Patent highlights February–March 2019

Hermann AM Mucke*,¹

¹H.M. Pharma Consultancy, A-1160 Wien, Austria

*Author for correspondence: h.mucke@hmpharmacon.com

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

WO/2019/024875

Use of substance directly or indirectly regulating YB-1 phosphorylation in preparation of drug for treating disease caused by inflammatory factors

Inventors: Liu B

Assignee: Jilin Zhong Tai Biotechnological Co. Ltd, Changchun (Jilin, China)

Y-box binding proteins are multifunctional nucleic acid-binding proteins with an evolutionary conserved cold shock domain. Their dysregulated expression can influence transcription and translation on many levels and has been linked to cancer and inflammatory diseases [1]. The best investigated Y-box binding protein, YB-1 (also known as YBX1), locates to cytoplasmic P granules and stress granules, and is considered a target for drug-resistant cancer therapy [2]. The signaling pathways involved in stress-induced YB-1 phosphorylation have recently been described [3]. It is well known that YB-1 is an early and central mediator of noncancer inflammation, especially in the context of renal conditions [4,5]. The inventor claims MK-2206 (an allosteric Akt inhibitor for which the US National Cancer Institute had completed a Phase II clinical study in 2017) and dexamethasone as agents that control YB-1 phosphorylation (and hence, inflammation of almost any type) either directly or indirectly (through phosphorylation of YB-1 inhibitors). Data from experiments with fresh human arterial tissue and murine arteriosclerosis models are presented.

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MeSH Keywords: arteriosclerosis / inflammation / Y-box-binding protein 1

WO/2019/025588

Methods of treating behavior alterations

Inventors: Maes T, Rottlant Pozo D, Grinan Ferre C, Pallás Lliberia M, Nadal Alemany R, Armario García A

Assignee: Oryzon Genomics S.A., Madrid (Spain)

Social behavior disturbances represent a broad field of symptoms that is found across ICD-10 Chapter V but extends to additional segments of neuropsychiatry, with their core symptoms oscillating between aggression and withdrawal. Their pathogenesis is also diverse; social behavioral disorders can be genetically predisposed, precipitated by psychological trauma or developmental and neurodegenerative disorders. It is not immediately apparent how a single drug should be able to treat what obviously is a common final syndrome rooted in many causes. Nevertheless, the inventors claim a range of compounds that inhibit Lsd1/Kdm1a, a lysine-specific epigenetic demethylase, as a treatment for both withdrawal and aggression. The data focus on what is identifiable as Oryzon's vafidemstat (ORY-2001; disclosed in Oryzon's WO/2012/013728) for which the company has commenced the REIMAGINE Phase IIa open label clinical trial (EUDRA-CT: 2018-002140-88) investigating it for aggression in neuropsychiatric disorders, and is preparing for ETHERAL-US (NCT03867253), a Phase IIa study in Alzheimer's disease. The rationale is that active DNA demethylation in postmitotic neurons, once thought to be absent or essentially irrelevant, could modulate mental illness [6,7]. Specific splice variants of Lsd1/Kdm1 seem to be present in neurons [8]. The strategy is not without risk; even with selective epigenetic enzyme inhibitors, off-target effects on

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gene expression can be assumed to occur [9]. For related cyclopropylamines see WO/2014/086790, discussed in Vol. 3 issue 5 of the *Pharmaceutical Patent Analyst*.

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MeSH Keywords: aggression / histone demethylases / social behavior

WO/2019/032563

Inhibitors of base excision repair activity & therapeutic methods based thereon

Inventors: Kool ET, Tahara Y

Assignee: The Board of Trustees of the Leland Stanford Junior University, Stanford (USA)

