Patent highlights August–September 2017

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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/2017/129558

Methods for predicting or treating myelopoiesis-driven cardiometabolic disorders & sepsis

Inventors: Yvan-Charvet L, Viaud M, Guinamard R

Assignee: Institut National de la Santé et de la Recherche Médicale (INSERM), Paris (France); Université Nice Sophia Antipolis, Nice (France)

MeSH Keywords: Apolipoproteins E • Glucose Transporter Type 1 • Glycolysis • Hematopoiesis, Extramedullary

Expansion of hematopoietic stem and multipotential progenitors and the associated myelopoiesis is associated with hypercholesterolemia-induced atherosclerosis in mice and humans [1,2]. However, the rate of ATP generation required for cell proliferation and differentiation cannot be directly accounted for by cholesterol, and requires alternative sources of energy [3]. Increased hematopoietic metabolic activity can be visualized by ^{18}F FDG PET-CT imaging, not only in inflamed atherosclerotic plaques but also in the spleen of patients with cardiovascular diseases, reflecting an extramedullary hematopoiesis [4]. Having found that the upregulation of Glut1 expression in ApoE $^{-/-}$ hematopoietic stem and multipotential progenitors was not due to an alteration of the oxygenation status of the bone marrow but rather was dependent on Ras signaling downstream of the GM-CSF/IL-3 receptor driving glycolytic substrate utilization by mitochondria, the inventors transplanted bone marrow from mice with single or combined deficiencies of ApoE or Glut1 into ApoE-knockout mice. Consistent with their hypothesis, knockouts receiving ApoE $^{-/-}$ Glut $^{\pm}$ bone marrow showed reduced HSPC proliferation and expansion, myelopoiesis and atherogenesis compared with mice that had received ApoE $^{-/-}$ bone marrow. A causal relationship between the enhanced hematopoietic glycolytic activity in ApoE $^{-/-}$ mice and their myelopoiesis through regulation of HSPC expansion and fate is proposed, offering novel therapeutic perspectives for inhibitors of glucose transport (e.g., those described in WO/2011/119866, WO/2013/182612 and WO/2015/112581) or glutamate-oxaloacetate transaminases, for example, compounds of the aminooxyacetic acid class. Expression inhibitors and antibodies directed at these two proteins are also claimed.

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WO/2017/130933

Therapeutic agent for neurodegenerative diseases

Inventors: Tanihara H, Iwao K, Nakao M, Hayashi H & et al.

Assignee: National University Corporation Kumamoto Unniversity, Kumamoto (Japan)

MeSH Keywords: Histone demethylases • Low tension glaucoma • Monoamine oxidase • Tranlylcypromine

Primary open-angle glaucoma, once thought to be caused solely by increased intraocular pressure that slowly compromises the optical nerve head, has been proven to be a much more complex and highly localized neurodegenerative disease that does not require elevated pressure in the eye. In East Asians, normal tension glaucoma is actually diagnosed more frequently than the classical type. The inventors have turned to epigenetics, specifically to inhibitors of LSD1, a nuclear enzyme that modulates gene expression by removing the methyl group from the mono- and di-methylated lysine 4 of histone H3. There are good reasons for this because recent research has shown that Rcor2, a co-repressor of LSD1 that is mainly expressed in the central nervous system (of which the optic

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nerve is a part) plays a key role in epigenetic regulation of neurogenesis [5]. LSD1 inhibitors also protect cochlear neurons against platinum toxicity [6]. A rat glaucoma model employing NMDA-induced excitotoxicity demonstrated that intravitreal administration of tranylcypromine (an MAO inhibitor antidepressant that also inhibits LSD1) significantly saved retinal ganglion cell numbers. (Notably, ORY-2001 – a LSD1/MAO-B dual inhibitor from Oryzon Genomics SA [Barcelona, Spain] – is being developed for suppressing leukemia stem cells and for Alzheimer's disease). Investigating two main candidate routes for this neuroprotection, the inventors found that, while expression of Akt and the expression and phosphorylation of total p38MAPK were unchanged by 100 μ M tranylcypromine, glutamate-induced suppression of p38MAPK γ expression was recovered by tranylcypromine. For the companion peer review paper see [7]. There is a caveat: A few months ago, it was reported that LSD1 is required for the terminal differentiation of rod photoreceptors, and that its pharmacological blockade increases expression of genes associated with other retinal cell types [8].

