

AVAILABLE PORTFOLIOS  
**LIFE SCIENCES**

<b>PS 510</b>	<b>TRANSDERMAL LISURIDE FOR PARKINSON'S DISEASE &amp; RESTLESS LEGS SYNDROME (RLS)</b> <i>ETV Capital Ltd.</i>
<b>PS 560</b>	<b>P450-BASED GENE-DIRECTED ENZYME PRODRUG THERAPY (GDEPT)</b> <i>Oxford Biomedica (UK) Limited</i>
<b>PS 576</b>	<b>TOPICALLY APPLIED DRUG PREPARATION &amp; METHOD FOR TRANSDERMAL DELIVERY</b> <i>Richlin Doherty, LLC</i>
<b>PS 582</b>	<b>MANUFACTURING TECHNIQUES FOR SILICA-BASED NANOCRYSTALLITES</b> <i>Sami Daoud</i>

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## TRANSDERMAL LISURIDE FOR PARKINSON'S DISEASE AND RESTLESS LEGS SYNDROME (RLS)

*ETV Capital Ltd.*

Dopaminergic therapy is the treatment of choice for Parkinson's disease (PD) and Restless Legs Syndrome (RLS).

For oral dopamine agonists (DAs), there is no clinical evidence that one compound is superior to another; however, the majority of clinical experts treating both PD and RLS patients agree that a certain number of patients respond well to one DA but not to another. Lisuride, which has an outstanding affinity for all dopamine receptors, (10<sup>-8</sup> – 10<sup>-10</sup> molar) has been launched as an oral DA for the treatment of PD. Since that time, a positive benefit risk evaluation has been observed, based on nearly 500,000 patient years of long-term use.

**Value Proposition:** To address the issue of short half-life and TID daily dosing with oral lisuride, Axxonis Pharma has developed a transdermal lisuride in the form of a 20 cm<sup>2</sup> patch, to be applied every other evening) as add-on therapy in advanced PD. The pivotal TULIP IIb study of transdermal lisuride as add-on therapy to stable high-dosed levodopa in advanced PD has confirmed the therapeutic effect of lisuride in PD. All primary and secondary efficacy parameters showed very robust, significant, and clinically relevant superiority over placebos. These results, which could never be achieved so rapidly with any oral DA, were obtained with a very low single digit rate of systemic adverse events (AEs). Reversible local reactions, which in some patients resulted in drop-outs, were the only prominent AEs in this study and will be addressed by modifying the formulation. The high efficacy of transdermal lisuride in RLS was also confirmed in the first ever three-armed comparative double-blind study vs. oral ropinirole (the only approved DA at the time of this study) and vs. placebo, over 12 weeks (TULIR 03). Corrected for the placebo effect, transdermal lisuride improved the IRLS by 7.5 and oral ropinirole by 4.9 points. The difference between both treatments came close to significance. In conclusion, very good dopaminergic efficacy has been demonstrated in both PD and RLS with a new transdermal application form of lisuride. There are many known advantages of transdermal application forms, including an easy dosing schedule, no interference with the GI system or liver metabolism and a low rate of typical systemic dopaminergic adverse events. The favorable benefit/risk profile for transdermal lisuride in both PD and RLS should interest both pharma and specialty pharma companies interested in launching products in these areas of unmet clinical need.

**Priority Date:** 05-18-1991

**Forward Citing Companies:** Siemens, Bayer, Axxonis Pharma, Novartis

**Representative Claim:** US 7,258,871 – Claim #1

A method of treating Parkinson's disease, Parkinsonism, and Restless Legs Syndrome, the method comprising the step of administering two or more discrete compositions of a dopamine agonist, wherein said discrete compositions comprise a first composition and a second composition, wherein said first composition comprises a transdermal therapeutic system (TTS) containing first

**TECHNOLOGY**  
PHARMACEUTICALS

**NOVELTY**  
ADVANCED TREATMENTS FOR PARKINSON'S DISEASE AND RESTLESS LEGS SYNDROME WITH LOW ADVERSE EFFECTS

**IMPORTANCE**  
PORTFOLIO HAS SIGNIFICANT POTENTIAL IN THE MULTI-BILLION DOLLAR US PHARMACEUTICALS MARKET

**NUMBER OF ASSETS**

*Please inquire for a complete asset listing.*

dopamine agonist and wherein said second composition comprises a second preparation of said first dopamine agonist, wherein said second preparation is selected from the group consisting of an oral preparation of the first dopamine agonist, a parenteral preparation of the first dopamine agonist, and mixtures thereof, wherein the second composition is administered within the duration of the administration of the first composition.

