Patent highlights April–May 2015

A snapshot of noteworthy recent developments in the patent literature of relevance to pharmaceutical and medical research and development.

WO/2015/042685

Inhibitors of polynucleotide repeat-associated RNA foci and uses thereof Chartrand P & Querido E

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Keywords: biological availability

- cytochrome P-450 CYP3A inhibitors
- HIV protease inhibitors • ritonavir

Polynucleotide expansions in specific genes can result in toxic excitatory proteins (as in Huntington's disease), but the resultant mRNA can also be directly toxic. Myotonic dystrophy type 1 (DM1; the most common autosomal dominant muscular dystrophy) is such an RNA-mediated disease where aggregates formed by CUG-expanded mRNA (coding for the DMPK kinase) and regulatory RNA-binding proteins form distinct, primarily nuclear foci [1,2]. Disrupting these foci and promoting the nuclear export of CUG-rich transcripts should reduce the mis-splicing that occurs as a result of the sequestration of essential regulatory proteins that interact with CUG nucleotides on normal mRNAs. The inventors have demonstrated that their compounds reduce the formation of mutant DMPK mRNA foci in DM1 patient myoblasts, have the capacity to correct the stabilization of the CUGBP1 alternative splicing factor in DM1 myoblasts, and correct the mis-splicing of specific mRNAs in DM1 cells, without acting as general regulators of splicing. Primary DM1 myoblasts were treated for 7 days with a 20 μ M concentration of candidate drugs. Total RNA was extracted, and used in real-time polymerase chain reactions to quantify the splicing of the endogenous mRNA. A parasulfonamide and a benzyl methylthio-

phene amide were identified as promising lead structures, and structure-activity relationships were established based on 49 derivatives. The inventors, who have published a single peer review paper on nuclear CUG-repeat RNA aggregates [3], do not mention specific molecular targets for their compounds (For progress on potential antisense oligonucleotide therapies for DM1 see [4]).

Published 2 April 2015

WO/2015/044395

Organometallic N-2-cyano-1-hydroxypropan-2-yl for use as anthelmintics

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Keywords: anthelmintics • *Haemonchus* • organometallic compounds
• *Trichostrongylus*

Worldwide, one in six humans is a chronic carrier of at least one parasitic helminth; the resultant global socioeconomic burden is greater than that of cancer and diabetes. Some helminths even have carcinogenic excretions. This invention claims organometal derivatives of monepantel (Novartis Animal Health's Zolvix®) [5] which can be full or half metal sandwich complexes with iron, cobalt, manganese, or ruthenium; (2-cyano-1-[5-cyano-2-(trifluoromethyl)phenoxy]propan-2-yl)ferroceneamide is one particular compound which had about 70% effectivity against *Haemonchus contortus* (the barber's pole worm of sheep and goats) and *Trichostrongylus colubriformis* (a common gastrointestinal nematode in humans

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and herbivores) *in vitro* at 10 mg/ml. Its IC₅₀ value for cytotoxicity against HeLa human cervical cancer cells was 93 µM, which the inventors interpret as indicative of anticancer potential. No comparative results for monepantel, which has also been reported as having anticancer activity [6], are presented. It would also be extremely interesting to see if the new compounds are mechanistically different from monepantel, which appears to act through acetylcholine receptors of the DEG-3 subfamily which do not occur in mammals [7]. Ferrocenyl derivatives of the popular antihelminthic, praziquantel have been reported by the same team in 2012 [8].

