months (a period during which the animals progressed to severe impairment), the compound completely prevented agitation-like behavior in an open-field paradigm, and significantly improved performance versus controls in three cognitive paradigms: Y maze for short-term memory, nonspatial long-term memory in the novel object recognition task and spatial learning in the Barnes maze. Hippocampal PSD-95 protein (a surrogate for synaptic density) was also close to wild-type levels. When the agent was replaced with vehicle after 6 months of treatment, behavioral and synaptic density benefits persisted for at least 1 month, indicating a disease-modifying action. Yet another set of experiments showed that the compounds also ameliorated anxiety- and depression-like behavior in a Gulf War syndrome animal model. Such compounds might also be useful in schizophrenia and alcoholism. For the peer review companion papers see Foster *et al.* [9,10].

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MeSH keywords: Alzheimer's disease • excitatory amino acid transporter-2 • glutamic acid • Persian Gulf syndrome

WO/2019/236750

Targeted treatment of autism spectrum disorder & other neurological or psychiatric disorders

Inventors: I Draper, AS Kopin, D Slonim

Assignee: Tufts Medical Center, Inc. (MA, USA)

Autism spectrum disorder (ASD; the umbrella term for autism and Asperger syndrome) has enormous genetic heterogeneity; almost 900 affected genes have been identified. A substantial fraction of ASD brains possess distinct transcriptomic signatures, which are in part a consequence of altered neuronal activity and have a particular impact on pre-mRNA alternative splicing patterns [11]. This invention claims the steps of identifying an ASD subject having a splicing defect in a gene having an heterogeneous nuclear ribonucleoprotein L-binding site, and administering to the subject a spliceopathy rescue agent such as ascochlorine [12], or its derivatives (e.g., 4-O-methylascochlorin) and analogs. A long list of such genes that were already claimed in US patent no. 9,662,314 is excluded, leaving as the highest scorers in a bioinformatics analysis the neurofibromatosis gene *NF1*, the tuberous sclerosis complex genes *TSC1* and *TSC2* and genes in the SHANK/TSC/mTOR/ERK signaling pathway [13], all of which have been shown to be associated with ASD. A screening assay for splice-repair compounds that affect heterogeneous nuclear ribonucleoprotein L levels is described, but no biological data are presented.

Published: 12 December 2019

MeSH keywords: autism spectrum disorder • heterogeneous-nuclear ribonucleoprotein L

WO/2019/241469

Nonmuscle myosin II inhibitors for substance use relapse

Inventors: C Miller, P Griffin, T Kamenecka et al.

Assignee: The Scripps Research Institute (CA, USA)

Dependence on psychotropic drugs is not only a matter of receptor expression or sensitization; the psychological component is much more difficult to treat. During drug consumption, associative memories form that connect the drug experience not only with immediate drug paraphernalia but also with items that are not directly related to the drug, as well as behaviors and social constellations during which the substance is consumed. Re-exposure to such context-based cues can trigger craving after successful withdrawal and is among the most important mediators of relapse. Five years ago, the inventor team had already identified actin polymerization dynamics as a factor in memories associated with methamphetamine, but not with food or fear. Because actin polymerization inhibitors would interfere with cardiac and skeletal muscle function, they shifted their focus upstream to nonmuscle myosin II, and found that a single injection of its inhibitor, blebbistatin ([S]-3a-hydroxy-1-phenyl-1,2,3,3a-tetrahydro-4H-pyrrolo[2,3-*b*]quinolin-4-one) into the basolateral amygdala complex disrupted methamphetamine-related memory storage [14,15]. In this document they push onwards with analogs of blebbistatin, BPN-0025915, BPN-0025001 and BPN-0026555 being the preferred ones. Their selectivity for nonmuscle myosin II relative to cardiac myosin II is >3.0 (for the parent compound, 0.79). For selected compounds *in vitro* results are backed up by cardiac safety tests in Sprague-Dawley rats at intravenous doses of 0.5 mg/kg, with measurements including fractional shortening, ejection fraction, heart rate and cardiac output.