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WO/2017/134265

Use of inhibitors of ADAM12 as adjuvants in tumor therapies

Inventors: Peduto L, Di Carolo S

Assignee: Institut Pasteur, Paris (France)

MeSH Keywords: ADAM12 Protein • Mesenchymal Stromal Cells • Neoplasms

Mesenchymal stromal cells developing in tumors (carcinoma-associated fibroblasts) play an essential role in creating an immunosuppressive and protumorigenic environment, favoring drug resistance. ADAM12, one of the disintegrin and metalloproteinase domain-containing membrane proteases, is highly expressed in a specific subset of such tumor-associated cells. It participates in tumor–stroma crosstalk in prostate, breast and colon cancer [9], apparently by proteolytically activating growth factors such as EGFR and VEGF [10], and is also involved in fibrotic and neurodegenerative diseases [11]. Although ADAM12 is a surface protease, it is not a widely addressed therapeutic target, and no small molecule inhibitors seem to have been reported. The inventors propose, among many other approaches that include chimeric antigen receptor strategies, immunoconjugates comprising anti-ADAM12 monoclonal antibodies or antibody fragments and tumor-specific or tumor-associated antigens as targeting agents. The ADAM12 inhibitors are supposed to disrupt the tumor stromal capsule for improving the vasculature, tumor perfusion and T cells infiltration in the central region of the tumor, and for limiting macrophage polarization toward an immunosuppressive M2 phenotype. One of several examples shows that depletion of ADAM12⁺ carcinoma-associated fibroblasts improves T-cell infiltration into the tumor, promotes M1 macrophages, and limits tumor growth.

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WO/2017/134301

Clec9A binding agents

Inventors: Kley N, Tavernier J, Cauwels A, Gerlo S

Assignee: Orionis Biosciences NV, Zwijnaarde (Belgium); VIB VZW, Gent (Belgium); Universiteit Gent, Gent (Belgium)

MeSH Keywords: CLEC9a protein, human • Dendritic Cells • Neoplasms • Tumor Necrosis Factor-alpha

This invention relates to agents (preferably, single domain antibodies) that bind to, but do not functionally modify, Clec9A (DNCR-1), a C-type lectin-like receptor expressed primarily on dendritic cells that excel in cross-presentation of exogenous antigens [12,13]. Therefore, these agents can, directly or indirectly, recruit dendritic cells to a site of interest while still allowing them to signal via Clec9A, presenting antigens by both MHC class I and II to antigen-specific T cells. In various embodiments, the Clec9A binding agents further comprise a signaling agent (e.g., an interferon, an interleukin or a tumor necrosis factor), that may be modified to attenuate activity. Additional targeting moieties that bind to tumor-specific or pathogen-specific antigens or receptors can be included. Mice were inoculated subcutaneously with B16 melanoma cells to induce tumors, and were subsequently given perilesional treatments with chimeric Clec9A VHH nanobodies specific for mouse Clec9A fused with a modified human IFN- α 2 (Q124R) mutant, with or without TNF. Combined treatment using the chimeric Clec9A VHH and TNF elicited potent antitumor effects with no tumor recurrence by day 38, was well tolerated, and induced no hematological toxicity. Another experiment evaluated whether a single-chain antibody specific for mouse Clec9A fused to a modified human IFN (Q124R) could induce proliferation of CAR T cells *in vivo*. T-cell

receptor transgenic CD8⁺ T cells which recognize the melanocyte differentiation antigen gp100 on tumor cells were adoptively transferred to mice bearing B16 melanomas. T-cell division was substantially induced, likely mediated via dendritic cell activation. This could be important for CAR T-cell therapy of solid cancers, whose microenvironment often contains immunosuppressive cytokines, regulatory modulators and co-inhibitory receptors. For related work from the USA NIH, see Li *et al.* [14].

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WO/2017/137003

Compound for treating respiratory syncytial virus infection & preparation method & use thereof

Inventors: Altmeyer R, Cao J

Assignee: Shandong University, Shandong (China)

MeSH Keywords: Hedgehog Proteins • Respiratory Syncytial Viruses • Smoothed Receptor • Veratrum Alkaloids

Cyclopamine is a teratogenic steroidal alkaloid that is so named because it can induce cyclopia in the offspring of sheep grazing on a certain plant. Its inhibition of Hedgehog signaling, and its direct antagonism of the transmembrane receptor Smoothed, has made it a template for the development of drugs that are associated with this pathway, mainly cancers [15,16]. Recently, it had been reported that up-regulated Hedgehog pathway activity during hepatitis C infection promotes an environment conducive to viral replication [17], and cyclopamine itself has been found to inhibit RSV replication *in vitro* and *in vivo* [18]. The inventors have designed a series of derivatives that retain this effect, but are no longer teratogenic. They are effective in the low micromolar range.

