Patent highlights October–November 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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WO2017172476

Potent inhibitors of aspartate N-acetyl transferase for the treatment of Canavan disease

Inventors: Viola RE, Thangavelu B, Mutthamsetty V & Wang Q

Assignee: The University of Toledo, Toledo (OH, USA)

MeSH keywords: acetyltransferases • Canavan disease • demyelinating diseases • rare diseases

Although a rare disease by definition, Canavan disease – one of the leukodystrophies, or ‘white matter-diseases’ – is one of the most common degenerative cerebral diseases of infancy, characterized by degeneration of myelin in the phospholipid layer insulating the axon [1]. It is caused by a deficiency of aspartoacylase which metabolizes N-acetylaspartate (NAA), but in a complex fashion that complicates development of a gene therapy [2]. Whether the resulting lack of acetate or the accumulation of the substrate is responsible for the symptoms of the condition remains a matter of debate [3]. In animal models, knocking out the *NAT8L* gene that codes for aspartate N-acetyltransferase, the enzyme that synthesizes NAA, can reverse demyelination but also decreases survival [4]. The inventors have designed N-derivatives of amino acids (preferably aminomalonic, aspartic, glutamic and aminoadipic acid) that are potent aspartate N-acetyltransferase inhibitors, and are supposed to reduce NAA levels without completely eliminating it. N-[(Benzyloxy)carbonyl]-L-aspartic acid has a K_i value of 17 μM . Extensive structure–activity relationships studies showed that, while changes at the α -carboxyl group are not well tolerated, even fairly extensive modifications to the α -amino moiety can result in significantly improved affinity. No animal data are presented. For the peer review companion paper, see Thangavelu *et al.* [5].

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WO/2017/174716

Methods of modulating BCKDH

Inventors: Carayol J, Hager J & Valsesia A

Assignee: Nestec SA, Vevey (Switzerland)

MeSH keywords: amino acids, branched-chain • leptin • obesity

Several attempts have been made to control body weight pharmacologically, with moderate success, and sometimes with considerable side effects. Elevations in branched-chain amino acid plasma levels in human obesity were first reported in the 1960s; they are among the earliest biomarkers for emergent diabetes and are reduced by surgical weight loss intervention [6]. Therefore, the inventors’ discovery of a link between branched-chain alpha-keto acid dehydrogenase (BCKD; an enzyme in the inner mitochondrial membrane which is involved in the metabolism of leucine, isoleucine and valine), and the physiological appetite suppressor, leptin is not particularly surprising. A protein quantitative trait loci analysis on data from DIOGENES (a pan-European randomized and controlled study investigating the effects of dietary protein and glycaemic index on weight loss and its maintenance in obese and overweight families [7]) was conducted. In the initial low-calorie diet phase, the genomic loci best associated with leptin differential expression were located in the regulatory region of the *BCKDH6* gene, which encodes the E1B subunit of BCKD. Mutations in this multiplexed subunit have been associated with several genetic conditions, including maple-syrup urine disease [8]. Agents that increase BCKD activity should increase levels of leptin, and

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support weight loss and/or maintenance. These agents can be polynucleotides coding for the E1B subunit; amiodarone; carbamazepine or valproic acid; resveratrol; 2,4-dinitrotoluene, benzo(a)pyrene, tetrachlorodibenzodioxin, 17-ethynyl-5-androstene-3,7,17-diol and even candidate compounds as unlikely as acetaminophen, atrazine and ammonium chloride. Because BCKD activity is controlled by a specific kinase, inhibiting activity of this kinase is also a mode of the invention. Linkage disequilibrium and metabolomics data are provided, but not data showing activity of the agents mentioned above. Note that a very recent paper found no association between branched-chain amino acids and leptin [9].

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WO/2017/180530

Inhibition of SCUBE2, a novel VEGFR2 co-receptor, suppresses tumor angiogenesis

Inventors: Yang R-B & Lin Y-C

Assignee: Academia Sinica, Taipei (Taiwan)

MeSH keywords: angiogenesis inhibitors • neovascularization, pathologic • SCUBE2 protein, human • vascular endothelial growth factor receptor-2

