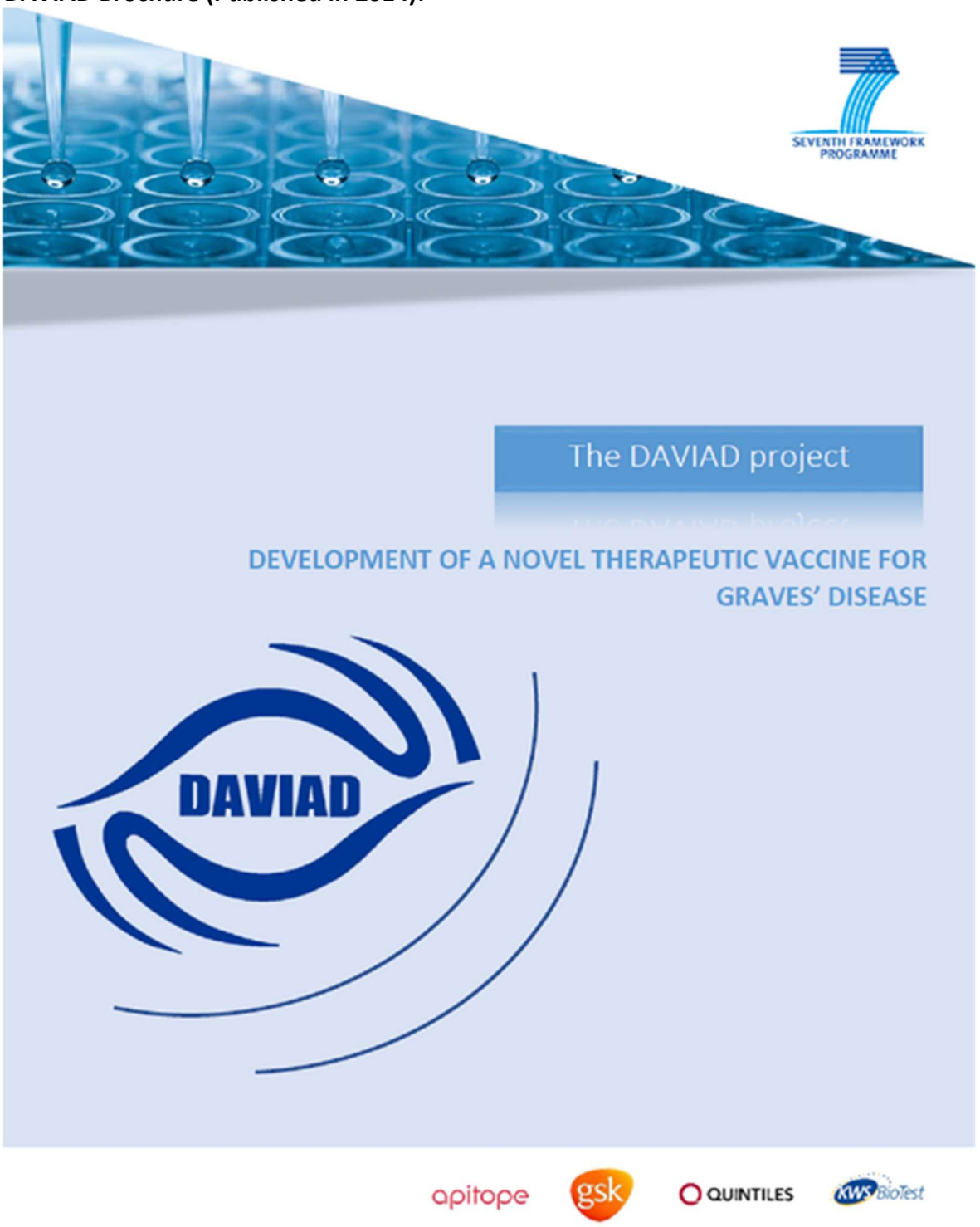
DAVIAD – Example Dissemination Tools

DAVIAD Brochure (Published in 2014):



Project Summary

This aim of the DAVIAD project is to develop a therapeutic vaccine for Graves' disease (GD) that has an improved safety and efficacy profile than current treatments. There is a high level of unmet need in the treatment of Graves' disease especially in patients with Graves orbitopathy (GO) and children and adolescents (who generally suffer from the most chronic form of the disease). Autoimmune diseases arise as a consequence of a break of the immunological tolerance to self-antigens. The therapeutic vaccine will change the ongoing destructive autoimmune response by immune modulation to reinstate the immune tolerance, leading to a down regulation of Graves' disease progression. This project focuses on the development of an antigen specific therapy to reinstate the immune tolerance to Graves' disease.

