For reprint orders, please contact reprints@future-science.com

Patent Highlights

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

Hermann AM Mucke*

WO2013030670

Tissue targeted

Fusobacterium antigenic
activation of the immune
response to treat intestinal
cancers

Gunn HD

Qu Biologics, Inc.

Few pathogens (primarily human papilloma virus, hepatitis viruses B and C, and *Helicobacter pylori*) are unequivocally known to cause cancers. The association of *Fusobacterium nucleatum*, a Gram-negative anaerobe previously linked to inflammatory bowel syndrome and appendicitis, with colorectal carcinoma (CRC) [1,2], directly visualized by FISH and confirmed by quantitative PCR and 16S rDNA sequence analysis, attracted considerable attention. The relation is probably not one of direct pathogenesis; mucosa-associated microbiota potentially affects CRC risk, primarily through direct interaction with the host [3], and opportunistic colonization of established CRC tissue by *Fusobacterium* also seems conceivable. This invention exploits this association by administering a therapeutic vaccine based on whole killed *Fusobacterium* cells to sites distant from the cancer tissue, so that modulation of the immune response from a M2-like macrophage response to a M1-like response is achieved. Extensive molecular biology data confirm the association of *Fusobacterium* with human intestinal tumors and its invasiveness towards cultured human colonic epithelial cells, but not the therapeutic claims.

Published: 7 March 2013

WO2013032893

The use of prolyl hydroxylase
inhibitors as a radioprotective
drug for the lower
gastrointestinal tract

Giacchia A, Taniguchi C

The Board of Trustees of Leland Stanford
Junior University

Under normoxic conditions, HIF1 α is hydroxylated by oxygen-dependent prolyl-hydroxylase domain proteins, which serve as oxygen sensors, leading to its proteosomal degradation and clearance from the cell. Its transcriptional regulatory pathway is activated by hypoxia, a condition that frequently occurs in tumors where HIF1 α is constitutively expressed, and which also show resistance against radiation therapy. While radiosensitizers that reduce HIF1 α have been the subject of other inventions, this document pursues the opposite goal: prolylhydroxylase inhibitors such as dimethyloxallylglycine (DMOG) should be able to serve as a radioprotectant. This is especially important in the gastrointestinal epithelium, whose radiation sensitivity is a dose-limiting factor in abdominopelvic radiation therapy. When mice were treated with 8 mg of DMOG prior to irradiation with a single fraction of 20 Gy to the whole abdomen, and received daily doses of DMOG until they were sacrificed 4.5 days post-irradiation, microcolony analysis showed a

*H.M. Pharma Consultancy e.U., Enenkelstrasse 28/32, A-1160 Wien, Austria; Tel.: +43 664 101 0121; E-mail: h.mucke@hmpharmacon.com

twofold increase of the regeneration capacity of intestinal stem cells versus saline. Treatment with DMOG also resulted in a 3.5-fold decrease in the uptake of fluorescein isothiocyanate-dextran from gut to serum, an indicator of gastrointestinal leakage. The August 2011 priority date of this patent application predates a paper from an apparently competing group at the Dana-Farber Cancer Institute [1] by only a few weeks. Meanwhile it has also been shown that pretreatment of mice with DMOG before sublethal 9.0 Gy irradiation improves blood recovery and massively enhances quiescent hematopoietic stem cell survival in the bone marrow, leading to quicker recovery [2].

Published: 7 March 2013

WO2013035906

Method for preventing & treating *Salmonella typhimurium* infection

Yoon SJ, Jun SY, Paik HR *et al.*
Intron Biotechnology, Inc.

