Patent highlights February–March 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/2020/024071

Pharmaceutical composition for the treatment of addiction to psychoactive substances &/or the prevention of relapse to said addiction

Inventors: Ezquer F, Ezquer M, Israel Jacard Y, Quintanilla González ME, Morales Retamales P, Herrera Marschitz M

Assignee: Universidad del Desarrollo, Santiago, Chile; Universidad de Chile, Santiago, Chile

Drug treatment of drug addiction is not a very dynamic field of pharmaceutical R&D; most of the widely used agents (such as naltrexone or acamprosate) just repress acute craving and have been in use for decades. Vaccination approaches have been investigated for nicotine and cocaine, but none have reached the market. A rather unconventional approach consists of injection of mesenchymal stem cells – not to regenerate neurons damaged by drugs [1], but to reduce their consumption, an application the inventors have pioneered for alcohol [2,3], later showing intranasal administration to be equally effective, also for nicotine self-administration of rats [4]. The key innovation is the use of exosomes prepared from preconditioned adipose tissue-derived stem cells (in essence, their secretome proteins), which can be intravenously or intranasally delivered. The nature of the preconditioning process is broad; one example described by the inventors involved addition of TNF- α and IFN- γ to the culture medium for 48 h. Animal data show 60–78% reduction of alcohol self-administration, and 80% reduction of nicotine self-administration in rats addicted to the respective substance after intranasal administration. Few if any other groups seem to publish in this field. For related work by others see Li *et al.* [5].

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MeSH keywords: exosomes • intranasal administration • mesenchymal stem cells • substance-related disorders

WO/2020/027137

Medicine composition for treating cerebral infarction

Inventors: Kakizuka A, Kinoshita H, Maki T, Takahashi R

Assignee: Kyoto University, Kyoto, Japan

Small-molecule patenting for ischemic stroke, which had been popular in the 1980s and 90s, is nowadays reduced to a low baseline. It is therefore of particular interest to see a patent application claiming valosin-containing protein ATPase (also known as p97 ATPase or Cdc48) as a drug target in this condition, which contributes a large part of the morbidity and mortality in the geriatric population. VCP ATPase dislocates polyubiquitinated proteins (mostly misfolded ones) from complexes or membranes and transfers them to the proteasome or segregates them from binding partners for downstream activity [6,7]. The compounds, preferably 4-amino-3-[6-(4-fluoro-2-methylphenyl)pyridin-3-ylazo] naphthalene (KUS121; claimed in WO/2012/014994), are intended for administration before or immediately after reperfusion. Primary cerebrocortical neurons are protected against ATP depletion under oxygen-glucose-deficient culture conditions and also against tunicamycin-induced endoplasmic reticulum stress, as had to be expected considering earlier findings in retinal ischemia [8]. In a mouse model of focal ischemic stroke, KUS121 (50 mg/kg ip. or 100 mg/kg iv.) administered 24 h after middle cerebral artery occlusion significantly prolonged residence time on the rotarod compared with vehicle and reduced infarct volume.

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MeSH keywords: brain ischemia • reperfusion injury • valosin-containing protein • VAT ATPase

WO/2020/028686

Targeting Piezo1 for treatment of cancer & infectious diseases

Inventors: Miller G, Aykut B

Assignee: New York University, NY, USA

Immune checkpoints act as negative regulators of T-cell function that tumors and many chronic viral infections co-opt as a major strategy of immune evasion. This disclosure demonstrates that Piezo1, a nonselective cation channel involved in mechanosensory transduction [9], is a vital regulator of innate and adaptive immune responses, acting as the primary sensor of mechanical stress in both myeloid and T cells. Global inhibition of Piezo1 resulted in reduced monocyte infiltration and expanded T-cell activation *in situ* and was protective against both cancer and septic shock. Its selective deletion in T cells resulted in higher IFN- γ responses, tumor-protection *in vivo*, enhanced clearance of lymphocytic choriomeningitis virus and activation of Akt-mTOR signaling, which triggered Myc-dependent increased nutrient consumption and accentuation of immunogenic responses. In myeloid cells, selective deletion of Piezo1 protected against cancer and increased survival in poly-microbial sepsis. At the time of the priority date (1 August 2018; predating the peer review papers on innate immunity from competing groups by 1 year [10], although Piezo1 involvement in T-cell activation had been reported earlier [11]) Piezo1 has not been intensively studied in cancer, which changed immediately thereafter [12].

