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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Aptamers that inhibit interaction between antibody & second extracellular loop of human β -1 adrenergic receptor

[Schimke I, Haberland A, Kage A et al.](#)

Autoantibodies directed against certain receptors can contribute to diseases by activating or blocking these receptors. In dilated cardiomyopathy, especially idiopathic forms or those caused by Chagas disease, this factor can be significant because cardiac β 1-adrenoceptors are permanently stimulated by autoantibodies in these conditions [1]. The multicentric Etiology, Titre-Course and Survival study is currently investigating these factors [2]. Instead of attempting removal of such antibodies by immunoadsorption, which can improve the disease course [3] but is complicated and costly, the inventors propose to neutralize them with nucleic acid aptamers that capture antibodies directed to the second (but not the first) extracellular loop of the β 1-receptor protein. Preferably, the aptamer has an IC_{50} value of <100 nM and neutralizes antibodies directed against a specific epitope on the second loop, defined by the amino acid sequence ESNEARRCYNDPK. In the supporting experiments with cultured rat cardiomyocytes and the agonistic goat anti-ADBR1 antibody, the delta beating rate of the cells after an incubation of approximately 1 h was compared with the basal beating frequency. The companion peer-reviewed paper to this patent application is [4].

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WO2012001099,
WO2012001100 &
WO2012001101

Enterovirus vaccines for preventing or treating Type I diabetes

[Hyöty H, Knip M, Laitinen O et al.](#)

Autoimmune (Type I) diabetes is robustly associated with enterovirus infection, although the exact nature of the link remains unclear [1]. Enteroviruses infect cultured human pancreatic β -cells [2] and cause diabetes in animal models; a polymorphism in the *IFIH1* gene, which encodes interferon-induced helicase 1 (domains of which can bind enteroviral nucleic acids), influences predisposition to Type I diabetes [3]. Certain other viral infections, when encountered at the right time and infectious dose, can prevent its development [4]. The '099 document reports associations between coxsackie-A virus serotypes 4, 5 and 6 and echovirus E18. Stool analysis (4184 samples from 359 children; 102 cases and 257 controls) shows that the risk is greatest if the infection is suffered in very young age and

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especially if the child has the moderate risk *HLA* genotype. The '100 and '101 documents focus on coxsackie-B viruses, where those infected with serotype 1 had an increased risk of contracting Type I diabetes, while strains 3 and 6 reduced the risk. In total, the most marked risk or protection was associated with the coxsackie B group. All three documents present extensive supporting data and claim vaccines. Note that [5] (by Vactech Oy, Sanofi Pasteur's co-assignee in these applications) claims an oral inactivated poliovirus, as well as nonpolio enteroviruses, including those claimed in the pertinent applications, against Type I diabetes [5].

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Photosensitive cardiac rhythm modulation systems

Parker KK & Brigham MD

Implantable pacemakers and defibrillators electrically stimulate and synchronize the contractions of myocardial cells, either to maintain a cardiac sinus rhythm or to induce an 'emergency reset' in the heart of persons suffering from arrhythmia and/or occasional fibrillation. Such devices are unresponsive to autonomic heart rate modulation, are susceptible to strong external magnetic fields, and require surgery to replace their power source. Biological means, in the form of genetically engineered tissues or cellular implants, could avoid all these drawbacks but would introduce a new one because they cannot be modulated from outside the patient's body. As a remedy, the inventors claim an engineered myocardial tissue that is capable of depolarizing, generating an action potential, and beating (or in the case of a defibrillator application, is capable of hyperpolarizing, suppressing generation of an action potential, and suppressing beating) in response to photostimulation. Photoresponsiveness is achieved by expressing a light-gated ion channel and/or a light-driven ion pump, preferably a rhodopsin. In another embodiment, cardiac myocytes are co-cultured with retina-derived cells from invertebrates and lower vertebrates. In such tissue constructs light of different wavelengths, transmitted through fiber-coupled diode laser modules, can selectively stimulate or silence myocardial action potentials. See [1,2] for very similar work carried out by two different teams, building on earlier general concepts [3].