SCUBE2 is one of three variants of a signal peptide-complement protein that additionally contains CUB and EGF domains. SCUBEs can anchor themselves on cell surfaces as peripheral membrane proteins, by either electrostatic or lectin–glycan interactions. SCUBE2 can form a heteromeric complex with SCUBE1, and both variants are rapidly downregulated in endothelial cells after IL-1 β and TNF- α treatment *in vitro* and after lipopolysaccharide injection *in vivo* [10]. In 2009, the inventors had reported that SCUBE2 suppresses breast cancer cell growth by antagonizing bone morphogenetic protein [11]; it also suppresses the β -catenin pathway [12]. Others have reported that all SCUBE proteins cooperate to drive synovial angiogenesis in rheumatoid arthritis [13]. The inventors took this further, and have discovered that SCUBE2 is a co-receptor that potentiates VEGF binding to VEGFR2 and augments MAPK/Akt pathway activation signaling and angiogenesis from this receptor. Although physiological angiogenesis remained normal in mice with *SCUBE2* gene ablation, pathological angiogenesis in experimental tumors was diminished. Anti-SCUBE2 and anti-VEGF monoclonal antibodies synergized in their growth-inhibitory effects on xenografted lung tumors. In well-established analogy to cancer, a combination of the anti-SCUBE2 SPB1 monoclonal antibody and bevacizumab suppresses pathological vessel growth in and under the retina making SCUBE2 antagonists potential candidates for neovascular eye diseases. For the peer review companion paper, see Lin *et al.* [14].

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WO/2017/180862

GPNMB compositions for treatment of skin wounds

Inventors: Kim M-H, Safadi F & Yu B

Assignee: Northeast Ohio Medical University, Rootstown (OH, USA)

MeSH keywords: diabetes mellitus • GPNMB protein, human • macrophages • wound healing

Chronic wounds are a major and growing healthcare problem, mainly for the long-term bedridden and for diabetics. The process of wound repair requires the coordinated participation of macrophages and mesenchymal stem cells, which are sequentially recruited to the site of injury during the healing process. The nature of the dynamic interplay between these two cell types is still not completely understood. The inventors had reported in a 2014 paper [15] that expression of GPNMB (glycoprotein nonmelanoma clone B, glycoprotein nonmetastatic melanoma B or osteoactivin) in macrophages from wild-type mice negatively correlates with the gene expression levels of the pro-inflammatory cytokines that induces macrophages to polarize into the inflammatory (M1) or regenerative (M2) phenotypes, and that polarized macrophages from db/db mice exhibited higher M1 markers and reduced M2 markers as compared with litter mate controls. Using a mouse model of skin wound healing, they now provide evidence that macrophage-derived GPNB is functionally important in promoting the recruitment of mesenchymal stem cells to the site of injury. This modulates inflammatory response by directing the M2 polarization of macrophages in acute wound healing. The inventors further demonstrate that GPNMB signaling is impaired in the diabetic wound environment. Finally, they show that topical administration of recombinant GPNMB can promote wound closure in diabetic mice. For the peer review companion paper see Yu *et al.* [16]. GPNMB is also considered a candidate agent for the treatment of neurodegenerative diseases [17], and as an emerging therapeutic target in cancer [18].

Published: 19 October 2017

WO/2017/184751**Compositions & methods for treating & preventing hypertension***Inventors: Desai A & Garcia JGN**Assignee: Arizona Board of Regents on behalf of the University of Arizona, Tucson (AZ, USA)**MeSH keywords: familial primary pulmonary hypertension • GADD45 protein, human • UCHL1 protein, human*

This document is not about common high blood pressure but addresses idiopathic pulmonary hypertension (PAH) – the cardiorespiratory condition that arises from progressive narrowing of the pulmonary artery lumen. In pulmonary artery endothelial cells, Akt plays a role similar to that in cancer [19]; indeed inhibitors of that kinase, and therapies that limit its expression, are being developed for the treatment of PAH. As in cancer, promoting Akt degradation through its post-translational modification could be an alternative [20]. Deficiency of Akt1, but not Akt2, attenuates the development of PAH [21]. A mechanism linking decreased Akt1 protein levels in human pulmonary artery endothelial cells with depletion of Gadd45a (a well-established DNA demethylating mediator) involving reductions in Uchl1 (a deubiquitinase), resulting in greater Akt1 protein degradation in lung injury has been reported [22]. Because *UCHL1* minor allele frequencies and prevalence of PAH are also linked, the inventors hypothesized that Uchl1 deficiency would promote protection from the development of chronic forms of pulmonary vascular disease via sustained reductions in Akt activity. This proved correct: *GADD45a* knockout mice (an ‘epigenetic’ model of Uchl1 deficiency) and wild-type mice administered a Uchl1-specific inhibitor (LDN 57444), demonstrated reductions in right ventricular systolic pressures, right ventricular hypertrophy and pathological and cancerous-like lung vascular remodeling when exposed to chronic hypoxia (a conventional murine model of PAH) compared with their controls.

