



### **Technologies for Out-licensing**

1. POTENTIATION OF ERYTHROPOIETIN ACTION BY MEMBRANE STEROID RECEPTOR AGONISTS
2. A NOVEL INDICATION FOR CRH ANTAGONISTS: TREATMENT OF CHRONIC INFLAMMATORY DISEASES
3. NOVEL SPIROSTEROID MOLECULES WITH POTENT NEUROPROTECTIVE, AND NEUROREGENERATIVE ACTIVITIES

# POTENTIATION OF ERYTHROPOIETIN ACTION BY MEMBRANE STEROID RECEPTOR AGONISTS

## LICENSING OPPORTUNITY

### OFFERING HIGHLIGHTS

- Novel technology targeted at the potentiating the function of erythropoietin (EPO)
- Enhancers of the action of EPO can be used in conjunction with lower doses of EPO in the treatment, for example, of anemia in cancer patients.
- Discovery addressing the FDA suggestion to use the lowest possible dose of EPO
- Specific steroid membrane receptor agonists are available for licensing
- The patented steroid membrane receptor agonists are currently in clinical development for cancer treatment
- Seeking worldwide licensee of novel use of novel steroid membrane receptor agonists as potentiators of EPO action.

### COMPANY PROFILE

Bionature EA, Ltd., headquartered in Nicosia, Cyprus, is a privately held biomedical research and pre-clinical development company established in 2003. Bionature seeks to discover new technologies that will enable the diagnosis, prevention, and treatment of diseases that contribute to chronic diseases and human aging. The Company focuses on the following main areas:

- Oncology, anti-tumor therapy
- Neuroprotective activities of natural and synthetic compounds
- Chronic inflammatory conditions
- Clinical diagnostics

Bionature seeks to achieve these goals by in-licensing discovery stage technology, building the intellectual property, performing pre-clinical development, and ultimately out-licensing the technology at the late pre-clinical / early clinical development stages. Bionature leverages its partnerships with academic centers to create synergy in applied and clinical research in the biomedical sciences, and in the development, testing and marketing of innovative pharmaceuticals and other biomedical products. Bionature currently has a strategic partnership with Emergo, an international private equity company, as well as a research partnership with the University of Crete Medical School. Bionature is actively looking for licensing partners.

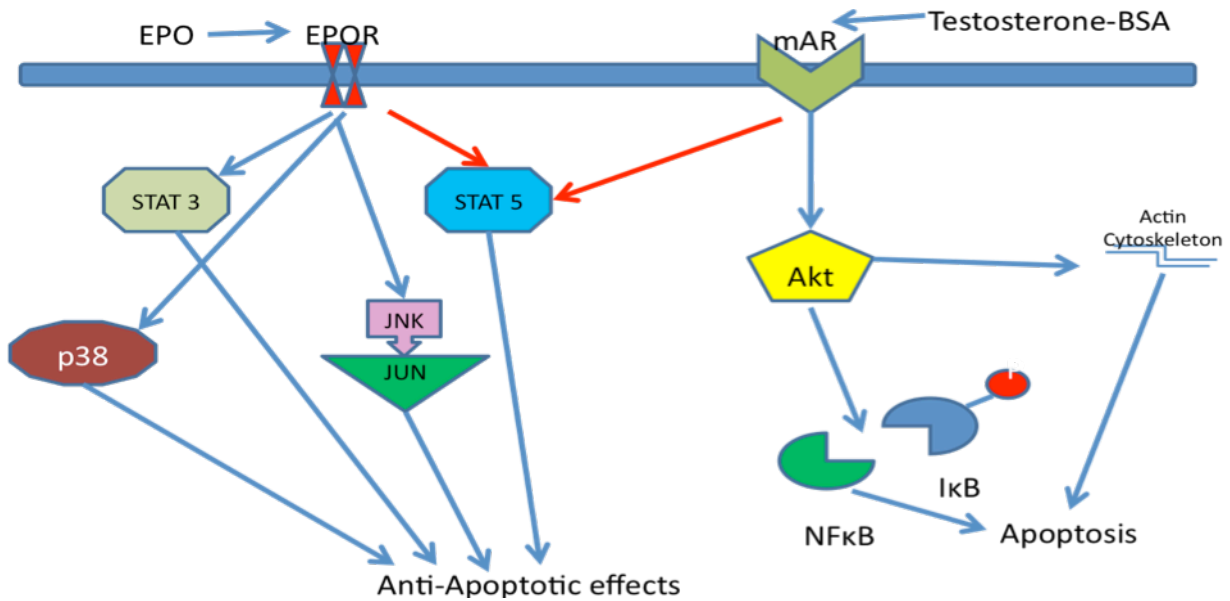
### TECHNOLOGY OVERVIEW:

