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TWS
TOM WAHLIG
STIFTUNG

ACTIVE DURING LOCKDOWN

Over the past few months, people's daily lives in Germany, Europe, and around the world have changed significantly – we all have to cope with unfamiliar limitations and are experiencing feelings of uncertainty. An entire year has gone by, in which the number one news topic has been a single virus that has brought a lot of things to a standstill: Covid 19. Although the virus has caused much suffering, however, it has also moved things forward. One of the developments the pandemic has brought to the fore is:

Science and research have become a major focus for people around the world

People suddenly had to cope with an extreme reduction in social activities, and were able to observe how expert opinions became much more prominent in politics and the media: the public has been listening more closely and extensively than ever to what virologists and epidemiologists, medical experts, as well as experts on ethics, education, and legal issues have to say. With their help, politicians are trying to find the right direction for their actions and decisions; at the same time, expectations are great for the surprisingly quickly developed vaccines. We can see that, to fight the pandemic, it is not enough to sit and wait what others are going to do. To get the virus under control, we all have to use face masks, practice good hygiene, and reduce our social contacts. For 23 years, we at TWS have been intent on learning to understand HSP in detail, develop causal treatments, and increase patients' chances of recovery. Ever since we embarked on our mission more than two decades ago, we have been aware that without an extensive network of scientists on the one hand, and the help of individuals on the other – HSP patients who bravely tell their stories, family members who regularly organize (virtual) meetings, friends who support us with donations – we would never be able to achieve a breakthrough.

It takes an entire community to achieve scientific success! In this sense, we hope you enjoy the new digital version of our MAGAZINE.

Sincerely,

Yours Henry & Susanne Wahlig,
Tom Wahlig and the TWS Team

NEW PATRONESS

CLAUDIA ROTH, VICE-PRESIDENT OF THE BUNDESTAG, IS THE NEW PATRONESS OF TWS

Photo: Stefan Kaminski

Overjoyed to get celebrity support , we welcome Claudia Roth, Vice-President of the Bundestag onboard who became patroness of the Tom Wahlig Foundation on January 1st, 2021. By supporting us, she is honoring our foundation's great commitment to the HSP cause.

„TWS shows in an impressive manner how much of a change a single person's commitment can make. People with rare diseases and their families are often neglected by research and left alone with their predicament. Not only has the Foundation raised awareness of HSP, it has also given hope to patients fighting a battle that once seemed hopeless. It is an honor to be able to support the Foundation's work as its patroness."

Claudia Roth is one of the most famous politicians in Germany. The long-time leader of the Green Party "Bündnis 90 / Die Grünen" has been Vice-President of the Bundestag since 2013, thus holding one of the top offices of State in the country. TWS is happy about the politician's support. Founder Tom Wahlig says:

„We are very happy and proud to have Claudia Roth onboard. On behalf of the Foundation and everybody suffering from HSP, I would like to thank her for lending us her name to further increase awareness of HSP".

Beside Claudia Roth, Christoph Strässer will also remain patron of TWS. The long-time member of the Bundestag from Münster, and Human Rights Officer of the German government, has been patron of the Foundation since October 2015.
In addition to becoming patroness, Claudia Roth is also joining our TWS team of PaceMakers, a network of celebrities taking symbolic steps for people suffering from HSP.

Other PaceMakers on our team include singer Roland Kaiser, actresss Eleonore Weisgerber and writer Gaby Hauptmann.

HENRY'S WALKING CHALLENGE

BROUGHT IN A BREATHTAKING 22,000 EUROS IN DONATIONS

Just like many other organizations, TWS was unable to realize many of its original plans for this year. Luckily, however, we were able to go through with Henry's Walking Challenge in August, and it got a lot of media attention! Not only did many regional and national papers cover Henry's Walking Challenge, even a TV crew shows up on site to make a special report. For his Walking Challenge, Henry Wahlig pledged to walk 18.48 km (an analogy to the founding year of his favorite soccer club VfL Bochum) around the soccer stadium in Bochum in 14 days, in spite of suffering from HSP, and met with incredible support and solidarity:

More than 250 people donated over 22,000 Euros to TWS, making this the most successful fundraising event in over 20 years of TWS history. At 1,848 Euros each, the biggest individual donations came from Hutzel Vollkorn-Bäckerei in Bochum and Dietmar Schruck in Essen.

In spite of his significant walking impairment that forces him to sit in a wheelchair for most of his daily life, Henry managed to walk over 25 km in two weeks.

He reached the actual finish line of his challenge ...

Photo: Nils Eden

Photo: Nils Eden

... after only 11 days. For the overall distance, he spent 26 hours walking through Bochum, either supported by walking sticks or by his daughter's stroller.
Henry gathered most of his supporters from among the rows of his favorite soccer Club, VfL Bochum. Several supporters, fan clubs, and the club itself are supporting Henry and his goal to gather donations for research on his presently incurable disease. On the final day, Thomas Eiskirch, Lord Mayor of the City of Bochum came to congratulate Henry on successfully completing his challenge.

