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Patent Highlights

Snapshot of key developments in the patent literature accompanied by explanatory synopses

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WO2013063388

Diatom-based vaccines

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Among the many natural and artificial antigen carriers and expression vectors that have been investigated by vaccine developers, diatoms are certainly unique. With funding from the US National Institute of Food and Agriculture and the Air Force Office of Scientific Research, the inventors have developed the carrier/vector system for protective immunization not only in man and domesticated mammals, but also birds and fish. Marine diatoms from the *Thalassiosiraceae* family are preferred. The antigen is attached to the surface of the diatom, or is recombinantly expressed as a fusion protein with a surface-expressed polypeptide endogenous to the diatom (e.g., frustulins that can also act as a metal chelators [1,2]), driven by a diatom-specific promoter such as the ribosomal protein L41 promoter or the fucoxanthin chlorophyll-binding protein promoter. The claims extend to antigens from virtually all pathogenic bacteria and bovine viruses. The silica in the diatom cell wall acts as an adjuvant; if necessary immunostimulatory adjuvants such Cholera Toxin B subunit, *Escherichia coli* heat-labile toxins, Toll-like receptor agonists or other protein adjuvants can be co-expressed. Evaluation of a *Vibrio cholerae* toxin B vaccine is described, but *in vivo* data are provided only for a combined bacterial/viral bovine respiratory disease vaccine. Diatoms replicate in sea water as well as fresh water, at ambient temperature with sunlight and require minimal nutrients, making inexpensive production feasible in under-developed countries. Diatom vaccines could also be sonicated to form nanoparticles for inhalation, or can be lyophilized for long-term storage.

Published: 2 May 2013

WO2013063496

Biomarkers of response to
NAE inhibitors

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Malignant cell cycle progression and prevention of stress-induced apoptosis of cancer cells require the tightly controlled destruction of specific intracellular proteins by the ubiquitin-proteasome system. This is accomplished by the Skp, Cullin, F-box containing complex multisubunit complex E3 ubiquitin ligase (cullin-RING ligase), which requires modification of the cullin protein with a ubiquitin-like protein called 'neural precursor cell expressed, developmentally down-regulated 8' (NEDD8).

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Millennium Pharmaceuticals is developing the NEDD8-activating enzyme (NAE) inhibitor, ((1*S*,2*S*,4*R*)-4-(4-((1*S*)-2,3-dihydro-1*H*-inden-1-ylamino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2-hydroxycyclopentyl)methyl sulfamate (MLN4924) as a first-in-class drug for cancer [1,2]. The inhibited enzyme can no longer NEDDylate the E3 cullin-RING ligases; this results in the stabilization of proteins regulated by the proteasome, leading to cell death [3]. This patent application claims modifications of the genes expressing neurofibromin 2 (*NF2*), mothers against decapentaplegic homolog 4 (*SMAD4*), lysine-specific demethylase 6A (*KDM6A*), tumor protein p53 (*TP53*), cyclin-dependent kinase inhibitor 2A (*CDKN2A*), cyclin-dependent kinase inhibitor 2A p14 variant (*CDKN2A* [p14]), and retinoblastoma protein 1 (*RBI*) as predictive treatment response biomarkers for MLN4924 and related 1-substituted methyl sulfamates. Measurement of more than one signature characteristic can provide a prognosis if the biologies of the results are consistent with each other. Two large cancer cell line panels were exposed to MLN4924 and cell viability data (IC_{50} , EC_{50} and percentage of control) were calculated. *RBI* and *TP53* mutations were linked to resistance, mutations in all other genes mentioned above indicated responsiveness to MLN4924.

Published: 2 May 2013

WO2013065913

Gene therapy for diabetic neuropathy using an HGF isoform

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HGF does much more than promote liver regeneration; it has been known for more than a decade that its concentration in cerebrospinal fluid is elevated in almost all degenerative diseases of the CNS [1], and it had been shown in 2005 that gene transfer of human HGF can improve diabetic neuropathy in rats [2]. ViroMed's VM202, a nonviral naked plasmid DNA construct expressing two isoforms of human HGF when injected intramuscularly, is the most advanced product candidate. In neuropathy, its directly neuroprotective effects [3] could combine with its angiogenic and antifibrotic action. ViroMed has completed a Phase I/II clinical trial [4] with VM202 in patients with painful diabetic neuropathy that indicated this gene therapy to be safe, well tolerated and sufficient to provide long-term symptomatic relief and improvement in the quality of life (for the peer-reviewed companion paper, see [5]), and is recruiting patients for a Phase II study [6]. The company has conducted a Phase I trial [7] in subjects with critical limb ischemia and is investigating VM202 for ischemic heart disease [8] under a co-development agreement with Cordis Corp., a Johnson & Johnson Company.