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WO/2017/140728

TAF1 inhibitors for the therapy of cancer

Inventors: Sdelci S, Kubicek S

Assignee: CEMM – Forschungszentrum für Molekulare Medizin, Wien (Austria)

MeSH Keywords: BRD4 protein, human • neoplasms • transcription factor TFIID

Compounds targeting the two bromodomains of BRD4, such as JQ1 [19], are promising templates for cancer therapeutics. Using a library of 89,355 small molecules, the inventors designed a strategy allowing the unbiased scouting of high diversity chemical space for modulators of a bromodomain 4-dependent inactive chromatin state. One such compound, CeMMEC1 (N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxamide), functioned by binding and potently inhibiting the second bromodomain of the transcription initiation factor TAF1, the largest component of the TAF subunits contained in the TFIID core. TAF1 is part of the Class II transcription preinitiation complex, and serves to recognize the TATA box and correctly place RNA polymerase II for transcription initiation [20]. By investigating the properties of this compound and its derivatives, the inventors found a strong synergy between the targeting of TAF1 and BRD4, which resulted in efficient killing of BRD4-dependent cancer cells. Another hit structure, CeMMEC2 (N-(2-(cyclohex-1-en-1-yl)ethyl)-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-6-amine), proved to be a novel direct BRD4 inhibitor. The patent literature describes compounds related to CeMMEC2 to inhibit BRD4 (WO/2014/191894; WO/2014/076146; US 2014/0135336; WO/2014/191896; US 2014/0349990; WO/2012/174487). For the peer-reviewed companion paper, see Sdelci *et al.* [21].

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WO/2017/143104

Modulation of hypoxia associated with stroke

Inventors: Le Moan N, Krotolica A, Leung P, Cary SPL

Assignee: Omniox, Inc, San Carlos, CA (USA)

MeSH Keywords: Brain Ischemia • Hemeproteins • Nitric Oxide • Reperfusion Injury

NOX enzymes are electron-transporting NADPH oxidases whose primary function is the generation of reactive oxygen species for antimicrobial defense; they are major contributors to oxidative damage in ischemic conditions such as stroke. The H-NOX family is something different: these are highly conserved nitric oxide-sensing hemeproteins, some of which also bind oxygen while some do not [22]. Although, H-NOX proteins are present in mammals (soluble guanylate cyclase is one of them [23]), almost all investigations address the bacterial forms. The affinity of H-NOX proteins for O₂ and NO, their ability to discriminate between these ligands and the O₂ on-off rates can be

altered by introducing one or more amino acid mutations [24]. The inventors attempt to apply these oxygen-carrier properties to prevent or ameliorate hypoxia in ‘penumbra’ brain areas after strokes and transient ischemic attacks, primarily with the objective to prevent reperfusion injury upon recanalization of the affected vessels. In a proximal middle cerebral artery occlusion rat model that generates a consistent infarct in cortical and subcortical structures, a single dose of trimeric H-NOX L144F mutant protein (240 mg/kg) quickly accumulated in the peri-infarct brain parenchyma, while it remained restricted to vessels in the contralateral nonischemic brain hemisphere. Hypoxia and caspase 9 activity were reduced 6-h postocclusion, indicating that trimeric H-NOX L144F, probably in PEGylated form, might be promising for treating stroke. In weighing these findings, it has to be considered that over the past three decades dozens of agents that had shown comparable or better effect in animal models have failed in clinical trials.

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WO/2017/143397

Inhibitors of beta-arrestin: neurokinin-1 receptor interactions for the treatment of pain

Inventors: Bunnett N

Assignee: Monash University, Victoria (Australia)

MeSH Keywords: Clathrins • Dynamin • Neurokinin-1 Receptor Antagonists • Visceral Pain

The substance P/neurokinin 1 receptor mediates pain and inflammation, but antagonists are ineffective treatments for chronic inflammatory pain because the receptor rapidly and completely desensitizes and internalizes at sites of pain transmission upon interaction with β -arrestin [25,26], promoting nuclear ERK1/2 activation and proliferation [27]. Formation of stable receptor/ β -arrestin complexes that persist inside the cell impedes receptor resensitization, and the aberrant formation of these complexes may play a role in diseases such as visceral pain syndromes [28]. The inventors have found that siRNA inhibitors of dynamin and clathrin (two key players in endocytosis) inhibit the interaction between β -arrestin and the intracellular C-terminus of the activated neurokinin 1 receptor. When injected intrathecally in rats and mice, they prevent receptor endocytosis and also suppress capsaicin-evoked hyperalgesia. Both phases of the nocifensive response to intraplantar formalin were also inhibited, and reversed the sustained mechanical hyperalgesia measured 37–40 h after intraplantar complete Freund’s adjuvant. For the peer-reviewed companion paper, see Jensen *et al.* [29].