Published: 19 December 2019

MeSH keywords: blebbistatin • nonmuscle myosin type IIB • substance-related disorders

WO/2019/243273

Gold(I)-phosphine 1,2,3-triazole derivatives with antibiotic properties

Inventors: G Mislin, I Schalk, P Pleasiat, A Paulen

Assignees: Université de Strasbourg (Strasbourg, France); Centre National de la Recherche Scientifique (Paris, France); Centre Hospitalier Régional Universitaire de Besançon (Besançon, France); Université de Franche-Comté (Besançon, France)

Investigations of gold complexes as antimicrobials go back to R Koch who demonstrated activity of potassium dicyanidoaurate(I) against *Mycobacterium tuberculosis* at the end of the 19th century. Increasing spread of antibiotic resistance has reinvigorated this line of research in recent years [16]. Gold(I)-phosphine coordination complexes, which can be regarded as analogs of auranofin (an antirheumatic agent that also has antimicrobial properties [17]), have always been of particular interest, including those with heteroaryl phosphine ligands [18]. Auspherix Ltd, Stevenage, UK, a company specialized in this field, had disclosed 1,2,3-triazole ligands in WO/2017/093545; however, regioisomerism seems to have produced mixtures of compounds, with the gold (I)-phosphine attached to different nitrogen atoms. The present inventors used click chemistry to synthesize compounds where the aurophosphine (preferably triethylphosphine) is attached to one of the two carbon atoms of the triazole heterocycle while the other one bears various substituents. Antibacterial activity was evaluated on a panel of Gram-positive (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Enterococcus faecium*, *Clostridium difficile*) and Gram-negative strains (*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*) with known features of antibiotic resistance. MIC values were close or lower than for ampicillin and were also effective against multiresistant strains.

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MeSH keywords: antibacterial agents • organogold compounds • triethyl phosphine gold

WO/2019/243653

Use of tyrosine hydroxylase inhibitors for the treatment of aortic aneurysm

Inventors: J Martínez Gonzáles, E Cañes, C Rodríguez Sinovas

Assignees: Consejo Superior Investigaciones (Madrid, Spain); Fundacio Institut de Recerca de l'Hospital de la Santa Creu I Sant Pau (Barcelona, Spain)

Abdominal aortic aneurysm results from a weakness of the vessel wall that usually develops over decades, with few if any symptoms; in men over 65 years old, prevalence can reach around 8%, especially in smokers. Ruptures are

fatal in 80% of cases and associated with extreme disability if survived [19]. No specific pharmacological treatment is available during the asymptomatic stage, although COX-2 inhibitors could be expected to have some effect on aneurysm growth and in preventing or delaying wall dissection [20,21]. The inventors have shown increased expression of tyrosine hydroxylase (the rate-limiting enzyme in catecholamine synthesis) in samples of patients with abdominal aortic aneurysm. In transgenic mice expressing the nuclear receptor Nr4a3 and in *APOE* knockout mice (two aortic aneurysms models), strong induction of tyrosine hydroxylase expression was seen in the aorta. These mice could be made partially resistant against aneurysm development triggered by infusion of angiotensin II by the tyrosine hydroxylase inhibitor α -methyl-p-tyrosine (100 mg/kg ip. twice daily). The effect became significant after 14 days of treatment; vascular remodeling and collagen deposition induced by angiotensin-II was attenuated. Interest in tyrosine and tryptophan hydroxylases as therapeutic targets has increased since nonclassical cardiovascular functions of monoamine neurotransmitters, as well as roles in energy and bone homeostasis, gastrointestinal motility, hemostasis and liver function have been described [22]. A 30-year-old report has described significantly elevated levels of dopamine, serotonin and 5-HIAA in the cerebrospinal fluid of patients with subarachnoid aneurysm before its rupture [23].

Published: 26 December 2019

MeSH keywords: abdominal aortic aneurysms • tyrosine 3-monooxygenase

WO/2020/006489

New molecular tweezers against neurological disorders & viral infections

Inventors: T Schrader, J Münch, C Heid et al.

Assignees: The Regents of the University of California (CA, USA); Universität Duisburg-Essen (Duisburg, Germany); Universität Ulm (Ulm, Germany)

Molecular tweezers are linear polycyclic molecules in which benzene and norbornadiene rings alternate; a hydroquinone sits in the center of symmetry of this backbone, which forms a well-defined hydrophobic cavity with a negative surface potential, allowing them to accommodate certain cationic guest molecules through a unique combination of electrostatic and hydrophobic interactions. When interacting with proteins, tweezers accommodate only the sidechains of lysine and arginine, making them potential agents to prevent pathologic protein aggregation such as in Alzheimer's and prion disease, and amyloidotic polyneuropathy [24,25]. Additionally, molecular tweezers have been found to disrupt the lipid-raft-rich membranes of enveloped viruses but not those of normal mammalian cells [26]. Their main drawback is that limited functionalities have been incorporated into them. In the present invention, the German–American team has continued work on the tweezer compounds it had claimed in WO/2010/102248, which had included the lead compound CLR01 (a.k.a. TW 1). They provide new derivatives with symmetrical dialkyl diphosphates and unsymmetrical diphosphate monoester substituents on the hydroquinone, with improved pharmacokinetic characteristics (including blood–brain barrier penetration) and antiviral activity. Most IC_{50} values with respect to Zika virus are in the millimolar range and are sometimes lost in the presence of serum, suggesting that more work will be needed to develop them into potential antivirals. In addition, a broad range of lipofuscin-related rare diseases (including macular degeneration and Stargardt disease) and lysosomal storage disorders are claimed as potentially responsive, with no data presented.