Published: 10 May 2013

WO2013066374

Humanin protection of dopaminergic neurons

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Humanin is regarded as the first small peptide of a putative set of mitochondrial retrograde signal peptides, which communicate back to the cell nucleus [1], mediating stress resistance through broad anti-apoptotic actions [2]. It does not only prevent formation of A β (1–42) fibrils *in vitro*, but also disaggregates preformed fibrils, which makes humanin a promising candidate for therapy of Alzheimer's disease [3]. Its heterotrimeric receptor appears to have additional endogenous ligands, such as the calmodulin-like skin protein, with stronger neuroprotective action than humanin itself [4]. Analogs of humanin are also known [5]. The present invention is directed to Parkinson's disease, with [Gly14]humanin (HNG; sequence: MAPRGFSCLLLTGEIDLVPVKRR) as

the preferred embodiment but with other humanin analogs, including those containing D-amino acids, also claimed. The data presented show a decrease in levels of endogenous humanin with age in the rat midbrain and demonstrate that rattin (the rat homolog of humanin) is present in this brain region. It is also expressed in MN9D, a dopaminergic cell line that humanin protects against the effects of serum withdrawal, peroxide and rotenone (a specific inhibitor of mitochondrial complex I). The cAMP-activated protein kinase (AMPK) can be activated in the MN9D cell line in response to HNG. The peptides of the invention could be particularly useful in advanced Parkinson's disease where L-DOPA therapy keeps the remaining dopaminergic neurons functional but also exposes them to additional oxidative stress.

Published: 10 May 2013

WO2013068836

A DDR1 antagonist or an inhibitor of *DDR1* gene expression for use in the prevention or treatment of crescentic glomerulonephritis

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The discoidin domain receptor-1 (DDR1; formerly known as CD 167a) is a transmembrane tyrosine kinase that is activated by specific types of collagens in their native triple-helical structure [1]. DDR1 is expressed in the GI tract, brain, lung, mammary gland, kidney and on human megakaryocytes. Upregulation of DDR1 induced by collagen I may contribute to the invasiveness of solid tumors [2]. It had been shown before that knocking out *Ddr1* in COL4A3^{-/-} Sv129 mice (an animal model for progressive renal fibrosis in Alport syndrome, a hereditary type IV collagen disease) delays and ameliorates the onset of disease [3]. However, the inventors are presumably correct in stating that no study had so far provided the evidence that DDR1 interfered with the progression of crescentic glomerulonephritis, a life-threatening autoimmune disease for which corticosteroids, immunosuppressants and plasma exchange are the only available therapies. When the condition was induced in Sv129 mice by injection of sheep nephrotoxic serum, the knockouts fared much better than the wild-type mice. Biopsies of rapidly progressive glomerulonephritis from three patients with Goodpasture's syndrome and two patients with lupus nephritis demonstrate the relevance in human disease. For the companion paper, see [4].

Published: 16 May 2013

WO2013072265

1-Pyridazinyl-hydroximino-3-phenyl-propanes as GPAR1 agonists

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When stimulated by bile acids, the G-protein-coupled bile acid receptor 1 (GPBAR1, also known in the literature as TGR5, and more rarely as M-BAR or BG37) promotes postprandial co-secretion of the incretins, glucagon-like peptide-1 and peptide YY from intestinal L-cells [1]. Activation of GPBAR1 by small molecules that mimic the effects of bile acids should be beneficial for the treatment of diabetes, obesity and metabolic syndrome [2,3]. In a cAMP generation FRET assay based on CHO cells deficient in dihydrofolate reductase activity and expressing human GPBAR1 cDNA, EC₅₀ values for the compounds of the invention were 0.5–100 nM. No *in vivo* data are presented. The Markush structures disclosed here seem to cover RO5527239, the GPBAR1 agonist described in the most recent Roche paper on the subject [4], although this compound is not among the explicit examples. For 2-phenoxy-nicotinamide GPBAR1 agonists from Roche see [5].