Published: 26 October 2017

WO/2017/185027**A gene therapy-based antidepressant***Inventors: Han Y & Lyman K**Assignee: Northwestern University, Evanston (IL, USA)**MeSH keywords: depressive disorder, major • genetic therapy • hyperpolarization-activated cyclic nucleotide-gated channels • TRIP8b protein, human*

Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels modulate neuronal membrane potential and input resistance, and are influenced by interacting proteins [23,24]. Knockout mice lacking the HCN channel auxiliary subunit TRIP8b display increased lysosomal HCN channel degradation, motor learning deficits and enhanced resistance to those multiple tasks of behavioral despair that are considered surrogate measures of antidepressant efficacy in animal models [25]. Since this seminal paper was published in 2011, the inventors have been on the forefront of research to elucidate the molecular mechanisms underlying the impact of HCN channel expression and trafficking on depression. Having reported small molecule inhibitors disrupting the interaction between HCN and TRIP8b that is required for the dendritic cell targeting of HCN channels that is responsible for the antidepressant-like effects [26,27], they have now developed a viral gene therapy that delivers a mutated form of TRIP8b that also blocks one of the two interacting TRIP8b-binding sites. Because TRIP8b expression is limited to the brain, such an antidepressant strategy would not interfere with cardiac HCN channels, which have an important pacemaker role. The AAV-TRIP8b/N13A construct employs the human synapsin promoter that is enhanced by the WPRE post-transcriptional element. Its delivery shortens immobility time in the classical rodent tail suspension and forced swim paradigms without increasing general locomotor activity, as was shown in the open field test.

Published: 26 October 2017

WO/2017/187176**Treatment of impulsivity-related disorders***Inventors: Rogers RD & Sharp T**Assignee: Oxford University Innovation Ltd (Oxfordshire, UK)**MeSH keywords: impulsive behavior • myo-inositol-1 (or 4)-monophosphatase*

Off-label use of antipsychotics and stimulants left aside, the only drug with established efficacy in impulse control disorders is lithium – which, at the doses used, is sufficiently toxic to require constant monitoring and has many side effects. The compounds of the invention (which include ebselen and volinanserin, a highly selective 5-HT 2A receptor antagonist of subnanomolar potency and putative antipsychotic, never marketed and now a research tool) have been previously shown to inhibit IMPase and to have utility in bipolar disorder (see WO/2012/107735 by Isis Innovation Ltd, Oxford, UK). The inventors say that the link between inhibition of this enzyme and impulse control disorders had not been established. This line of reasoning formally holds, but only barely: it was reported in 1995 that lithium inhibits IMPase activity at low millimolar concentrations [28]; IMPase inhibitors have been called lithium mimetics for the past 20 years [29]; in 2003, dampening effects of volinanserin on impulsivity measures were reported [30]; and in late 2015, a report on the stabilizing effect of ebselen on human emotional processing was available [31]. The application's priority date is 28 April 2016. Results for either compound in rodent gambling tasks and in the Choice Serial Reaction Time Task with or without cocaine mostly show favorable trends but no high significance. However, related compounds that are covered by the Markush formula might prove more promising.

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WO/2017/190009

Use of Jumonji C demethylase inhibitors for the treatment & prevention of chemotherapy resistance & radioresistance in cancer

Inventors: Dalvi MP, Martinez ED, Minna JD, Bayo-Fina J & Das A

Assignee: The Board of Regents of the University of Texas System, Austin (TX, USA)

MeSH keywords: Jumonji domain-containing histone demethylases • neoplasms

The Jumonji C (JmjC) domain-containing proteins are a diverse superfamily containing a conserved β -barrel structure with binding sites for Fe(II) and α -ketoglutarate. Most of these proteins have histone lysine demethylase activity [32]. The inventors have found that progressively chemoresistant cancer cells, especially taxane-platinum resistant non-small-cell lung cancer cells, develop increasing sensitivity against inhibitors of this activity. JmjC demethylase inhibitors, especially those targeting histones H3K4, H3K9 and/or H3K6, can also block effective DNA repair in cancer cells, sensitizing them to radiation therapy. Treatment with the JmjC inhibitor JIB-04 (E-isomer; the Z-isomer is inactive in this respect) [33] causes upregulation of pro-apoptotic genes and downregulation of proliferative or oncogenic genes, slows DNA double strand repair kinetics and inhibits nonhomologous end joining and homologous recombination repair. This is achieved at nanomolar concentrations in a cancer-selective manner that is not related with changes in G2-M checkpoint arrest or cell cycle distribution. In rodents bearing radioresistant tumor xenografts, the inhibitor significantly increased survival. For the peer review companion paper see Dalvi *et al.* [34] – this finding could offer promising perspectives for the neoadjuvant chemotherapy of early stage lung cancer patients. However, the effects of JmjC inhibitors on nonmalignant cells with high proliferation rates need to be investigated.

