Neuromuscular diseases: the results

The IOP Genomics project focuses on developing llama derived antibody fragments that recognise specific biomolecules in neuromuscular diseases. The small size, structure, specificity, stability and flexibility of the variable part heavy chain (VHH) of these antibodies proved to be very suitable to unravel pathogenic mechanisms. Furthermore, the use of these antibodies brings the development of diagnostics and therapeutics one step closer.

"The development of llama derived antibody fragments against different biomolecules in different diseases has created many spin-offs and follow-up projects", says Professor Silvère van der Maarel, project leader of two consecutive IOP genomics projects on llama antibodies. The first IOP project ended in 2006, but the research in this field has been extended and is going full speed ahead.

Two patents

The use of llama derived antibodies in diagnosis, prevention and/or treatment of diseases associated with protein aggregates has been patented. To date the patent has been licensed to two companies, Philips Medical Systems and Ablynx, the latter being specialised in the production of antibodies.

In this first IOP project, a remarkable result was obtained in the research on oculopharyngeal muscular dystrophy (OPMD). Specific llama antibodies were developed against the mutant protein that causes nuclear aggregates which are possibly involved in the pathogenesis. These antibodies were able to prevent the formation of aggregates in a cellular OPMD model.

The researchers realised that these antibodies could possibly be the basis for therapeutics for preventing protein aggregates.

In an EU financed project, the research on OPMD was continued together with a French research group (Dr. M. Simonelig, Montpellier). The groups developed transgenic OPMD fruit flies which also carried the gene coding for the protein aggregate antibody. In the majority (93%) of these flies the phenotype was rescued. Van der Maarel: "Of course we also want to know if the antibodies can prevent formation of aggregates in mice and ultimately in humans. Presently we are involved in research on OPMD mice."

Continuing funds

Van der Maarel and colleagues also investigated how and where the anti-aggregate antibody binds to the protein aggregate. Based on their results, they set up a model which predicts how the anti-aggregate antibodies can prevent the formation of aggregates. The research on OPMD has generated three manuscripts which have been submitted. Van der Maarel hopes that this part of the research can be continued by a NWO grant, for which an application has been filed. Based on this work, Van der Maarel also received funding from the American Muscular Dystrophy Association (MDA) to further understand the pathophysiology of the aggregation process.

In addition, the llama derived antibodies were used to analyse a specific protein, dysferlin. Dysferlin probably plays a role in muscle membrane repair. Mutations in dysferlin are associated with the group of limb girdle muscular dystrophies. The discovery of other proteins bound to dysferlin in skeletal muscle may shed light on damage protection and damage repair pathways in muscle cells. The follow-up of this project is financed by the Princess Beatrix Fund. So far Van der Maarel and colleagues have found two different components (calpain 3 and AHNAK) which play a role in the dysferlin complex. Further research is needed to discover their precise role and the role of yet undiscovered components. "We presently also participate in a large European network of researchers (www.proteomebinders.org) who are all specialists in the field of affinity binders for detection of the human proteome", says Van der Maarel. The aim of the network, financed by the EU, is to provide a set of consistently characterised binders, required to detect all the relevant human proteins in tissues and fluids in health and disease.

IOP Genomics project IGE01019

Period 2002-2006

Purpose To gain insight into structural and functional genetic variations in muscle and nerve diseases. To develop improved diagnostics, treatments and new intervention strategies in neuromuscular diseases.

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Key results

- participation in EU-financed network (www.proteomebinders.org)
- a second IOP Genomics project (IGE05005)
- continued OPMD research (EU project and MDA project)
- continued dysferlin research (Princess Beatrix Fund)
- development of antibodies for early diagnosis of breast and prostate cancer, EU financed
- (licensed) patent: VHH for the diagnosis, prevention and treatment of diseases associated with protein aggregates
- participation in two recent Alzheimer's disease programmes (CTMM and CMBS)
- new promising applications of llama derived antibodies (detection of HIV virus and for use in microbiocides)