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A RUSSIAN PSYCHOSTIMULANT FOR FIBROTIC DISEASES

International Patent Application WO/2020/191503, *Methods and Uses of Bromantane and Derivatives Thereof for Treating Lung Disease, Fatty Liver Disease, and Kidney Disorders* (Inventor: Williams M; applicant: Algernon Pharmaceuticals, Inc., Vancouver, Canada; published: October 1, 2020).

Bromantane (adamantylbromphenylamine) is an anxiolytic psychostimulant developed and used in Russia at doses of 50–100 mg for what used to be called neurasthenia. It also is a banned doping agent.¹ Its scientific literature, found almost exclusively in Russian journals, refers to it an “actoprotectant,” that is, a compound that improves physical performance without increasing oxygen consumption or heat production.² Its pharmacology is complex, dose dependent, and insufficiently characterized; dopaminergic, cholinergic, and adrenergic neurotransmission are affected.³ In addition, bromantane seems to increase adaption to hypoxia,⁴ which is suggestive of a downregulation of hypoxia-inducible factor 1- α (HIF-1 α). It is the last-mentioned feature that prompted the inventors to investigate bromantane in mouse models of fibrotic complications of nonalcoholic fatty liver disease (NAFLD), kidney injury, and lung diseases: all these conditions have HIF-1 α involvement.^{5–7} The results presented in this document are quite convincing, but translational success in the preventive setting will strongly depend on the required human doses.

A NONRESORBABLE ANTIBIOTIC PREVENTS SICKLE CELL VASO-OCCLUSIVE CRISES

International Patent Application WO/2020/198136, *Use of Rifaximin on Circulating Aged Neutrophils in Sickle Cell Disease* (Inventor: Lim SH; applicant: New York Medical College, Valhalla, New York, USA; published: October 1, 2020).

Activated and circulating aged neutrophils (CANs) are pivotal for the pathogenesis of vaso-occlusive crises in sickle cell disease: they adhere to vascular endothelium and form the nidus for sickled red blood cells to aggregate on. In mice

neutrophil aging is modulated by the intestinal microbiome,^{8,9} which probably is a runaway consequence of the intestinal injury and increased gut permeability caused by the recurrent hypoxia-reperfusion injury induced by vaso-occlusive crises.¹⁰ In these earlier experiments, treatment of sickle cell disease (SCD) mice with an oral cocktail of ampicillin, neomycin, metronidazole, and vancomycin had induced a reduction in CAN counts and protection from fatal vaso-occlusive crises, but absence of a systemic effect of these antibiotics had not been demonstrated. By using rifaximin, a minimally absorbed oral antibiotic for intestinal infections, it has now been shown that the controlling effect on CANs is indeed owing to antibiotic modulation of the intestinal microbiome. Long-term use of rifaximin is an established treatment and does not increase the risk for the development of *Clostridium difficile* infection, against which SCD patients enjoy a degree of protection.—For the peer review companion paper see Lim *et al.*¹¹

A FREE RADICAL SCAVENGER FOR FATTY LIVER DISEASE

International Patent Application WO/2020/199650, *Application of Edaravone in the Treatment or Prevention of Nonalcoholic Steatohepatitis* (Inventors: Ding H, Zhou Y; applicant: Suzhou Auzone Biological Technology Co., Ltd, Suzhou, Jiangsu, China; published: October 8, 2020).

Edaravone is a free-radical scavenger that was developed by Mitsubishi Tanabe Corp. It received Japanese approval as a once-monthly intravenous infusion treatment for amyotrophic lateral sclerosis in 2015 and by the U.S. Food and Drug Administration (US FDA) (as Radicava[®]) in 2017; the European marketing authorization application was withdrawn in 2019. To date it remains the only agent of this type with explicit treatment approvals for a specific disease.¹² Based on the ubiquitous involvement of free radicals it has also been investigated (so far without convincing results) in other neurological diseases¹³ and in many diseases associated with ischemia-reperfusion injury.¹⁴ A Chinese company has now added nonalcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH) to this catalog. This is not surprising given that considerable clinical data have been amassed for edaravone in hepatic diseases, and the fact that its pharmacokinetics are almost unaffected even by severe hepatic

impairment is an additional bonus.¹⁵ Surprisingly, although the role of oxidative stress and free radicals in NAFLD and NASH is well known,¹⁶ there seem to be no reports of studies with edaravone. The inventors compared it (at oral doses of 90 mg/kg) with Gilead's candidate Ask1 inhibitor selonsertib (now presumably discontinued) in the commonly used rabbit model of NASH; edaravone was superior in reducing NASH scores (the sum of the scores of steatosis, inflammation, and cell ballooning), elevated liver enzymes, and histopathology.