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WO/2017/192761

Propionyl-CoA carboxylase compositions & uses thereof

Inventors: Kraus JP, Majtan T & Collard R

Assignee: The Regents of the University of Colorado, Denver (CO, USA)

MeSH keywords: enzyme replacement therapy • propionic acidemia • rare diseases

The coenzyme A derivative of propionic acid is a metabolite of fatty acids and of three aminoacids (valine, isoleucine and methionine), and a precursor compound for the citric acid cycle. The first step toward this biosynthetic pathway is accomplished by propionyl-CoA carboxylase, a biotin-dependent mitochondrial enzyme that produces (S)-methylmalonyl CoA. Over 80 loss-of-function mutations have been detected in each of the two genes that code for the two subunits constituting the heterododecameric human enzyme [35]. The resulting propionic acidemia, a rare disease most frequently seen in the Arab world, is inherited in an autosomal-recessive fashion, and primarily affects hepatic mitochondria; the only available treatment consists of a low dietary intake of proteins and propiogenic substrates, supplemented with L-carnitine [36]. The invention provides recombinant α and β subunits or fragments thereof, with natural mitochondrial leader sequences or other mitochondrial-penetrating sequences. Immunofluorescence shows such a construct (TAT-PCCAB, containing the enzyme subunits linked to the transactivating transcriptional activator) being imported in patient-derived enzyme-deficient fibroblast cell lines, restoring

propionyl-CoA carboxylase activity in cell lysates. When hypomorphic mice that had their *PCCA* gene replaced by the human transgene bearing the A138T mutation [37] were injected with the TAT-PCCAB construct (20 mg/kg ip.), their propionyl-/acetyl-carnitine ratio decreased for a period of 9 h. For a related patent application from the University of Pittsburgh, see WO/2017/184583.

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WO/2017/197104

YAP1 inhibitors & methods

Inventors: Yun K & Zhai H-X

Assignee: The Jackson Laboratory, Bar Harbor (ME, USA)

MeSH keywords: neoplasms • porphyrins • YAP1 protein, human

Verteporfin, a benzoporphyrin, is broadly known a photosensitizer for photodynamic therapy in age-related macular degeneration (Visudyne®; QLT Therapeutics, BC, Canada/Novartis, Basel, Switzerland). It is less well known that verteporfin also is a YAP inhibitor that disrupts its interactions with the TEAD transcription factor family [38], and promotes trypsin cleavage of YAP at nanomolar concentrations. This makes it interesting as a potential antiangiogenic oncology drug, the therapy field for which it had been originally envisaged. For example, verteporfin can reverse paclitaxel resistance in YAP-overexpressing colon cancer cells entirely without photoactivation [39]. However, verteporfin is almost insoluble in water and physiological buffers. The invention presents 30 verteporfin derivatives (T1-T30) of which many are improved over the parent compound in terms of solubility, cellular uptake and potency toward YAP (e.g., T13: IC₅₀ = 74 nM; verteporfin: IC₅₀ = 494 nM). Microphotographs show the effect of T13 compared with verteporfin (both at 10 μM) on SMO-M2:GFAP-cre tumor cells. For related work from the French Jean-Pierre Aubert Research Center, see Gibault *et al.* [40].

Published: 16 November 2017

WO/2017/197243

Cblb inhibition for treating fungal infections

Inventors: Zhang J & Rappleye C

Assignee: Ohio State Innovation Foundation, Columbus (OH, USA)

MeSH keywords: CBLB protein, human • invasive fungal infections • pattern recognition receptors • ubiquitination

Disseminated infections by *Candida* yeast species are frequent life-threatening complications in patients with a weakened immune system. The inventors have found that the E3 ubiquitin ligase Cbl-b [41,42] targets K48-linked poly-ubiquitination of Dectin-1 and Dectin-2 (two key pattern recognition receptors for sensing *Candida albicans* [43]), leading to loss of these receptors through their internalization and degradation. Silencing the *CBLB* gene protects mice from systemic infection with this yeast, even at infectious doses that are lethal otherwise, and its knockdown in human macrophages significantly increases TNF-α and IL-6 production – innate immune responses – upon infection. The possibility that the enhanced antifungal immune response in the absence of Cbl-b might result from heightened adaptive T-cell responses is excluded by the observation that *CBLB/RAG1* double knockout mice (which do not have T and B cells), phenocopy that of *CBLB* knockouts after *C. albicans* infection. siRNAs are claimed as suitable agents. The invention claims two priority dates, in May and September 2016. Between those dates researchers working in China and at the University of Texas MD Anderson Cancer Center published a paper [44] that seems to negate the later date. The patent examiner did not cite this paper, but challenged novelty of the invention based on Apeiron Biologics' WO/2012/089736 which, although primarily dealing with Cbl-b inhibition in cancer, also mentions application to mycoses. For a review of current host-directed strategies promoting resistance to systemic *C. albicans* infection, see Carpino *et al.* [45].