The selected peptides behave as apitopes® (antigen processing independent epitopes) and bind to MHC class II molecules in the correct confirmation to induce tolerance.

The consortium has the expertise required to effectively and efficiently take the proposed vaccine through clinical development and eventual commercialisation. A disease modifying therapy for GD would address a serious unmet need and potentially offer a therapy that can change the way this disease is treated, offering better quality of life for sufferers and reducing burden on health services.

About the consortium

apitope

Apitope is a privately owned European biotech company developing antigen specific therapeutic peptides for the treatment of allergy and autoimmune diseases, including Multiple Sclerosis, Graves' Disease, Uveitis and others.

gsk

GlaxoSmithKline is a science-led global healthcare company that researches and develops a broad range of innovative medicines and brands.

QUINTILES

Quintiles is the world's largest provider of biopharmaceutical development and commercial outsourcing services with a network of more than 28.000 employees conducting business in approximately 100 countries

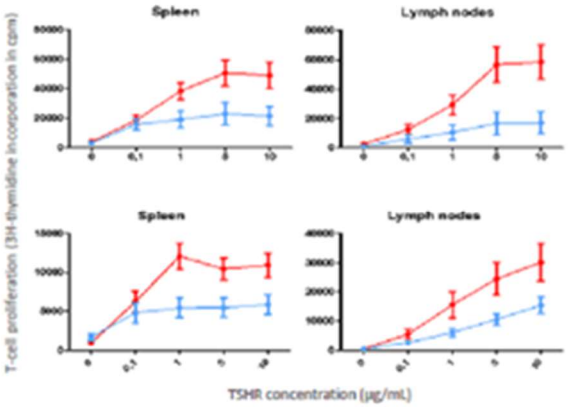
KWS BioTest

KWS Biotest is an established preclinical contract research organization that brings together internationally renowned scientific expertise in a commercially managed environment for the testing of prophylactic and therapeutic agents as treatments for human diseases.

DAVIAD project objectives

Further characterise the candidate apitopes® in appropriate human and mouse cell systems

DAVIAD will further characterise process-independent soluble synthetic tolerogenic peptides for the treatment of GD which have been previously shown to be efficacious in animal tolerance models. The previously identified Thyroid Stimulating Hormone Receptor (TSHR) specific peptide (in blue) could reduce the proliferative response to TSHR by 50% - 70% versus a PBS control (in red) in lymph nodes and splenocyte preparations from DR3 transgenic mice (see the efficacy of two individual tolerogenic peptides in the figure below).



Prior to initiating clinical studies with DAVIAD vaccine, DAVIAD will complete preclinical activities including toxicity studies, development of analytical methods, Chemistry, Manufacturing & Control (CMC) and regulatory activities.

Develop GMP grade Investigational Medicinal Product for use in toxicity studies and in a Phase I/IIa clinical programme

It is anticipated that the DAVIAD vaccine will be a lyophilised product. The main objective is to develop a formulation that is suitable for intradermal injection in man when reconstituted and ensures that the investigational medicinal product remains within specified limits for at least 24 months when stored at 2-8°C or preferably 15-25°C and is thus suitable for use in supporting the Phase I/IIa clinical programme.

A range of formulations will be evaluated against pre-defined criteria including:

- Stable cake
- Solubility of each peptide at >1mg/mL
- Physiological formulation
- Suitable for freeze drying
- Fully reconstitutable and stable for at least 8 hours

Preferred formulations will be evaluated for initial stability under the proposed long-term storage and accelerated conditions.

Assess the effects of the DAVIAD vaccine peptides in at least one relevant toxicology species sufficient to support a Phase I/IIa clinical programme in patients with GD and obtain regulatory approval for a Phase I /IIa clinical study in GD patients.