ASTHMA DRUGS TREAT ANEURYSMS AND RELATED VASCULAR DISEASES

International Patent Application WO/2020/207165, *Compound for Treating Vascular Malformation* (Inventors: Shan H, Pang P, Mao J, Hu X, He H, Xiao F; applicant: The Fifth Affiliated Hospital of Sun Yat-Sen University, Zhuhai, Guangdong, China; published: October 15, 2020).

Aneurysms are routinely treated by surgery, but research into pharmacological treatments has accelerated during recent years: somatic gene therapies, epigenetic therapies (WO/2019/046791), but also small molecule agents (e.g., tyrosine hydroxylase inhibitors, WO/2019/243653; or S1P receptor agonists, WO/2014/175287) have appeared in the patent literature. The genetics of aneurysm propensity are also under intense study.¹⁷ However, the spectrum of vascular malformations extends beyond aneurysms. In earlier work the inventors examined four generations of a family suffering from what they named multiorgan venous and lymphatic defect (MOVLD) syndrome. Using cell culture models and zebrafish knockouts they determined that single nucleotide polymorphism mutations in *DDX24*, a gene coding for a DEAD box helicase, are responsible not only for the MOVLD syndrome but could also be found in some sporadic cases of vascular malformation, and that *DDX24* is involved in early vascular development.¹⁸ In this patent document the inventors proceed to identify antagonists of the cysteinyl leukotriene receptor-1 as agents to treat or prevent such malformations. These are the asthma drugs based on the "lukast" class of agents (motelukast, zafirlukast, and pranlukast) but also the older necrodomil. See the directly competitive work from the Karolinska Institute, prepublished almost 7 months before the April 2019 priority date of this patent application.¹⁹

TANDOSPIRONE FOR L-DOPA INDUCED DYSKINESIA: A MATTER OF ADMINISTRATION

International Patent Application WO/2020/218487, *Therapeutic Drug for Dyskinesia* (Inventors: Kurita M, Ikeda Y, Nakato M; applicant: Sumitomo Dainippon Pharma Co., Ltd., Osaka, Japan; published: October 29, 2020).

Even three decades after the launch of the first selective dopamine receptor agonists for the treatment of Parkinson's disease, L-dopa remains a mainstay of therapy, although 30%–50% of patients develop dyskinesia within 5 years. Articles reporting and discussing 5-HT_{1A} agonists, which originally carried high hopes for the treatment of anxiety and depression, as treatments for dyskinesia have been published for almost two decades,²⁰ also for tandospirone, which is the subject of this patent application.²¹ The inventors apparently believe that patenting is still possible with transdermal administration of tandospirone, based on the different pharmacokinetics and release kinetics, given that L-dopa is orally administered. This is supported by data from a 6-OHDA lesioned rat model of L-dopa dyskinesia. The effect of the tandospirone metabolite, 1-(2-pyrimidyl)piperazine (which is not generated with transdermal administration) was also evaluated, and revealed potential for rebound dyskinesia with oral dosing.

AN ALLERGIC RHINITIS DRUG FOR DEMENTIA

International Patent Application WO/2020/222799, *A Method of Treating Mental, Behavioral, Cognitive Disorders* (Inventors: Wang J, Cui G; applicant: La Pharma Tech, Inc., Blacksburg, Virginia, USA; published: November 5, 2020).

The anti-allergic agent, azelastine, has a wider range of pharmacologic effects on mediators of inflammation (including leukotrienes, kinins, platelet-activating factor, tumor necrosis factor alpha [TNF- α], and inflammatory cell migration) than other histamine H₁ receptor antagonists and histamine release blockers of its class.^{22,23} Thirteen years ago a Japanese group published results from a blinded 4-week trial with 2 $\times$ 1 mg azelastine in 30 patients with mild-to-severe dementia²⁴; behavioral and psychological symptoms improved but cognition did not. The inventors (and the examiner) do not cite this article but in any case this line of investigation has now been followed up using an unusually high dose of azelastine (12 mg once daily) for 6 months in two elderly patients with advanced dementia. Measurable improvements set in after 6 weeks. If supported by controlled trials this would be remarkable because no anti-inflammatory drug has yet shown efficacy in prospective dementia trials. Azelastine is almost devoid of anticholinergic effects²⁵ that would mask or overcompensate beneficial behavioral effects of other antiallergic medications. If the high doses reported here are really required, it would rule out the intranasal route used in azelastine preparations for allergic rhinitis.

