Patent Highlights

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

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WO2011135332

NMN modulators
for the treatment of
neurodegenerative disorders
[Coleman M & Conforti L](#)

Nicotinamide phosphoribosyltransferase (also known as Nampt or visfatin) is the rate-limiting enzyme in the nicotinamide adenine dinucleotide (NAD⁺) salvage pathway. It catalyzes the condensation of nicotinamide with 5-phosphoribosyl-L-pyrophosphate to yield nicotinamide mononucleotide, the precursor to NAD⁺. Nampt inhibitors such as *N*-[4-(1-benzoyl-4-piperidinyl)butyl]-3-(3-pyridinyl)-2E-propenamide (FK866; [1]) and *N*-(6-chlorophenoxyhexyl)-*N*'-cyano-*N*''-4-pyridylguanidine (CHS828; [2]) are developed as cancer therapeutics because they can 'starve' cancer cells (which have high DNA-synthesis rates, and therefore higher nucleotide requirements than less rapidly growing tissue) by depleting NAD⁺ [3]. In this disclosure, an alternate use is presented for these two compounds: axonal protection in Wallerian degeneration (Alzheimer's and Parkinson's disease, multiple sclerosis, diabetic neuropathy and glaucoma). In neurites grown *in vitro* from explanted murine superior cervical ganglia, protection against the effects of cut injury or of the cancer therapeutic vincristine is evident at FK866 concentrations of 100 nM. The science behind these interesting findings is not new: a paper by Mack *et al.* is probably the first published evidence [4]. Two papers from a group at Washington University School of Medicine [5,6] were also published before this application's April 2010 priority date. FK866 is under development by TopoTarget while Leo Pharma is developing a CHS828 prodrug.

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WO2011138449

Antagonists of SEMA3E/
PlexinD1 interaction as
anticancer agents
[Royet A, Mann F, Chauvet S *et al.*](#)

Binding of semaphorin (Sema) proteins to their plexin transmembrane receptors activates plexin's intrinsic GTPase-activating protein; this is an important step in organogenesis, differentiation and cell motility [1]. PlexinD1, the sole and somewhat divergent member of the vertebrate-specific PlexinD subfamily, has only recently been fully characterized [2]. Its primary ligand is semaphorin 3E, and a role for the Sema3E/PlexinD1 signaling pathway in cancer and metastasis has been shown [3], with aberrantly upregulated Sema3E affecting integrin-mediated adhesion to fibronectin and motility inhibition of prostate cancer cells [4]. At the molecular

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level, this involves the association of PlexinD1 with R-Ras and concomitant activation of Arf6, which affects the status of integrins and their intracellular trafficking [5]. Against this background (some of which had not been published at the May 2010 priority date) the inventors have designed a peptide (SD1) comprising the *N*-terminal sema domain of approximately 500 amino acids from PlexinD1, which antagonizes the Sema3E/PlexinD1 interaction and subsequent signaling. Extensive *in vitro* and *in vivo* data obtained with SD1 expressed in HEK293T cells are presented, including viability reduction of the mouse metastatic mammary tumor cell line 4T1 and metastatic behavior in a syngenic Balb/c murine breast cancer model, (from which 4T1 cells were derived). SD1 is a large peptide and would not be suitable as a cell-penetrating drug, but it could serve as an important template.

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WO2011140639

Modulation of scleraxis using a dominant negative scleraxis mutant with a basic DNA binding

Czubryt MP

The sclerotome-related helix-loop-helix transcription factor (scleraxis [Scx], first described in 1995) is involved in pathological fibrosis of collagen-rich tissues such as tendons or cardiac valves [1], and probably the lungs. This appears to take place either directly or in response to increased TGF- β signaling [2], especially in overstrained or infarcted tissues. At the core of the invention claimed here is the discovery that mutants of the murine *Scx* gene express proteins with a deleted basic binding domain (designed ScxABD) lacking this activity, act as Scx antagonists and should therefore be useful for inhibiting collagen synthesis. Data from cultured NIH 3T3 fibroblasts transfected with an *Scx* expression vector from Scx knockout mice, and from Scx-GFP mice subjected to aortic banding surgery demonstrate the molecular mechanism of Scx in these settings. However, it does not seem clear how native Scx could be modulated in systemic or organ sclerosis, apart from administering doses of ScxABD that are high enough to displace Scx from collagen gene promoters. The inventor has published extensively on myocyte biology and cardiac remodeling.

