Multi-Functional Anti-Inflammatory Drugs (MFAIDs):
Novel, non-steroidal, multifunctional approach to treating inflammatory/allergic diseases

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Background:
The initiation of inflammatory/allergic processes involves two key activities:
1. Degradation of cell membrane lipids by the enzyme phospholipase A2 (PLA2), leading to a cascade of inflammatory lipid mediators (ILM), which includes two main families: prostaglandins (PGs) and leukotrienes (LTs), produced via the COX and LOX pathways respectively.
2. Degradation of the cell-surface protective layer composed of glycosaminoglycans (GAG) that protects cells and tissues from damaging agents, such as free radicals, endotoxins, and enzymes that promote the formation of cancer metastasis.

A common and conventional approach to treating inflammatory processes has been the development of drugs that suppress the ILM formation or action, focusing primarily on the PG-producing COX pathways (COX inhibitors), assumed to be the predominant one(s). However, deleterious ILM are produced also by the other pathways. Therefore, the selective COX inhibition, represented by NSAIDs, has not been successful, and related drugs (e.g., VIOXX from Merck) have been withdrawn from the market. On these grounds, the approach of "inclusive pathway inhibition" has been proposed, aiming at containing the ILM production by all pathways, by controlling the PLA\textsubscript{2} activity.

At the same time, while the pharmaceutical industry has focused on the ILM production, the role of the cell-surface GAGs in inflammatory/allergic pathology has been ignored.

To address both needs (controlling ILM production and enriching the cell surface GAGs), we have designed and synthesized a platform of novel and unique compounds composed of PLA2-inhibiting lipid moieties conjugated to GAGs. This structure enables the inhibiting lipid component to incorporate into the surface and anchor the conjugated GAG to the cell membrane. These lipid-conjugates exert a dual protective effect: the PLA2-inhibiting lipid moiety suppresses the ILM production, and the membrane-anchored GAG enriches the cell surface protective layer. This presents a platform of multi-functional anti-inflammatory drugs (MFAIDs) for the treatment of diseases associated with lipid mediator production and/or damage to cell surface. The MFAIDs excellent safety been demonstrated in both pre-clinical and clinical data generated with over 200 subjects that have been treated with MFAIDs in clinical trials.

Results:
Selected MFAIDs have been tested and found effective in the suppression of inflammatory/allergic processes in different cell types (see List of Selected Publications below), as well as in inhibiting the production and action of metastasis-promoting enzymes by human cancer cells. Subsequently, the MFAIDS have been tested and found effective in treating diverse inflammatory conditions, in animal models and clinical studies, as follows:

In animal models:

Sepsis: Amelioration of endotoxin (LPS and LTA)-induced sepsis in rats (mortality and level of blood cytokines), by IP or IV administration of MFAID.

Inflammatory bowel disease (IBD): Ameliorating intestinal inflammation (models of colitis and Crohn’s disease) in rats and mice, treated with MFAID IP and orally.
Central nervous system inflammation: Amelioration of Experimental allergic encephalomyelitis (EAE, a model for multiple sclerosis), in rats and mice.

Cancer: Inhibition of melanoma-induced lung metastases in mice.

Clinical Trials (studies with patients and with human tissues):

1. Contact dermatitis: Two clinical studies (presenting Phase I and Phase IIa/IIb, double blind) showed excellent safety and efficacy in treating patients with contact dermatitis by topical application of MFAID.

2. Atopic Dermatitis (concluded on February 2015): Phase II clinical trial performed at Sheba Hospital in which patients with atopic dermatitis were treated with topical formulation (cream) of an MFAID (one dose). Results showed no toxicity or adverse effects, but no significant efficacy (should be retested using an appropriate formulation enabling a better penetration rate).

3. Airway pathologies (see below)

Airway Pathologies:

1. Clinical Studies:
   A. Allergic Rhinitis in allergic patients (in South Africa), treatment by intra-nasal (IN) administration (spraying) of MFAID solution (saline) – one dose (Slides 23-28 in the presentation).