Published: 23 May 2013

WO2013077680

Development of novel macromolecule transduction domain with improved cell permeability & method of using same

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Many techniques have been developed to introduce macromolecules into cells: microinjection, electroporation, calcium or DEAE-dextran, packaging into liposomes that can fuse with the target cell membrane, and cell-penetrating peptides derived from the human immunodeficiency virus Tat protein [1,2]. Nanotechnology has opened yet another frontier of targeted macromolecular drug delivery, but the potential of approaches that use purely biological means are far from exhausted. This invention presents improvements of the South Korean inventors' macromolecule transduction domain (MTD [3]). Because the prototypical MTD is mainly composed of hydrophobic amino acids, it creates a microenvironment that can cause precipitation of its payload; the inventors attempt to improve this by attaching two amino acids (a terminal methionine and a pre-terminal arginine, histidine or lysine). The delivery capacity to HCT116 human colon cancer cells and HEK293 human embryonic kidney exceeded that of a system using the prototypical MTD by 40–90%. Improvements were also seen in the EpiOral skin permeation model.

Published: 30 May 2013

WO2013079487

Pharmaceutical composition for use in the treatment of dysfunction associated with aging

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In 1998 the peptide apelin was identified as the endogenous ligand for an orphan G-protein-coupled receptor, APJ [1]. The various apelin isoforms have sequence similarities with angiotensin II, and are among the most potent endogenous positive inotropic substances yet identified [2]. Apelin is required for the maintenance of insulin sensitivity [3], and because APJ can act as a co-receptor for the human and simian immunodeficiency viruses, apelins can prevent cell entry of these retroviruses [4]. But even that is not all, as the inventors have shown: apelins (and presumably, all direct APJ receptor agonists) promote mitochondrial biogenesis and mitochondrial lipolysis in skeletal muscle cells, thereby counteracting the development of sarcopenia (the age-related loss of muscle mass, strength and function that contributes to frailty). Data on the effects of chronic intraperitoneal apelin injections (0.1 $\mu\text{mol/kg/day}$) on muscle mass of insulin-resistant mice, fatty acid oxidation, long-chain acylcarnitine levels and insulin-stimulated glucose uptake are presented. All beneficial metabolic effects appear to be almost entirely attributable to mitochondrial respiratory capacity. For the peer-reviewed companion paper, see [5].

Published: 6 June 2013

WO2013086200

Composition and method for neuropeptide S receptor (NPSR) antagonists

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Human Neuropeptide S (NPS) is a 20-residue neurotransmitter peptide (SFRNGVGTGMKKTSTFQRAKS) that binds to the former orphan receptor GPR154 [1]. While NPS is expressed predominantly in a small group of brain neurons located near the locus ceruleus and the lateral parabrachial nucleus, co-localized with corticotrophin releasing-factor, its receptor is expressed throughout the CNS and is involved in the balance of arousal and sleep, anxiety, and food intake. The NPS system has shown some promise as a target for non-sedating anxiolytics [2], and for the therapy of otherwise nonresponsive insomnia or narcolepsy. The 3,4,6,7-tetrahydrofuro[3,4-c]pyridines that are presented here (the R060039 series, on which only chemical data are disclosed) are very similar to the NPS receptor blocker SHA-68 from the University of Ferrara [3]. For earlier work from the Research Triangle Park team, see [4].

Published: 13 June 2013

WO2013087090

Treatment of tinnitus through modulation of chloride co-transporter NCC1 in the auditory system

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Chronic tinnitus (the perception of 'phantom' noise without external acoustic stimulation) is a benign condition in itself, but in approximately 1% of the population, it is so pronounced that it seriously impacts the ability to sleep, relax or to concentrate. According to current understanding – which is far from complete – tinnitus is caused by overexcitation of the auditory nerve and signal misprocessing in the dorsal cochlear nucleus [1]. GABAergic agents (baclofen, gabapentin, valproate and benzodiazepines) have been tested for their efficacy to treat tinnitus to no (or very limited) effect. Here the inventors take an indirect route by manipulating chloride homeostasis. Small changes in intracellular chloride concentrations could exert significant leverage on the transmembrane gradient, which would affect how ion currents through GABA-A or glycine receptor channels further modify the neuronal membrane potential. One Na–K–2Cl co-transporter, NKCC1, which transports chloride into astrocytes, oligodendrocytes and Schwann cells, and is known to be involved in the auditory process, is the immediate target. NKCC1 blockade results in an upregulation of the activity and/or expression of another closely related neuronal ion channel, KCC2, which extrudes chloride [2]. Preferred NKCC1 antagonists of the invention include bumetanide thioesters and thioacid salts; however, the experiments on noise-damaged Wistar rats were conducted with unmodified bumetanide delivered intra-aurally from a gel-foam pellet inserted into the round window niche. Note that NKCC1 has also been proposed as a target to treat neonatal seizures [3].