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WO2011145777

Pharmaceutical composition including an HIF-2A inhibitor as an active ingredient for preventing or treating arthritis

Chun J-S & Yang SJ

The hypoxia-inducible factors (HIFs) have a very clear physiological role – they allow the metabolism to respond to low oxygen partial pressures by regulating acute functions such as breathing, blood pressure and glucose metabolism, as well as by initiating longer term responses such as angiogenesis and erythropoiesis. Beyond these classical functions, there are others that take place under normobaric conditions and modulate inflammation; different HIFs might have opposing roles. This disclosure is the companion patent application to [1] where the inventors describe HIF-2 α (one component of the dimeric HIF-2; the other is HIF-1 β) as a key factor in articular cartilage loss during the development of osteoarthritis. This paper had been published back-to-back with a competing one from Tokyo University [2], and both were hailed as a breakthrough in research on chronic joint degeneration. Briefly, the patent application claims that inhibition of HIF-2 α would decrease the expression level of cartilage-degeneration factors and the phosphorylation of MAP kinase. There are few, if any, selective small-molecule inhibitors available for the HIFs, but Kyowa Hakko Kirin Co., Ltd has a recent patent application [3] claiming antisense nucleic acids directed against HIF-2 α .

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WO2011146619

Systems & methods for
identifying drug targets using
biological networks

Wang W & Chang R

In the search for new drug targets inferences must be made from pre-existing sets of data (the so-called ‘priors’) that incompletely describe the properties of this unknown target. Moreover, this novel target will not be isolated but will act as a node in some biological signaling network. This implies that its modulation by ligands could have various effects elsewhere, including complicated feedback regulations. Systems biology-based algorithmic target discovery strategies heavily build on Bayesian-type network approaches to machine learning that are frequently developed in interaction with ligand-discovery technologies. The inventors present a novel method for combining qualitative prior knowledge with training data that is said to address some of the major shortcomings of current approaches, including cross-distribution inequality constraints. This is accomplished by using a soft parameter score instead of hard constraints, and by sampling directly on parameter space. The new algorithm was applied to the (partially) known transcriptional regulatory networks of yeast and human embryonic stem cells, producing results that correlated well with experimental data. The inventors have published similar algorithms for predicting breast cancer cell growth rate based on manipulating (anti)cancerous marker genes and proteins [1]. For other related work see [2–4].

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WO2011150300

Prevention of pancreatic
β-cell degeneration

Reaume AG, Saporito MS &
Ochman AR

At first sight this highly formalized application would appear to be just another addition to the small but constantly expanding set of inventions claiming causative Type 1 diabetes therapies, which would be interesting enough in itself. However, the assignee, Melior Pharmaceuticals is specialized in drug repurposing and the claims are constructed around compounds such as 5-(3-methylphenoxy)-2,4(1H,3H)-pyrimidinedione (compound 102 in the application), which was claimed as 5-m-toloxoyuracil for the treatment of peptic ulcers in Pfizer’s 1978 patent US4080454. This is tolimidone (now MLR-1023), which Pfizer had in clinical trials in the 1980s. Under a June 2008 agreement, Pfizer paid Melior an undisclosed sum and provided access to its data on tolimidone, in exchange for an exclusive option to negotiate a license to the molecule in new indications. Diabetic db/db mice treated daily for 56 days with 30 mg/kg tolimidone showed an attenuated rise of blood glucose levels and a significantly slower decrease of serum insulin levels. In the same setting, but at 100 mg/kg, mice expressed significantly higher levels of pancreatic immunostaining for insulin than vehicle-treated mice, and had better preserved islet cell structure. At 30 mg/kg tolimidone also improved the acute response of diabetic Zucker rats to an oral glucose challenge. This continues Melior’s work from [1] where tolimidone and related compounds are disclosed to be inhibitors of Lyn, a Src family kinase that is activated by diverse pancreatic stimulants [2].