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Treatment of alkaptonuria & tyrosinemia type 1

Inventors: Santucci A, Bernardini G, Laschi M, Manetti F, Petricci E

Assignee: Universita degli Studi di Siena

MeSH Keywords: 4-hydroxyphenylpyruvate dioxygenase • Alkaptonuria • Nitisinone

Alkaptonuria is caused by genetic deficiency of homogentisate 1,2-dioxygenase, leading to defective tyrosine metabolism, accumulation of homogentisic acid and formation of a polymeric pigment that gives the urine a dark coloration. Eventually, the polymer deposits in connective tissues, especially in cartilage, resulting in early and severe arthritis, heart damage and motor disability [30]. The only therapy with any effect is the 4-HPPD inhibitor nitisinone, originally a herbicide, which had been repurposed for the treatment of hereditary tyrosinemia type 1 (caused by fumarylacetoacetate hydrolase deficiency) [31]. The biochemical pathway rationale for using nitisinone in alkaptonuria has been confirmed in terms of the reduction in plasma homogentisic acid in four clinical trials [32], and the European Medicines Agency has issued an approval; however, the drug is problematic in many ways. The inventors have screened a commercial compound library of nitisinone analogs, and found several 4-HPPD inhibitors with a superior profile – lower IC_{50} and cytotoxic LD_{50} values in primary human fibroblasts, and lower intracellular tyrosine accumulation. Three compounds – the herbicides tembotrione, mesotrione and the most promising candidate 2-(2-chloro-4-nitro-benzoyl)-5,5-dimethyl-cyclohexane-1,3-dione – were investigated further in various *in vitro* assays. The patent document also includes data on nitisinone that had not been published before. For related work from this group see Bernini *et al.* [33].

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WO/2017/151687**Compositions & methods for reducing prion levels***Inventors: Schaetzl HM, Abdulrahman B, Gilch S, Zukiwski A, Proniuk S**Assignee: Arno Therapeutics, Inc, North Flemington, NJ (USA); UTI Limited Partnership, Calgary, Alberta (Canada)**MeSH Keywords: Autophagy • OSU-03012 • Prion Diseases*

Although prion diseases did not nearly reach the epidemic prevalence that had been predicted in the 1990s, every year about 8000 people die of sporadic and genetic forms of such diseases [34]. While individuals with genetic susceptibility to prion infection can be diagnosed long before the onset of clinical disease presentation, attempts to develop drugs have met huge hurdles in terms of efficacy and safety [35]. This invention claims AR-12 (OSU-03012, a derivative of the COX-2 inhibitor celecoxib and PDK-1 inhibitor) which has been previously shown to exhibit antitumor, antiviral, antifungal and antibacterial activity [36]. It is thought that AR-12 is a host-cell-directed agent that induces autophagy of cells harboring viruses or intracellular microbes [37]. However, the antiprion activity of AR-12 has not been previously shown. When persistently prion-infected CAD5 or ScN2a murine neuronal cells or embryonic fibroblasts were exposed to AR-12 at nontoxic conditions (1–5 μ M for 72 h), immunoblots of cell lysates showed that the compound induced clearance of the PrP^{Sc} prion protein as opposed to merely inhibiting its propagation. Additional data demonstrate that the mechanism was autophagy induction, as with bacteria and fungi. For the peer-reviewed companion paper, see Booth *et al.* [38].