Once the peptides have been successfully characterised in the in vitro and in vivo assays and formulated, they will be subjected to a set of toxicity studies to confirm a suitable safety profile for conducting clinical trials. Where appropriate the studies will be conducted to GLP, using appropriate grade peptide.

The peptides in the DAVIAD vaccine have been designed and shown to specifically interact with human MHC Class II molecules on the surface of APCs. Therefore, traditional toxicology species with species specific MHC Class II molecules may not be relevant for the assessment of on-target toxicology. Therefore studies will be conducted to determine whether a 'wild type' species has a phamacodynamic response to the peptides. The strategy for the non-clinical testing of the DAVIAD vaccine will be based on the regulatory guidelines ICH M3 (R2), ICH S6, EMA/CHMP/SWP/28367/07 and CHMP/SWP/1042/99 with a focus on the specific mode of action of the DAVIAD vaccine.

DAVIAD's non-clinical testing strategy and subsequent in vivo data will be discussed with relevant competent authority(ies) through national Scientific Advice procedures.

Develop, validate and execute study specific clinical assays to support patient eligibility and assess secondary exploratory endpoints; design and execute a Phase I/IIa trial in GD patients to provide a clear assessment of safety and preliminary proof of principle

In order to assess the efficacy and safety of the DAVIAD vaccine it will be necessary to develop and validate clinical laboratory assays to assess whether repeat administration of the DAVIAD vaccine to patients induces an antibody response to the individual vaccine peptides and whether the vaccine impacts TSHR induced Peripheral Blood Mononuclear Cell proliferation and other immunological markers. Once validated, each study specific clinical analytical method will be considered to be fit for purpose and if so, approved for use in the clinical programme.

The DAVIAD project will undertake a Phase I/IIa clinical trial in treatment-naive GD patients in order to provide initial evidence that the vaccine is safe and well tolerated in a GD population. This is essential before any further studies can be undertaken in those patients identified as having a high unmet medical need, e.g. paediatric GD or moderate to severe GO. The secondary endpoint of the clinical trial will provide initial evidence that the DAVIAD vaccine elicits the appropriate clinical responses required for efficacy in this disease population.

This Phase I/IIa clinical trial is the foundation for a series of subsequent clinical trials that will provide the definitive evidence of efficacy for the aforementioned sub-groups. Specifically, this clinical trial will provide further evidence that antigen-specific immunotherapy can be employed in a clinical situation to reinstate tolerance to an auto-antigen and decrease pathological antibody levels. This will build on the DAVIAD knowledge of the benefits of antigen-specific immunotherapy in T-cell mediated as well as T-cell/antibody mediated autoimmune diseases.

Potential Impacts of the project

- Health

GD is a chronic autoimmune disease in which the thyroid is overactive, producing a serious metabolic imbalance known as hyperthyroidism. Patients can experience a wide range of symptoms and suffer major impairment in most areas of health-related quality of life (HRQL). Current treatments for GD patients often fail to provide long-term remission or expose those patients with more severe forms of GO to drugs with a broad immunosuppressive effect and associated problems. A novel and effective vaccine strategy will have a major impact for patients, society and public health systems.

GO patient with typical overactive and enlarged goiter

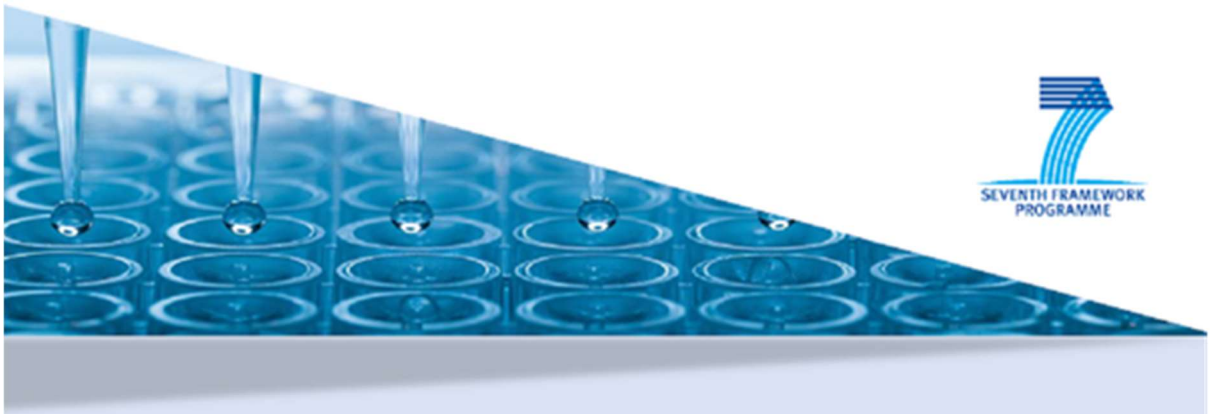
Proptosis in GO patient ("Marty Feldman" by AVRO - Beeld en Geluidwiki)