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Methods & compositions for treatment of lipogenic virus-related conditions

Atkinson RL, Lee ZP-L & He J

This patent application concerns adenovirus-36 (Ad-36) [1], a subtype that did not attract much attention until more than 20 years after its first description, when it was claimed to promote obesity, probably by stimulating preadipocyte differentiation [2] and by a direct effect of the viral *E4orf1* gene on lipogenic enzymes [3]. Many serological, metabolic and epidemiological investigations have been published since then and although the majority of the papers support the association, others did not corroborate it [4,5]. This document wraps up newer insights on potential mechanisms for Ad-36 (and for subtypes 2 and 37, also claimed to be lipogenic) and proposes treatments with antivirals such as didox or tridox (10–100 μ M), or luteolin, which seems to act synergistically with the antidiabetic metformin. There are no data to show that antiviral treatment reduces adiposity in Ad-36-infected animals, which would be the true test. In a separate line the inventors also found that Ad-36 infection enhances the malignant potential of human breast (MCF-7) and lung epithelial (A549) cancer cell lines (also through *E4orf1*), and that Ad-36 seropositivity is more than twice as high in women with breast cancer than in controls. The abovementioned antivirals reduced the cytopathic effect of Ad-36 in A549 cells, and reduced expression of FAS

protein (a cancer biomarker) the MCF-7 cells. There is clearly some potential here, but more research is needed.

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The role of PI3K p110 δ signaling in retroviral infection & replication

Katsikis PD, Boesteanu AC & Turner M

The p110 δ isoform of PI3K is essential for the development and function of B cells [1], memory T cells [2], and for natural killer-cell maturation [3]. This patent application extends the role of PI3K-p110 δ to HIV infection, claiming that preventing its activation or signaling by any type of inhibitor would prevent infection or reduce virus loads. A wide variety of known small-molecule PI3K inhibitors are named (specifically, the highly selective IC87114 [4], created by ICOS Corp. and now in Phase II studies for Hodgkin's lymphoma by Gilead Sciences under compound code GS-1101); siRNAs and antibodies are also included. The *in vivo* data that are presented concern exclusively mice infected with influenza virus A, which is not a retrovirus (although it is a single-stranded negative-sense RNA virus). However, there are also data showing that primary human peripheral blood mononuclear cells infected with HIV-1 *in vitro* reduced their expression of p24 (the HIV core protein) by approximately 80% when treated with IC87114 (10 μ M). So far the peer-reviewed literature include no explicit reports concerning a potential utility of PI3K-p110 δ inhibitors to any viral infection. In spite of the good murine data, the application does not claim such inhibitors for influenza.

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Medicaments based on dinuclear arene ruthenium complexes comprising bridging thiolato, selenolato or alkoxo ligands

Süss-Fink G, Therrien B, Gras M *et al.*

Ruthenium complexes, once considered exotic examples of organometal chemistry and later used as catalysts and photosensitizers, are attracting considerable interest as anticancer agents [1]. See, for example, [2] and [3] for Ru(diene)carboxylate salts and *trans*-[tetrachlorobis(1H-indazole)ruthenate(III)] complexes, respectively. Thus far, this has not translated into advanced development: clinicaltrials.gov lists only one study conducted with a ruthenium complex (Niiki Pharma's NKP-1339). The present application claims cationic bitetraedric complexes based on diruthenium sulfide or selenate, where each of the three sulfur or selenium atoms carries a benzyl substituent, sandwiched between the π electron systems of two substituted benzyl moieties. The idea behind using such substituted arene rings is that they would not only coordinatively bind to DNA, but would also undergo hydrophobic interactions, triggering kinds of damage in the rapidly replicated tumor cells that differ from those induced by cisplatin [4]. The compounds were tested on the human ovarian cancer cell line A2780 and its cisplatin-resistant derivative A2780cisR. The most active entity was found to be $[(p\text{-}^i\text{PrC}_6\text{H}_4\text{Me})_2\text{Ru}_2(\text{S-}p\text{-C}_6\text{H}_4\text{Me})_3]^+$. Its cytotoxic mechanism is not DNA intercalation, but rather the oxidation of cysteine and glutathione-free sulfhydryl bonds. Coordination of the ruthenium complexes with cysteine and glutathione was not observed, indicating that their action is purely catalytic. For the companion peer-reviewed paper see [5].