Published: 8 September 2017

WO/2017/153982**Method for modulating myelination***Inventors: Peles E, Hyunjeong Y**Assignee: yeda research & development Co. Ltd, Rehovot (Israel)**MeSH Keywords: Demyelinating Diseases • GPR37 receptor, human • Oligodendroglia*

The myelin membrane, produced by Schwann cells in the peripheral nervous system, and by oligodendrocytes in the central nervous system, provides essential trophic support to maintain axonal integrity and survival. This patent application claims methods to enhance the myelinating activity of oligodendrocytes or their progenitors, by ligands binding to GPR37 (also known as PAEL-R, an endothelin B receptor-like nervous system orphan receptor that does not bind endothelins but is associated the E3 ubiquitin ligase parkin [39]), or a polynucleotide encoding GPR37 or one of its upstream activators, effecting up-regulation ERK1/2 [40]. The inventors first demonstrated that knocking out GPR37 in mice results in faster differentiation of oligodendrocytes and precocious hypermyelination of the corpus callosum and thicker myelin sheaths in the spinal cord, and that GPR37-dependent inhibition of oligodendrocyte differentiation is mediated by ERK phosphorylation and nuclear translocation. They proceeded to show that the absence of GPR37 prevents the chronic progression of demyelination in the mouse experimental autoimmune encephalomyelitis model of multiple sclerosis, mitigates T-cell accumulation in the lumbar spinal cords in these animals, and allows extensive remyelination of focal demyelination lesions. The potential implications for the treatment of multiple sclerosis and leukodystrophies are obvious, although it has not been shown that the remyelination is physiological and functional. For the peer-reviewed companion paper, see Yang *et al.* [41]; for related work see Smith *et al.* [42].

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WO/2017/161140**Oxo-M & 4-PPBP induction of tenogenic differentiation of perivascular stem cells***Inventors: Lee CH, Tarafder S, Chen E**Assignee: the trustees of Columbia University in the city of New York, New York, NY (USA)**MeSH Keywords: 4-PPBP • Oxotremorine • Stem Cells • Tendon Injuries*

Healing and regeneration of damaged connective tissue remains a challenge, and this is particularly true for tendons. While CTGF induces perivascular tendon stem and progenitor cells to differentiate into tendon cells, and helps to recruit these multipotent CD146⁺ cells to the site of injury following tendon rupture [43,44], the clinical use of CTGF remains limited. The inventors have now shown that a combination of two small molecule compounds – oxotremorine, a nonselective muscarinic acetylcholine receptor agonist that can elicit FAK signaling in neuronal cells [45], and the sigma receptor agonist 4-phenyl-1-(4-phenylbutyl) piperidine (4-PPBP) which phosphorylates ERK1/2 [46] activate the same signaling pathway that regulates CTGF-mediated differentiation

of perivascular tendon stem and progenitor cells. Their combination can be more effective than even CTGF at increasing expression of tendon markers. In a rat model of fully transected patellar tendons, administration of oxotremorine (1 mM) + 4-PPBP (10 μ M) 1 week after transection resulted in reduced gaps and more aligned collagen structure, as compared with the disorganized scar-like tissue seen in controls. At 2 weeks, treatment with the combination resulted in significantly improved healing with densely aligned fibers, while treatment with the individual agents at the same concentrations produced scar-like healing with disrupted collagen structure. Pharmaceutical compositions incorporating the combination into a graft or patch could be adapted for tendon or ligament therapy, and for soft tissue research applications.

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WO/2017/162284

Homovanillic acid ester for reducing or inhibiting fatty acid absorption in the small intestine

Inventors: Hans J, Lieder B, Geissler K, Hentschel F, Ley JP, Somoza V

Assignee: Symrise AG, Holzminden (Germany)

MeSH Keywords: Anti-Obesity Agents • Phenylacetates

Most pharmacological antiobesity medications approach the problem by attempting to reduce appetite, by promoting satiety, or by interfering with fatty acid metabolism. The lipstatin derivative orlistat (Xenical[®], Roche; Basel, Switzerland), an inhibitor of pancreatic lipases, represented the first drug based on the more fundamental strategy of reducing intestinal fat absorption [47]. Strategies that act further downstream by reducing uptake of fatty acids or glucose by adipocytes remain experimental, although phytochemistry has provided highly interesting leads [48]. The inventors have identified homovanillic acid esters that reportedly have low sensory potential, making them suitable for administration with food, or for inclusion in medicated nutrition. 2-phenylethyl-2-(4-hydroxy-3-methoxy-phenyl)acetate and alkyl-2-(4-hydroxy-3-methoxy-phenyl)acetates (where the alkyl moiety can be branched, which improves efficacy) are among the preferred compounds. 1-methylpentyl-2-(4-hydroxy-3-methoxy-phenyl)acetate reduced uptake of the fluorescent fatty acid analog BODIPY-docecanic acid by Caco-2 cells to 90% at 1 μ M, and to 53% at 100 μ M (controls = 100%).

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