Salmonella ssp. bacteria (including *Salmonella enterica* serotype Typhimurium), the major pathogens of food-borne illnesses, are transmitted through ingestion of trace fecal matter from mammals, birds and reptiles. Increasing resistance to fluoroquinolones and third-generation cephalosporins has become a pervasive problem since the millennium. This disclosure contributes to the revival of the concept of using highly specific lytic bacteriophages – in this case, of a new type named STP-1 – as a purely biological causal therapy for bacterial enteral infections. The sequence of STP-1, which has been deposited in the Biological Resource Center, Korea Research Institute of Bioscience and Biotechnology, under accession number KCTC 12012BP, is disclosed, and data obtained in 20-day-old piglets are provided. Another *S. enterica* var. Typhi bacteriophage, named Vi1, has been known for decades [1], and protection of mice against *S. enterica* serovar Paratyphi B by Phage f1 has recently been reported [2]

Published: 14 March 2013

WO2013036383

Oral delivery for hemoglobin based oxygen carriers

Wong BL & Kwok SY
Inventors are applicants

Safe whole blood or packed erythrocyte preparations for transfusion are in short supply, and so far the oxygen and carbon dioxide binding, carrier and release characteristics of hemoglobin can only be approximated by synthetic oxygen carriers. Acellular recombinant hemoglobin preparations, if developed to regulatory approval, could go a long way towards alleviating this problem for trauma patients in intensive care, but there remains the challenge of increasing tissue oxygenation outside the acute hospital setting – in particular, for preventing or treating high-altitude syndrome. The present invention claims to have solved the challenge of oral delivery of intact hemoglobin by encapsulating it in nanoparticles consisting of an anionic polymer – preferably, a poly(methacrylic acid)-poly(methyl methacrylate) copolymer, hydroxyl propylmethylcellulose phthalate or poly(γ -glutamic acid) - and chitosan. This appears to resemble a delivery system that has been reported for oral insulin [1]. Ascorbic acid or *N*-acetyl cysteine are added as stabilizers. In a Caco-2 cell culture model of intestinal transepithelial transport, enteric-coated capsules containing such nanoparticles that were exposed to simulated intestinal fluid provided absorption through the cell layer within 2–4 h. In addition to delivering oxygen, the heme group delivered in these formulations provides iron to aid in the production of more erythrocytes under hypoxic conditions. There seems to be very little patent or peer-reviewed literature on orally bioavailable hemoglobin.

Published: 14 March 2013

WO2013038189

New enzyme inhibitor compounds

Carley A & Simpson I

Proximagen Ltd

Semicarbazide-sensitive amine oxidase (SSAO) is an activity associated with VAP-1 or AOC3. Known substrates include endogenous methylamine and aminoacetone, as well as some xenobiotic amines such as benzylamine. Since most of its reaction products (aldehydes, hydrogen peroxide and so on) promote inflammation and/or oxidative stress, VAP-1 is a promising anti-inflammatory and anti-angiogenic target; its activity in plasma is elevated in conditions such as congestive heart failure, diabetes and Alzheimer's disease [1,2]. This invention discloses a new class of SSAO inhibitors, for the most part 4-[1-(4-chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-3-yl]-N-[(1-alkylpiperidin-4-yl)alkyl]piperidine-1-carboxamides. IC₅₀ values are disclosed in three categories (<100 nM, 100–500 nM and 500–2500 nM). For a survey of patents related to SSAO, see Dunkel *et al.* [3].

Published: 21 March 2013

WO2013041246 &**WO2013041247**

Yersinia outer protein M (YopM) in the treatment of psoriasis; *Yersinia* outer protein M (YopM) in the treatment of psoriasis induced by imiquimod

Rüter C, Schmidt A

Westfälische Wilhelms-Universität Münster

The *Yersinia* ssp. outer protein M (YopM), a bacterial virulence factor, belongs to the class of cell-penetrating peptides. After its autonomous translocation into the host cell it downregulates the transcription of pro-inflammatory cytokines, priming the suppression and reprogramming of the immune system to infect lymphatic tissues [1,2]. The present invention exploits this, together with the 'self-delivering' capability of YopM, to treat psoriasis; approximately 2 µg/cm², delivered via the topical, subcutaneous or intradermal routes, is most preferable. Immunohistochemical data from the mouse model of imiquimod-induced psoriasis are presented. With topical application, no systemic distribution was observed. The WO2013041247 patent focuses on psoriasis induced by imiquimod therapy of actinic keratosis in immunocompetent adults but is otherwise identical. The search reports cite the inventors' earlier congress report [3], and their earlier patent application [4], as anticipating prior art.