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MeSH keywords: antiviral agents • lipofuscin • pathological protein aggregation • rare diseases • Zika virus

WO/2020/007342

Application of biphenyl phosphate compound as Gpr84 antagonist

Inventors: F Nan, X Xie, Y Xiad, Q Zhang, L Chen, Y Fang

Assignee: Shanghai Institute of Materia Medica, Chinese Academy of Sciences (Shanghai, China)

Gpr84 is a medium-chain fatty acid receptor expressed on immune cells that mediates pro-inflammatory and immunostimulatory effects [27]. It remains insufficiently characterized; it seems to have three separate ligand-binding sites [28] and the few small-molecule activators that have been reported have pronounced off-target actions [29]. Reasonably selective antagonists (which are scarce; see Galapagos' WO/2013/092791 and WO/2014/095798) are expected to be anti-inflammatory; more specifically, they might be able to break the link between hyperlipidemia, obesity and inflammation. PBI-4050 (2-[3-pentylphenyl]acetic acid; a dual Gpr40/Gpr84 antagonist) reduces hepatic stellate cell activation and liver fibrosis [30]. Here the inventors introduce a new chemical class of Gpr84 antagonists where two substituted phenyl or naphthyl residues are connected via a cyclic phosphodiester. The

compounds (the XYF series) were tested in a fluorescence assay for inhibition of agonist-stimulated calcium influx on human HEK293 cells expressing Gpr84 and Gα16; more than two dozen had IC₅₀ values in the nanomolar or even high-picomolar range. Also see the applicant's WO/2018/161831 where the phosphodiesterases do not form a connecting ring.

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MeSH keywords: G protein-coupled receptor 84, human • inflammation

WO/2020/009551

Graphene quantum dot as therapeutic agent for disease associated with abnormal fibrillation or aggregation of neuroprotein

Inventors: BH Hong, JM Yoo

Assignee: Seoul National University R&D Foundation (Seoul, Korea)

Pharmaceutical patent applications claiming quantum dots as therapeutic agents [31] are few and far between, and in most cases the dots are used as photosensitizers or in photodynamic therapy. Occasionally they are claimed for drug delivery (see WO/2018/167618) or for sophisticated applications such as manipulation of mitochondrial function (WO/2018/007801). Instead, the present invention uses graphene quantum dots (0.5–10 nm diameter, 0.1–3 nm thickness, with a negative surface charge) for inhibiting the fibrillar aggregation of α-synuclein (one of the key proteins in neurodegenerative disorders) and even for decomposing existing fibrils by binding to their C-terminus, without light and without a 'guest' drug (although they can carry functional groups, and are biotinylated in some embodiments to allow immunostaining). They permeate the blood–brain barrier easily, and are said not to accumulate in the body, thereby avoiding the toxicity that has been reported for graphene oxide dots [32]. This is a fascinating new application for graphene quantum dots, whose major biomedical application is in sensor technology [33].

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MeSH keywords: pathological protein aggregation • quantum dots • synucleinopathies

WO/2020/014261

RNA programmable epigenetic RNA modifiers & uses thereof

Inventors: DR Liu, CG Wilson, PJ Chen

Assignees: The Broad Institute, Inc. (MA, USA); President & Fellows of Harvard College (MA, USA)

RNA comprises many more naturally occurring nucleotide variants than DNA. There are about 140 alternative nucleotide forms, and this diversity that can impact RNA structure, folding patterns, splicing, protein-binding properties and RNA translation into encoded proteins. Epigenetic marks, such as the N⁶-methyladenosine modification [34] or other methylations, are introduced into RNA by enzymes and cofactors known as 'writers'. The reverse process is performed by 'erasers', such as Fto (a fat mass and obesity-associated protein) and AlkB homolog 5 demethylase. Full control over these editing steps would allow extensive RNA efficacy modulation and pretranslational editing of proteins [35]. The present disclosure provides for fusion proteins (comprising RNA binding and effector domains) that act as programmable editors of RNA methylation that can modify reporter and endogenous mRNA transcripts with high efficacy in both nucleus and cytoplasm. The effector domain can have various activities, including making N6-methyladenosine, N1-methyladenosine, or 5-hydroxymethylcytidine modifications in the RNA. In particular embodiments, the RNA target may be a β-actin, a GAPDH or an ADAM19 mRNA with an adenosine at a particular locus. This could allow for the correction of a broad variety of hereditary diseases and cancers but has much broader implications as well. Techniques that allow reversible reprogramming of living cells equal the CRISPR/Cas9 technology for permanent genetic mutations in importance.