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MeSH keywords: neoplasms • PIEZO1 protein, human • sepsis

WO/2020/032076

Osteoclast differentiation inhibitor

Inventors: Terkawi MAHS, Kayoda K, Takahashi D, Iwasaki N

Assignee: National University Corporation Hokkaido University, Sapporo, Japan

Inhibitors of the Rankl/Rank/Opg pathway can block osteoclast differentiation and prevent bone resorption. However, this pathway is also involved in several other critical areas including immune tolerance, and it would be preferable to treat osteoporosis by means that do not simply block it. The inventors believe that a solution could be offered by the cardiotrophin-like secretory cytokine Clcf1 which – as has now been found – suppresses only the Rankl-induced induction of monocyte differentiation into osteoclasts. *In vitro* data obtained with human peripheral mononuclear blood cells and dentin slices show clear effects: bone resorption was observed in about 40% of the slice surface in the absence of Clcf1, but almost no bone resorption occurred in the presence of the cytokine in the nanogram per milliliter range. The effect was confirmed in a mouse model of calvarial osteoporosis (C57/B6 CLEA Japan mice injected with 0.1 mg/kg/day Rankl with or without 0.1 mg/mg/day Clcf1). Clcf1 used to be regarded as a relatively minor cytokine, mainly in the context of its mutational inactivation in the rare cold-induced sweating syndrome [13]. Meanwhile it has also been reported to modulate mesenchymal stem cell differentiation into osteoblasts [14], indicating that its effects on osteoporotic bone metabolism might be even higher than suggested by the current patent document. Clcf1 also is a strong inducer of macrophage-foam cell transition, suggesting that it might be a target for atherosclerosis [15].

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MeSH keywords: CLCF1 protein, human • osteoporosis • RANK ligand

WO/2020/033577

Methods & compositions for increasing the activity in the CNS of hexosaminidase A, acid sphingomyelinase & palmitoyl-protein thioesterase 1

Inventors: Pardridge WM, Boado RJ

Assignee: Armagen, Inc., CA, USA

This invention provides bifunctional fusion antibodies binding to an endogenous blood–brain barrier receptor and carrying one of three brain lysosomal enzymes: hexosaminidase A (deficient in Tay Sachs disease), acid sphingomyelinase (deficient in Nieman Pick Disease), palmitoyl-protein thioesterase 1 (deficient in neuronal ceroid lipofuscinosis 1) and others. Preferably the fixed domain of the fusion antibody binds to the extracellular domain of the insulin receptor, allowing the intravenously injected construct to be transported into the CNS by receptor-

mediated transcytosis [16], while retaining enzymatic activity. Alternatively, the construct catalyzes breakdown of the GM2 gangliosides, sphingomyelin or protein fatty acyl conjugates that accumulate in the respective genetic diseases. The inventors encountered several unpredictabilities; for example, fusion of β -glucuronidase (to treat Sly syndrome, MPS-VII) to the amino terminus of the human insulin receptor antibody heavy chain, resulted in retention of glucuronidase activity, but almost annihilated binding to the insulin receptor. Fusion to the carboxyl terminus of the heavy chain achieved the exact opposite: this construct bound to the receptor, but its glucuronidase activity was decreased by >95%. A prophetic example delineates treatment of neuronal ceroid lipofuscinosis type 1 (the infantile form of Batten disease) where intrathecal injection of the recombinant PPT1 enzyme would not be effective because it is rapidly exported from the cerebrospinal fluid into the blood pool. An intravenous dose of 3 mg/kg of the HIR Ab-PPT1 fusion protein as per the invention is expected to replace 2.6 mU/g, equaling 2.2% of endogenous activity. While this might seem minuscule it is expected that small increases in residual enzyme activity can significantly alter disease progression [17].

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MeSH keywords: blood–brain barrier • insulin receptors • lysosomal storage diseases • rare diseases