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WO2011153531

Method of treating skeletal
dysplasias using vessel dilator

Vesely DL

The 39-kD cardiac hormone named vessel dilator is expressed from the atrial natriuretic peptide (*ANP*) gene [1], but in contrast to ANP and C-natriuretic peptide (CNP) it is linear, and has a much longer biological half-life of approximately 100 min in man. All three peptides share the same cGMP-mediated MAP kinase-dependent mechanism of action. In addition to being hypotensive and diuretic, ANP and especially CNP are also known to regulate proliferation and differentiation of osteoblasts and chondrocytes [2]. CNP has been suggested as a treatment for achondroplasia [3], a dwarfism syndrome that is caused by a point mutation in

the fibroblast growth factor receptor-3 gene, and is unresponsive to human growth hormone. Using the CRL-11372 human osteoblast cell line the inventor has shown that not only does the vessel dilator peptide stimulate osteoblasts but does so at concentrations that are three orders of magnitude lower than those required for CNP (doses in the fg/kg body weight should be sufficient), with the *in vivo* effects presumed to last >6 h (compared with <30 min for CNP or ANP). A four-times daily infusion schedule, while certainly not comfortable for the patient, would be practical as a treatment. The companion paper to this patent disclosure is [4].

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WO2011151395

Transglutaminase 2 inhibitors for use in the prevention or treatment of rapidly progressing glomerulonephritis

Tharaux P-L & Fligny C

Owing to its ubiquitous expression in the human body and its transamidating, protein disulphide isomerase and nucleotide binding and hydrolyzing activities, transglutaminase 2 (Tg-2) has been called 'a molecular Swiss army knife' [1]. It has already been suggested as a biomarker for renal pathology, especially IgA nephropathy [2], several years ago. The present claims are for a common type of acute kidney failure that occurs as a complication of massive infection or systemic lupus. Among the preferred Tg-2 inhibitors is monodansylcadaverine, which is shown to significantly block proliferation and migration of podocytes in primary cultures and in the murine urinary kidney space. Other inhibitors mentioned include the monoclonal antibody 6B9, antisense nucleotides and several sets of small molecules claimed as Tg-2 inhibitors in earlier patents. The inventors have built the novelty rationale of the present application on their description of a novel immunostimulatory function of Tg-2, and focus their claims on autoimmune renal diseases.

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WO2011155983

Opsin-binding ligands, compositions & methods of use

Garvey DS, Larosa GJ, Greenwood JR *et al.*

The first step in the vertebrate vision process is purely chemical: in the rod cells of the retina, the pigment rhodopsin (which consists of the G-protein-coupled receptor protein opsin, covalently coupled to the retinoid 11-cis-retinal) is split upon exposure to light by photoisomerization of the retinoid component to the all-trans form, which is released from the activated protein. In the dark it is regenerated into 11-cis-retinal and can then reconstitute the chromophore by binding to opsin [1]. This visual cycle can be disturbed by accumulation of toxic reaction products of all-trans retinal (e.g., lipofuscin), or opsin can be misfolded as a consequence of a mutation. Most frequently, this is the P23H point mutation [2], which does not allow correct insertion of opsin into the membrane of the rod cell. The result is photoreceptor degeneration, either in the form of dry macular degeneration or retinitis pigmentosa. In this invention, computational techniques have been applied to predict the hydration of the opsin retinal binding pocket. Extremely hydrophobic environments were identified that, upon binding of a small-molecule ligand, should lower the energy of the ligand/protein complex. A total of 239 potential ligands are described in full chemical detail. For a subset of 81 compounds data are provided that show improved folding of recombinant P23H mutant opsin as measured by rhodopsin-regeneration studies. 2-fluoro-4-(hydroxy(2,6,6-trimethylcyclohex-1-enyl)methyl) benzonitrile and 4-chlorophenyl(3,3-dimethylcyclohex-1-enyl)methanone are among the compounds with the lowest effective concentration (10 mM). Such concentrations might not be achievable in chronic therapy, but might be an option in eye surgery where brief periods of very bright illumination are required that can further

damage vision if opsin is already compromised. See [3] and [4] for earlier applications from Bikam Pharmaceuticals, and [5,6] for documents from its corporate competitors, Acucela and Revision Therapeutics.