Published: 28 March 2013

WO2013042833

Pharmaceutical composition for the prevention or treatment of a prion disease containing an active ingredient in the form of the *Prnp* gene using recombinant adenovirus vector

Jeong JK, Moon MH, Lee YJ *et al.*

Industrial Cooperation Foundation,
Chonbuk National University

The discovery of prions (mutated forms of a normally neuroprotective membrane glycoprotein, PrP^C) that convert to a self-replicating state (PrP^{Sc}) as quasi-infectious agents of transmissible spongiform encephalopathies was a milestone of modern biology. Interfering with this pathological folding with small molecules has not proven very successful, and presently the hopes lie in immunotherapy and gene therapy, or a combination of both [1,2]. This patent application aims at restoring the 'folding balance' by delivering PrP^C through an adenovirus expression vector. Lactate dehydrogenase and annexin-V expression data from a transfected murine neuronal cell line (Zpl 3–4, which has the *PNNRP* gene knocked out) are presented, and show that normal neuronal characteristics are restored. The inventors are part of a tight-knit research group that has published an impressive number of peer-reviewed papers on potential therapeutics for prion diseases [3–5] and other matters.

Published: 28 March 2013

WO2013049200

Methods of treating
periodontal inflammation
& periodontal bone loss

Hajishengallis G, Chavakis T

University of Louisville Research
Foundation, US Department of Health
& Human Services

The peptide Del-1 is an endothelial-derived anti-inflammatory factor that is dependent on the integrin LFA-1, and antagonizes integrin-dependent leukocyte adhesion [1]. Its physiological roles appear to include the endocytotic clearance of phosphatidylserine-expressing platelet-derived microparticles by endothelial cells of the vasculature and in the lungs [2], and modulation of angiogenesis after cerebral ischemia [3]. Even though the involvement of inflammation and integrins in bone loss caused by rheumatoid arthritis or infection is well known, it is innovative to see Del-1 applied to tooth loss caused by periodontitis, which probably is the most prevalent disease in mankind (and in many of its companion animals). The data presented show: how decreased periodontal expression of Del-1 in aged mice correlates with increased neutrophil influx; that Del-1 deficient mice have increased osteoclastic activity in the periodontium, which does not occur in mice without the *IL-17* receptor gene; and that administration of Del-1 inhibits periodontal bone loss in old C57BL/6 wild-type mice. For the peer review companion paper see Eskan *et al.* [4].

Published: 4 April 2013

WO2013049350

Smac mimetic (birinapant)
for use in the treatment of
proliferative diseases (cancer)

Weng D, Chunduru S & Graham M

Tetralogic Pharmaceuticals Corp.

Smac (also known as DIABLO) is an intracellular protein that antagonizes apoptosis-inhibiting proteins. Small-molecule mimetics of Smac, which typically mimic the structure of its four N-terminal amino acids, enhance tumor cell death in a variety of cancers [1]. Birinapant (TL32711), which Tetralogic had disclosed before [2], is currently in a Phase II clinical trial for advanced gynecological cancers (NCT01681368 [3]). Two 2013 peer-reviewed papers report single-agent efficacy in two patient tumor-derived *in vitro* models of inflammatory breast cancer (an aggressive subset of breast cancer with an extremely poor survival rate) [4], and against melanoma cell lines with acquired resistance to BRAF inhibitors when combined with TNF- α [5]. The patent application predates these two papers as an 'IP wrapper' but adds interesting details concerning greater-than-dose-proportionality in a melanoma xenograft model (a fourfold increase in dose resulted in a 14-fold increase in exposure), the increased efficacy without compromised tolerability in combination with carboplatin and paclitaxel, and the nonsuperiority of a biweekly versus the established weekly dosing schedule.