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Vaccines against pregnancy-associated malaria

Tuikue Ndam N, DeLoron P, Gnitéhou SUAC *et al.*

Plasmodium falciparum infection in pregnancy can compromise placental development and function, which causes fetal malnutrition and growth restriction [1]. The standard sulfadoxine/pyrimethamine intermittent drug regimen to prevent malaria is teratogenic and must not be employed before the 20th week of pregnancy. While mefloquin prophylaxis can be initiated in the second trimester of pregnancy, use of any antimalarial chemoprevention in women with childbearing potential remains precarious and, hence, of questionable efficacy [2]. The recently thriving field of malaria vaccine development is, therefore, paying particular attention to the modulation of the immune response to *P. falciparum* during pregnancy [3]. The inventors have created a recombinant vaccine based on the DBL1x, Id1 and DBL2x domains of the N-terminal portion of the VAR2CSA antigen from *P. falciparum* strain, FCR3. This is the minimal fragment that will elicit high-affinity antibodies to block the binding of VAR2CSA-expressing infected erythrocytes to chondroitin sulfate A in the placenta, which is the key event in 'placental malaria'. Using the minimal sufficient antigenic epitope seems crucial because antibodies to a full-length VAR2CSA immunogen do not cross-inhibit different placental-type parasite isolates [4]. Extensive immunological data from mice and rabbits are presented and relate to affinity-purified immunoglobulin G from a pool of plasma from ten multigravid malaria-exposed women who had naturally acquired immunity. DNA vaccines, which might ultimately be the best approach in this case, are also claimed. For the companion peer-reviewed paper see [5].

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Carbon nanohorns comprising dendrimers on their surface as non-viral vectors for gene therapy

Ceña Callejo V, Sánchez Verdú M, Merino Guijarro S *et al.*

Carbon nanohorns are single-walled graphene tubules of 30–50 nm in length and 3–5 nm in diameter, with conical closed tips where the carbon rings are pentagonal; they form aggregates where these tips stand out like horns. Since they were first reported in 1999, nanohorns, which can be filled with fluids and are amenable to many chemical modifications, have drawn attention as potential high-capacity drug carriers [1]. However, this patent document appears to document their first application in nucleic-acid delivery. The inventors have 'grown' poly(amidoamine) dendrimers – tree-like nanostructures with a background in experimental gene-therapy vector delivery [2] – from the surface of nanohorns. This combines the most-desired properties of both elements; the surface dendrimers can form complexes with a siRNA payload, while the nanohorn carrier allows the entire aggregates to be internalized by the target cells. Flow cytometry with nanohorn concentrations in the 1–8-μM range in combination with 100-nM fluorescence-labeled siRNA showed no significant cytotoxicity; this achieved transfection rates of up to 40% and partial silencing of cofilin expression in cultured cortical neurons. The therapeutic applications would be limited only by the types of cells that can be transfected.

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Preparation for treatment of spinal cord injury

Medea M, Kishino A, Sano A *et al.*

After spinal cord injury, chemoattractant and chemorepulsive guidance factors act against each other in the attempts to regenerate the axon connections [1]. Among the major limiting agents is semaphorin 3A (Sema3A), which binds with high affinity to neuropilin-1 on nerve growth cone tips [2]. In mice deficient in the Sema3 key receptors, PlexinA3 and PlexinA4, complete spinal cord transections do not regenerate more quickly than in wild-type controls [3]. The obvious conclusion

would be that compounds that inhibit this interaction would be useless in terms of promoting functional regeneration. Not so, says this document from Dainippon Sumitomo Pharma and Keio university: controlled release formulations of vinaxanthone (SPF-3059-5; Ro 09-1450; 5,7-diacetyl-6-(5-carboxy-6,7-dihydroxy-4-oxo-4H-chromen-3-yl)-2,3-dihydroxy-9-oxo-9H-xanthene-1-carboxylic acid), based on drug-impregnated silicon sheets in which the injured spinal cord is wrapped, can restore the motor functions in female Sprague–Dawley rats with thoracic spinal cord cuts. Kinematic analysis showed remarkable recovery in terms of average step length and step cycles after 1–3 months. This was matched by immunostaining data showing an increased density of neurons that were positive for GAP-43 (a nerve regeneration marker) and that had also regenerated their myelin sheaths. Vinaxanthone has been reported as an antibacterial enoyl-ACP reductase inhibitor [4] and as a phospholipase C inhibitor [5], but it is also a simple derivative of xanthofulvin, which is a strong Sema3A inhibitor [6].