A DRUG FOR NAUSEA AND VOMITING ALSO TREATS MALARIA

International Patent Application WO/2020/225283, *NK1 Inhibitors for the Treatment of Malaria* (Inventor: Salinas-Marín MV; applicant: Plus Vitech, S. L., Sevilla, Spain; published: November 12, 2020).

This patent application is yet another example of an inadvertent discovery of a repurposing opportunity. An immunosuppressed patient with chemotherapy-refractory lymphoma was given the antiemetic NK1 receptor blocker, aprepitant as an off-label compassionate treatment based on available evidence.^{26,27} Initial doses of 250/160/160 mg t.d.s. were increased to 935/935/980 mg t.d.s. without adverse events except fatigue and heartburn. Shortly after treatment commenced, the patient was identified as also suffering from malaria. Standard antimalarial drugs triggered severe adverse reactions, and had to be discontinued on day 6. However, treatment with aprepitant was continued and, surprisingly, also resulted in an effective and nontoxic treatment of the patient's malaria after 3 weeks. The inventors speculate that aprepitant either directly causes extensive lysis of the *Plasmodium* parasite, or by activating the immune system, or a combination of both. This is supported by *in vitro* experiments with cultures from several chloroquine-resistant *Plasmodium falciparum* strains exposed to aprepitant concentrations between 5 and 50 μ M, and by successful parasite count reduction in *Plasmodium berghei*-infected mice treated with the prodrug, fosaprepitant (2.5–40 mg/kg for 7 days). Maropitant was also effective. For both drugs, intermediate doses worked best, achieving >75% parasite count suppression.—The literature has no reference for NK1 antagonists in malaria, but aprepitant has been reported to show effects in other diseases caused by protozoan parasites, such as cryptosporidiosis²⁸ and trypanosomiasis.²⁹

A PEPTIDE USED FOR CELIAC DISEASE COULD RESTORE SALIVA AND TEAR FLOW

International Patent Application WO/2020/227341, *Compositions and Methods for Treating Sjögren Syndrome* (Inventors: Madan JP, Sivils KL, Deshmukh U, Radhakrishnan B, Woodard K, Bagavant H; applicants: 9 Meters Biopharma, Inc., Raleigh, North Carolina, USA; Oklahoma Medical Research Foundations, Oklahoma City, Oklahoma, USA; published: November 12, 2020).

In Sjögren syndrome lymphocyte infiltration and auto-antibodies damage ductal and acinar epithelial cells in exocrine glands, resulting in their dysfunction that causes loss of

saliva and tear production, along with other symptoms including leaky gut syndrome.³⁰ It is no surprise that these last-mentioned intestinal Sjögren symptoms can be treated with larazotide, an octapeptide that protects tight junctions by blocking zonulin receptors,³¹ and can therefore restore intestinal impermeability in celiac disease.³² Combination with aminosalicic acids, commonly used in intestinal inflammatory diseases, is also obvious. However, treatment of the more classical symptoms—dry eye and dry mouth—reflects a higher degree of innovation and has not been reported, although larazotide has been investigated in many inflammatory conditions.³³ An *in vitro* assay system to measure tight junction integrity was established using PAR-C10 cells (an immortalized rat acinar epithelial cell line), which mimics the biochemical and functional characteristics of primary salivary gland acinar cells. Monolayers were incubated for 24 h with 3 ng/mL of interferon gamma and TNF- α to cause tight junction disruption. Larazotide acetate (1 and 5 mM) or any one of 4-aminosalicylic acid (4-ASA), 4-amino-phenyl-acetic acid (4-APAA), and 4-acetyl amino-phenyl-acetic acid (4-Ac APAA) (5 or 10 mM) was added to the apical surface and the cells were allowed to grow for an additional 24 h, which restored cytokine-disrupted trans-epithelial electrical resistance to varying significant degrees. Such concentrations are achievable with eyedrops and in the oral cavity.

AN ANTIDEPRESSANT FOR YET ANOTHER TYPE OF HEADACHE

International Patent Application WO/2020/229388, *Mirtazapine for Use in Medication Overuse Headache Based on Tension-Type Headache* (Inventors: Pause A, Bedtsen L, Jensen R, Olesen J; applicants: Curatis AG, Liestal, Switzerland; Rigshospitalet—Glostrup, Glostrup, Denmark; The University of Copenhagen, Copenhagen, Denmark; published: November 19, 2020).