One of the most frequent types of potentially mutagenic free radical damage to DNA is the oxidation of guanine to 8-oxo-7,8-dihydroguanine (8-OG). The primary enzyme for repairing this type of damage is OGG1, a glycosylase which generates an abasic deoxyribose, ultimately leading to strand cleavage that can be repaired through the base excision repair mechanism [10]. Selective OGG1 inhibitors reported so far mostly are simple hydrazides and hydrazones [11] that tend to hydrolyze spontaneously. Approximately 26,000 compounds were subjected to initial high-throughput screening [12] at 20 μ M, resulting in over 300 initial hit compounds with varied chemical structures, whose validation by titration over an eightfold concentration range focused the structure–activity optimization on the tetrahydroquinoline sulfonamide scaffold. A compound (SU0268) carrying an amidobiphenyl substituent was found to be the most potent competitive inhibitor, with an IC_{50} value of 59 nM. SU0286 does not bind to DNA and has negligible activities against other DNA repair enzymes that process either 8-OG nucleotides, bind nucleotides or DNA, or employ base excision mechanisms. For the peer review companion paper see Tahara *et al.* [13] The obvious application is in cancer sensitization, but note that another OGG1 inhibitor, TH5487 has recently been reported to suppress lung inflammation by preventing TNF- α -induced OGG1-DNA interactions at guanine-rich promoters of pro-inflammatory genes [14].

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MeSH Keywords: DNA repair enzymes / oxoguanine glycosylase 1, human

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The use of Cxcl12 for therapy after prostate surgery

Inventors: Williams JK

Assignee: Wake Forest University Health Sciences, Winston-Salem (USA)

The chemokine Cxcl12 and its receptor, Cxcr4 have recently attracted interest as potential pharmacological targets to treat multiple sclerosis [15] and Alzheimer's disease [16]. Additional potential could be found in treating peripheral nerve disorders and surgical trauma because Cxcl12 plays a major role in peripheral and bone marrow progenitor cells trafficking and homing of progenitor cells to sites of injury. It is also crucial for muscle regeneration [17]. The inventor's team has developed a cynomolgus monkey model of persistent erectile and urinary dysfunction following radical prostatectomy [18] to investigate whether Cxcl12, injected into the periurethral space at the level of the vesiculo-urethral anastomosis, might address these widespread problems associated even with nerve-sparing excision of the prostate. 6 weeks following open radical prostatectomy, 1 ml of saline containing 125 ng of human recombinant Cxcl12 was injected transrectally at each side of the urethra. This restored abdominal leak point pressure, which radical prostatectomy had reduced from 80 ± 20 to 15 ± 5 cm H_2O , to 50 ± 7 cm H_2O . Two months after the injection, the vesiculo-urethral anastomosis was still fibrotic, but muscle fibers were beginning to re-appear. Sexual behavior was monitored at baseline, 3 and 6 months postoperative. In the three monkeys receiving Cxcl12 injections, the ability to achieve erection sufficient for mating was either completely or partially restored.

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MeSH Keywords: chemokine CXCL12 / penile erection / prostatectomy / urinary incontinence

WO/2019/035919

Compositions & methods for inhibition of L-plastin activity in osteoclasts to reduce bone loss

Inventors: Chellaiiah M

Assignee: University of Maryland, Baltimore (USA)

An ideal therapeutic approach for osteoporosis would decrease osteoclast activity without interfering with osteoblast-driven bone formation – a goal that bisphosphonates accomplish only incompletely: long-term treatment causes a

reduction in osteoblast-mediated bone formation, resulting in atypical fractures. One alternative approach could be to interfere with the cytoskeleton of osteoclasts; specifically, with the formation of the ‘sealing ring’ – a dynamic and structurally elaborate actin ring, composed of podosomes that form a cohesive superstructure [19] – which is a requirement for their bone resorption activity. Osteoclasts deficient in gelsolin remain capable of bone resorption but the resorbed areas are small due to the absence of podosomes and the hypomotility resulting from the retarded remodeling of the actin cytoskeleton [20]. The present patent application exploits yet another possibility along the same line, interfering with L-plastin, an actin-bundling protein. The inventor has designed peptide inhibitors that prevent phosphorylation of serine residues of L-plastin. The peptides comprise the first 10 N-terminal residues of L-plastin (MARGSVSDEE; optionally with serine-to-alanine mutations at positions 5 and 7), or the first 45 N-terminal residues. Fusion peptides with a cell transduction domain are also possible. These inhibitors reduce the resorptive activity of osteoclasts from C57/BL6 mice without interfering with osteoblasts *in vitro*. When encapsulated in polylactic-co-glycolic acid 150 nm nanoparticles, such peptides were released over 3 weeks after injection into mice and decreased the formation of nascent sealing zones. For the peer review companion papers see Chellaiah *et al.* [21,22]

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MeSH Keywords: L-plastin / osteoclasts / osteoporosis / podosomes