Published 2 April 2015

WO/2015/048567

Spirocyclic EBI2 modulators

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Keywords: autoimmune diseases • cardiovascular diseases • human GPR183 protein • neoplasms

The Epstein–Barr virus-induced G-protein coupled receptor 2 (EBI2; previously known as orphan receptor GPR 183) has recently emerged as a potential therapeutic target in autoimmune conditions, cancer and cardiovascular disease. Its expression on B cells is highly induced upon activation. Its endogenous ligands are oxysterols such as 7α,25-dihydroxycholesterol [9], previously known to bind nuclear receptors. B cells with *EBI2* knocked out exhibit defective migration, resulting in strongly impaired T-cell-dependent antibody responses. Selective EBI2 antagonists, such as ML401 which has a central piperazine core, have been reported [10], and also a spirocyclic inverse agonist (GSK682753 from GlaxoSmithKline, Brentford, UK) [11] on which the compounds of this invention have been modeled, probably aiming at increasing the metabolic stability beyond that of GSK682753. Biological data are all but absent, although a cell-based luminescent assay is stated to have shown IC₅₀ values ‘below 100 nM’ for many of the compounds that were chemically identified in detail. This allows no effective comparison, considering that an IC₅₀ of 1 nM for EBI2 antagonism, and an IC₅₀ of 6 nM in a chemotaxis assay, had been reported for ML401. However, the EBI2 target seems to attract more and more interest; Novartis (Basel, Switzerland) and Johnson & Johnson (NJ, USA) are also known to pursue programs.

Published 2 April 2015

WO/2015/051166

Use of COX-3 binding molecules for modulating autophagy

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Keywords: autophagy • cyclooxygenase-3 • innate immunity • phagosomes

Because acetaminophen is a weak inhibitor *in vitro* of both cyclooxygenase-1 and 2, the existence of another putative isoform, COX-3, had been postulated in 2000 [12]. This isozyme indeed exists; it is translated from a splice variant of the COX-1 messenger RNA that retains intron 1, and therefore the protein is also known as COX-1b [13]. Creating novel analgesic and antipyretic drugs was not on the inventors’ agenda; rather, they focused on the fact that nucleobindin, an autoimmunity- and apoptosis-associated protein known to interact with cyclooxygenases, which participate in the retention of nucleobindin within the lumen of the endoplasmic reticulum [14], also forms complexes with COX-3. Catalytically active glycosylated cyclooxygenases are translated from rat COX-3 mRNA through translational recoding mechanisms of ribosomal frameshifting and translation initiation at alternative start codons, which produces other rat COX-3 proteins (identified as rc57, rc50 and rc44 based on their electrophoretic mobility) that are cytosolic, are unglycosylated, do not catalyze prostaglandin synthesis, and function in innate immunity at the cellular (rather than tissue or organ) level. Moreover, they are members of the critical ATG9 chaperone complex that governs formation of autophagosomes [15]. Also, rc57, rc50 and rc44 act synergistically with nucleobindin to form mega-autophagosomes, which are implicated in virus replication. Virtually any conceivable type of agent that specifically inhibits the expression level and/or enzymatic activity of COX-3 protein or its isoforms, or interferes with COX-3 protein interaction with nucleobindin, is claimed; but the essential claims are the opposite ones – those for induction of autophagy to treat cancers and viral infections. While more work is certainly needed to further elucidate the role of these COX-3 derivatives in innate immunity, the potential seems exciting.

Published 9 April 2015

WO/2015/051340

Methods for treating breast and other cancers by targeting argininosuccinate synthetase 1 – deficiency

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Keywords: arginine deiminase • argininosuccinate synthase • breast neoplasms

Multiple types of cancer have been reported to be deficient in argininosuccinate synthetase (ASS), a metabolic defect that renders them unable to internally synthesize arginine – although their demand for this amino acid is actually higher than that of normal cells. An early cross-sectional study showed ASS expression varying greatly with the tumor type and tissue of origin [16]. This cancer-specific auxotrophy could be exploited by depleting external supplies of arginine. The inventors have found that abundance of ASS1 was either low or absent in more than 60% of 149 random breast cancer samples, potentially making this frequent carcinoma a very good candidate for arginine starvation therapy; especially those types that do not overexpress the HER2 antigen or the estrogen receptor. The present document has been filed to obtain intellectual property for Polaris Group's lead therapeutic candidate, ADI-PEG 20 (pegylated arginine deiminase) in this particular application; many data obtained in MDA-MB-231 cells, in pathology samples, and from analysis of clinical response data are presented. ADI-PEG 20 has already received orphan drug designation for the treatment of malignant pleural mesothelioma in the USA and in the EU; in a recently published study ASS was undetectable in more than 50% of high-grade pulmonary neuroendocrine carcinomas [17]. Primary acute myeloid leukemia cells also tend to be ASS1-deficient, and their cytotoxic response to cytarabine is enhanced by concomitant ADI-PEG 20 treatment [18].