WO/2020/037030

Methods for targeting pain directed at metabolic pathways

Inventors: Melemedjian OK

Assignee: University of Maryland, ML, USA

Current treatment options for chemotherapy-induced painful peripheral neuropathy are vastly inadequate. The invention is based on increasing the expression of the Asct2 neutral amino acid transporter [18], in lumbar dorsal root ganglia through administration of a tRNA (translation-enhancing RNA), which binds to the upstream open reading frame of the Asct2 mRNA, facilitating translation of the primary open reading frame [19]. This innovative strategy targets the increased glutamine uptake by damaged neurons resulting from energy production through glycolysis, a mechanism that leads to increased extrusion of lactate and protons into the extracellular space and by extension, increased sensitization of sensory neurons through various ion channels. In the mouse model of post-incision allodynia induced by PGE2, L4-6 dorsal root ganglia showed increased expression of Asct2 and the glutamine catabolizing enzyme Gls1 only during the primed phase. Single intrathecal injections of 1 μ g of tRNA produced a robust increase in Asct2 protein in these sites and alleviated the subsequent tactile hypersensitivity for at least 7 days. Sham-treated mice receiving mismatched tRNAs did not display any change in their tactile thresholds. Two-way repeated-measure ANOVA revealed a main effect for time ($p < 0.001$) and group ($p < 0.001$) interaction. Humans have three Asct2 variants and would likely require more than one tRNA species for treatment. For a recent discussion of the ‘glutamosome’ in pain, see Gegelashvili and Bjerrum [20].

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MeSH keywords: amino acid transport system ASC • peripheral nervous system diseases • untranslated RNA

WO/2020/041333

Methods for treating cardiac valve disease

Inventors: Theodoris C, Srivastava D

Assignee: The David J. Gladstone Institutes CA, USA; The Regents of the University of California, CA, USA

Calcific aortic valve disease, the third-leading cause of adult heart disease, is a progressive disorder that ranges from mild valve thickening without obstruction of blood flow, to severe calcification with impaired leaflet motion. There is no pharmacological treatment for the underlying biomineralization process, which is more complex than atherosclerotic plaque formation [21,22]. Haploinsufficiency of the membrane-bound transcription factor Notch1 has been identified as a genetic predisposition [23], and most recently Notch1 suppression by miRNA-34a was shown to have a similar effect [24]. A network-based drug screen was performed to identify small molecules that correct the gene network dysregulated by Notch1 haploinsufficiency in human iPSC-derived endothelial cells from patients affected by calcific aortic valve disease. As expected, molecules targeting atherosclerotic and osteogenic pathways had the largest corrective impact on the network. The hits included XCT-790, an inverse agonist at the estrogen-related receptor $ERR\alpha$ originally intended for the treatment of triple-negative breast cancer [25]; the Clk1/Sty splice factor kinase inhibitor, TG-003 [26]; GSK-837149A, a reversible fatty acid synthase inhibitor [27]; and also naloxone and biperiden, among other known compounds. XCT-790 had the strongest restorative effect

on central regions of the network and most closely mimicked the effects of direct siRNA targeting Sox7 and Tcf4, two key regulatory nodes upregulated in Notch1 haploinsufficiency. It acted complementary to GSK-837149A, indicating that these compounds might be synergistic in combination.

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MeSH keywords: aortic valve stenosis • receptor, Notch1

WO/2020/044067

Pharmaceutical combination to modify the effect of beta-receptor blockers & reduce side effects

Inventors: Literati NP

Assignee: N-Gene Research Laboratories, Inc., NY, USA

Beta adrenergic receptor antagonists are traditional items on the WHO List of Essential Medicines; they revolutionized the treatment of cardiovascular disorders in the mid-1960s and remain indispensable for treating cardiac arrhythmia and secondary prevention of myocardial infarction. The well-known side effects of old nonselective beta blockers, such as fatigue, exacerbation of obstructive pulmonary diseases and male sexual dysfunction, can often be circumvented by using more recent cardioselective members of this drug class combined with proper dose adjustment. However, side effect potentials remain, and it would be ideal if co-administration of another drug could prevent them. N-Gene believes that could be possible by combining bisoprolol with hydroxamic acid Parp inhibitors such as iroxanadine, NG-094, NG-50 or BGP-15 (claimed for Type 1 diabetes in WO/2000/007580, for mitochondrial neogenesis in WO/2005/123049, in WO/2006/079910 for periodontitis, and in WO/2009/074835 to reduce psychiatric side effects of cannabinoid CB1 receptor antagonists). No data are provided in support of the claims and no indication of the potential mechanism is suggested. Parp inhibitors, originally developed to treat cancer, can protect stressed cells and organelles in multiple ways [28,29].