Bionature's erythropoietin (EPO) invention relates to the use of membrane steroid receptor agonists as potentiators of the action of the best-selling erythropoiesis agent, EPO. More specifically, macromolecular conjugates of steroids with proteins of any kind (serum albumin, antibodies, or other proteins, which do not permit them to enter the cell and therefore designate them as agonists of the membrane receptors) or micromolecules, acting as agonists on these specific sites, are used as enhancers of the action of EPO in haemopoietic or extra-haemopoietic tissues. The invention claims that EPO and the membrane receptor agonists may be used conjointly in a kit, in order to decrease the administered doses of EPO and to minimize its side-effects, to control proliferation, differentiation, migration and regeneration of cells, in different organs and tissues. For example, EPO is commonly given to cancer patients to alleviate fatigue and to counter anemia, the most common cancer-associated morbidity. A growing body of evidence suggests that EPO may shorten survival in cancer patients and might possibly fuel tumor cell growth. In March 2007, the FDA added a black-box warning to EPO's prescribing information that included a warning that EPO "may cause thrombotic events... .. and increase the risk of death..." It warned physicians to "... use the lowest dose...". Bionature's discovery could help reduce the dosage of EPO required to have the desired anti-anemic effects and thus reduce the risks associated with the higher doses of EPO in cancer patients.

### PARTNERSHIP / LICENSING OPPORTUNITIES

Bionature EA, Ltd. is currently seeking worldwide strategic partners to continue development of its EPO technology for the safer treatment of patients currently receiving EPO. The opportunity also exists for the licensing of specific membrane steroid receptor agonists that are being developed as anti-tumor agents. Bionature has several patent applications filed in the USA and in the EU.

## Proposed mechanism of interaction between the EPO and steroid receptor agonist signaling pathways



- EPO market at \$10 billion in the USA (2006) and rising
- Data from recent clinical studies with patients who received EPO prompted the FDA to approve new labeling for the use of EPO products in patients with cancer
- Bionature's product could help reduce the dose of EPO required in cancer patients to have the desired effects.
- Accomplished scientists in the fields of chemistry, endocrinology, and pharmacology
- Bionature's scientists published more than 250 peer-reviewed scientific papers

### BRIEF MARKET OVERVIEW

The total US sales for erythropoietins (EPO) in 2006 were \$10 billion up from \$6.4 billion in 2004. The recent attention to safety concerns notwithstanding, sales of EPO and the number of dispensed prescriptions were 4% higher in the first quarter of 2007. Johnson & Johnson, AMGEN and Hoffman La Roche, all have blockbuster EPO products on the market. An estimated 300,000 patients take EPO each year.

Further to the approval by the FDA of new labeling for EPO products strengthening the Boxed Warning and Warnings sections of the labeling, there is a demand for agents that would help mitigate the risks associate with EPO administration to cancer patients.

### MANAGEMENT TEAM

#### *Achilleas Gravanis, PhD*

Dr. Gravanis is Professor of Pharmacology at the University of Crete Medical School. His special research interests include modulation of the proliferation, apoptosis, and differentiation of neural and neuroendocrine normal and tumor cells. In addition, his interests lie in neurodegenerative diseases and neuroprotective agents.

Dr. Gravanis has published more than 100 papers in MedLine journals.

#### *Elias Castanas, MD, PhD, DSc*

Dr. Castanas is currently a Professor of Experimental Endocrinology, at the University of Crete Medical School and Director of the Endocrinology Laboratory at the University Hospital of Heraklion in Crete. Special research interests: Modulation of the proliferation of hormone sensitive tumours by biologically active substances (opioid peptides and analogues, antioxidant polyphenols, and neuroactive steroids).