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WO/2017/198590

A specific trifluoroethyl quinoline analog for use in the treatment of APDS

Inventors: Allen RA, Armstrong MJ, Cavazzana M, Kracker S, Mchale DP & Payne AC

Assignee: UCB Biopharma SPRL (Brussels, Belgium)

MeSH keywords: activated PI3K-delta syndrome • immunologic deficiency syndromes • rare diseases

This document claims N-{(R)-1-[8-Chloro-2-(1-oxypyridin-3-yl)quinolin-3-yl]-2,2,2-trifluoroethyl}-pyrido[3,2-d]pyrimidin-4-ylamine, a PI3K inhibitor that had been explicitly disclosed for a broad range of medical

conditions in UCB Pharma's WO/2012/032334, for a new use: therapy of the activated phosphoinositide 3-kinase delta syndrome (APDS; also known as PASLI). This is a primary immunodeficiency, caused by gain of function mutations in the *PIK3CD* gene which codes for the PI3K δ subunit (APDS1), or by a loss-of-function mutation in *PIK3R1* which encodes the p85 α regulatory subunit (APDS2) [46]. There is currently no efficient treatment, which makes PI3K δ inhibitors a potentially attractive option that might have been forgotten when UCB first claimed this compound, which is shown here to inhibit the increase of PI3K signaling in T cells from both APDS1 and APDS2 in the presence or absence of T-cell activation. The mean IC₅₀ values (adjusted for free concentration) in T lymphoblasts derived from three APDS1 patients were 51, 56 and 41 nM for CD3⁺, CD8⁺ and CD4⁺ cells, respectively. The UCB compound, which has been advanced into Phase I clinical trials, is chemically and pharmacologically very similar to duvelisib, a PI3K $\gamma\delta$ inhibitor under investigation for hematologic cancers by Verastem Inc. (MA, USA). Another PI3K δ inhibitor, Novartis Pharmaceuticals' leniolisib (CDZ173), also is in clinical trials APDS/PASLI [47].

Published: 23 November 2017

WO/2017/201585

Modulators of Dux4 for regulation of muscle function

Inventors: Rickard A, De La Garza A, Schmidt U & Kiselyov A

Assignee: Genea IP Holding Pty Ltd (Sydney, Australia)

MeSH keywords: DUX4 protein, human • histone-lysine N-methyltransferase • muscular dystrophy, facioscapulohumeral • rare diseases

Facioscapulohumeral dystrophy, an autosomal-dominant and highly variable neuromuscular disease [48], comes in two major genetic forms. In *FSHD1*, a 3.2 kb tandem-repeat region at the subtelomeric 4q35 chromosomal region is partially deleted; this D4Z4 repeat region seems to contain only one gene, *DUX4* which codes for a protein that is normally repressed but is inappropriately expressed in patients, and activates the homeodomain transcription factor PITX1. *FSHD2* has no deletions in D4Z4 but mutations in genes encoding D4Z4 chromatin repressors, also causing *DUX4* upregulation [49]. One of the currently considered treatment options involves antisense oligonucleotides directed against *DUX4* mRNA [50]. The present disclosure attempts interference with *DUX4* expression further upstream, using histone methyltransferase inhibitors (e.g., GSK126, CPI-360, EPZ5676, UNC1999 and tazemetostat) or epigenetic modifiers such as DNA methyltransferases. The inventors speculate that once-monthly administration of such a drug should produce a clinical effect within a few months. On the other hand, DNA methyltransferase inhibitors such as decitabine that induce *DUX4* expression can be used to create FSHD models that are suitable for candidate compound screening and characterization of *DUX4* derepressor compounds. Also see WO/2017/009644 claiming kinase inhibitors including sunitinib and vandetanib for the treatment of FSHD.