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MeSH keywords: adrenergic beta-antagonists • drug-related side effects and adverse reactions • poly(ADP-ribose) polymerase inhibitors

WO/2020/047186

Small-molecule stimulators of steroid receptor-coactivator-3 & methods of their use as cardioprotective &/or vascular regenerative agents

Inventors: O'Malley BW, Lonard DM, Song Y

Assignee: Baylor College of Medicine, TX, USA

Preventing detrimental remodeling of cardiac tissue, ideally by regenerating moderately affected myocardium, pragmatically by preserving tissue that is still functional, is the first strategic call after a myocardial infarction. A major hurdle to this is the adult heart's limited and restricted regenerative potential, which poses a barrier to therapies designed to promote tissue reprogramming and repair. The inventors' proposed solution to this challenge is the stimulation of Scr-3, a nuclear co-receptor for steroids. The preferred compound is SYC-944, known in the literature as MCB-613 – a 'super-stimulator' intended to induce excessive endoplasmic reticulum stress coupled to the generation of reactive oxygen species in cancer cells [30]. The inventors show that the *NCOA3* gene that codes for Src-3 is expressed at low levels in human adult hearts (suggesting that Scr-3 activation should have limited side effects), and that Src-3 induces the proliferation of non-cardiomyocytes in hearts within 9 days. Adenovirus-derived Src-3 was injected into the left ventricular free walls of wild-type adult mice, which were fed 5-ethynyl-2'-deoxyuridine-treated water as a cell proliferation marker. MCB-613 or saline was administered 2 h after ligation and for six additional days every 24 h. Repeat injections were given three times per week at weeks 8 and 16. Comprehensive single cell transcriptional profiling and single-cell sequencing of nonmyocyte cells was performed on noncardiomyocytes in hearts at 10 weeks post-myocardial infarction. Cell clusters were generated based on t-distributed stochastic neighbor embedding (tSNE) analysis and identified by gene expression signatures. It should be kept in mind that the strong expression of Src-3 in cancers implies that its activation should be strictly localized to the diseased heart. Src-3 might have additional roles in malignancies [31], and when expressed in bone marrow mesenchymal stem cells it could promote the development of multiple myeloma [32].

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MeSH keywords: myocardial infarction • nuclear receptor coactivator 3

WO/2020/049475**Use of exfoliated black phosphorus for the treatment of bone cancers***Inventors: Raucci MG, Ambrosio L, Fasolino I, Caporali M, Serrano Ruiz M, Peruzzini M**Assignee: Materias s.r.l., Napoli, Italy*

Cancer deaths due to bone and joint malignant neoplasms represent about 9% of all childhood and adolescent cancer deaths. The most frequent of these childhood bone cancers is osteosarcoma [33]. The standard therapy – surgical resection followed by chemotherapy for micrometastases – cures only about 65% of the cases. The inventors have found that nanosheets of black phosphorus (one of the ‘two-dimensional’ novel materials [34], the phosphorus equivalent of graphene sheets), a well-known candidate for cancer photothermal and photodynamic therapy [35], could offer interesting benefits in osteosarcoma – but without any radiation. The metabolic activity of Saos-2 osteosarcoma cells is inhibited and apoptosis is induced (apparently through production of reactive oxygen species), while both the proliferation and the osteogenic differentiation of human pre-osteoblast (HOb) cells and mesenchymal stem cells are promoted. Moreover, exfoliated black phosphorus increases IL-10 secretion and inhibits IL-6 in a Saos-2/HOb co-culture model, suggesting anti-inflammatory potential in osteosarcoma. The substance can be formulated as an injectable composition for minimally invasive surgery, comprising inorganic salts, such as calcium phosphate, and/or polymeric materials, such as gelatin, hyaluronic acid, cellulose or chitosan.

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MeSH keywords: nanogels • osteosarcoma • phosphorus

WO/2020/051375**Papd5 inhibitors & methods of use thereof***Inventors: Agarwal S, Nagpal N**Assignee: Children's Medical Center Corp., MA, USA*

Short telomeres, due to genetic disease or insults, cause a loss of cellular self-renewal and result in (or contribute to) life-threatening diseases such as aplastic anemia, pulmonary fibrosis, hepatic cirrhosis, bone marrow failure and rare genetic diseases for which there are few, if any, effective medical therapies. Poly(A) ribonuclease (Parn) mutations can result in the accumulation of 3'-oligo-adenylated forms of nascent Telomerase RNA component (Terc) transcripts, which are targeted for destruction, thus causing telomerase deficiency and telomere diseases. Disruption of the noncanonical poly(A) polymerase-associated domain containing 5 (Papd5; also known as Trf4-2) may restore Terc levels, telomerase activity and telomere elongation in Parn-mutant patient cells [36]. The lead compound of the invention, DHQ-1 (a dihydroquinolizinone also known as RG7834) inhibits recombinant Papd5-mediated RNA oligonucleotide extension *in vitro*, restoring Terc 3'-end processing and Terc RNA steady state levels in CD34⁺ primary cells of dyskeratosis congenita patients. This was confirmed by xenotransplanting these cells into immunodeficient NBSGW mice and treating them with RG7834, a compound that was originally described as a highly selective hepatitis B virus inhibitor with a novel mechanism of action [37]. Papd5 is a cellular host factor required for stabilization of HBV RNA, but not other viral RNAs [38].