- Economic

GD imposes significant economic burden on the health and social services organisations across EU27. A German study estimated the total costs related to GD in Germany alone to be approximately 1 billion euro. Given the pressure throughout the EU and worldwide on the growing health budget requirements, therapeutics that can modify the course of diseases or avoid long-term treatment of patients are sought by governmental authorities. Significant saving in the costs associated with GD is likely if the therapeutic peptides being developed by the DAVIAD project achieve the anticipated levels of efficacy.

- Social

GD in general and in particular GO and paediatric GD have physical, psychological and economic impacts on the patient and also on caregivers, friends, family, healthcare systems and society. Several studies have shown that GO is an invaliding and disfiguring disease affecting appearance and functioning of the eyes. Furthermore the majority of caregivers are family members as it is preferable to eliminate the need for professional and costly levels of care. The successful implementation of the DAVIAD project will help to improve the HRQL for patients suffering from GD, their families and the caregivers. The project will also help national healthcare systems by reducing the cost of caring for the patients.



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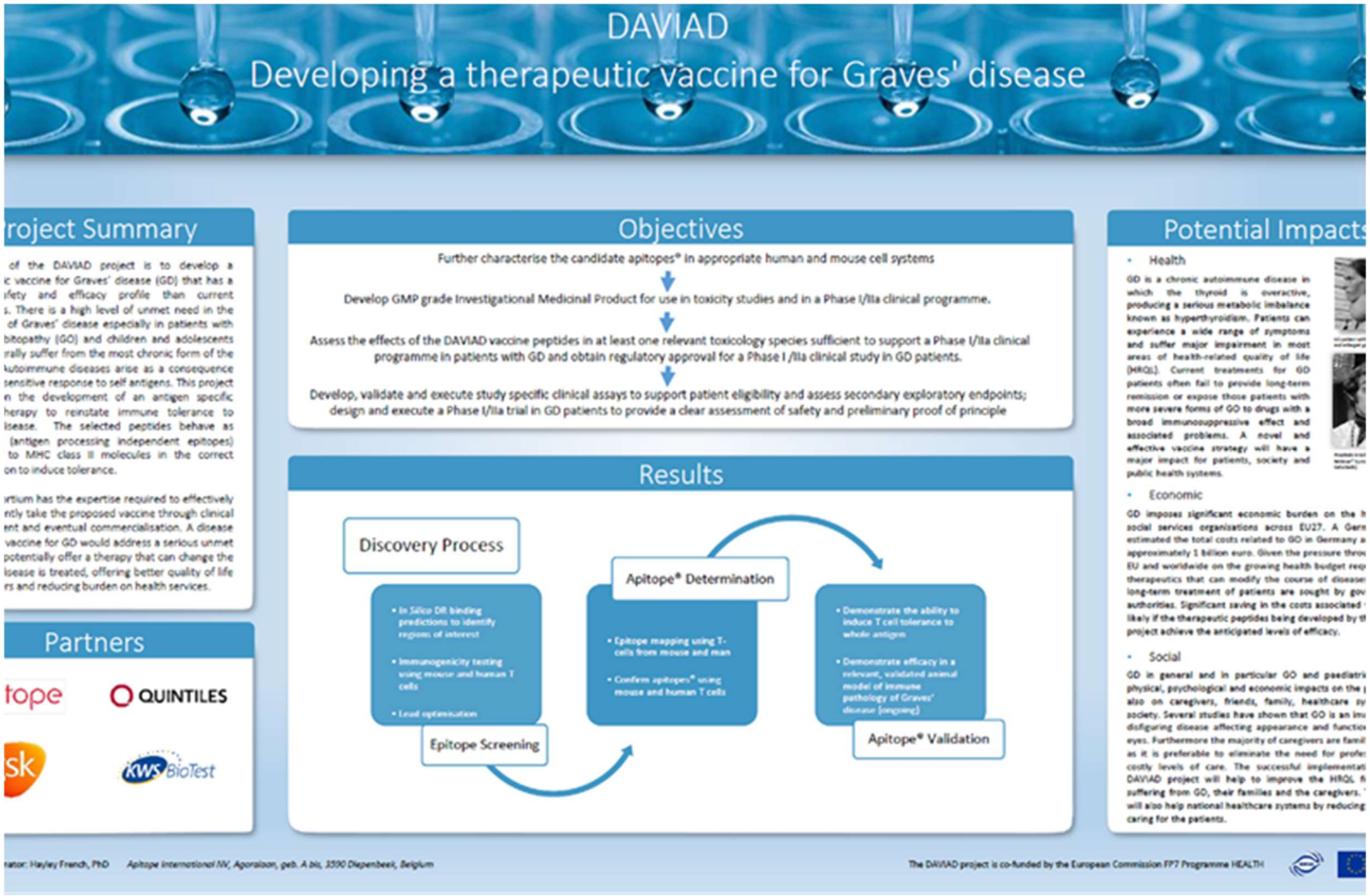
DAVIAD Logo:

DAVIAD Website:

WWW.daviad.eu

DAVIAD Poster (Published in 2014):



DAVIAD Example press releases

Apitope Led Consortium Receives up to €6M FP7 Funding to Develop Novel Therapeutic Vaccine for Graves' Disease

Bristol, UK and Hasselt, Belgium – 8th January 2014 – Apitope, the drug discovery and development company focused on treating the underlying cause of autoimmune diseases, today announces that the consortium, led by Apitope, which includes GSK Vaccines, Quintiles and KWS Biotest Limited, has been awarded prestigious Framework Programme 7 (FP7) Health Innovation funding by the European Commission to develop its Graves' disease therapeutic vaccine, including a Phase I first-in-man study in Graves' disease patients. Graves' disease is an immune system disorder that eventually results in the overproduction of thyroid hormones (hyperthyroidism). While a number of disorders may result in hyperthyroidism, Graves' disease is the most common cause affecting 2% of the female population. Symptoms of hyperthyroidism can include increased heart rate, muscle weakness, disturbed sleep, and irritability. Patients may also develop bulging eyes (proptosis). The disease affects multiple systems of the body, including the skin, heart, circulation and nervous system. Apitope's antigen-specific disease modifying peptide therapy uses epitopes designed to shut down the abnormal immune responses to the causative agent in a highly selective manner, re-instating the normal immune balance, thereby avoiding global immune suppression. As a result, the peptides taken into clinical evaluation by Apitope offer the potential to have limited side effects and a good probability of efficacy.

Dr. Keith Martin, CEO of Apitope stated: "Graves' Disease is a disease with serious implications particularly for those with Graves' orbitopathy who are at risk of blindness. Current treatments for this disease may result in abnormally low thyroid activity levels, requiring further medications, and do not treat the fundamental cause of Graves' disease nor reduce the long term cardiac risks. This funding will allow a team of experts to develop a much needed therapy that may address the cause of this serious condition rather than simply treating the symptoms and removing the need for other medications."

Professor Neil Williams, CSO of KWS BioTest said: "This is a really exciting approach to the treatment of an important human disease, which builds on the successes that Apitope has seen in its MS programme. We are looking forward to applying our expertise in the preclinical immunology and inflammation areas to help drive the project forwards into the clinic. The award of the EU grant helps to cement the close drug discovery partnership in the consortium."

Apitope Progresses Graves' Disease Treatment Initiates Preclinical Development of Peptide Therapy

Diepenbeek, Belgium – 21st June 2014 – Apitope, the drug discovery and development company focused on disease-modifying treatments for patients with autoimmune and allergic diseases, announced today that it has started preclinical development of its novel peptide therapy ATX-GD-459 for the treatment of Graves' disease.