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Polypeptide vaccine

Carling-Wright J, Birnie R, Heath AW *et al.*

Human pappalysin-1 (also metzincin metalloproteinase pregnancy-associated plasma protein-A [PAPP-A]) is a multidomain zinc metalloprotease that promotes cell growth by liberating insulin-like growth factors (IGFs) from their binding proteins, which are proteolytically cleaved [1]. Overexpression of pappalysin has been shown to promote tumor growth *in vivo* [2], which is not surprising if the role of IGFs in cancer is considered. PAPP-A knockout mice have an extended lifespan because fatal neoplasias and age-related degenerative changes are delayed or avoided [3]. Instead of attempting to develop selective small-molecule inhibitors (very difficult with metalloproteinases), the inventor team opted for an immunization approach. C57/B16 female mice were subcutaneously injected with a peptide fragment of pappalysin (AQVATSGEQVGGIFSLTQKC) coupled to an anti-CD40 monoclonal antibody acting as an adjuvant, and were then challenged subcutaneously with 5×10^5 B16 melanoma cells transfected with full-length murine pappalysin. A single immunization was able to slow tumor growth. Pappalysin mRNA in resected tumors was also reduced.

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Benzotriazolodiazepine compounds inhibitors of bromodomains

Bailey JM

Chromatin-associated proteins and many nuclear histone acetyltransferases contain small (1–10 amino acid) domains that bind to acetylated lysine residues. These conserved elements, known as bromodomains, alter chromatin-aggregation status and are therefore crucial for the regulation of protein–protein interactions in gene transcription [1]. This makes them interesting drug targets for cancer, obesity, diabetes and inflammation, as well as disorders involving epigenetic modifications [2]. A novel class of compounds has been found that inhibits the binding of the BET family of bromodomains to acetylated lysine residues, which is a focus area of GlaxoSmithKline's research in this field [3]. Four compounds, including (S)-2-(6-(4-chlorophenyl)-1-methyl-8-(4-(pyrrolidin-1-ylmethyl)phenyl)-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-N-ethylacetamide, were tested in an *in vitro* assay of lipopolysaccharide-induced release of the key inflammation mediator, interleukin-6 from whole blood, and were found to have a $\text{pIC}_{50} \geq 5.5$. *In vivo* experiments are outlined, but no results are presented. Research on very closely related selective BET inhibitors can be found in [4] where JQ-1 (a thieno-triazolo-1,4-diazepine) is presented, and in Mitsubishi-Tanabe Pharma's patent [5], which discloses a broader series of thienotriazolodiazepines.

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WO2011161282

Use of rapamycin for the treatment of the cognitive deficits associated with Down's syndrome

Montesinos-Gutiérrez M, Troca-Marín JA & Alves-Sampaio AM

The serine/threonine protein kinase mTOR, long known for its importance in oncology, has only recently been linked to neurological diseases [1]. In this patent application, a companion to [2], the Spanish inventors claim the use of the immunosuppressant macrolides rapamycin (sirolimus), temsirolimus, everolimus or deforolimus (ridaforolimus; AP23573; MK-8669) for Down syndrome (trisomy 21). This is quite in line with the fact that hyperactivation of the mTOR pathway has been described for one of the most common causes of mental retardation, fragile X syndrome [3] and in Alzheimer's disease [4] for which several key genes reside on chromosome 21. Rapamycin also reverses learning deficits in a mouse model of tuberous sclerosis [5]. Confocal microscopy was used by the inventors to show how rapamycin 20 nM, administered for 10 min or 24 h, significantly lowers levels of phosphorylation of mTOR in neurons of Ts1Cje mice (a trisomy 16 model for Down syndrome [6]) leading to levels similar to those in neurons of normal mice under basal conditions. No cognitive experiments with mTOR inhibitors are reported, but this would have required a rat-equivalent model of Ts1Cje mice. With the exception of ridaforolimus, which is in a Phase III clinical study program by Merck & Co. and ARIAD Pharmaceuticals, the drugs that are claimed here are all approved for transplant rejection and/or various cancers. Repurposing studies for Down syndrome might be relatively straightforward if no doses higher than the approved ones are required. However, it seems unlikely that existing neurological deficits could be reversed and immunosuppression would be a problem.

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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.

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