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## **P450-BASED GENE-DIRECTED ENZYME PRODRUG THERAPY (GDEPT)**

*Oxford Biomedica (UK) Limited*

Cyclophosphamide (CPA) is one of a group of drugs that is taken by the patient in the form of an inactive prodrug. In fact CPA has been used widely in clinical practice since the 1950's and therefore there is broad familiarity in the oncology community. CPA remains a treatment option for several cancers and has been used in high dose regimens, for example in metastatic breast cancer. CPA travels through the body to the liver where the active metabolite is generated. The enzyme P450 (CYP2B6), which is predominantly expressed in the liver, converts the prodrug CPA to a 4-hydroxy intermediate. The intermediate is dispersed via the circulation to the tumor target where it transits the cell membrane and further converts into the toxic metabolites acrolein and phosphoramidate mustard. The phosphoramidate mustard interacts with DNA to form crosslinks.

This has limited effects on quiescent cells but, once the cell divides, the cross-links result in DNA fragmentation and damage, which result in cell death by both apoptosis and necrosis. Although this mechanism of killing is highly potent, the short half-life of the metabolite means that the effective concentration of the drug at the tumor site is diminished by both transit times as well as by system dilution. In addition, the systemic toxicity caused by the active metabolite limits the dose that can be administered. Local efficacy at the tumor is therefore limited by systemic toxicity. Genetic delivery of cytochrome P450 to the tumor site (GDEPT) provides a clear path to optimising the potency and therapeutic index of CPA. The objective is to achieve high concentrations of activated CPA locally in the tumor.

**Value Proposition:** This intellectual property portfolio represents a novel approach for the treatment of cancer by targeting prodrug activation to the tumor site. Oxford BioMedica has broad intellectual property, covering various aspects of this field, which is of value in achieving freedom to operate in the field and protecting both gene-based and cell-based prodrug products. Oxford BioMedica has exploited its prodrug and viral vector IP estate through the development of a gene-based product (MetXia) and a cell-based product (MetXia-MG). The concept behind GDEPT is to exploit a metabolic conversion that would not normally occur to any significant level in the target cells. An appropriate vector (typically viral) is used to achieve insertion and expression of a prodrug-activating enzyme within tumor cells. Following administration of the otherwise non-toxic (or minimally toxic) prodrug, this is converted to an active, toxic metabolite in transduced cells. These are subsequently killed. Bystander, untransduced cells might also be killed following prodrug activation, by mechanisms that include direct transfer of an activated drug, ingestion of apoptotic bodies from killed cells, effects on tumor vasculature, or immunological responses.

MetXia is currently in phase II clinical development and MetXia-MG is at the pre-clinical stage. A commercial partner may have the option of acquiring the P450-based GDEPT technology with or without a commitment to develop further MetXia or MetXia-MG, subject to the development plans for the technology set out by the partner.

### Clinical Results (MetXia)

- Completed Phase I/II trials in 19 patients with accessible metastatic lesions
- All endpoints met
- Safe and well tolerated in all patients with dose dependent gene transfer

### **TECHNOLOGY**

BIOPHARMACEUTICALS

### **NOVELTY**

CANCER TREATMENT VIA  
TARGETED PRODRUG  
ACTIVATION TO THE  
TUMOR SITE

### **IMPORTANCE**

STRATEGIC IP FOR  
COMPANIES INVOLVED IN  
CANCER TREATMENT

### **NUMBER OF ASSETS**

44

### **PATENTS (42)**

US 5,688,773 EP 0772689  
US 5,591,624 EP 0776161  
US 5,716,832 EP 0953052  
US 5,888,502 ES 0772689  
US 6,241,982 FR 0772689  
US 6,333,195 FR 0776161  
US 6,013,517 FR 0953052  
AT 0772689 GB 0772689  
AT 0776161 GB 0776161  
AU 665176 GB 0953052  
AU 690427 IE 0772689  
BE 0772689 IE 0776161  
BE 0776161 IE 0953052  
CA 1341585 IT 0772689  
CA 2197677 JP 4092278  
CH 0772689 JP 4303315  
CH 0776161 JP 4509221  
CH 0953052 LI 0772689  
DE 0772689 LI 0776161  
DE 0776161 LI 0953052  
DE 0953052 LU 0772689

### **APPLICATIONS (2)**

US 12/699,509  
EP 07011311

- Reductions in cutaneous tumor nodule size
- Phase I-II trial in unresectable pancreatic cancer is ongoing
- Twenty three of approximately 29 patients treated to date
- Disease stabilization and associated stabilization of tumor markers
- Cancer-specific systemic immune responses, improvements at distant uninjected tumor sites and reductions in tumor markers