WO/2019/036562

Estrogen receptor-related orphan receptor inverse agonists

Inventors: Burris T, Walker JK, Hampton CS, Haynes KM, Griffett K, Billon C, *et al.*

Assignee: Saint Louis University, St. Louis (USA)

The estrogen receptor-related orphan receptors (ERRs), which do not bind endogenous estrogen receptor ligands and interact with a DNA response element that is quite distinct from that of the estrogen receptors, were the first orphan nuclear receptors to be identified. ERR- γ target genes including both metabolic and angiogenic genes are substantially downregulated in the mdx mouse model of Duchenne muscular dystrophy [23]. By controlling hepatic glucose production, ERR- γ is a major contributor to hyperglycemia under diabetic conditions [24], and it is also a key regulator of hepatocytic fibrinogen gene expression [25]. Starting from a reported co-crystal structure of the ERR- γ ligand binding domain with the agonist, GSK4716 the inventors developed a docking model and designed a series of disubstituted heteroaromatic compounds. These were screened in a thermal shift assay to determine if they bound directly to the receptor. Compounds that dose-dependently affected the melting point of ERR- γ to a greater or comparable degree than the standards were evaluated in a cell-based luciferase assay of ERR- γ activity. The resulting molecules, for example, N-(2-fluorophenyl)-5-(4-(2,2,2-trifluoroacetyl)phenyl)thiophene-2-carboxamide, typically achieved submicromolar EC₅₀ values. They are chemically quite distinct from the tamoxifen derivatives recently reported by Korean researchers [26]. Claims are for obesity, diabetes, muscular dystrophy, nonalcoholic fatty liver disease and neurological disorders.

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MeSH Keywords: diabetes mellitus / ESRRG protein, human

WO/2019/038772

Roundabout (Robo) receptor inhibitors & uses thereof

Inventors: Opatowsky Y, Barak-Fuchs R, Guez-Haddad J, Yom-Tov G

Assignee: Bar-Ilan University, Ramat-Gan (Israel)

Humans have three long Robo receptors (Robo 1–3), and one shorter Robo (Robo 4) paralog, which serve as cognate receptors for the Slit guidance factors, which are secreted glycoproteins. Slit/Robo signaling provides a repulsive signal for precise axon path finding and cell migration that guarantees correct organ morphogenesis during embryonic development. In the adult organism, this pathway is important in nerve regeneration [27]. It also acts as a tumor suppressor: Slit/Robo interaction is frequently inactivated in cancer [28], facilitating uncontrolled angiogenesis. Its general role can be described as control of tissue barrier transgression [29]. The high affinity of Robo toward Slit, combined with the high local concentration of Slit factors at the signaling sites, make the development of competitive inhibitors difficult. The inventors have identified the extracellular Ig-like domain 4 (D4) as a Robo receptor dimerization domain and have determined D4-mediated dimerization to be critical for Robo receptor activity: a hydrophobic surface on D4 mediates homotypic close contacts with a reciprocal D4, with a dissociation

constant of 16.9 μM . A secondary Robo receptor dimerization site was identified in the extracellular Ig-like domain 3. The invention's dimerization inhibitors (mostly single-chain antibody fragments) bind to one or more of these Robo2 interface sites. Data from a rodent dorsal root ganglion growth cone collapse assay are presented, along with actin cytoskeleton structure data in COS-7 cells. For the peer review companion papers see Barak *et al.* [30] and Yom-Tov *et al.* [31].

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MeSH Keywords: neoplasms / nerve tissue proteins / roundabout protein

WO/2019/043139

Fused [1,2,4]thiadiazine derivatives which act as Kat inhibitors of the Myst family

Inventors: Morrow BJ, Foitzik RC, Camerine MA, Lagiakos HR, Walker SR, Bozikis YEB, et al.

Assignee: CTXT Pty Ltd., Parkville (Australia)

Lysine acetylation of proteins regulates histones, oncoproteins, tumor suppressors and transcription factors. Acetylation of histone residues is a crucial epigenetic modulator, generally associated with transcriptional activation although repression has also been observed in some cases [32]. Lysine histone acetyl transferases (systematic name: Kat proteins) bear a catalytic Myst domain, which contains an acetyl-CoA binding motif and a zinc finger. Translocations affecting Myst acetyltransferases can lead to cancer; Kat inhibitors might treat such tumors with minimal side effects [33]. Some such inhibitors have been reported, including anacardic acid-derived salicylates [34] with IC_{50} values for the Kat proteins Tip60 and MoF in the midmicromolar range – which is suboptimal for use as drugs. The inventors have synthesized (and in part, characterized using histone acetylation marker assays for the various Kats) hundreds of [1,2,4]thiadiazine-3-carboxamide 1,1-dioxides, some of which are much more potent *in vitro*. This opens an entirely new section of the chemical space for Myst acetyl transferases. Claims are limited to cancer therapy, but Kat inhibitors are likely to have broader applications, for example, in regulating mitochondrial activity [35].