Dr Castanas published more than 100 papers in peer-reviewed journals and several US and European patents.

#### *Constantinos Neophytou, PhD*

Dr. Neophytou is a portfolio manager with the private equity group, Emergo and is the Managing Director of Bionature. He holds a B.A. and an M.A. in Natural Sciences at Cambridge University and a Ph.D. in Neuroscience from University College London. He was a post-doctoral fellow at Harvard Medical School as a Wellcome Trust Prize Scholar. Prior to joining Emergo, he worked for three years as the General Manager of a financial services group and the venture capital firm BOC Ventures in Cyprus. He is on the BOD of a number of emerging Companies, in the biomedical sector and in the information and communication technology sectors.

Dr Neophytou has close to 10 years experience in private equity transactions in the biomedical sector.

# A NOVEL INDICATION FOR CRH ANTAGONISTS: TREATMENT OF CHRONIC INFLAMMATORY DISEASES

## LICENSING OPPORTUNITY

### OFFERING HIGHLIGHTS:

- Novel technology currently targeted at treatment of a wide range of inflammatory disorders.
- Existing safety data ensures low risk and/or expedited process through phase I trials.
- Patent protected through issued and pending patent applications.

- Treatment of Inflammatory diseases through Corticotropin-Releasing Hormone (CRH) and Urocortin (UCN) systems.
- Regulation of monocyte and macrophage cell activity pathways.
- Synthetic CRH-R1 antagonists inhibit the activity of macrophages.
- Product has excellent safety profile.

- Seeking world wide licensee of novel CRH pathway for the treatment of inflammatory diseases

### COMPANY PROFILE:

Bionature EA, Ltd., currently headquartered in Nicosia, Cyprus, is a private biomedical research and pre-clinical development company founded in 2003. Bionature seeks to discover new technologies that will enable the diagnosis, prevention, and treatment of diseases that contribute to chronic diseases and human aging. The company's focuses on the following main areas:

- Oncology, anti-tumor therapy
- Chronic inflammatory conditions
- Clinical diagnostics
- Neuroprotective activities of natural and synthetic compounds
- Pharmacogenomics

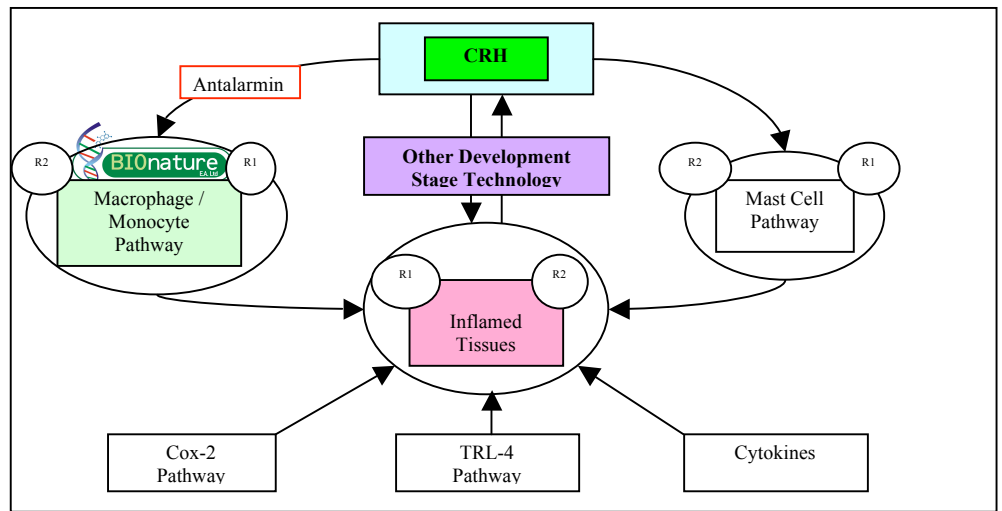
Bionature seeks to achieve these goals by in-licensing discovery stage technology, building the intellectual property, performing pre-clinical development, and ultimately out-licensing the technology at the late pre-clinical / early clinical development stages. Bionature leverages its partnerships with academic centers to create synergy in applied and clinical research in the biomedical sciences, and in the development, testing and marketing of innovative pharmaceuticals and other biomedical products. Bionature currently has a strategic partnership with Emergo, an international private equity company, as well as a research partnership with the University of Crete Medical School. Bionature has successfully out-licensed several projects to European biotechnology firms.