Published 9 April 2015

WO/2015/051422

New pradimicin derivatives for the treatment of diseases caused by kinetoplastids

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Keywords: anthracyclines • *Leishmania* • pradimicin S • *Trypanosoma*

The pradimicin family of antibiotics is unique among natural products in their ability to bind carbohydrates in a calcium-dependent manner; these benzonaphthacenequinones have created particular interest as potential entry inhibitors against viruses with highly glycosylated envelopes [19]. However, the surface of bloodstream *Trypanosoma brucei* (the causative agent of sleeping sickness) is also covered by densely packed variant surface glycoproteins that

protect the cell from effectors of the host immune system, physically and by mediating immune evasion [20]. A comparable situation exists in *Leishmania* spp., another kinetoplastid parasite [21]. The concept of targeting surface glycoproteins of these two important human pathogens is not new [22], but apparently nobody has thought of pradimicins in this context. They are active *in vitro* in the low micromolar range against *T. brucei*. Administration of pradimicin-S to infected BALB/c mice starting at the 3rd day postinfection, when parasitemia reached 10 million cells/ml, resulted in a dramatic decrease of parasitemia after the first dose of 50 mg/kg or after the third dose of 25 mg/kg; only the higher dose prevented relapse and secured survival of mice for at least 90 days. Pradimicin-S and pradimicin-A were active at low micromolar concentrations against amastigotes and promastigotes of *Leishmania donovani*. No toxicity was observed in macrophages ($EC_{50} > 100 \mu\text{M}$).

Published 16 April 2015

WO/2015/055240

Soluble Fc gamma receptor for treatment of autoimmune bullous diseases

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Keywords: autoantibodies • IgG • receptors • vesiculobullous skin diseases

In autoimmune bullous diseases such as bullous pemphigoid and epidermolysis bullosa acquisita, the host immune system disrupts intercellular adhesion molecules or components of the basement membrane in the skin and mucosal surfaces, typically leading to blister formation. Autoreactive IgG antibodies that bind to structural dermal elements including desmogleins, integrins, and type VII collagens subsequently trigger infiltration of inflammatory cells in the skin, complement activation, and release of proteases at the dermal–epidermal junction. This is mediated through an interaction of their Fc portions with Fc gamma receptors [23]. Immunosuppressive and anti-inflammatory steroids, and intravenous immunoglobulin (IVIG), which modulates the equilibrium between activating and inhibitory Fc gamma receptors [24] are used; all are nonspecific therapies. The inventors improve on the IVIG approach by showing that soluble Fc gamma receptor has a similar beneficial effect, apparently by competing with membrane-bound Fc receptors for the pathogenic autoantibodies. While the utility of soluble Fc gamma RII receptor (sCD32) for treating autoimmune diseases where immune complexes occur in the blood is known, it has not been reported in skin. The

murine animal model used to generate the data has been published [25]. sCD32 treatment led to a 20% reduction in circulating antigen-specific autoantibodies compared with controls ($p = 0.048$; t -test), while total IgG levels were not significantly different.