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WO/2017/205610

Use of angiotensin II receptor agonists in the treatment & prevention of stroke

Inventors: Sumners C, Bennion DM & Steckelings UM

Assignee: University of Florida Research Foundation Inc., Gainesville (FL, USA); Institute for Molecular Medicine, University of Southern Denmark (Odense, Denmark)

MeSH keywords: cerebral infarction • intranasal drug administration • drug delivery systems • neuroprotection • receptor, angiotensin, type 2

Although the angiotensin-II type 1 (AT1) receptor is responsible for most of the physiological actions of angiotensin, there is also an AT2 receptor which is upregulated in pathological conditions, including ischemic stroke where AT2 agonists are neuroprotective even when administered after the event, significantly attenuating superoxide anion production and expression of proinflammatory cytokines [51,52]. This makes the AT2 receptor part of the so-called protective arms of the renin–angiotensin system in neurological disease [53]. The novel element in the present disclosure is the intranasal transolfactory route, using a device that delivers up to 0.75 μ g/kg of an AT2 receptor agonist and can be applied by medically untrained persons. This mode of delivery essentially bypasses the blood–brain barrier, allowing peptides to be delivered to the brain very quickly through olfactory neurons, as has been shown for nerve growth factor [54]. One suitable agent is N-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)5-iso-butylthiophene-2-sulfonamide ('compound 21' or 'C21'; see WO/2002/096883 by Vicore

Pharma AB, Uppsala, Sweden). Among the nasal delivery devices deemed suitable are those developed by Impel NeuroPharma (WA, USA) and Optinose (PA, USA). Extensive data are provided showing that C21 can be delivered to the rat brain through the olfactory route, and is neuroprotective in the model of endothelin-induced ischemic stroke while having no effect on blood pressure, heart rate or animal activity when delivered at 1.5 or 30 µg/kg.

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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.

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References

- Hoshino H, Kubota M. Canavan disease: clinical features and recent advances in research. *Pediatr. Int.* 56(4), 477–483 (2014).
- von Jonquieres G, Spencer ZHT, Rowlands BD *et al.* Uncoupling N-acetylaspartate from brain pathology: implications for Canavan disease gene therapy. *Acta Neuropathol.* 135(1), 95–113 (2017).
- Appu AP, Moffett JR, Arun P *et al.* Increasing N-acetylaspartate in the brain during postnatal myelination does not cause the CNS pathologies of Canavan disease. *Front. Mol. Neurosci.* 10, 161 (2017).
- Maier H, Wang-Eckhardt L, Hartmann D, Gieselmann V, Eckhardt M. N-acetylaspartate synthase deficiency corrects the myelin phenotype in a Canavan disease mouse model but does not affect survival time. *J. Neurosci.* 35(43), 14501–14516 (2015).
- Thangavelu B, Mutthamsetty V, Wang Q, Viola RE. Design and optimization of aspartate N-acetyltransferase inhibitors for the potential treatment of Canavan disease. *Bioorg. Med. Chem.* 25(3), 870–885 (2017).
- Giesbertz P, Daniel H. Branched-chain amino acids as biomarkers in diabetes. *Curr. Opin. Clin. Nutr. Metab. Care.* 19(1), 48–54 (2016).
- Larsen TM, Dalskov S, van Baak M *et al.* The diet, obesity and genes (diogenes) dietary study in eight European countries – a comprehensive design for long-term intervention. *Obes. Rev.* 11(1), 76–91 (2010).
- Evarsson A, Chuang JL, Wynn RM, Turley S, Chuang DT, Hol WG. Crystal structure of human branched-chain alpha-ketoacid dehydrogenase and the molecular basis of multienzyme complex deficiency in maple syrup urine disease. *Structure* 8(3), 277–291 (2000).
- Connelly MA, Wolak-Dinsmore J, Dullaart RPF. Branched chain amino acids are associated with insulin resistance independent of leptin and adiponectin in subjects with varying degrees of glucose tolerance. *Metab. Syndr. Relat. Disord.* 15(4), 183–186 (2017).
- Yang RB, Ng CK, Wasserman SM *et al.* Identification of a novel family of cell-surface proteins expressed in human vascular endothelium. *J. Biol. Chem.* 277(48), 46364–46373 (2002).
- Cheng CJ, Lin YC, Tsai MT *et al.* SCUBE2 suppresses breast tumor cell proliferation and confers a favorable prognosis in invasive breast cancer. *Cancer Res.* 69(8), 3634–3641 (2009).
- Lin YC, Chen CC, Cheng CJ, Yang RB. Domain and functional analysis of a novel breast tumor suppressor protein, SCUBE2. *J. Biol. Chem.* 286(30), 27039–27047 (2011).
- Yang M, Guo M, Hu Y, Jiang Y. Scube regulates synovial angiogenesis-related signaling. *Med. Hypotheses* 81(5), 948–953 (2013).
- Lin YC, Chao TY, Yeh CT, Roffler SR, Kannagi R, Yang RB. Endothelial SCUBE2 interacts with VEGFR2 and regulates VEGF-induced angiogenesis. *Arterioscler. Thromb. Vasc. Biol.* 37(1), 144–155 (2017).
- Yu B, Malcuit C, Safadi M, Kim M-H. The immunomodulatory role of glycoprotein nonmelanoma clone B (GPNMB) in macrophage polarization in diabetes (IRC10P465). *J. Immunol.* 192(Suppl. 1), 192.3 (2014).
- Yu B, Albosley T, Safadi F, Kim MH. Glycoprotein nonmelanoma clone B regulates the crosstalk between macrophages and mesenchymal stem cells toward wound repair. *J. Invest. Dermatol.* 138(1), 219–227 (2017).
- Budge KM, Neal ML, Richardson JR, Safadi FF. Glycoprotein NMB: an emerging role in neurodegenerative disease. *Mol. Neurobiol.* doi:10.1007/s12035-017-0707-z (2017) (Epub ahead of print).
- Taya M, Hammes SR. Glycoprotein non-metastatic melanoma protein B (GPNMB) and cancer: a novel potential therapeutic target. *Steroids* doi:10.1016/j.steroids.2017.10.013 (2017) (Epub ahead of print).
- Fan Z, Li C, Qin C *et al.* Role of the PI3K/AKT pathway in modulating cytoskeleton rearrangements and phenotype switching in rat pulmonary arterial vascular smooth muscle cells. *DNA Cell Biol.* 33(1), 12–19 (2014).
- Chan CH, Jo U, Kohrman A *et al.* Post-translational regulation of Akt in human cancer. *Cell Biosci.* 4(1), 59 (2014).
- Tang H, Chen J, Fraidenburg DR *et al.* Deficiency of Akt1, but not Akt2, attenuates the development of pulmonary hypertension. *Am. J. Physiol. Lung Cell Mol. Physiol.* 308(2), L208–L220 (2015).
- Mitra S, Sammani S, Wang T *et al.* Role of growth arrest and DNA damage-inducible α in Akt phosphorylation and ubiquitination after mechanical stress-induced vascular injury. *Am. J. Respir. Crit. Care Med.* 184(9), 1030–1040 (2011).