Published: 4 April 2013

WO2013052736

Methods of treating or
preventing blood loss during
surgery using the serine
protease inhibitor MDCO-2010

Van de Locht A, Dietrich W, Englberger L
et al.

The Medicines Company

Perioperative bleeding is a serious complication that adversely affects the morbidity and mortality of cardiac surgery, and consumes approximately 20% of a typical western industrial nation's allogeneic blood supply. The only prophylactic antifibrinolytic agent associated with reduced mortality, a decreased incidence of stroke and shortened hospital stay in the context of cardiac surgery is aprotinin, which has some renal toxicity and safety issues [1]. Safety issues have also been reported for a synthetic lysine analog, tranexamic acid [2]. MDCO-2010 is a peptidomimetic small molecule (consisting of two unnatural amino acids, D-phenylpropylglycine and 3-aminomethyl-L-phenylalanine) that is an active-site directed reversible inhibitor of serine proteases (primarily kallikrein and plasmin; but also factors Xa and XIa as well as activated protein C). It has been developed specifically for cardiac surgery. The bolus infusion dose is 5–50 $\mu\text{g}/\text{kg}$, followed by a maintenance dose of 10–100 $\mu\text{g}/\text{kg}/\text{h}$. Results from a Phase IIa dose-escalation study are presented. For the peer review companion paper see Kim *et al.* [3].

Published: 11 April 2013

WO2013054153

Nutlin compounds for use in the treatment of pulmonary hypertension

Adnot S
INSERM

In pulmonary arterial hypertension (PAH) the pulmonary artery smooth muscle cells in the vessel wall proliferate in response to increased right ventricular pressure, a process that has much in common with cancer. This invention investigates the role of *cis*-2,4,5-triphenyl-imidazolines (nutlins), which prevent the interaction of ubiquitin ligase MDM2 with the p53 tumor suppressor protein [1,2] in PAH. When primary human pulmonary artery smooth muscle cells were exposed to nutlin-3a (2.5–10 μ M), levels of p53 protein and of mRNA coding for its target genes *p21*, *Bax* and *PUMA* were elevated. Cell proliferation stimulated by 0.2% fetal calf serum or 50 ng/ml PDGF was dose-dependently inhibited, with an increased fraction of senescent cells as determined by the percentage of β -galactosidase stained cells. While nutlin-3 also partially reversed PAH symptoms in transgenic SM22–5-HTT+ mice (which express the human serotonin transporter gene in smooth muscle and develop PAH spontaneously), it was ineffective in p53 and p21 knockout mice that developed PAH under hypoxia, indicating that the pathways controlled by these proteins are required for the PAH-mitigating effect of nutlins. For the peer-review companion paper, see Mouraret *et al.*, [3].

Published: 18 April 2013

WO2013055913

PGAM1 inhibitors & methods related thereto

Chen J, Hitosugi T & Kang S
Emory University

Cancer tissues appear to coordinate glycolysis and anabolic biosynthesis of macromolecules to provide an overall metabolic advantage to cancer cell proliferation and disease development. The Warburg effect (the enhanced aerobic glycolysis and lactate production that allows cancer cells to generate more ATP more rapidly than normal cells that rely on oxidative phosphorylation) was the first key metabolic insight in oncology. PGAM1 converts 3-PG to 2-PG during glycolysis; it is up-regulated in tissues that have lost the p53 tumor suppressor gene. 3-PG and 2-PG can directly affect the catalytic activity of enzymes involved in the pentose phosphate pathway, and new insights into the intricacies of this feedback mechanism constitute the essence of this invention. 3,4-dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-sulfonic acid (a derivative of alizarin Red S), its sulfonamide prodrug PGM1-004A and a monoclonal antibody to a PGAM1 epitope phosphorylated at aminoacid Y26 are among the PGAM1 inhibitors presented, along with extensive biological data. For related research, see Vander Heiden *et al.* and Hallows *et al.* [1,2]; for the peer-review companion paper, see Hitosugi [3].