When mirtazapine, a tetracyclic piperazine-azepine antidepressant, was launched in the 1990s it was marketed as a noradrenergic and specific serotonergic antidepressant (NaSSA) to distinguish it from the dominant selective serotonin reuptake inhibitors (SSRIs). Actually its pharmacological activity spectrum is almost as broad as that of the tricyclic psychotropic drugs; it antagonizes α -adrenergic, serotonin 5-HT₂, and histamine H₁ receptors but does not inhibit neurotransmitter reuptake.³⁴ In long-term treatment it induces tonic activation of postsynaptic 5-HT receptors.³⁵ As most non-SSRI antidepressants mirtazapine is also an analgesic and there have been many reports of its use in various types of

headache; it is considered a second-choice drug in the most common form, tension-type headache.³⁶ There is no great surprise in the fact claimed here, namely its efficacy in medication overuse headache—which is defined as headache occurring on >15 days per month in patients with a primary headache disorder (frequently migraine) who regularly overuse one or more headache medications for more than 3 months.³⁷ According to the invention there is no need to discontinue the overused drugs before initializing mirtazapine. Data from two patients given 15–30 mg mirtazapine per day for 8 weeks show headache reduction scores and intake of overused medication reduced by up to 80%.

AN ANTIBIOTIC AS A TREATMENT FOR A RARE GENETIC DISEASE

International Patent Application WO/2020/234496, *Moxifloxacin for Use in the Treatment of Spinal Muscular Atrophy* (Inventors: Artero Allepuz R, Konieczny PT, López Castel A, Pérez Alonso M; applicants: Universitat de València, Valencia, Spain; Fundación Incliva, Valencia, Spain; published: November 26, 2020).

Almost all spinal muscular atrophy (SMA) patients have a deletion, mutation, or other type of homozygous change in the *SMN1* gene, but all nevertheless carry one or more copies of the functional *SMN2* gene, whose coding region differs from *SMN1* by only one C-to-T nucleotide change in an exon 7 splicing enhancer region.^{38,39} However, *SMN2* can compensate for *SMN1* loss only to a minimal degree because this change causes predominant skipping of its exon 7 using two separate mechanisms. This is what moxifloxacin, a commonly used fluoroquinolone antibiotic, is supposed to correct according to the present invention—at a tiny fraction of the cost of the antisense oligonucleotide, nusinersen (Spinraza®). Quantification of Smn protein levels in fibroblasts derived from patients with SMA, treated with moxifloxacin at 500 µM (the maximum nontoxic concentration) for 72 h, showed an 70% increase. Moxifloxacin was also successfully evaluated in HeLa cells to determine the existence of Smn aggregates colocalized with Cajal's bodies, which would indicate the presence of functional protein. Treatment with moxifloxacin also allows recovery of fusion capacity in SMA patient myoblasts to levels similar to that of healthy myoblasts.—In their peer review companion article,⁴⁰ the inventor described the screening of 1,100 drugs from the Prestwick Chemical Library in an *in vivo* SMN2 minigene reporter system in *Drosophila* motor neurons. SMA is considered a disease for which drug repositioning has particular potential.⁴¹

FROM RAVE DRUG TO TREATMENT FOR AN ULTRA-RARE GENETIC DISORDER

International Patent Application WO/2020/247615, *Ketamine and Ketamine/Nap for Treatment of ADNP Syndrome and Related Neurological Conditions* (Inventors and applicants: Sermone S, Davis MC, USA; published: December 12, 2020).

Activity-dependent neuroprotective protein syndrome (Helsmoortel-Van der Aa syndrome) is an ultra-rare genetic condition in the spectrum of autism with intellectual disability, caused by loss-of function mutations in the *ADNP* gene.⁴² These trigger two distinct epigenatures,⁴³ which correlate only modestly with the clinical phenotype. The Activity-dependent neuroprotective protein (ADNP) protein contains an NAP motif (NAPVSIPQ) that binds to microtubules, which seems to be the structural basis for its pivotal role in neurodevelopment.⁴⁴ The N-methyl-D-aspartate receptor blocker, ketamine increased levels of the pro-apoptotic enzyme-activated caspase-3 (Ac3) in the somatosensory cortex of neonatal mice, an effect that could be reversed by the NAP peptide.⁴⁵ On the contrary, sub-anesthetic doses of ketamine induce ADNP expression and are neuroprotective in a similar paradigm.⁴⁶ The inventors cite both articles (published 2012 and 2015, respectively) but argue that the mice and rats used in these studies did not carry an *ADNP* mutation, and that claims for treating ADNP syndrome with low-dose ketamine are therefore novel.—Both inventors have offspring afflicted with ADNP syndrome. Sandra Sermone is President and Executive Director at ADNPkids Research Foundation; Matt Davis is a neurologist.