Published 23 April 2015

WO/2015/061294

Use of STING agonists to treat chronic hepatitis B infections

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Keywords: hepatitis B virus • innate immunity • signal transducing adaptor proteins

Recently a cytosolic DNA signaling pathway that is dependent on the endoplasmic reticulum adaptor and cyclic dinucleotide sensor protein, STING (STimulator of INterferon Genes) has been identified as an important innate immune sensing mechanism [26]. STING is an adaptor of multiple cytoplasmic DNA receptors and a pattern recognition receptor recognizing bacterial second messengers, cyclic diadenosine monophosphate (c-di-AMP) and cyclic diguanosine monophosphate. STING agonists can stimulate an innate cytokine response in macrophages, dendritic cells, liver nonparenchymal cells, or any combination thereof. Although much of the attention generated by the STING pathway focuses on cancer [27], its involvement in innate antiviral responses was identified early [27,28]. The STING agonists claimed here for chronic hepatitis B virus (HBV) infection are flavonoids: 10-(carboxymethyl)-9(10H)acridone (CMA); 5,6-dimethylxanthenone-4-acetic acid (DMXAA); methoxyvone; 4'-methoxyflavone and 6,4'-dimethoxyflavone; 3',6'-dihydroxyflavone and 7,2'-dihydroxyflavone; daidzein; formononetin, retusin 7-methyl ether and xanthone. A cell-based assay mimicking the environment of the HBV-infected liver was developed: AML12HBV10 immortalized mouse hepatocytes harboring HBV (which do not express detectable level of STING) were exposed to conditioned media from RAW 264.7 mouse macrophages that had been treated with the test compounds. CMA and DMXAA were the most active compounds in this assay. The crystal structure of the human STING protein, which provides structural delimiters for ligands, has been claimed in WO/2015/017652 (for a discussion, see [29]). A companion paper [30] has been published, followed by more related work by some of the inventors [31].

Published 30 April 2015

WO/2015/063177

Stable pantetheine derivatives for treatment of pantothenate kinase-associated neurodegeneration (PKAN) and method for the synthesis of such compounds

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Keywords: inborn genetic diseases • pantothenate kinase-associated neurodegeneration • prodrugs

Pantothenate kinase-associated neurodegeneration (PKAN), also known as Hallervorden-Spatz syndrome, is a rare disease caused by mutations in the *PANK2* gene coding for pantothenate kinase 2, the mitochondrial enzyme which phosphorylates pantothenate to 4'-phosphopantothenate in the *de novo* biosynthesis pathway of coenzyme A [32]. Although pantethine (two molecules of pantothenic acid linked by cysteamine) rescues the *Drosophila* [33] and mouse [34] models of PKAN, it is only marginally suitable for human therapy because serum pantetheinases rapidly break it down. As the inventors have found, (S)-acyl-4'-phosphopantetheines (compounds that were described as intermediates in the synthesis of coenzyme A derivatives in WO2012/17400) should serve the purpose much better; and their thioester or bis(pivaloyloxymethyl) ester prodrugs (where the negatively charged phosphate is masked) should ensure better cell membrane penetration. They have superior rescue potential in the *Drosophila* PKAN cell model and in *Drosophila* S2 cells treated with the chemical inhibitor hopanthenate, and they are also less cytotoxic towards human HEK293 cells compared with pantethine.

Published 7 May 2015

WO/2015/069669

Nanostructure conjugates for modulation of location-specific subtypes of receptors and ion channels

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Keywords: adamantane • glutamic acid • nanoparticles • nerve degeneration • N-methyl-D-aspartate receptors • synapses

Glutamate, one of the most ubiquitous neurotransmitters, binds to neuronal receptors that are present both inside and outside the synapses. Their location is not fixed; lateral receptor mobility in and out of the synapses occurs in response to neuronal activity. In the case of N-methyl-D-aspartate (NMDA) receptors, physiological synaptic activity is supported by

synaptic receptors, while many pathological activities are caused by elevated ambient glutamate concentrations outside the synapses that activate extrasynaptic NMDA receptors [35,36]. If these could be selectively blocked it could support neuroprotective pathways. Instead of employing complicated pharmacology, the inventors have simply tethered adamantane compounds (this cage-like molecular structure is found in NMDA antagonists such as memantine or amantadine) to gold particles with an effective hydrodynamic diameter of 20–40 nm. Because this is also the average width of the clefts of common excitatory synapses, the constructs cannot reach synaptic NMDA receptors for steric reasons. Gold–memantine conjugates (50 nM) prevented dendritic spine loss in hippocampal slices from YFP-transgenic mice exposed for 10 days to β -amyloid oligomers (A_{1-42} ; 500 nM), while spontaneous synaptic activity in cerebrocortical neurons was not inhibited. Even at an $A\beta$ oligomer concentration of 5 μ M, 50 nM of the conjugate was more protective than 10 μ M free memantine. Whole-cell voltage-clamp recordings confirmed that synaptic NMDA receptors remained essentially unaffected. Caution is advisable here because gold nanoparticles of that size, though chemically inert, have been reported to increase neuronal excitability [37].