Published: 18 April 2013

WO2013057251 & WO2013057253

Heteroaryl hydroxamic acid derivatives & their use in the treatment, amelioration or prevention of a viral disease; Pyrimidin-4-one derivatives and their use in the treatment, amelioration or prevention of a viral disease

Classen-Houben D, Wolkerstorfer A, Szolar O *et al.*

F Hoffmann-LaRoche AG; Savira Pharmaceuticals GmbH; European Molecular Biology Laboratory

The development of 'universal' preventive influenza vaccines is currently at the center of pharmaceutical attention, while drugs such as neuraminidase inhibitors or M2 ion channel inhibitors (adamantanes) are mostly considered a stop-gap measure. However, the virus has an additional promising target: the mRNA cap-binding domain in the PB2 subunit of its RNA-dependent RNA polymerase, which carries out the initial copying of the single-stranded virion RNA into viral mRNAs and its replication. 'Cap' designates a 5'-terminal 7-methylguanosine residue, which is linked to the first transcribed nucleotide through a 5'-5'-triphosphate bond, and normally serves to initiate cellular protein synthesis upon binding of the elongation factor eIF-4E. The viral polymerase 'hijacks' this sequence using the so called 'cap-snatching' transcription mechanism, binding to the 'cap' of cellular mRNA molecules and cleaving it off, together with a stretch of 10–15 nucleotides. The capped eukaryotic RNA fragments then serve as primers for the synthesis of viral mRNA. The compounds presented here are believed to inhibit the endonuclease function of the viral polymerase by directly interfering with its N-terminal part, which is responsible for this activity. Although the focus of these compounds is on influenza viruses, they should be effective against other ssRNA viruses (arenaviridae, bunyaviridae and tenuiviridae) that also use cap-snatching [2]. For earlier closely related patenting and peer-review publishing from this group see Kowalinski *et al.* [3] and [4]

Published: 25 April 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.

References

■ WO2013030670

- 1 Kostic AD, Gevers D, Pedamallu CS *et al.* Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma. *Genome Res.* 22(2), 292–298 (2012).
- 2 Castellarin M, Warren RL, Freeman JD *et al.* *Fusobacterium nucleatum* infection is prevalent in human colorectal carcinoma. *Genome Res.* 22(2), 299–306 (2012).
- 3 Chen W, Liu F, Ling Z *et al.* Human intestinal lumen and mucosa-associated microbiota in patients with colorectal cancer. *PLoS ONE* 7(6), e39743 (2012).

■ WO2013032893

- 1 Ayrapetov MK, Xu C, Sun Y *et al.* Activation of Hif1 α by the prolylhydroxylase inhibitor dimethoxyglycine decreases radiosensitivity. *PLoS ONE* 6(10), e26064 (2011).
- 2 Forristal CE, Winkler IG, Nowlan B *et al.* Pharmacologic stabilization of HIF-1 α increases hematopoietic stem cell quiescence *in vivo* and accelerates blood

recovery after severe irradiation. *Blood* 121(5), 759–769 (2013).

■ WO2013035906

- 1 Ackermann HW, Berthiaume L, Kasatiya SS. Ultrastructure of Vi phages I to VII of *Salmonella typhi*. *Can. J. Microbiol.* 16(6), 411–413 (1970).
- 2 Capparelli R, Nocerino N, Iannaccone M *et al.* Bacteriophage therapy of *Salmonella enterica*: a fresh appraisal of bacteriophage therapy. *J. Infect. Dis.* 201(1), 52–61 (2010).