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Treatment of penetrative injury to the brain

Tymanski M, Lu P & Garman JD

While patenting frequently addresses traumatic brain injury, these applications are almost always for closed head trauma – patents that specifically claim compounds to treat gunshot wounds or other skull-penetrating injuries are very rare. The present invention makes use of the postsynaptic density-95 protein (formerly known as synapse-associated protein 90), a member of a family of membrane-associated guanylate kinase proteins that regulate the synaptic localization of ionotropic glutamate receptors such as the NMDA receptor and couple it to other neuroexcitatory pathways by binding to one or more of its subunits [1]. While inhibitors of this interaction have been proposed for percussion injuries and stroke, the inventors have shown that certain peptides are also effective in ameliorating secondary neurological damage in a rat model of penetrative ballistic injury to the brain. The agents can be coupled to an internalization peptide, particularly to the human immunodeficiency virus tat peptide, to give chimeric agents such as the preferred Tat-NR2B9c (YGRKKRRQRRRLSSIESDV; also designated NA1 and claimed as an analgesic [2]). When administered (0.5 mg/kg intravenously) to rats 30 min after a simulated ballistic wound to the right frontal brain, neurological deficits were significantly reduced at 3 and 7 days post-injury, especially in terms of motor functions as seen in beam balance and rotarod paradigms. Memory retention as determined in the Morris water maze was improved twofold over controls. The compounds are also claimed to be of use in preventive high-risk settings, such as for administration to soldiers immediately prior to combat or to law enforcement personnel preparing to confront armed criminals. Obviously, this would require the current need for intravenous administration to be overcome, perhaps by small molecules such as those known from [3].

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TAM receptors & TAM receptor ligands in detection & modulation of neuropathological disease

Kilpatrick T, Perreau VM, Field J *et al.*

The tumor-associated macrophage (TAM) family of receptor tyrosine kinases has three known members that are designated Axl, Mer and Tyro3. Their common natural ligands are protein S and the Gas6 protein, which is secreted by macrophages under the influence of tumor cells. Besides offering a potential new approach to cancer, this intriguing kinase family has a role in autoimmune diseases because its members are activated by Toll-like receptor and type I interferon signaling during the innate immune response [1] and in the initiation of phagocytosis. These are central mechanisms in the demyelination events of multiple sclerosis (MS), and given that both protein S and Gas6 are expressed in the human central nervous system MS is increasingly seen as another potential area where TAM ligands could be useful, as two of the present inventors had pointed out earlier [2]. The present disclosure teaches that although TAM receptors and their ligands are upregulated during inflammatory demyelination events in MS (shown in 11 patients presenting with their first demyelinating event), promoting TAM-mediated signaling through agonistic ligands should be able to ameliorate the symptoms. In Gas6-knockout mice subjected to the demyelination inducer cuprizone (0.2% for 3 weeks), initial remyelination after discontinuation of cuprizone was comparable to that observed in wild-type mice, but continued recovery appeared compromised. *In vitro*, recombinant human Gas6 (100 ng/ml) promoted both the survival of oligodendrocytes ($39.3 \pm 3.1\%$ vs $11.8 \pm 2.4\%$; $p = 0.00005$) and reduced markers of activation in purified cultures of microglia (TNF α expression reduced 48%; $p < 0.05$). The claims include agonistic antibodies and cell-based diagnostics. Since the Australian patent application underlying this international disclosure was filed, the inventors have copublished an association study to identify single nucleotide polymorphisms in TAM or TAM ligand genes that are associated with MS [3].

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

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