THYROXIN FOR AN INNER EAR DISORDER

International Patent Application WO/2020/254587, *Thyroid Hormone or Metabolite for Use in the Treatment of a Peripheral Vestibulopathy* (Inventors: Tighilet B, Chabbert C, Rastoldo G, Pericat D; applicants: Centre National de la Recherche Scientifique, Paris, France; Université d'Aix-Marseille, Marseille, France; published: December 24, 2020).

There are many types of vestibular disorders that are characterized by gait instability, head motion intolerance, and nystagmus.⁴⁷ If these symptoms occur without a demonstrable central lesion and no non-age-related auditory deficit the condition is usually labeled peripheral vestibulopathy, and ascribed to a deafferented vestibular environment.⁴⁸ After the acute manifestation compensatory mechanisms set in, aiming at neurogenesis⁴⁹ and at modulation of excitability of the remaining functional afferents to restore the electrophysiological balance between the homologous left and right

vestibular nuclei. The inventors observed that after a left-side vestibular neurectomy in rats, treatment with thyroxine (T4) at a dose of 10 µg/kg administered just after lesioning and at days 1, 2, and 3 significantly reduced the vestibular deficits, including the general behavioral alterations during the acute phase, accompanied by improvement of walking and speed motion over several days. The inventors, who have published extensively on animal models of vestibular dysfunction, do not disclose what prompted them to test thyroid hormone in this application, but their reasoning is not difficult to retrace: there is a clear relationship between thyroid autoimmunity (which lowers T4 levels) and vestibular disorders.⁵⁰

A CANKER SORE DRUG FOR HEPATITIS

International Patent Application WO/2020/259706, Use of Amlexanox in Preparing Anti-hepatitis Virus Drug (Inventors: Wang X, Yang J, Xu X, Li L, Zhao C, Wang Y, et al.; applicant: Marine Biomedical Research Institute of Qingdao Co., Ltd., Qingdao, Shandong, China; published: December 30, 2020).

Amlexanox is an anti-inflammatory immune modulator in widespread use for aphthous ulcers, onto which it is applied as an adhesive paste. In Japan, it is used topically and systemically for a variety of allergic conditions. It seems to have multiple mechanisms among which inhibition of Tbk1 and IKKε (which activate the innate immune response via the interferon response regulator Irf3) are prominent. The pivotal involvement of these kinases in many diseases has caused amlexanox to be investigated in various cancers,⁵¹ acute lung and liver injury,^{52,53} myocardial infarction,⁵⁴ multiple sclerosis,⁵⁵ and other conditions. So far viral infections have not been reported as a possible application. The inventors show that amlexanox inhibits hepatitis B virus (HBV) replication in the HepG2 hepatocyte cell line (at 10 µM) and in mouse models (at 50 mg/kg/day) with an efficacy comparable with that of lamivudine and tenofovir. This is surprising because hepatitis viruses (and other viruses, including dengue and vesicular stomatitis virus) also suppress the Tbk1/IKKε/Irf3 axis to evade interferon induction.⁵⁶

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Abbreviations Used

4-Ac APAA = 4-acetyl amino-phenyl-acetic acid
 4-APAA = 4-amino-phenyl-acetic acid
 4-ASA = 4-aminosalicylic acid
 Ac3 = activated caspase-3
 ADNP = Activity-dependent neuroprotective protein
 CANs = circulating aged neutrophils
 HBV = hepatitis B virus
 HIF-1 α = hypoxia-inducible factor 1-alpha
 MOVLD = multiorgan venous and lymphatic defect
 NAFLD = nonalcoholic fatty liver disease
 NASH = nonalcoholic steatohepatitis
 NaSSA = noradrenergic and specific serotonergic antidepressant
 NMDA = N-methyl-D-aspartate
 SCD = sickle cell disease
 SMA = spinal muscular atrophy
 SSRIs = selective serotonin reuptake inhibitors
 TNF- α = tumor necrosis factor alpha
 US FDA = U.S. Food and Drug Administration
 VSV = vesicular stomatitis virus