■ WO2013036383

- 1 Sonaje K, Chen YJ, Chen HL *et al.* Enteric-coated capsules filled with freeze-dried chitosan/poly(gamma-glutamic acid) nanoparticles for oral insulin delivery. *Biomaterials* 31(12), 3384–3394 (2010)

■ WO2013038189

- 1 Tábi T, Szökő E, Mérey A *et al.* Study on SSAO enzyme activity and anti-inflammatory effect of SSAO inhibitors in animal model of inflammation.

J. Neural. Transm. 120(6), 963–967 (2013).

- 2 Dunkel P, Gelain A, Barlocco D *et al.* Semicarbazide-sensitive amine oxidase/vascular adhesion protein 1: recent developments concerning substrates and inhibitors of a promising therapeutic target. *Curr. Med. Chem.* 15(18), 1827–1839 (2008).
- 3 Dunkel P, Balogh B, Meleddu R *et al.* Semicarbazide-sensitive amine oxidase/vascular adhesion protein-1: a patent survey. *Expert Opin. Ther. Pat.* 21(9), 1453–1471 (2011).

■ WO2013041246 & WO2013041247

- 1 Rüter C, Buss C, Scharnert J *et al.* A newly identified bacterial cell-penetrating peptide that reduces the transcription of pro-inflammatory cytokines. *J. Cell Sci.* 123(Pt 13), 2190–2198 (2010).
- 2 Aepfelbacher M, Trasak C, Ruckdeschel K. Effector functions of pathogenic *Yersinia* species. *Thromb. Haemost.* 98(3), 521–529 (2007).

- 3 Poceva M, Rueter C, Loser K *et al.* YopM as a bacteria-derived anti-inflammatory cell-penetrating peptide (CPP) in a murine psoriasis model. *Int. J. Med. Microbiol.* 301(Suppl. 47), 26 (2011).
- 4 Universitätsklinikum Münster: WO2009115531 (2009).

■ WO2013042833

- 1 Roettger Y, Du Y, Bacher M *et al.* Immunotherapy in prion disease. *Nat. Rev. Neurol.* 9(2), 98–105 (2013).
- 2 Moda F, Vimercati C, Campagnani I *et al.* Brain delivery of AAV9 expressing an anti-PrP monovalent antibody delays prion disease in mice. *Prion* 6(4), 383–390 (2012).
- 3 Jeong JK, Moon MH, Lee YJ *et al.* Autophagy induced by the class III histone deacetylase Sirt1 prevents prion peptide neurotoxicity. *Neurobiol. Aging* 34(1), 146–156 (2013).
- 4 Park YG, Jeong JK, Moon MH *et al.* Insulin-like growth factor-1 protects against prion peptide-induced cell death in neuronal cells via inhibition of Bax translocation. *Int. J. Mol. Med.* 30(5), 1069–1074 (2012).
- 5 Jeong JK, Seo JS, Moon MH *et al.* Hypoxia-inducible factor-1 α regulates prion protein expression to protect against neuron cell damage. *Neurobiol. Aging* 33(5), 1006.e1–10 (2012).

■ WO2013049200

- 1 Choi EY. Inhibition of leukocyte adhesion by developmental endothelial locus-1 (del-1). *Immune Netw.* 9(5), 153–157 (2009).
- 2 Dasgupta SK, Le A, Chavakis T *et al.* Developmental endothelial locus-1 (Del-1) mediates clearance of platelet microparticles by the endothelium. *Circulation* 125(13), 1664–1672 (2012).
- 3 Fan Y, Zhu W, Yang M *et al.* Del-1 gene transfer induces cerebral angiogenesis in mice. *Brain Res.* 1219, 1–7 (2008).
- 4 Eskin MA, Jotwani R, Abe T *et al.* The leukocyte integrin antagonist Del-1 inhibits IL-17-mediated inflammatory bone loss. *Nat. Immunol.* 13(5), 465–473 (2012).