### TECHNOLOGY OVERVIEW:

Bionature's CRH technology relates to the use of the Corticotropin-Releasing Hormone (CRH)—Urocortin (UCN) System for the treatment of inflammatory diseases. The CRH technology targets the inflammatory process by regulating the monocyte & macrophage cell activity pathways. Macrophages are among the primary initiator cells during an inflammatory response and they are the main source of a series of pro-inflammatory cytokines. These inflammatory cells are activated by the binding of CRH to the CRH-R1 receptor sites. By directly blocking the cell activity of macrophages, synthetic CRH-R1 antagonists present a novel approach to the treatment of inflammatory disorders. Synthetic CRH-R1 antagonists and/or CRH-R2 agonists (UCN) have the potential to be as efficacious as Cox-2 inhibitors, but without the toxicity of a Cox-2 inhibitor. The CRH technology could ultimately be utilized as an alternative to Cox-2 inhibitors, providing a novel replacement product for the controversial Cox-2 inhibitor products. Another advantage to the currently pre-clinical stage CRH technology offered by Bionature is the large body of safety data that currently exists around the use of both Corticotropin-Releasing Hormone and the CRH antagonists. This data suggests that an established safety profile already exists for this technology, which increases the probability of successfully advancing through to Phase II trials.

### PARTNERSHIP/LICENSING OPPORTUNITIES:

Bionature EA, Ltd. is currently seeking world wide Strategic Partners to continue development of its CRH technology for the treatment of chronic inflammatory disorders, by regulating the monocyte & macrophage cell activity pathways. The opportunity also exists for the licensing of the CRH technology, which is currently ready for IND application in the United States.



- Anti-inflammatory market is projected to grow to \$50 billion by 2010.
- Many patients continue to be refractory to current treatments.
- Wide scope of anti-inflammatory market provides extensive opportunity for novel medications
- CRH Technology represents a potential alternative to Cox-2 inhibitors.

- Experienced scientists in the fields of chemistry, endocrinology, and pharmacology
- Over 250 scientific papers have been published by the Bionature team of scientists.

### MARKET OVERVIEW:

The market for anti-inflammatory drugs in 2005 was approximately \$31 bln and is projected to swell to around \$50 bln by 2010. The market in 2005 was dominated by treatments for asthma and chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, multiple sclerosis, psoriasis, and inflammatory bowel disease. The fastest growing markets in the next five years will be for the treatment of psoriasis and rheumatoid arthritis, both with average annual growth rates of over 13 percent (BCC Research 2006). The anti-inflammatory market was dramatically altered in 2004 by the withdrawal of Merck's blockbuster anti-inflammatory product, Vioxx<sup>®</sup>, and the subsequent increased scrutiny by the FDA of the entire class of Cox-2 inhibitors. Although competition in the treatment of inflammatory disorders is high, there is still a demand for novel treatments to be developed and pharmaceutical and biotech companies are looking to develop safer and more effective alternatives to the Cox-2 inhibitor class of drugs. Bionature's CRH system represents a novel approach to the treatment of neurogenic inflammatory disorders.

### MANAGEMENT TEAM:

#### **Achilleas Gravanis, PhD**

Dr. Gravanis is Professor of Pharmacology at the University of Crete Medical School. His special research interests include modulation of the proliferation, apoptosis, and differentiation of neural and neuroendocrine normal and tumoral cells. In addition, his interests lie in neurogenerative diseases and neuroprotective agents. Dr. Gravanis has published more than 100 papers in MedLine journals.

#### **Elias Castanas, MD, PhD, DSc**

Dr. Castanas is Professor of Experimental Endocrinology at the University of Crete Medical School. His special research interests include modulation of the proliferation of hormone sensitive tumors by biologically active substances. Dr. Castanas has published more than 100 papers in MedLine journals.