Published 14 May 2015

WO/2015/070122**Protein disulfide isomerase inhibiting anticancer agents**

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Keywords: multiple myeloma • protein disulfide-isomerases • ubiquitin-activating enzymes

Despite innovations such as the proteasome inhibitor, bortezomib (Millennium/Takeda's and Janssen's Velcade®) and lenalidomide (Celgene's Revlimid®), multiple myeloma remains one of the most serious challenges in cancer therapy. This is mostly due to its genetic instability: activation of multiple survival programs in one clone, switch between clones, and intraclonal development of new 'survival strategies' converge in the highest-risk myelomas [38]. The inventors have developed a mechanistically unbiased assay to identify drug candidates that simultaneously informs about antimyeloma activity in the context of cell barriers; bone marrow stromal support; short, kidney-clearance-like exposure tolerability by normal bone marrow; and stability towards liver enzymes. The lead compound, CCF642 had submicromolar IC_{50} values in all eight multiple myeloma cell lines tested where it triggered increase of protein ubiquitination, depletion of survival factors c-myc, IRF4, NF- κ B, and

apoptosis with degradation of all ubiquitinated proteins. Mechanistic studies with an active biotinylated analog suggested it exerts most of its action via inhibition of protein disulfide isomerase, the enzyme which is responsible for post-translational folding of newly synthesized proteins through reductase, oxidase, isomerase and chaperone functions in the endoplasmic reticulum. CCF642 interacted with ubiquitin activating enzyme UBA1 [39] with covalent, cysteine dependent binding that could be reversed by ATP and ubiquitin. In an immunocompetent systemic mouse myeloma model (C57BL/KaLwRij mice injected with syngeneic 5TGM1-luc myeloma cells [40]), CCF642 (7.5 mg/kg three times per week) was well tolerated and about as effective as bortezomib.

Published 14 May 2015

WO/2015/077753**Inhibitors of ERCC1-XPF and methods of using the same**

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The enhanced DNA repair that is observed in cancer

Keywords: DNA repair enzymes • endonucleases • ovarian neoplasms • platinum compounds

treatment occurs early in the development of resistance, and appears to be one of the first mechanisms activated in response to pharmacotherapy. It is evident in nearly all cases of high cisplatin resistance, such as are frequently observed in ovarian carcinomas – sometimes even before chemotherapy commences. This is where the ERCC1-XPF complex comes into play – a structure-specific endonuclease that is essential for the repair of DNA damage by the nucleotide excision repair pathway but is also involved in the repair of interstrand cross-links and double-strand breaks [41]. The hypersensitivity of testis tumor cells is attributable to their low level of ERCC1-XPF expression [42]. Only a small region of the XPA peptide interacts with ERCC1 to form a stable complex [43]; small molecule inhibitors of ERCC1/XPA interaction have been identified [44]. The compounds claimed by the present inventors, centered around 4-amino-5-([4-methylbenzenesulfonyl]oxy) naphthalene-2,7-disulfonic acid as a lead compound, occupy a different chemical space. The tosyl moiety is necessary for the compounds' ability to inhibit DNA repair; the IC_{50} of the lead compound for ERCC1/XPA inhibition (as determined by an *in vitro* fluorescence incision assay, is 400–500 nM. Co-encapsulation with the antineoplastic platinum agents might be the most effective way of administering these inhibitors.

Published 28 May 2015

Financial & competing interests disclosure

The authors have 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 employ-

ment, 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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