23. Sartiani L, Mannaioni G, Masi A, Novella Romanelli M, Cerbai E. The hyperpolarization-activated cyclic nucleotide-gated channels: from biophysics to pharmacology of a unique family of ion channels. *Pharmacol. Rev.* 69(4), 354–395 (2017).
24. He C, Chen F, Li B, Hu Z. Neurophysiology of HCN channels: from cellular functions to multiple regulations. *Prog. Neurobiol.* 112, 1–23 (2014).
25. Lewis AS, Vaidya SP, Blaiss CA *et al.* Deletion of the hyperpolarization-activated cyclic nucleotide-gated channel auxiliary subunit TRIP8b impairs hippocampal Ih localization and function and promotes antidepressant behavior in mice. *J. Neurosci.* 31(20), 7424–7440 (2011).
26. Han Y, Lyman K, Clutter M *et al.* Identification of small-molecule inhibitors of hyperpolarization-activated cyclic nucleotide-gated channels. *J. Biomol. Screen.* 20(9), 1124–1131 (2015).
27. Han Y, Heuermann RJ, Lyman KA, Fisher D, Ismail QA, Chetkovich DM. HCN-channel dendritic targeting requires bipartite interaction with TRIP8b and regulates antidepressant-like behavioral effects. *Mol. Psychiatry* 22(3), 458–465 (2017).
28. Vadnal R, Parthasarathy R. Myo-inositol monophosphatase: diverse effects of lithium, carbamazepine, and valproate. *Neuropsychopharmacology* 12(4), 277–285 (1995).
29. Atack JR. Inositol monophosphatase inhibitors – lithium mimetics? *Med. Res. Rev.* 17(2), 215–224 (1997).
30. Winstanley CA, Chudasama Y, Dalley JW, Theobald DE, Glennon JC, Robbins TW. Intra-prefrontal 8-OH-DPAT and M100907 improve visuospatial attention and decrease impulsivity on the five-choice serial reaction time task in rats. *Psychopharmacology (Berl.)* 167(3), 304–314 (2003).
31. Singh N, Sharpley AL, Emir UE *et al.* Effect of the putative lithium mimetic ebselen on brain myo-inositol, sleep, and emotional processing in humans. *Neuropsychopharmacology* 41(7), 1768–1778 (2016).
32. Accari SL, Fisher PR. Emerging roles of JmjC domain-containing proteins. *Int. Rev. Cell. Mol. Biol.* 319, 165–220 (2015).
33. Wang L, Chang J, Varghese D *et al.* A small molecule modulates Jumonji histone demethylase activity and selectively inhibits cancer growth. *Nat. Commun.* 4, 2035 (2014).
34. Dalvi MP, Wang L, Zhong R *et al.* Taxane-platin-resistant lung cancers co-develop hypersensitivity to JumonjiC demethylase inhibitors. *Cell Rep.* 19(8), 1669–1684 (2017).
35. Wongkittichote P, Ah Mew N, Chapman KA. Propionyl-CoA carboxylase – a review. *Mol. Genet. Metab.* 122(4), 145–152 (2017).
36. Shchelochkov OA, Carrillo N, Venditti C. Propionic Acidemia. In: *GeneReviews*®. Adam MP, Ardinger HH, Pagon RA *et al.* (Eds). University of Washington, WA, USA, 1993–2018 (2012).
37. Guenzel AJ, Hofherr SE, Hillestad M *et al.* Generation of a hypomorphic model of propionic acidemia amenable to gene therapy testing. *Mol. Ther.* 21(7), 1316–1323 (2013).
38. Wei H, Wang F, Wang Y *et al.* Verteporfin suppresses cell survival, angiogenesis and vasculogenic mimicry of pancreatic ductal adenocarcinoma via disrupting the YAP–TEAD complex. *Cancer Sci.* 108(3), 478–487 (2017).