#### Preclinical Results

- MetXia has shown significant reduction in tumor burden and delayed tumor growth
- MetXia-MG has shown targeted invasion of tumors and survival benefit
- No toxicity was observed in any animal model with MetXia or MetXia-MG

#### Materials

- MetXia comprises the P450 type 2B6 (CYP2B6) gene, the most efficient activator of cyclophosphamide prodrug class, using an advanced, 'minimal' retrovirus vector derived from murine leukemia virus (MLV)
- MetXia-MG comprises isolated macrophages transduced by an adenoviral vector containing the genes encoding cytochrome P450 type 2B6 and P450 reductase which are controlled by a hypoxia-regulated promoter

**Priority Date:** 03-21-1988

**Forward Citing Companies:** Novartis, Bristol Myers Squibb, Roche, Sempra Energy, Vertex Pharmaceuticals

**Representative Claim:** US 6,241,982 – Claim #1

A method for treating a tumor in a human patient comprising: (a) administering a replication defective retroviral or adenoviral vector, which infects human cells, directly to a tumor in a human patient in need of treatment for said tumor, said replication defective retroviral or adenoviral vector being free of producer cells and encoding a conditionally lethal gene product which activates a prodrug into a cytotoxic agent, said gene being operatively linked to a control element for expression in said tumor, said gene product being E. coli guanine phosphoribosyl transferase; and (b) providing said tumor with said prodrug, whereby said gene product converts said prodrug to a cytotoxic agent, whereupon cells of said tumor are destroyed.

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## TOPICALLY APPLIED DRUG PREPARATION & METHOD FOR TRANSDERMAL DELIVERY

Richlin Doherty, LLC

This patent portfolio discloses a preparation method for a therapeutic agent that can be applied topically for delivery into a patient's skin. While a number of drugs have been marketed for relief of minor muscular aches and pains, none appear to address moderate-to-severe pain (e.g., acute, post-traumatic, and chronic pain). Also, a scarcity exists for topically applied agents/drugs for the relief of various chronic pain conditions. Thus there is need for safe and reliable analgesic drugs or therapeutic agents.

**Value Proposition:** This patent portfolio discloses a preparation of a therapeutic agent that is topically applied and a method for its transdermal delivery through a patient's skin to target the inciting tissues or structures. The agent is mainly comprised of a skin penetration enhancer (e.g., lecithin or dimethylsulfoxide), and vasoconstrictor. Further, the agent includes a local anesthetic (e.g., bupivacaine, mepivacaine, levobupivacaine, ropivacaine, chloroprocaine, procaine, lidocaine, etidocaine, benzocaine, tetracaine, or prilocaine) for reducing/blocking neural transmission of pain and non-steroidal anti-inflammatory agents for prompt and long-lasting relief. The penetration enhancer carries the therapeutic agent and the vasoconstrictor through a patient's skin to sites of desired action; the vasoconstrictor retards the vascular dispersion of the agent from the site. Therefore, the vasoconstrictor prolongs the duration of the agent's effect and reduces the dosage frequency. This therapeutic agent is efficient in relieving moderate-to-severe pain while also avoiding the adverse systemic effects associated with use of oral and other systemic analgesic/adjuvant drugs. Effective use of this preparation may afford opportunities to reduce or eliminate concurrent opioid use.

**Priority Date:** 06-03-2004

**Representative Claim:** A preparation for topically delivering and localizing at least one therapeutic agent, comprising: a vasoconstrictor for retarding vascular dispersion of a therapeutic agent, selected from the vasoconstrictor group consisting of at least one of: phenylephrine, ephedrine sulfate, epinephrine, naphazoline, and oxymetazoline; and a penetration enhancer for facilitating penetration of said vasoconstrictor and said therapeutic agent through a patient's intact skin, selected from the penetration enhancer group consisting of at least one of: lecithin and dimethylsulfoxide; wherein: said therapeutic agent is selected from at least one therapeutic agent in at least one of the following therapeutic agent groups: (a) a local anesthetic selected from the group consisting of: bupivacaine, mepivacaine, levobupivacaine, ropivacaine, chloroprocaine, procaine, lidocaine, etidocaine, benzocaine, tetracaine, and prilocaine; (b) a rapid-onset, short-acting non-steroidal anti-inflammatory agent [NSAID] selected from the group consisting of: ketoprofen, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, and tolmetin; (c) a long-acting non-steroidal anti-inflammatory agent selected from the group consisting of: piroxicam, celecoxib, meloxicam, nabumetone, naproxen, oxaprozin, rofecoxib, sulindac, and valdecoxib; (d) an antiviral agent selected from the group consisting of: 2-deoxy-d-glucose, podoflox, acyclovir, penciclovir, and docosanol.

