Patent Highlights

A snapshot of recent key developments in the patent literature of relevance to the advancement of pharmaceutical and medical R&D

Hermann Mucke*

WO2012055814

Compound inducing LBPA accumulation for inhibiting cell-to-cell transmission of HIV

Record M, Chapuy-Regaud S, Izoped J *et al.*

Transmission of HIV occurs not so much through free virus but rather through infected blood cells, which constitute a reservoir with persistent low-level viral replication. The intracellular 'storage facility' is the endosomal compartment with its multivesicular bodies where lysobisphosphatidic acid (LBPA; also *bis*(monoacylglycerol)phosphate), is specifically located. LBPA interacts with the protein Alix, which is associated with the endosomal sorting complex required for transport and can also bind HIV [1]. The inventors have used U18666A (3- β (2-diethylaminoethoxy)androst-5-en-17-one) [2], an inhibitor of two enzymes in the cholesterol biosynthesis pathway (oxidosqualene cyclase and C8–C7 isomerase) to demonstrate that altering cholesterol metabolism and distribution, or inhibiting phospholipase A2 (PLA2), induces the formation of large multivesicular bodies which accumulate LBPA. This was accompanied by a decrease in virus release; the particles being sequestered within intracellular vesicles. Moreover, the transfer of HIV from human monocyte-derived macrophages to autologous lymphocytes by direct cell–cell contact was inhibited, as was the shedding of assembled HIV into the medium, although the HIV replication cycle was not affected. Progesterone and the PLA2 inhibitor methyl arachidonyl fluorophosphonate have a similar effect. The inventors point out that this might be mediated by sigma-1 receptors on which progesterone acts as an antagonist and which are linked to PLA2 downstream, potentially accounting for the crosstalk between cholesterol, progesterone and PLA2 observed at low-micromolar concentration of the inhibitors. One should note that a different group has recently shown that U18666A inhibits dengue virus entry and replication [3].

Published: 3 May 2012

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WO2012055971

Microvesicles derived from atheroprotective endothelial cells for the treatment & prevention of atherosclerotic diseases

Dimmeler S, Boon R & Hergenreider E

Krüppel-like factor 2 (KLF2) is a transcription factor for which many roles have been described. One of these is the maintenance of the endothelial cell phenotype that develops under shear stress from fast steady-state laminar blood flow and protects against atherosclerosis [1]. Atherosclerotic lesions develop preferentially at sites where the blood flow is disturbed and becomes turbulent [2]. Although the atheroprotective effects of KLF2 have been extensively described, this knowledge could not be exploited for therapeutic purposes. It was also known that a bicistronic cluster of miRNAs, comprising miR-143 and miR-145, is of crucial importance for proper smooth muscle cell function [3]) as they are integral components of the regulatory network that controls cytoskeletal remodeling and phenotypic switching of these cells during vascular disease.

The invention is based on a finding that links these two pieces of information: endothelial cell cultures that are treated with statins to induce KLF2 expression produce submicrometer-sized vesicles containing miR-143/145 and shed them into the culture supernatant, from where they can transmit the RNAs to co-cultured smooth muscle cells to exert an atheroprotective effect. The microvesicles are sufficiently stable to be isolated using a multi-step ultracentrifugation procedure. Using a lentiviral shRNA construct, the inventors also demonstrate that silencing of KLF2 impairs the shear stress-mediated induction of miR-143/145 to a similar extent as endothelial nitric oxide synthase, a direct transcriptional target of KLF2. At the priority date of the invention, miR-143/145 expression had only been described in muscle cells. This is the first compelling evidence that intercellular transport of miRNAs can influence atherogenesis. For the companion peer-reviewed paper, see [4]. The recently reported fact that these miRNAs might be involved in tumor formation and invasiveness could limit their therapeutic applicability [5].

Published: 3 May 2012

WO2012057421

Cancer-metastasis suppression by means of increased TASK-3 potassium channel expression