Apitope, through its innovative discovery platform, has selected three peptides in ATX-GD-459 that have the potential to treat and prevent the production of stimulating antibodies against TSHR (thyroid stimulating hormone receptor) that lead to Graves' disease.

Graves' disease is an autoimmune disorder that impacts over 7.5 Million people worldwide. Patients with Graves' disease typically develop goitre and serious medical issues such as increased heart rate, muscle weakness, disturbed sleep, and irritability. It affects multiple systems of the body, including the skin, heart, circulation and nervous system with potential long term morbidity. Some 30-50% of Graves' disease patients develop the medically challenging Graves' orbitopathy characterised by bulging eyes (proptosis), while 3-5% of such patients suffer from a sight- threatening form of Graves' orbitopathy.

Graves' disease is linked to the thyroid gland and the overproduction of the thyroid hormones thyroxine (T4) and triiodothyronine (T3). The overproduction of thyroid hormones is caused by auto-reactive T and B lymphocytes targeting the primary auto-antigen, TSHR. This activation of the thyroid cells through the auto-antibodies results in the typical Graves' disease hyperthyroidism and respective symptoms.

Dr. Keith Martin, CEO said "Apitope is developing innovative products based on therapeutic peptides to treat a range of life-threatening autoimmune and allergic diseases, including rare conditions. We are delighted to progress the development of these innovative peptides which have the potential to help Graves' disease patients. We now have seven programmes in clinical, and preclinical development and discovery as we continue to maximise the potential of our innovative discovery platform."

The development of ATX-GD-459 is part of the DAVIAD project (www.daviad.eu) co-financed by the European Commission in the 7th Framework Programme, FP7-HEALTH-2013-INNOVATION-1, 602779. The DAVIAD consortium is comprised of Apitope as coordinator, GlaxoSmithKline Biologicals SA, Quintiles Benefit and KWS Biotest Limited.

Prof David Wraith, CSO and Founder of Apitope, added, "Bringing this latest product through into preclinical development is another important milestone event for Apitope and provides further evidence that our discovery platform can generate new potentially life changing therapies for development and validates further the scientific basis of our approach."

Apitope Treatment Approach Published in Nature Communications – Scientists discover how to 'switch off' autoimmune diseases

Diepenbeek, Belgium – 4th September 2014 – Apitope, the drug discovery and development company focused on disease-modifying treatments for patients with autoimmune and allergic diseases, announced today that Bristol University research led by Apitope Founder and CSO, Prof David Wraith, on its treatment approach to autoimmune diseases, such as Multiple Sclerosis (MS), has been published in Nature Communications.

The researchers at the University of Bristol reported an important breakthrough in the fight against debilitating autoimmune diseases such as Multiple Sclerosis. Rather than the body's immune system destroying its own tissue by mistake, researchers have discovered how cells convert from being aggressive to actually protecting against disease. It's hoped this latest insight will lead to the widespread use of antigen-specific immunotherapy as a treatment for many autoimmune disorders, including Multiple Sclerosis (MS), Factor VIII intolerance in haemophiliacs, Graves' disease (hyperthyroidism) and uveitis, conditions for which Apitope is developing important new therapies.

Commenting on the research, Dr. Keith Martin, CEO said: "Multiple Sclerosis affects around 100,000 people in the UK and 2.5 million people worldwide. This is an important breakthrough in our fight against debilitating autoimmune diseases by providing further important information on how to stop cells attacking healthy body tissue. This research further reinforces Apitope's treatment approach, which has already successfully completed two clinical trials in MS patients with MRI data showing a significant decrease in new lesions, and has the potential to improve the lives of millions of people worldwide. Importantly, we are now taking this approach into other serious autoimmune conditions as well as MS."

The reported study, funded by the Wellcome Trust, is published in Nature Communications. The article entitled "Sequential transcriptional changes dictate safe and effective antigen-specific immunotherapy" that describes how researchers have managed to "switch off" autoimmune disease as a breakthrough for Multiple Sclerosis (MS) treatment, can be viewed here:http://www.nature.com/ncomms/2014/140903/ncomms5741/full/ncomms5741.html