■ WO2013049350

- 1 Emeagi PU, Thielemans K, Breckpot K. The role of SMAC mimetics in regulation of tumor cell death and immunity. *Oncoimmunology* 1(6), 965–967 (2012).
- 2 Tetralogic Pharmaceuticals Corp.: WO2011002684 (2011).
- 3 ClinicalTrials Database: NCT01681368 <http://clinicaltrials.gov/show/NCT01681368>
- 4 Allensworth JL, Sauer SJ, Lyerly HK *et al.* Smac mimetic birinapant induces apoptosis and enhances TRAIL potency in inflammatory breast cancer cells in an IAP-dependent and TNF- α -independent mechanism. *Breast Cancer Res. Treat.* 137(2), 359–371 (2013).
- 5 Krepler C, Chunduru SK, Halloran MB *et al.* The novel smac mimetic birinapant exhibits potent activity against human melanoma cells. *Clin. Cancer Res.* 19(7), 1784–1794 (2013).

■ WO2013052736

- 1 Henry D, Carless P, Fergusson D *et al.* The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis. *CMAJ* 180(2), 183–193 (2009).
- 2 Murkin JM, Falter F, Granton J *et al.* High-dose tranexamic acid is associated with nonischemic clinical seizures in cardiac surgical patients. *Anesth. Analg.* 110(2), 350–353 (2010).
- 3 Kim H, Szlam F, Tanaka KA *et al.* The effects of MDCO-2010, a serine protease inhibitor, on activated clotting time in blood obtained from volunteers and cardiac surgical patients. *Anesth. Analg.* 115(2), 244–252 (2012).

■ WO2013054153

- 1 ElSawy KM, Verma CS, Joseph TL *et al.* On the interaction mechanisms of a p53 peptide and nutlin with the MDM2 and MDMX proteins: a Brownian dynamics study. *Cell Cycle* 12(3), 394–404 (2013).
- 2 Secchiero P, Bosco R, Celeghini C *et al.* Recent advances in the therapeutic perspectives of Nutlin-3. *Curr. Pharm. Des.* 17(6), 569–577 (2011).

- 3 Mouraret N, Marcos E, Abid S *et al.* Activation of lung p53 by nutlin-3a prevents and reverses experimental pulmonary hypertension. *Circulation* 127(16), 1664–1676 (2013).

■ WO2013055913

- 1 Vander Heiden MG, Locasale JW, Swanson KD *et al.* Evidence for an alternative glycolytic pathway in rapidly proliferating cells. *Science* 329(5998), 1492–1499 (2010).
- 2 Hallows WC, Yu W, Denu JM. Regulation of glycolytic enzyme phosphoglycerate mutase-1 by Sirt1 protein-mediated deacetylation. *J. Biol. Chem.* 287(6), 3850–3858 (2012).
- 3 Hitosugi T, Zhou L, Elf S *et al.* Phosphoglycerate mutase 1 coordinates glycolysis and biosynthesis to promote tumor growth. *Cancer Cell* 22(5), 585–600 (2012).

■ WO2013057251 & WO2013057253

- 1 Guilligay D, Tarendeau F, Resa-Infante P *et al.* The structural basis for cap binding by influenza virus polymerase subunit PB2. *Nat. Struct. Mol. Biol.* 15(5), 500–506 (2008).
- 2 Reguera J, Weber F, Cusack S. Bunyaviridae RNA polymerases (ι -protein) have an N-terminal, influenza-like endonuclease domain, essential for viral cap-dependent transcription. *PLoS Pathog.* 6(9), e1001101 (2010).
- 3 Kowalinski E, Zubieta C, Wolkerstorfer A *et al.* Structural analysis of specific metal chelating inhibitor binding to the endonuclease domain of influenza pH1N1 (2009) polymerase. *PLoS Pathog.* 8(8), e1002831 (2012).
- 4 Savira Pharmaceuticals: WO2011000566 (2011).