Kang DW & Han JH

In this companion patent to [1], the Korean inventors demonstrate that increasing the expression of the two-pore domain acid-sensitive K(+) type 3 (TASK-3) channels (a product of the *KCNK9* gene) through means such as activation of PKC can reduce the invasiveness of established solid tumors. It had been known for years that TASK-3 has oncogenic potential that is directly related to its potassium channel function and that reducing potassium efflux through neuronal TASK-3 channels can prevent apoptosis [2]. Expression of functional mitochondrial TASK-3 was reported to be integral to the proliferation and/or survival of cultured melanoma cells [3]. All of this would not suggest that TASK-3 could be a metastasis suppressor – which is what the inventors have demonstrated. Using a non-invasive (MCF-7) and an invasive (MDA-MB-231) breast cancer cell line, TASK-3 expression levels were compared using real-time PCR, western blot and immunohistochemistry, and were shown to be correlated with cellular migration potential in an *in vitro* cell-layer scraping and closure assay, and a 3D CytoSelect™ cell migration assay. Transformation with a TASK-3-expressing vector, or knockdown with siRNA directed against TASK-3, could change the migration behavior, which, in turn, could be modulated by PKC inhibitors. These findings could be of therapeutic interest in situations where preventing metastasis is paramount, for example, after debulking surgery of a primary tumor. Diagnosis of invasive potential is another aspect that this application covers extensively.

Published: 3 May 2012

WO2012061681

Control & characterization of memory function

Goshen I & Deisseroth K

Memory formation (which happens on the timescale of minutes to hours) and its consolidation over weeks to years to establish neuronal circuits that guide memory retrieval and associated behavior, is an extremely complex process that psychiatrists would like to modulate in different ways. For example, focal amnesia (the inability to retrieve certain memories while others remain accessible) is generally undesirable but is a central goal in the treatment of post traumatic stress disorder (the undesired and uncontrollable retrieval of specific fear memories). The present invention is based on the discovery that temporally and locally precise inhibition of neuronal circuits in the hippocampus (preferably in the dorsal CA1 field), the basolateral amygdala, or the anterior cingulate cortex can reversibly disrupt memory function. Preferably, this is achieved by expressing light-activatable proteins (e.g., opsins) in the cells of the neural circuit, but direct electrical stimulus or pharmaceuticals with temporally precise action are also claimed. In a series of complicated mouse experiments involving hippocampal expression of a lentiviral vector encoding the light-activated microbial halorhodopsin eNpHR3.1 fused in-frame to enhanced yellow fluorescent protein and optical fibers inserted through a double cannula system into the dorsal CA1 region, it was shown that optogenetic inhibition during behavioral entraining completely prevented contextual fear acquisition of eNpHR3.1-treated mice compared with controls (39 ± 5.4 v. $7.6 \pm 4.3\%$ behavioral freezing; means $\pm$ SEM, $P < 0.005$). When the same mice were tested with light delivery during recall, the memory that was present the day before became unavailable for recall (42.6 ± 10.1 v. $5.94 \pm 4.1\%$ freezing, $P < 0.01$). Surprisingly, CA1 inhibition during recall completely blocked remote fear memory in a reversible fashion. When the same mice were retested on the next day without illumination, the fear memory was fully expressed as in controls. Finally, when mice were bilaterally injected in the basolateral amygdala instead of hippocampus it was possible to optogenetically inhibit both contextual (65.5 ± 7.2 v. $9.6 \pm 5.5\%$ freezing; $P < 0.001$) and auditory-cued acquisition (69.5 ± 9.6 v. $24.5 \pm 13\%$ freezing; $P < 0.05$) in eNpHR3.0 ($n = 4$) mice, also a finding of high relevance [1]. The inventors conclude: *“The ability to reversibly shut down a remote fearful memory may open an exciting therapeutic avenue for post traumatic stress disorder patients, in which a recurring disturbing memory may be stopped as it appears, without permanently affecting other memories. Additionally, memories related to drugs of abuse can be inhibited to reduce drug seeking behavior.”* For a peer-reviewed companion paper see [2], for a companion patent application claiming optogenetic control of reward-related behaviors see [3], and for related work on conditional transgenic optogenetic silencing by another group see [4].

Published: 10 May 2012

WO2012062044

Small-molecule inhibitor syntelin against kinetochore motor protein CENP-E & use thereof

Yao X & Ding X

The mitotic kinesin-7 centromere protein E (CENP-E) is a slow-acting ATP-dependent motor protein that captures and stabilizes microtubule spindles during metaphase chromosome alignment and is crucial for correct mitosis [1,2], suggesting potential as a novel target for cancer therapy [3]. GlaxoSmithKline has published Phase I/II clinical study data for its CENP-E inhibitor, GSK-923295, in solid tumor patients [4]. By screening a library of structurally diversified compounds for lagging chromosome phenotypes and inhibition of CENP-E motility, the inventors identified $\{5-[(\{3\text{-amino-8-thia-4,6-diazatricyclo}[7.4.0.0.2,7]\text{trideca-1}(9),2,4,6\text{-teraen-5-yl}\}\text{sulfanyl})\text{methyl}\}4\text{-phenyl-1,2,4-triazol-3-yl}\}\text{sulfanyl}\}\text{acetic acid}$ (syntelin) that binds to different sites from those of GSK923295 with an IC_{50} value of 160 nM and inhibits CENP-E mutants resistant to GlaxoSmithKline's investigational compound [5]. This companion patent application adds information obtained with immunodeficient NOD/SCID mice that received luciferase-expressing

MDA-MB231 human breast cancer cells via tail vein injection. Therapeutic response to syntelin (as determined by bioluminescence imaging) was significantly better than with the standard first-line mammary carcinoma drug, paclitaxel. Syntelin broadens the known CENP-E inhibitor chemical template space that researchers are just beginning to explore.

