# MYASTERIX

**Endorsed by:** BIOVISION

**Focus:** Vaccines and immunotherapies

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## Brief summary:

MYASTERIX is an FP7, EU funded project that will advance a therapeutic vaccine candidate for the autoimmune disease myastenia gravis to clinical proof of concept studies.

## Project / initiative description (context and objectives):

The MYASTERIX project will advance a therapeutic vaccine candidate (designated orphan drug) indicated for the autoimmune disease myasthenia gravis (MG) to clinical proof of concept studies. MG is caused by T cell dependent antibodies that bind to and deplete acetylcholine receptors (AChR) at neuromuscular junctions causing muscle weakness by interfering with neuromuscular transmission and junction architecture. The vaccine candidate comprises two synthetic peptides designed to generate antibodies that bind to autoantibodies and T-cell receptors associated with MG. These peptides prevented or improved muscle fatigue in a rat model of MG and increased the remission rate to 75% in pet dogs (compared to 17% natural remission rate in historical controls). In both models, administration of the peptides resulted in reduced titres of anti-AChR antibodies and lower numbers of anti-AChR T-cells, based on the induction of antibodies that bound to the corresponding B and T cell antigen receptors. These results suggest that similar antigen receptor mimetic vaccination approaches could drive autoimmune diseases like MG into long-term remission.
The objectives of the project are to manufacture toxicology and clinical batches of the vaccine human formulation based on already developed and tested standard operating procedures, to carry out stability and regulatory toxicity testing of the GMP product, to conduct phase I and subsequently phase II clinical trials to demonstrate safety, tolerability and proof of mechanism of action/concept of the therapeutic vaccine.
The impact on MG patients will be to offer a targeted therapeutic approach requiring only three injections, bringing significant and lasting improvement or even a cure. MG is a model for many autoimmune diseases and the concept of targeted therapeutic vaccines could lead to a new class of drugs for the treatment of autoimmune diseases more generally, with a significant impact on innovation, competitiveness and society.

## Description of the existing or potential collaboration:

MYASTERIX is a five year collaborative research project that brings together five partners in 4 European member states.
Around CuraVac, a Belgian SME specialised in therapeutic vaccines for autoimmune diseases and scientific coordinator, the project includes the following partners:
- piCHEM an Austrian SME with specific expertise in peptise synthesis and conjugation and GMP accreditation to manufacture vaccines and therapeutic products clinical batches,
- Leiden University Medical Centre, a referral site for myastenia gravis in the Netherlands,
- Aepodia, a Belgian CRO with expertise in First in Man and early phase clinical trials,
- Inserm Transfert, a technology transfer and management company based in France.

## Project / initiative assets (type, originality, innovation...):

The vaccine candidate comprises two synthetic peptides. RhCA 67-16 is designed to generate antibodies (anti-idiotypic Abs) that bind autoantibodies (idiotypic antibodies, Id Abs) and RhCA 611-001 is designed to generate antibodies that bind T-cell receptors (TCRs). Each peptide is separately coupled to CRM197, a genetically detoxified diphtheria toxoid (DT) carrier. The conjugated peptides are mixed with a saline solvent and adsorbed to the alum adjuvant to constitute the vaccine.
Mechanism of action:
The proposed treatment follows the molecular logic of antigen receptor mimetic (ARM) vaccination for autoimmune diseases reviewed by Weathington and Blalock (2003).
For Myasthenia Gravis, the autoimmune assault on the nicotinic AChRs of skeletal muscles often causes a severe deficit in muscle function due to the destruction of muscular tissue architecture at the neuromuscular junction. The main B-cell epitope on the AChR (MIR) is probably targeted by molecular mimicry, leading to the loss of self-tolerance for the nicotinic AChR and the generation of Id Abs.
T-cell sensitisation to a T-cell epitope on the nicotinic AChR (?-subunit residues 100-116) is thought to promote cytokine-mediated B-cell isotype switching and the production of circulating anti-AChR IgG antibodies (detectable in ~90% of MG patients).
By vaccinating with the ARM vaccines for each epitope, we aim to generate antibody responses that react against the pathogenic Id Abs (anti-idiotypic Abs) and to the TCR for T-cell clones reactive to nicotinic AChR (anti-TCR Abs), thus reducing pathogenic anti-MIR antibody responses and restoring function at the neuromuscular junction.

It has been shown that the proposed therapeutic vaccine specifically targets the underlying immune disorder in the EAMG rat model and in the spontaneous MG canine model. The vaccine candidate therefore has the potential to preserve immune system function in MG patients while treating the underlying pathology. This will therefore represent significant progress beyond the state-of-the-art in the management of MG patients.

## Citizen benefits:

**Impact on MG patients**: During the project, we will evaluate the anticipated benefits of a targeted therapeutic approach for MG requiring only three injections which can bring significant and lasting improvement or even a cure to MG patients. We will compare this novel treatment to current options such as general immunosuppression, which cannot cure but only control the disease, and incomplete symptomatic relief, which can only be achieved by the frequent (every 4 hours) administration of drugs like acetylcholinesterase inhibitors. The side effects of the MG therapeutic vaccine are expected to be comparable to current prophylactic vaccines. The vaccine will therefore compare favourably to the current drugs used to treat MG, which cause numerous and severe side effects. For example, corticosteroids may cause osteoporosis, hypertension, diabetes mellitus, gastric ulcer, glaucoma and increase the severity of infections; immunosuppressive drugs may cause hypertension, kidney failure, liver dysfunction, abdominal pain, increased susceptibility to infection or even cancer; and acetylcholinesterase inhibitors may cause nausea, diarrhoea, profuse salivation, muscle twitching, cramps and weakness.
Myasterix, if successful, will therefore have an immense positive impact on the quality of life of MG patients.
**Medico-economic impact on patients and society:** Reviews that have evaluated the current treatment strategies for MG, their numerous and severe side effects (see above) as well as their costs (Juel et al., 2005), indicate that the total average cost of treatment including all known side effects is well above the average cost of MG medication alone. Many patients also remain significantly disabled, which reduces their quality of life and their ability to work, thus causing lost revenue not only for the patients but also for society as a whole.
Our approach could generate considerable benefits for patients and society by replacing all the primary and secondary costs with the sole cost of the vaccine and its straightforward three-injection procedure.

## Plannned schedule:

The general schedule is the following:
1) by the end of 2014, to manufacture according to good manufacturing practice (GMP) guidelines, batches of the human formulation of the vaccine for toxicology and clinical studies, based on detailed good laboratory practice (GLP) standard operating procedures (SOPs) that have already been established and tested;
2) by the end of 2014 also, to carry out preclinical toxicity testing of the product and initiate stability testing following the appropriate regulatory guidelines;
3) to gain approval for and perform a phase 1 clinical trial in 2015 and early 2016 followed by a phase 2 trial during 2017 and 2018 to demonstrate safety, tolerability and efficacy of the MG therapeutic vaccine candidate through proof-of-concept studies on a group of patients (up to 80 in total including 32 in phase 1 and 48 in phase 2).

By the end of the phase 1 clinical trial, which will be conducted on MG patients in 2015, the short term efficacy will be know on the basis of the following endpoints:
1) effect of the vaccine on the plasma level of acetylcholine receptor antibodies (the autoantibodies)
2) clinical efficacy using the MG Composite (MGC) scale (Burns et al., 2010), clinical evaluation and CD4+/CD25+ data in flow cytometry.
The patients will then be included in a long term follow-up study.

## What are you expecting from BIOVISION Catalyzer?

1 Visibility
2 Meeting potential partners
3 International reach
4 Other: investors for the other autoimmune vaccines