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MeSH Keywords: histone acetyltransferases / neoplasms / thiadiazines

WO/2019/045451

Cartilage regeneration composition containing Hapln1 as active ingredient

Inventors: Kim DK, Jang JM

Assignee: Chung-Ang University Industry-Academy Cooperation Foundation, Seoul (Korea)

Hapln11 is a protein that links hyaluronan and proteoglycan in cartilage. Although the gene family was described 15 years ago [36], and Hapln1 was cloned from zebrafish over 10 years ago [37], relatively little is known concerning its biology, especially if one compares it to what is known about other extracellular matrix components in the joints. According to the mouse data presented in this invention, Hapln1 can be used for cartilage regeneration by injecting it into the joint space, and even with repeated intraperitoneal injections. Hapln1 appears to act through TGF- β and the stabilization of its receptor, and through the expression of Sox9. In this context, it seems noteworthy that Runx proteins (transcription factors that are also associated with osteoblast differentiation) are the crucial transcription regulators for Hapln1 expression induced by luteinizing hormone periovulatory follicular matrix [38]. Note that the Hapln proteins are also key players in the organization of the perineuronal matrix in the adult brain [39].

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MeSH Keywords: arthritis / cartilage / link protein

WO/2019/046931

Compounds, pharmaceutical compositions & use thereof as inhibitors of Ran GTPase

Inventors: Wu JH, Batist G, Tian X, Li X, Mes-Masson A-M, Provencher D, et al.

Assignee: The Royal Institution for the Advancement of Learning - McGill University, Montreal (Canada); Val-Chum LP, Montreal (Canada)

The high-grade serous histotype of epithelial ovarian cancer has extremely high intratumoral heterogeneity even at early stages, which facilitates resistant tumor recurrence after initial response to treatment with platinum drugs or paclitaxel. Individual metastases can have different drug resistances. Complex karyotypes and aneuploidy are common characteristics, suggesting that strategies that specifically target aneuploidy might be successful. The inventors, who have built a large biobank of ovarian cancer tissue samples, have reported earlier that overexpression

of Ran, a small Ras-type GTPase that is specialized in nuclear trafficking and regulates mitotic spindle formation [40], is associated with a poor prognosis and that its downregulation induces caspase-3 associated apoptosis [41]. Because of the natural high affinity of GTP toward Ran, the binding-pocket itself is widely considered difficult to target effectively with small-molecule inhibitors. Instead, the inventors designed compounds that target the GDP-bound form of Ran, with the hypothesis that this would lock the protein in an inactive state, thereby depleting the active Ran population. *In silico* screening of the NCI chemical database using a surface binding site that includes the GDP-binding pocket and an allosteric subpocket was conducted, and a refined set of 45 hits was assessed by clonogenic assays using the aneuploid epithelial ovarian cancer cell line TOV112D. Two lead structures were identified and optimized, resulting in compounds of different chemical classes with submicromolar IC₅₀ values that recapitulate all effects of Ran siRNA but did not affect diploid ARPE-19 control cells.

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MeSH Keywords: aneuploidy / carcinoma, ovarian epithelial / Ran GTP-binding protein

WO/2019/053731

Succinate-regulating polypeptides & use thereof

Inventors: Ohana E

Assignee: B. G. Negev Technologies and Applications Lt., at Ben-Gurion University, Beer Sheva (Israel)