Published: 20 June 2013

WO2013088382

Therapy for subarachnoid hemorrhage & ischemia

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Intracranial hemorrhage, resulting from arterial aneurysms inside the brain (hemorrhagic stroke) or in the narrow space between the brain and the skull (subarachnoid hemorrhage [SAH]), are acute, life-threatening events with a poor prognosis. The course of SAH is characteristically biphasic: many patients survive the initial insult but succumb to the complications of cerebral vasospasm and hydrocephalus. The invention claims compounds that inhibit binding of PSD-95 to an NMDA receptor-2 subunit as having therapeutic value in delayed reactions to SAH. PSD-95 (a scaffold anchor protein of the post-synaptic density complex) mediates the specific coupling between NMDA receptor activation and nitric oxide production, and is involved in excitatory synaptic maturation [1,2]. The agent can be a chimeric peptide having an amino acid sequence XitSX2V, wherein t and S are alternative amino acids; Xi is E, Q, or A; X2 is A, Q, D, N, (N-ethyl)-A, (N-methyl)-Q, (N-methyl)-D, or (N-methyl)-N; and where the peptide carries an N-terminal internalization sequence. Examples include peptides such as KLSSIESDV or KLSSIETDV. Data from a clinical trial [3], which was conducted with a peptide identified as NA-1 provide evidence of significant benefit in subjects harboring an intracranial aneurysm in need of endovascular repair. Surprisingly, outcome was better in patients whose aneurysm had ruptured prior to the procedure causing SAH – this could also be useful in the much more frequent cases where ischemic stroke transforms to a hemorrhagic stroke as a result of thrombolytic reperfusion therapy.

Published: 20 June 2013

WO2013090524

Compositions associated with and methods of managing neutrophil movement using serum amyloid P (SAP)

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Serum amyloid P (SAP; a constitutive component of blood) is a member of the pentraxin family of proteins that is related to the C-reactive protein [1]. It is secreted by the liver, circulates as a stable pentameric complex, and binds to bacterial surface carbohydrates leading to their opsonization and engulfment. During the acute-phase inflammatory response, pentraxins limit neutrophil recruitment to a site of injury by binding to Fc- γ receptors that are expressed on neutrophils [2]. This is essential because activated neutrophils can recruit additional immune system cells, potentially triggering a runaway inflammatory response that is more harmful than the initial insult (e.g., in the acute respiratory distress syndrome). This invention claims SAP as a treatment for such conditions. On the other hand, the number of neutrophils in a body region can be increased by administering a SAP-binding agent to boost the local immune response. Extensive biological data show the effect on spreading, transmigration, hydrogen peroxide production and apoptosis of neutrophils; and on accumulation of Ly6G-positive cells in bleomycin-treated mouse lungs. Although SAP affects adhesion, it does not affect the granulocyte adhesion molecules CD11b, CD62L, CD18 or CD44. SAP also has no effect on the production of hydrogen peroxide by resting or stimulated granulocytes. For the peer-reviewed companion paper, see [3].

Published: 20 June 2013

WO2013091260

Carious tooth vaccine & preparation method

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Proposals for developing vaccines to prevent dental caries have been made and investigated for at least 45 years [1]. In the 1970s a vaccine against *Streptococcus mutans* reduced bacterial load in the oral flora and smooth-surface caries scores in monkeys, although salivary IgA antibody induction was modest [2]. The induced serum IgG antibodies cross-reacted with antigens on mammalian heart and skeletal muscle tissue, raising safety concerns, and were not equally protective against the main eight *S. mutans* serotypes. Hundreds of papers and several decades later, there is still no caries vaccine available. Meanwhile, Chinese researchers have taken the lead in the ongoing efforts, and have developed a mucosal DNA vaccine that expresses an antigen containing the A-P fragment of the *S. mutans* surface protein PAc as a fusion protein with *E. coli*-derived flagellin. When administered to rats intranasally in triple doses of a few micrograms each, the KF-rPAc vaccine reduced caries scores by two-thirds. For the peer-reviewed companion paper, see [3].

Published: 27 June 2013

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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