Published: 16 January 2020

MeSH keywords: epigenomics • genetic diseases, inborn • post-transcriptional RNA processing

WO/2020/018039

Highly potent Tacc3 inhibitor as a novel anticancer drug candidate

Inventors & applicants: E Banoğlu, B Calışkan, Ö Şahin, D Lengerli, Ö Arkebulut (Turkey)

Tacc3, one of the transforming acidic coiled coil containing protein family members, is a nonkinase microtubule binding protein. It plays a key role in centrosome regulation [36] and is a critical molecule for mitotic spindle

assembly, especially in cancer cells [37]. Two preclinical-stage inhibitors, KHS101 [38] and SPL-B, have been shown to reduce tumor growth in glioblastoma and ovarian cancer xenografts, respectively. However, neither seems to be suitable as a cancer drug without further optimization. The inventors from universities in Ankara and South Carolina have identified a new compound, 3-(4-methoxyphenyl)-N-(2-morpholinopyrimidin-4-yl) isoxazol-5-amine (BO-264), which showed a superior antiproliferative effect toward different breast cancer cell lines while having minor effects on normal breast cell lines. BO-264 also was highly cytotoxic, with GI_{50} values <1 pM in approximately 90% of various colon, melanoma, lung, CNS, ovarian, leukemia, renal and prostate cancer cell lines in the NCI-60 panel. Furthermore, BO-264 induced mitotic arrest, apoptosis and DNA damage at lower doses compared with the other two Tacc3 inhibitors. Its oral administration suppressed tumor growth in breast cancer xenografts in immunodeficient mice without affecting their nontumor body weight.

Published: 23 January 2020

MeSH keywords: microtubule-associated proteins • neoplasms • TACC3 protein, human

WO/2020/022789

Pharmaceutical composition for preventing, alleviating or treating osteoarthritis, containing rhodanine derivative as active ingredient

Inventors: MJ Kim

Assignee: Avixgen, Inc. (Seoul, Korea)

Since a 2012 paper from Korea University had reported a potent I κ B kinase- β inhibitor screening hit compound containing a rhodanine moiety, no additional reports have been published that mention this structural element in the context of rheumatoid arthritis or other autoimmune diseases. Here a company from Seoul takes up the slack. However, their target is osteoarthritis, where I- κ B kinase- β involvement in the activation of target genes that trigger extracellular matrix remodeling and terminal differentiation of chondrocytes has attracted attention recently [39]. Although it is not explicitly stated, it seems likely that the 41 rhodanine compounds presented here also rely on this mechanism. Extensive mouse model data show attenuation of synovitis and cartilage matrix loss.

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MeSH keywords: I-kappa B kinase • osteoarthritis • rhodanine

WO/2020/023813

Isoquinoline compounds & uses thereof

Inventors: J Liang, S Malhorta, RV Mendonca et al.

Assignee: F. Hoffmann-La Roche AG (Basel, Switzerland); Genentech, Inc. (CA, USA)

No proofreading enzymes exist for RNA, a fact which RNA viruses such as the influenza virus have made into an advantage for immune evasion. The influenza RNA-dependent RNA polymerase makes a single nucleotide insertion error roughly every 10,000 nucleotides, which is the approximate length of the viral genome; therefore, nearly every single newly assembled influenza virus will exhibit incremental antigenic drift. Moreover, the separation of the genome into eight separate segments allows mixing or reassortment of vRNAs if more than one viral strain has infected a single cell, allowing the virus to infect new host species and quickly overcome protective immunity. Aside from neuraminidase inhibitors, which are effective only in the earliest stages of infection, there is still no pharmacotherapy available. Developing inhibitors of RNA-dependent RNA polymerase that show a degree of target tolerance into drugs would be of huge importance because they might be effective not only against influenza but likely against many RNA viruses, including hemorrhagic ones (e.g., Ebola), coronaviruses (e.g., SARS-Cov2) and others. Examples include the investigational compounds favipiravir [40] and remdesivir [41]. The isoquinolines presented here fit into the PB2 cap-binding pocket of influenza polymerase [42,43], much in the way of pimodivir, which is an azaindole. With IC_{50} values of 25–50 μ M for the most active compounds this series does not seem to be very potent, but with RNA-dependent RNA polymerases not being of significance in humans, sufficient concentrations could be readily achievable, especially in the respiratory tract via inhalation.

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MeSH keywords: antiviral agents • influenza • isoquinolines • PB2 protein, influenza virus • RNA replicase

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