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### TECHNOLOGY

LIFE SCIENCES

### NOVELTY

TRANSDERMAL DELIVERY OF TOPICALLY APPLIED THERAPEUTIC AGENT/ DRUG TO EFFECTIVELY ELIMINATE MODERATE-TO-SEVERE CHRONIC PAIN

### IMPORTANCE

IMPORTANT PROFILE FOR ANALGESIC MANUFACTURERS

### NUMBER OF ASSETS

7

### PATENTS (2)

US 7,666,914  
AU 2005251740

### APPLICATIONS (5)

US 11/569,805  
BR P10511235-4  
CA 2569072  
EP 05757659.7  
IN 4460/CHENP/2006

PS  
576

## MANUFACTURING TECHNIQUES FOR SILICA-BASED NANOCRYSTALLITES

Sami Daoud

The patent portfolio discloses techniques for manufacturing silica-based nanocrystallites. Silica-based hydrogels such as aerogels, xerogels, nanogels, and ambigels are chemically inert and highly porous ceramic materials that are useful in many applications. They are commonly produced from a source of silica (e.g., silicate or alkoxide) by dispersing the silica source in a synthesis solvent and gelation catalysts. Products of silica hydrolysis then condense, forming a sol system having a network of linked silica particles. After the sol system reaches its gel point, the sol-gel is set aside to age, allowing hydrolysis and condensation of reactants to continue while the sol-gel self-assembles, strengthening the gel structure and increasing its density. During the aging process, the gel is contacted with a low surface tension topping agent such as alcohol to displace water of condensation present in the nanoporous structure of the gel. Then, the wet hydrogel is dried. Owing to the high capillary stress exerted on the wet gel network during drying, this product is at a high risk of compression, extended cracking, shrinkage, and pore collapse, particularly in highly porous, low density gel structures having relatively high surface areas. Therefore, if care is not taken in the drying process, the wet gels are prone to structural weakness and significant brittleness (friability) when dried. Improved techniques are therefore required for manufacturing silica-based nanocrystallites.

**Value Proposition:** This portfolio discloses a process for manufacturing silica-based nanocrystallites having a nanoporous 3-dimensional silica-based network of high water and oxygen permeability, and a granular, monolithic, or hybrid geometric structure. The disclosed process uses a substantially homogenous colloidal dispersion of silica source, catalyst, and surfactant to form the sol matrix. Also, the drying process for a wet hydrogel intermediate product includes a short-cycle drying period during which the liquids present in this hydrogel can be evaporated at ambient pressure and temperature ranges at or below a specified temperature. Therefore, the gel structure and especially gel porosity is preserved. The nanocrystallites produced by this process have excellent clarity, density, R-values, thermal conductivity, sound velocity, refractive indexes and bulk modulus.

**Priority Date:** 10-03-2006

**Representative Claims:** US 7,750,056 – Claim #1

A method for synthesis, manufacture, and production of a silica nanocrystallite material comprising a colloidal dispersion, produced by using high speed homogenization, wherein a base catalyst is added to a solvent to form a catalyst solution and homogenized, using high speed homogenization, wherein a surface-active agent (surfactant) is dispersed in the catalyst solution using high speed homogenization thus forming a low surface tension catalyst solution; wherein a precursor solution is mixed with the catalyst solution while at the same time high speed homogenization is carried out, thus forming oil-in-water (O/W) emulsion, wherein a hydrolysis-polycondensation reaction mechanism takes place instantaneously with the aid of the catalyst, thus forming a hydrogel; wherein a hydrophobing agent is added few seconds prior to formation of the hydrogel, while homogenizing is in progress, thus rendering the hydrogel a sol-gel with hydrophobic characteristics.

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### TECHNOLOGY

NANOTECHNOLOGY

### NOVELTY

IMPROVED  
MANUFACTURING  
OF SILICA-BASED  
NANOCRYSTALLITES

### IMPORTANCE

STRATEGIC PORTFOLIO  
FOR COMPANIES ENGAGED  
IN THE MANUFACTURING  
OF NANOPARTICLES OR  
NANOCRYSTALLITES

### NUMBER OF ASSETS

2

### US PATENTS (1)

7,750,056

### US APPLICATIONS (1)

60/848,631

PS  
582