Published: 18 May 2012

WO2012064340

Dual-action compounds targeting adenosine A2A receptor & adenosine transporter for prevention & treatment of neurodegenerative diseases

Liang C-M, Lin Y-L, Chern Y *et al.*

An adenosine A2A receptor agonist, CGS21680, has shown symptomatic benefit in animal models of Huntington's disease [1], probably because the resultant stimulation of the ubiquitin protease system tends to remove the neurotoxic huntingtin protein [2]. The human equilibrative nucleoside transporter-1 (ENT1), which shuttles purine and pyrimidine nucleosides across membranes [3], is expressed in the same striatal regions of the brain that express the A2A receptor and where mutant huntingtin aggregates. Remarkably, however, the peer-reviewed literature holds few indications of ENT1 having been explored in the context of neurodegenerative disease; the great majority of its literature body relates to cancer. The existence of synergistic A2A/ENT1 dual-action compounds, suggested by the similarity of the ligands/substrates, has likewise remained mostly unexplored. In this patent application such agents were rationally designed, based on the pharmacophores of A2A agonists such as CGS21680 and inhibitors of ENT1, a protein for which no crystal structure was available. Compounds (all based on adenosine) that exhibited good predicted properties towards both targets were synthesized, assayed for binding to guinea pig brain membrane fractions and for their ability to prevent apoptosis of serum-deprived PC12 neuronal cells. For the companion peer-reviewed paper see [4].

Published: 18 May 2012

WO2012065362

Myomegalin variant 8 & uses thereof

Wang Z & Qi RZ

Myomegalin is a large Golgi-associated leucine zipper protein that exists in several splice variants, interacts with phosphodiesterase 4D and targets it to particulate structures. Isoform 1 displays centrosome and Golgi-localizing patterns similar to CDK5 regulatory subunit-associated protein 2, a human microcephaly-related protein [1,2]. Isoform 4 has been shown to act as a cAMP-activated PKA-anchoring protein [3]. The present patent application claims the novel isoform 8 (MMG8) which regulates microtubule organization and nucleation at the Golgi apparatus by forming a complex with AKAP450. The inventors have generated a monoclonal antibody, 532C, which binds to its C-terminal region, which is different from all other MMG variants. Suppression of MMG8 expression by siRNA knockdown induces the accumulation of LAMP-1 (a marker of lysosomal storage diseases), reduces glycosylated mature CD44 antigen (a therapeutic target of metastatic tumors) and inhibits proliferation of HeLa and MCF-7 cancer cell lines without causing significant cell death. Although the claims cover potential therapeutic applications in glycosylation disorders and cancer, the primary focus seems to be on diagnostics for such conditions. These will likely not remain the only disorders in which myomegalin, on which slow but steady research progress has been made since its first characterization in 2000, could serve as a target. For example, new data suggest its involvement in retinal photoreceptor component trafficking [4].

Published: 24 May 2012

WO2012069870

A compound comprising α -MSH for use in endodontic regeneration

Benkirane-Jessel N,
Mendoza Palomares C & Fioretti F

Periodontitis – perhaps the most prevalent disease of mankind – is the primary cause of tooth loss in adults aged 35 years and older. Allowing teeth roots to re-anchor themselves in the bone after endodontic surgery is the major goal of regenerative oral medicine, pursued by stimulating the local regeneration of the dentin–pulp complex through various (and partially experimental) means that could include grafting, resorbable implants and/or the application of growth factors [1]. The inventors have studied nanostructured multilayer films incorporating α -melanocyte-stimulating hormone peptides (α -MSH and melanocortin) covalently coupled to poly-L-glutamic acid of 15–400 amino acid residues in length (which leaves the anti-inflammatory α -MSH C-terminal sequence Lys-Pro-Val accessible). Such films induce IL-8 and -10 secretion and promote proliferation of pulp fibroblasts cultured from human third molar germ tissue, while the presence of α -MSH alone, or of a poly(glutamic acid) alone, inhibits such proliferation without affecting viability. Once new dental pulp fibroblasts are formed, the film construct promotes their adhesion more strongly than each of its components. This could represent a significant advance in guided regeneration in cases where the dental pulp has been destroyed by infection and inflammation. For companion papers see [2,3].