39. Pan W, Wang Q, Zhang Y *et al.* Verteporfin can reverse the paclitaxel resistance induced by YAP over-expression in HCT-8/T cells without photoactivation through inhibiting YAP expression. *Cell Physiol. Biochem.* 39(2), 481–490 (2016).
40. Gibault F, Bailly F, Corvaisier M *et al.* Molecular features of the YAP inhibitor verteporfin: synthesis of hexasubstituted dipyrins as potential inhibitors of YAP/TAZ, the downstream effectors of the hippo pathway. *ChemMedChem* 12(12), 954–961 (2017).
41. Lutz-Nicoladoni C, Wolf D, Soppor S. Modulation of immune cell functions by the E3 ligase Cbl-b. *Front. Oncol.* 5, 58 (2015).
42. Liu Q, Zhou H, Langdon WY, Zhang J. E3 ubiquitin ligase Cbl-b in innate and adaptive immunity. *Cell Cycle* 13(12), 1875–1884 (2014).
43. Saijo S, Iwakura Y. Dectin-1 and Dectin-2 in innate immunity against fungi. *Int. Immunol.* 23(8), 467–472 (2011).
44. Zhu LL, Luo TM, Xu X *et al.* E3 ubiquitin ligase Cbl-b negatively regulates C-type lectin receptor-mediated antifungal innate immunity. *J. Exp. Med.* 213(8), 1555–1570 (2016).
45. Carpino N, Naseem S, Frank DM, Konopka JB. Modulating host signaling pathways to promote resistance to infection by *Candida albicans*. *Front. Cell Infect. Microbiol.* 7, 481 (2017).
46. Elgizouli M, Lowe DM, Speckmann C *et al.* Activating PI3Kδ mutations in a cohort of 669 patients with primary immunodeficiency. *Clin. Exp. Immunol.* 183(2), 221–229 (2016).
47. Rao VK, Webster S, Dalm VASH *et al.* Effective ‘activated PI3Kδ syndrome’ – targeted therapy with the PI3Kδ inhibitor leniolisib. *Blood* 130(21), 2307–2316 (2017).
48. Wang LH, Tawil R. Facioscapulohumeral dystrophy. *Curr. Neurol. Neurosci. Rep.* 16(7), 66 (2016).
49. Gatica LV, Rosa AL. A complex interplay of genetic and epigenetic events leads to abnormal expression of the *DUX4* gene in facioscapulohumeral muscular dystrophy. *Neuromuscul. Disord.* 26(12), 844–852 (2016).
50. Bao B, Maruyama R, Yokota T. Targeting mRNA for the treatment of facioscapulohumeral muscular dystrophy. *Intractable Rare Dis. Res.* 5(3), 168–176 (2016).

51. Min LJ, Mogi M, Tsukuda K *et al.* Direct stimulation of angiotensin II type 2 receptor initiated after stroke ameliorates ischemic brain damage. *Am. J. Hypertens.* 27(8), 1036–1044 (2014).
52. McCarthy CA, Vinh A, Callaway JK, Widdop RE. Angiotensin AT2 receptor stimulation causes neuroprotection in a conscious rat model of stroke. *Stroke* 40(4), 1482–1489 (2009).
53. Sumners C, Horiuchi M, Widdop RE, McCarthy C, Unger T, Steckelings UM. Protective arms of the renin–angiotensin system in neurological disease. *Clin. Exp. Pharmacol. Physiol.* 40(8), 580–588 (2013).
54. Vaka SR, Sammeta SM, Day LB, Murthy SN. Delivery of nerve growth factor to brain via intranasal administration and enhancement of brain uptake. *J. Pharm. Sci.* 98(10), 3640–3646 (2009).