   Excellent safety (better than placebo)

   Marked suppression of challenge-induced biochemical markers, IL-5, IL-13 TNF-α, MCP-1 and Eotoxin, as well as eosinophil level, in nasal lavage.

   11% improvement of symptoms.

   B. Chronic Rhinosinusitis (ex vivo), using Nasal polyps of patients suffering from Chronic Rhino-Sinusitis with polyps (CRSwP) (Slides 29-31 in the presentation).

   Nasal polyps (cell dispersion) of patients suffering from CRSwP were stimulated with super-antigen (SA = staphylococcus Aureus Enterotoxin).

   Treatment with MFAID markedly suppressed the SA-stimulated

   Production of IL-5, IL-13, IL-17 and to a lesser extent IFN-γ.

   Gene expression (mNBA) of secretory PLA2s gIB, gII (A, D &E), and gX

2. Human basophils: Suppression of IgE-stimulated histamine release (Slide 32).

3. Human lung Cystic fibrosis cells: Suppression of IL-8 production by hkPOA1-stimulated human CF cell lines (IB3 and C38) (Slide 33).
4. **Asthma model in rats** – Ovalbumin (OVA)-induced Experimental allergic bronchitis (EAB)  
   *(Ofer et al., Am.J.Physio, 2005; Shoseyov et al., Thorax 2005) (Slides 34-39 in the presentation)*

Inhaled MFAID (nebulized) ameliorated OVA-induced EAB, expressed by:

- **Prevention of broncho-constriction** by pre-challenge MFAID inhalation, in sensitized and treated rats.

- **Relief (prevention) of broncho-constriction (broncho-dilation)** by post-challenge MFAID inhalation in non pre-treated rats.

**Suppression of:**
- **Airway remodeling** (lung histology) in sensitized and challenged rats.

  - The broncho-constricting Cysteinyl-leukotrienes (CysLTs) level in broncho-alveolar lavage (

  - **Secretory PLA2 (sPLA2)** in lung tissue.

  - TNFα and NO production by BAL macrophages.

5. **Asthma model in mice** – Ovalbumin (OVA)-induced Experimental allergic bronchitis (EAB)  
   *(Mruwat et al., PlosOne, 2015) (Slides 40-47 in the presentation)*

Intra-nasal administration of MFAID (in saline) ameliorated OVA-induced EAB expressed by:

- **Prevention of OVA-induced broncho-constriction and airway resistance,** as well as infiltration of inflammatory cells (cellularity) in the lung (histology).

**Suppression of**

- The level of eicosanoids, including the broncho-constricting CysLTs, PGD₂ and TBX₂, in BAL

  - **5-lipoxygenase (5-LO)** protein expression in lung tissue.

  - **Gene expression (mRNA)** of PLA2s (including sPLA₂gX)

**Advantages:**
- A platform of molecules with potential to synthesize many APIs and formulations
- Multi-factorial anti-inflammatory/allergic mechanisms: Protecting cells from membrane phospholipid degradation, and enrichment of the protective layer of cell surface glycosaminoglycans (GAG).
- The technology is protected by a very extensive patent portfolio
- Human clinical trails

"According to leading experts in inflammatory/allergic diseases, who served on the Morria’s scientific advisory board before the change of management (Mark Feldman, Peter Barnes, Rod Flower and Charlie Serhan), the MFAID technology has great therapeutic potential in treating inflammatory/allergic conditions."

**History:**

In 2002 the company was founded by three co-founders, and the technology was licensed by the Hebrew University to *Morria Bioparmaceuticals*. From 2005-2012 the company raised over $13m from private investors as a private company. In March 2013 the company’s management was changed and renamed the company to *Celsus Therapeutics Plc.*, which started being traded on NASDAQ in late 2013.
On September 2015 Celsus reverted the entire respective IP to Yissum.

Selected relevant publications:


Reviews and Chapters in Books:


