

## Gene Signal: Pioneer in treating angiogenesis-based disease

Gene Signal is a clinical-stage biotechnology company pioneering the development of innovative therapies for angiogenesis-based diseases. Gene Signal's product candidates are precisely targeted angiostatic (inhibiting vascular growth) or angiogenic (inducing vascular growth) agents derived from genes that are exclusively involved with the angiogenesis process. Four molecules are in development for seven indications in ophthalmology, dermatology, vascular disorders and cancer.

The Company's lead product candidate, Aganirsen (GS-101), will complete in 2013 an international Phase III clinical trial for the treatment of neovascularisation-associated corneal graft rejection (NV-CGR). Aganirsen is an antisense oligonucleotide that targets unwanted neovascularisation by precisely blocking a key upstream protein, IRS-1 (Insulin Receptor Substrate 1). Excessive blood vessel growth in this part of the eye is a key contributor to corneal graft rejection. Aganirsen is also ready to enter Phase II trials for the treatment of age-related macular degeneration (AMD) and neovascular glaucoma (NVG) and is concluding a Phase IIA for psoriasis. Gene Signal's pre-clinical pipeline also includes four molecules in the discovery phase addressing indications in the field of vascular disease and oncology.

Gene Signal's discovery program leverages a patented gene discovery platform named GENE-MAAP (Gene Signal Multiple Angiogenesis, Angiostatic Platform). GENE-MAAP streamlines the identification process of genes exclusively involved in the regulation of angiogenesis and has allowed Gene Signal to identify and patent more than 94 genes involved in the angiogenic process.

## Angiogenesis based disease management

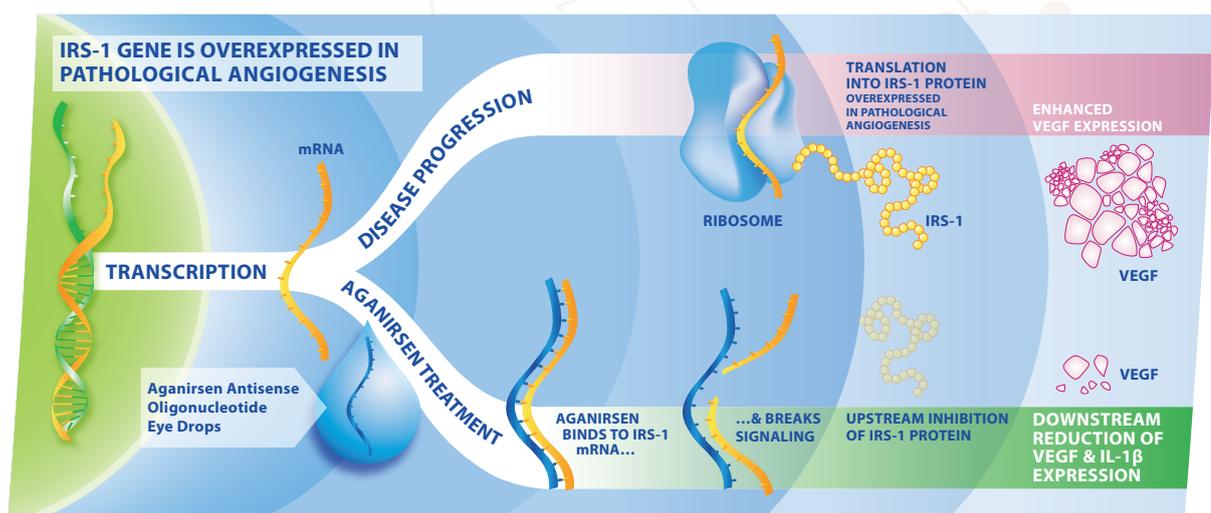
Angiogenesis is the growth of new capillary blood vessels. This natural process is controlled by a precise balance of growth and inhibitory agents produced in the body by healthy tissue for healing and reproduction. Abnormal blood vessel growth leads to many diseases including various ischemic and inflammatory diseases as well as cancer. According to the Angiogenesis Foundation, more than one billion people worldwide are believed to be affected by angiogenesis related conditions. In recent years, a concentrated research effort has been made to discover the specific pro- and anti-angiogenic molecules involved in the complex interactions of the angiogenesis process. According to Global Industry Analysts, the global market for Angiogenesis inhibitors and stimulators is expected to reach US\$ 53.5 Billion by 2015.

Gene Signal is dedicated to addressing important unmet needs in angiogenesis-based disease management. The current market challenge is to identify targeted agents that are specifically involved in the regulation of angiogenesis and are not widely expressed, nor play a role in unrelated physiological pathways. In addition, advancements need to be made in the design of optimal formulations and routes of administration for these innovative therapeutic agents.

## Aganirsen: First-in-class upstream inhibition of pathological angiogenesis

Gene Signal is adapting a unique approach to this disease area. Aganirsen, the Company's most advanced drug candidate, is a highly targeted angiostatic agent that regulates angiogenesis upstream of the VEGF pathway. Aganirsen inhibits angiogenesis by preventing the expression of Insulin Receptor Substrate 1 (IRS-1), a protein required for the formation and growth of new blood vessels. In vitro and in vivo data suggests that Aganirsen modulates selective transcriptional activities related to VEGF expression and has been shown to reduce levels of Interleukin IL-1 $\beta$ .

**Aganirsen (GS-101) penetrates the cell membrane to prevent upstream translation of mRNA into IRS-1 protein, leading to a downstream reduction in VEGF & IL-1 $\beta$  expression, thus inhibiting pathological (but not physiological) angiogenesis.**



# Gene Signal International Corporate Fact Sheet



Aganirsen is an antisense oligonucleotide administered in the form of eye drops. It is being developed for the treatment of progressive corneal neovascularisation to prevent Corneal Graft Rejection (CGR) in those patients with pathological neovascularisation not responding to the standard of care. Aganirsen is currently completing Phase III following very encouraging Phase II results. Interim analysis of Aganirsen eye drops (86 mcg /day) produced a highly significant regression of corneal neovascularisation ( $p = 0.0047$ ) together with a trend of an improvement of visual acuity. Compared to the placebo group, which showed 100% ongoing progression of corneal neovascularisation over the 3-month evaluation period, the Aganirsen group achieved 86% regression.

## GENE MAAP R&D platform delivers streamlined gene identification

Gene Signal's patented gene discovery platform, GENE-MAAP (GENE Signal Multiple Angiogenesis, Angiostatic Platform), streamlines the identification process of genes exclusively involved in the regulation of angiogenesis. GENE-MAAP allows Gene Signal to single out genes that are exclusively linked to the angiogenic and angiostatic process, taking into account a variety of factors, including inhibiting and inducing factors, extra-cellular matrix and human endothelial cells.

GENE-MAAP identifies both the gene coding for the angiogenesis regulatory factors and the gene coding for the cell constituents involved in the regulation of angiogenesis, thus allowing Gene Signal to identify highly specific targets. Gene Signal researchers are leveraging this proprietary scientific platform to conduct targeted drug development across a variety of disease areas.

## Diverse pipeline across 4 therapeutic areas

Gene Signal is developing a diverse pipeline of novel antisense oligonucleotides, proteins and monoclonal antibodies that are exclusively involved in the regulation of the angiogenic process. These development stage therapies aim to provide a more targeted approach by using genes that are exclusively involved in the process of angiogenesis.

### Gene Signal Pre-Clinical and Clinical Pipeline

#### Ophthalmology – Orphan

- GS-101 – Corneal Graft Rejection
- GS-101 – Neovascular Glaucoma
- GS-101 – Retinopathy of Prematurity

#### Ophthalmology – Non Orphan

- GS-101 – Age-Related Macular Degeneration
- GS-101 – Diabetic Retinopathy

#### Dermatology

- GS-101 – Psoriasis & Rosacea

#### Vascular

- GS-156 (small peptide) – Wound Healing

#### Oncology

- GS-497c – Lung Cancer
- GS-168 – Lung Cancer
- GS-101 – Bladder Cancer
- GS-156 – mAb

	PRE-CLINICAL DEVELOPMENT			CLINICAL DEVELOPMENT		
	Discovery	Proof of Concept	Pre-Clinical	Phase I	Phase II	Phase III
Ophthalmology – Orphan						
• GS-101 – Corneal Graft Rejection						Results 2013
• GS-101 – Neovascular Glaucoma				Start 2013		
• GS-101 – Retinopathy of Prematurity						
Ophthalmology – Non Orphan						
• GS-101 – Age-Related Macular Degeneration				Start 2013		
• GS-101 – Diabetic Retinopathy						
Dermatology						
• GS-101 – Psoriasis & Rosacea				Results Phase I/IIA 2013		
Vascular						
• GS-156 (small peptide) – Wound Healing						
Oncology						
• GS-497c – Lung Cancer						
• GS-168 – Lung Cancer						
• GS-101 – Bladder Cancer						
• GS-156 – mAb						

## Business strategy

Gene Signal maintains a broad discovery and development program, which enables the company to diversify risk and utilize its development capacity fully. Strategic partnerships for development and commercialization of its products will be used to maintain a balance of risk versus reward.

Gene Signal possesses the widest intellectual property portfolio on genes regulating angiogenesis. All patents are the exclusive property of Gene Signal and protection will not expire until 2022-2030.

**Gene Signal is looking to collaborate with a leading pharmaceutical partner to bring Aganirsen successfully through clinical development and to assume responsibility for product commercialization. Aganirsen holds Orphan Drug designation in Europe for Corneal Neovascularisation in Corneal Graft Rejection (CGR), Retinopathy of Prematurity (ROP) and Neovascular Glaucoma (NVG).**

## Management team

**Eric Viaud**, Chief Executive Officer  
**Salman Al-Mahmood**, Chief Scientific Officer  
**Dr. Eric Thorin**, Chief Development Officer  
**Dr. Antoine Ferry**, Chief Medical Officer  
**Sylvie Colin**, Head of Genomics  
**Marta Gehring**, BD&L and Chief Marketing Officer

## Key facts

**Main Focus:** Angiogenesis based diseases  
**Key Product:** Aganirsen (GS-101)  
**Development Stage:** Phase III  
**Company Status:** Private  
**Funding:** Network of private investors  
**Founded:** 2000  
**Locations:** Lausanne, Switzerland; Paris and Evry, France; Montreal, Canada

## Contact

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