Published: 31 May 2012

WO2012073214

New heptose derivatives
& biological applications

Gerusz V, Vincent S, Oxoby M *et al.*

Glycobiology drug targets enjoyed a brief period of prominence in the late 1990s but industry has waned since that time. The heptose biosynthesis pathway, which is essential for correct configuration of the inner core of the lipopolysaccharide component of the outer membrane of Gram-negative bacteria, could be a particularly attractive target for anti-infective drugs because the involved enzymes are unique, if only recently characterized [1,2]. A few bacterial heptosylation inhibitors have been reported, especially targeting enzymes known as HldE (a kinase involved in ADP heptose synthesis) and the two heptosyltransferases WaaC and WaaF. In this patent application, a series of D-glycero-D-manno-heptopyranose 7-phosphate (H7P) analogs is reported (H7P is the product of GmhA, which catalyzes the isomerization of D-sedoheptulose 7-phosphate into H7P, and the substrate for HldE [2]). Among the compounds with IC_{50} values $<100 \mu\text{M}$ for GmhA, which also showed at least 30% inhibition of *Escherichia coli* C7 LPS heptosylation at concentrations $<10 \text{ mM}$, are α -fluoro 7-O-phosphoryl-D-glycero- α -D-manno-heptopyranoside and 7-O-phosphoryl-1-deoxy-D-glycero-D-mannoheptapyranoside. At a time when antibiotic resistance is spreading to Gram-negative bacteria, compounds that inhibit the first committed step in the formation of ADP-heptose could prove valuable as antibiotic adjuvants and virulence modulators. The companion paper is [3].

Published: 7 June 2012

WO2012074120

Lissencephaly
therapeutic agent

Hirotsune S

Lissencephaly (Greek for ‘smooth brain’) is a rare embryonal development disorder of the brain, which, as a result of defective neuronal migration during the second trimester of pregnancy, fails to properly develop its normal surface folds [1]. As with the otherwise unrelated Down syndrome, there are many subtypes and a wide spectrum of medical consequences: many lissencephaly children fail to develop beyond a 3–5-month-old level and die before the age of 2, while others may have near-normal development and intelligence. Many cases are due to mutations in *LIS1*, an essential regulator of cytoplasmic dynein and hence, cell migration. The inventor and his colleagues at Osaka City University’s department of genetic disease research

(Japan) have discovered (fortuitously, as they state [2]) that a substantial fraction of the *LISI* gene product is proteolytically degraded by calpain after reaching the plus-end of microtubules. An experimental orally bioavailable peptide calpain inhibitor, Senju Pharmaceutical Co.'s SNJ-1945 (under investigation for ophthalmological applications [3]), re-established the migratory and chemotactic capacity of cerebellar neurons from *LISI* knockout mice and improved many behavioral and motor features. One would expect prenatal treatment possibilities, but claim 9 is directed at the treatment of lissencephaly patients by administering 50–1200 mg of a specific calpain inhibitor through 2–5 days, an astounding accomplishment if it can be clinically corroborated. At present, established lissencephaly shows no significant response to any type of treatment on the anatomical level, although some functions might improve through training.

Published: 7 June 2012

WO2012077051

Hydroxylated aminotriazole derivatives as ALX receptor ligands

Bur D, Corminbeuf O, Cren S *et al.*

The lipoxin A4 receptor (or formyl peptide receptor 2, FPR2/ALXR) has quite promiscuous ligand-binding characteristics: it also is a functional receptor for annexin A1, a fragment of the prion protein, a peptide derived from gp120 of HIV and serum amyloid A and β -amyloid(1–42). Implicated in inflammatory conditions as diverse as tendon repair and Alzheimer's disease, ALXR is among the most promising truly novel target for anti-inflammatory drugs at this time [1,2]. The challenge is to identify high-affinity agonists that are not peptides or peptidomimetics. Actelion, which has already disclosed aminotriazoles with this type of activity in an earlier patent application [3], has now made a valuable contribution to our understanding of the structure–activity relations in this niche of medicinal chemistry space. Tertiary alcohols demonstrated a high activity as ALXR agonists only if they were attached to the 4-position of an oxazol-2-yl radical. Other tested heteroaryl tertiary alcohol derivatives were significantly less active. This is in contrast to acetyl derivatives disclosed earlier, demonstrating high activities for a variety of different heteroaryl groups [3]. The claimed new compounds also had a significantly longer half-life in rat or human plasma *ex vivo*.