#### **Constantinos Neophytou, PhD**

Dr. Neophytou is a portfolio manager with the private equity group, Emergo and he serves as the Managing Director of Bionature. He received his B.A. and M.A. in Natural Sciences at Cambridge University and his Ph.D. in Neuroscience at University College London. He was a post-doctoral fellow at Harvard Medical School as a Wellcome Trust Prize Research Scholar. He has close to 10 years experience in private equity transactions in the biomedical sector.

# NOVEL SPIROSTEROID MOLECULES WITH POTENT NEURO-PROTECTIVE, AND NEURO-REGENERATIVE ACTIVITIES

## LICENSING OPPORTUNITY

### OFFERING HIGHLIGHTS

- Novel small synthetic compounds with strong neuro-protective activity
- International patent applications pending covering the structure and function of the novel compounds
- Neuro-protective compounds which lack endocrine activity

- Spectacular *in vitro* data demonstrating potent anti-apoptotic activity in neuronal cell lines and primary neurons
- Compounds tested in several animal models of neurodegenerative disease, including Multiple Sclerosis, macular degeneration and Parkinson's disease

- Seeking worldwide licensing partner for the clinical development of novel proprietary neuro-protective and neuro-regenerative molecules

### COMPANY PROFILE

Bionature EA, Ltd., headquartered in Nicosia, Cyprus, is a privately held biomedical research and pre-clinical development company established in 2003. Bionature seeks to discover new technologies that will enable the diagnosis, prevention, and treatment of diseases that contribute to chronic diseases and human aging. The Company focuses on the following main areas:

- Oncology, anti-tumor therapy
- Neuroprotective activities of natural and synthetic compounds
- Chronic inflammatory conditions
- Clinical diagnostics

Bionature seeks to achieve these goals by in-licensing discovery stage technology, building the intellectual property, performing pre-clinical development, and ultimately out-licensing the technology at the late pre-clinical / early clinical development stages. Bionature leverages its partnerships with academic centers to create synergy in applied and clinical research in the biomedical sciences, and in the development, testing and marketing of innovative pharmaceuticals and other biomedical products. Bionature currently has a strategic partnership with Emergo, an international private equity company, as well as a research partnership with the University of Crete Medical School. Bionature is actively looking for licensing partners.

### TECHNOLOGY OVERVIEW

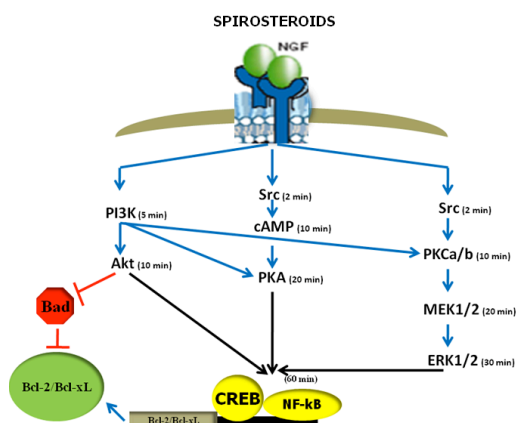
Neuronal cell death by apoptosis is the 'end-point' of many human neurological disorders, including Alzheimer's, Parkinson's and Huntington's diseases, stroke/trauma, multiple and amyotrophic lateral sclerosis. Additionally, brain ischemia and trauma induce necrosis of a small brain area, which then propagates neuronal cell loss by apoptosis to a larger brain area, due to the neurotoxic material released by the necrotic cells. Apoptotic neuronal cell loss is also observed in the ageing brain, as a physiological process. Currently, there is little or no treatment for most neurodegenerative diseases. A fundamental approach for reducing the burden of neurodegenerative diseases is to slow or halt progression, and ultimately, to prevent the onset of the disease process. Thus, strategies for neuroprotection, preventing apoptotic neuronal cell loss may offer new therapeutic interventions.

Bionature had developed novel spirosteroid molecules that possess anti-apoptotic, neuro-protective activity and are apparently devoid of any hormonal side effects. These molecules interact with NGF receptors, activating major pro-survival, anti-apoptotic signalling in degenerative neurons, addressing the pressing need for the discovery of new compounds for neural cell protection, repair and rescue. Bionature's research in a number of widely accepted mouse models of neurological disease and in stem cells has demonstrated that its proprietary molecules are effective in preventing neuronal apoptosis and in inducing neurogenesis.