Succinate, an intermediate of the citric acid metabolic cycle that is constantly present in human plasma at concentrations of 1–20 μM, also functions as a signaling molecule for local metabolic stress: a G-protein coupled receptor, *Sucnr1* (formerly *Gpr91*), was identified in blood vessels, cardiomyocytes and kidney epithelia [42]. In the kidney, there are also apical succinate transporters; one of these, *NaDC-1* forms an inhibitory complex with *Slc26a6*, a luminal Cl[−] dependent oxalate/HCO₃[−]/OH[−] exchanger. This limits renal oxalate and citrate concentration and prevents urolithiasis [43]. *Sucnr1* stimulation releases the protein *Irbit* which interacts with the transporter complex [44], ‘fine-tuning’ its activity. The present invention provides the data underpinning these insights as well as polypeptides representing partial amino acid sequences of *Slc26a6* or *Irbit* comprising a mutation that increases *NaDC-1* binding, stability of the polypeptide, stability of *NaDC-1* complex or a combination thereof to increase succinate reabsorption. Specifically, they inhibit electrostatic interaction between the Stas domain of *Slc26a6* and the H4c domain of *NaDC-1*. Antibodies and their fragments interfering with binding are also a subject of the invention. Besides kidney stones and hypertension, the potential applications extend to inflammatory bowel diseases (where gut microbiota that produce succinate are more abundant), nonalcoholic fatty liver diseases and primary sclerosing cholangitis and cholestasis.

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MeSH Keywords: dicarboxylic acid transporters / SLC13A2 protein, human / sodium-succinate-cotransporter / urolithiasis

WO/2019/054922

Methods for identifying therapeutic agents which interact with Stk24

Inventors: Mahlapuu M

Assignee: Alexera AB, Göteborg (Sweden)

Mst3 (also called *Stk24*) is among the kinases that regulate cell migration, cell polarity, apoptosis and metabolic regulation [45]. *Mst3* is important in the development of insulin resistance [46], is an unfavorable survival predictor when overexpressed in non-small-cell lung adenocarcinoma [47], and might be involved in the development of salt-induced hypertension [48]. A role in the regulation of lipid partitioning (specifically, in controlling the metabolic balance of lipid utilization vs lipid storage in peripheral tissues prone to lipotoxicity), as the inventors have shown using quantitative phosphoproteomics, has not been described in the peer review literature. siRNA knockdown of *Mst3* significantly reduced accumulation of neutral lipids in human hepatocytes. The document focuses on the identification of *Mst3* modulator compounds by determining activity *Mst3* (*in situ*, in tissue homogenates or *in vitro* with the recombinantly produced kinase or functional peptide fragments). This can be achieved by measuring lipid deposition, fatty acid oxidation and/or lipid secretion and/or synthesis or uptake of lipids; or by measuring insulin-stimulated glucose uptake. Enzymatic assays, such as TR-FRET or ADP hunter assays, can be adapted for *Mst3* assays, and can be used to determine the level of phosphorylation of the substrate. These findings highlight

Mst3 modulators as potential drug candidates for the prevention and treatment of nonalcoholic fatty liver disease and steatohepatitis.

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MeSH Keywords: diabetes mellitus / nonalcoholic fatty liver disease / STK24 protein, human

WO/2019/060260

Xpa protein inhibitor compounds & their use

Inventors: Turchi JJ, Gavande N, Vanvere-Carozza PS

Assignee: Indiana University Research and Technology Corp., Indianapolis (USA)

Induced overexpression of nucleotide excision repair proteins, of which Xpa is a critical one [49], is directly linked to platinum drug resistance of tumors. Xpa has a greater affinity for damaged DNA over undamaged DNA but does not possess any enzymatic activity; nevertheless, it is an integral component for which there is no redundant or compensatory protein: it builds the NER pre-incision complex in a modular fashion [50]. Surprisingly, despite the potential physiological significance of Xpa and the fact that the inventor team had made the 3D structure of its minimal DNA-binding domain, and also the first small molecule inhibitor (X80), available years ago [51], very little progress has been made to date to develop more drugs targeting Xpa. They have now expanded on the arylpyrazone template defined by X80. Docking studies with X80 revealed a large space-filling pocket around the aromatic carboxylic acid ring of the lead compound that can be exploited for further structural optimization. Compounds such as (*Z*)-3-(4-((5-(4-chloro-3-((4-fluorobenzyl)carbamoyl)phenyl)thiophen-2-yl)methylene)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)benzoic acid have IC₅₀ values in the low to very low micromolar range; competitive DNA intercalation assays showed that the agent bind to Xpa but not to DNA.

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MeSH Keywords: DNA repair enzymes / xeroderma pigmentosum group A protein

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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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