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MeSH keywords: rare diseases • RNA nucleotidyltransferases • telomere • TRF4-2 protein, human

WO/2020/055166**Composition for treating fibrotic diseases, comprising benzhydryl thioacetamide compound as active ingredient***Inventors: Suh S-H, Kim S-J**Assignee: Cellionbiomed Inc., Sejong, Korea*

This invention's compounds are intended to treat hepatic and pulmonary fibrosis by suppressing expression of the membrane protein forming the KCa2.3 and KCa3.1 calcium-gated potassium channels (which differ mainly in their tissue distribution). These channels and their antagonists have been studied in the context of fibrosis [39]. Remarkably, the compounds are derivatives and analogs of modafinil, an agent approved for the treatment of narcolepsy and daytime somnolence. Modafinil has been clinically investigated in primary biliary cirrhosis, but for the fatigue that accompanies this fibrotic disease; the literature does not seem to hold suggestions that it could directly treat fibrosis. The inventors tested some of their compounds in the mouse model of bleomycin-induced

pulmonary fibrosis, and present data showing expression levels of Timp-2 and Ccr2 being significantly reduced and fibrosis inhibited.

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MeSH keywords: benzhydryl compounds • fibrosis • potassium channels, calcium-activated

WO/2020/061279

Cdpk1 inhibitors, compositions & methods related thereto

Inventors: Hopper AT, Sibley LD, Janetka JW

Assignee: Vvera Pharmaceuticals, LLC, NY, USA; Washington University, WA, USA

Approximately a third of humankind is chronically infected with *Toxoplasma gondii*. Most strains are essentially harmless for immunocompetent individuals, but especially for those with a compromised immune system complications such as encephalitis and ocular disease can be devastating. The standard treatments for toxoplasmosis – pyrimethamine, usually in combination with a dihydropteroate synthase inhibitor (for example, sulfadiazine) – has quite severe gastrointestinal and hematological side effects [40] and does not eradicate the pathogen. Apicomplexans such as *T. gondii* contain from 6 to 11 related calcium-dependent protein kinases, which control parasite invasion and egress, or play other essential roles in bradyzoite development and cell division. Cdpk1 from *T. gondii*, *Neospora caninum*, *Sarcocystis neurona* and *Cryptosporidium* spp. is unique among parasite and mammalian kinases in containing glycine at the key ‘gatekeeper’ residue, which results in an expanded ATP-binding pocket. This can be exploited for the development of highly apicomplexan-specific inhibitors, such as the pyrazolopyrimidines presented here, which were designed to fill and block this binding pocket optimally. IC₅₀ values generally are in the nanomolar range. For the inventors’ closely related earlier work see Rutaganira *et al.* [41].

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MeSH keywords: apicomplexa • calcium-dependent protein kinase • toxoplasmosis

WO/2020/061477

Methods of treating creatinine transporter deficiency

Inventors: Muncipinto G, Jones LH, Rettenmaier TJ

Assignee: Jnana Therapeutics, Inc., MA, USA

The creatine phosphate system is needed for the storage and transmission of phosphate-bound energy, primarily in the brain and skeletal muscle. Creatine transporter deficiency, an X-linked disorder identified only in 2001 and caused by one or several of at least 80 known mutations in the *SLC6A8* solute carrier transporter 6 family gene [42], impedes the active uptake of creatinine through the blood–brain barrier [43], resulting in intellectual disability, delayed development and behavioral problems. Obviously, alimentary creatine (which can treat other forms of creatinine deficiency quite well) is of very limited use here [44]. The inventors propose to use guanidinoacetic acid, 3-guanidinopropionic acid, 4-guanidinobutyric acid or guanidinoethane sulfonic acid or a broad range of derivatives thereof, which apparently can act as surrogate substrate for the transporter protein, whereby they also increase creatine uptake into the brain. Several U-2 OS MEM-EA cell lines stably expressing *SLC6A8* CTD mutants were created, exposed to the compounds followed by labelled creatine; uptake was increased severalfold in many cases. Jnana Therapeutics, which specializes in solute carrier transporters, might have opened up a new field here.

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MeSH keywords: creatine deficiency, X-linked • creatine transporter • glycocyamine • guanidinopropionic acid • rare diseases • taurocyamine

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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.

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