### PARTNERSHIP/LICENSING OPPORTUNITIES

Bionature is currently seeking worldwide strategic partners to continue developing its neuroprotective compounds for the safe and effective treatment of neurodegenerative diseases, such as Multiple Sclerosis (three of Bionature's compounds efficiently reverse paralysis of EAE mice, modulating Th17 response and neuronal apoptosis). The invention provides pharmaceutical compositions and methods of treating various neurodegenerative diseases.

Bionature has several patent applications pending and is actively investigating the efficacy of its proprietary compounds in *in vitro* and *in vivo* experimental models.



## Testing of spirosteroids *in vivo*

In vivo animal model	Human Disease
Experimental Allergic Encephalomyelitis (EAE) mice	Multiple Sclerosis
MPTP mice	Parkinson's
NGF+/- mice	Alzheimer's
Retinal Ischemia rats	Retina Degeneration
Brain Cryolesion	Brain Trauma
Neural Stem cells	Neurogenesis

- The global pharmaceutical market for neurodegenerative diseases will grow to over \$30 billion in the next few years
- There is a pressing need for safe treatments that will be able to prevent neuronal damage very early on in conditions affecting neuronal survival and regeneration
- Bionature's products show great promise for the prevention as well as the treatment of neurodegeneration
- Accomplished scientists in the fields of chemistry, neuroscience, and pharmacology
- Bionature's scientists published more than 250 peer-reviewed scientific papers
- Research also in progress with *in vivo* models for other neurological conditions

## BRIEF MARKET OVERVIEW

Neurodegenerative disease (NDD) is a general term for a number of disorders that compromise the brain's function by damaging the neurons. Some of the most prevalent conditions are Alzheimer's disease, Parkinson's disease, Multiple Sclerosis and Retinal Degeneration. Many of the underlying mechanisms of damage to the nervous system are common to NDD and other acute diseases such as brain trauma and stroke. Neuroprotective treatments that can effectively prevent neurons from dying are rapidly becoming a major and important component of the NDD market.

The World Health Organization forecasts that NDD will become the world's second leading cause of death by the year 2040, overtaking cancer. Sales among current medicines for NDD total more than \$18.5 billion and are expected to increase 62% to \$29.7 billion by 2012. NDD patients have few treatment options, which often provide only limited effectiveness. Companies that can invest in and develop new, tolerable therapies, which improve the patients' quality of life, could see hundreds of millions — or even billions — of dollars in sales.

## MANAGEMENT TEAM

### *Achilleas Gravanis, PhD*

Dr. Gravanis is Professor of Pharmacology at the University of Crete Medical School. His special research interests include modulation of the proliferation, apoptosis, and differentiation of neural and neuroendocrine normal and tumor cells. In addition, his interests lie in neurodegenerative diseases and neuroprotective agents.

Dr. Gravanis has published more than 100 papers in MedLine journals.

### *Elias Castanas, MD, PhD, DSc*

Dr. Castanas is currently a Professor of Experimental Endocrinology, at the University of Crete Medical School and Director of the Endocrinology Laboratory at the University Hospital of Heraklion in Crete. Special research interests: Modulation of the proliferation of hormone sensitive tumours by biologically active substances (opioid peptides and analogues, antioxidant polyphenols, and neuroactive steroids).

Dr Castanas published more than 100 papers in peer-reviewed journals and several US and European patents.

### *Constantinos Neophytou, PhD*

Dr. Neophytou is a portfolio manager with the private equity group, Emergo and is the Managing Director of Bionature. He holds a B.A. and an M.A. in Natural Sciences from Cambridge University and a Ph.D. in Neuroscience from University College London. He was a post-doctoral fellow at Harvard Medical School as a Wellcome Trust Prize Scholar. Prior to joining Emergo, he worked for three years as the General Manager of a financial services group and the venture capital firm BOC Ventures in Cyprus. He is on the BOD of a number of emerging Companies, in the biomedical sector and in the information and communication technology sectors.

Dr Neophytou has close to 10 years experience in private equity transactions in the biomedical sector.