Published: 14 June 2012

WO2012080459, WO2012080460 & WO2012080461

miRNAs in joint disease

Heermeier K, Schneider JC, Leeuw T *et al.*

Rheumatoid arthritis (RA) and osteoarthritis (OA) are both characterized by progressive degeneration of articular cartilage, ultimately leading to a functional inability of the affected joint; however, while inflammation is the primary factor in RA it is only a secondary one in OA, where age-related synovial erosion and subsequent bone remodeling result primarily from extended physiological and mechanical strains. Also, quite contrary to RA, there are no validated laboratory markers to aid in the early diagnosis of OA, which has to rely on joint damage that is severe enough to be visible on an x-ray. In the present three patent applications, Sanofi inventors claim three microRNAs as early-stage indicators of joint tissue status and drug response: mir-22, associated with osteogenic differentiation of mesenchymal stem cells [1] (discussed in the '459 document); the inflammation-associated mir-146a ('460) [2]; and mir-199a which is involved in the senescence of chondrocytes ('461) [3]. The effects of mir-22 overexpression or knockdown on collagens II and X, aggrecan, the Sry-related high-mobility group box transcription factor Sox9, cartilage-derived retinoic acid-sensitive protein, and matrix metalloproteases 1 and 3 were analyzed in chondrocytes and stem cells during their cultivation as well as in

chondrogenically differentiated bone marrow stem cells after infecting them with pseudoviral particles encapsulating the respective DNA. Nucleic acid antagonists of these miRNAs are claimed as therapeutics but the most important aspect of this work is its contribution to the intensely investigated field of experimental OA biomarkers which have rarely involved nucleic acids so far [4].

Published: 21 June 2012

WO2012083261

Blood–brain barrier-
penetrating oximes for
cholinesterase reactivation

Cashman JR & Kalisiak J

The so-called nerve gas agents (and also the organophosphate and carbamate pesticides) permanently inactivate cholinesterase by forming covalent bonds with amino acid residues in the active center of these enzymes, leading to overstimulation of the cholinergic system via postsynaptic muscarinic acetylcholine receptors. Countermeasures consist of autoinjectors, which deliver atropine and an anticonvulsant, together with the actual antidote. This is an oxime component containing a pyridinium quaternary nitrogen atom that can reactivate the enzyme by forming a diffusible adduct with the bound nerve agent through a nucleophilic reaction [1,2]. None of these antidote oximes are equally effective against all nerve agents and many are compromised by a short half-life in solution. This document presents new oximes whose amidine or guanidine groups, while enabling them to react with their targets, do not contain a permanent positive charge. This allows them to penetrate into the brain and reactivate central cholinesterases which conventional antidotes do not regenerate to a substantial extent. Pretreatment with 2-(hydroxyimino)-*N,N*-dimethyl-*N'*-propylacetimidamide HCl protected mice against toxicity of Sp-GDC (a nerve agent model compound) much more effectively than an equivalent dose of pralidoxime, an older antidote that is stable and, therefore, widely used in military settings. While much of the original oxime antidote research was originally classified, the arising need of terrorism countermeasures has drawn such work almost completely into the public arena.

Published: 21 June 2012

WO2012085789

Agents for clearing
biomolecules from circulation

Rossin R, Laeppchen T,
van den Bosch SM *et al.*

In the overwhelming majority of cases where pharmacokinetics needs to be overridden by drug-delivery technology, the objective is to extend the compound's plasma half-life. In some cases where short or ultrashort action is desired (e.g., with insomnia agents or anesthetics), molecular drug design can be brought into play to achieve rapid clearance. However, targeted imaging agents that are designed for high affinity for receptors, structural proteins, or intracellular metabolic pathways might need additional clearing agents that can rapidly remove the unbound imaging agent from circulation by binding or complexing, or the desired contrast would not be achieved. Other examples are antibody–toxin conjugates, or pre-targeting approaches such as antibody-directed enzyme prodrug therapies, where it would be beneficial to remove any antibody conjugate from circulation prior to administering the prodrug [1]. Here, Philips researchers provide new strained cyclooctene dienophiles (conjugated to hexose moieties and/or tetrazines) as clearing agents that can react with diene target molecule groups, for example, in a Retro Diels–Alder reaction [2]. These reactions are bio-orthogonal, i.e., they can occur in the living body without affecting its biochemistry. Many proteins, including recombinant antibody fragment constructs and cytokines, can be targeted in this fashion. Extensive chemical and biological data are provided.

Published: 28 June 2012

Financial & competing interests disclosure

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.

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

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