Henry Wahlig is happy about how it went and impressed with the result:

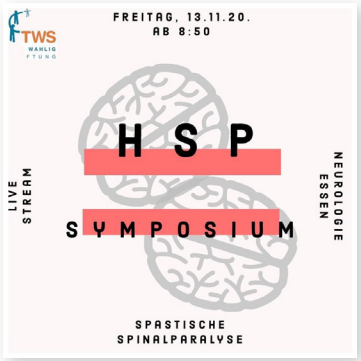
„I feel overwhelmed how many people I have touched with this idea. I would like to thank everybody for their donations, their supportive comments in the social media, and their kind words of encouragement during my walk. It was all this support that carried me through this extremely exhausting challenge. I really hope, the awareness we managed to raise for people with disabilities will last beyond this challenge."

Thomas Eiskirch (Lord Mayor of Bochum), Ilja Kaenzig (Management Spokesperson VfL Bochum 1848), Henry Wahlig, Sebastian Schindzielorz (Head of the Sports Division, VfL Bochum 1848), Frank Althaus (Owner of Hutzel Vollkorn-Bäckerei)

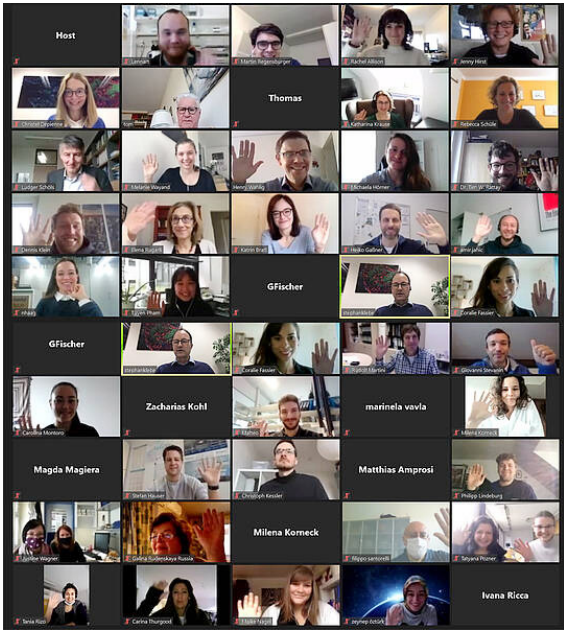
Photo: Nils Eden

19TH TWS-SYMPOSIUM – FIRST LIVESTREAM EDITION…

…AND 2000 PEOPLE WATCHING!



Due to the pandemic, the annual TWS Symposium could not take place in the usual format. The original plan was to hold a regular symposium in Baden-Baden at the end of March. After a lot of careful thinking, we finally decided to organize our first online symposium featuring a livestream on November 13th. Once again, top HSP researchers from around the world came together to introduce and talk about their latest projects. Instead of coming together in one location, this time, more than 50 researchers came together virtually, via Zoom.
A livestream was made available for viewers, and viewer numbers vastly exceeded our expectations.



Nearly 2000 viewers from around the world tuned into our livestream throughout the day, the greatest number of people that have ever watched an event centered on the rare disease of HSP.

This also showed the immense significance of the TWS symposium for this particular research area. We would like to thank Prof. Christel Depienne and Prof. Stephan Klebe from the University Hospital in Essen for supervising the scientific aspects of the symposium, and Thomas Stender and his company Blickpunkt Münster for implementing the livestream.

The successful use of technology and the positive reaction to this year's digital edition of the symposium have opened up new perspectives for how it might be organized in the future. We do hope, however, that at the next symposium in 2021, we will be able to meet in person once again - planning in progress.
For more up-to-date information, see our website at:

www.hsp-info.de

TWS RESEARCH FUNDING

INTRODUCING CURRENT PROJECTS

Research funding is the central focus of our work. At our symposium in Weimar in **March 2019**, we presented awards to three of 14 projects.

Dennis Klein (Würzburg), **Rebecca Schüle** and **Ulrike Ulmer** (Tübingen), and **Christel Depienne** (Essen) received 12,500 Euros each for their research.

In **2020**, three of nine project applications were selected:

Amir Jahic (Berlin) received 12,930 Euros, **Coralie Fassier** (Paris) and **Maria Magiera** (Orsay) 16,000 Euros, and **Ivana Ricca** (Pisa) 17,500 Euros.

The six winning projects will be introduced in the following pages.

As we are working on the publication of this newsletter, the jury is already looking at eleven new applications. We are looking forward to their reports.

For more information on our research funding and the application process, please see: *www.hsp-info.de/en/researchers.html*

FUNDED RESEARCH PROJECTS 2019

DENNIS KLEIN | WÜRZBURG

Physiotherapy as a possibly treatment for spastic paraplegia type 2 (SPG 2)

Spastic paraplegia type 2 (SPG2) is a neurodegenerative disease of the central nervous system (CNS) and is caused by mutations in the gene for proteolipid protein 1 (PLP1). This protein is part of an insulating layer that surrounds the nerve fibers (axons) and plays a vital role in the functioning and survival of axons. Damage to the insolating layer, such as that caused by PLP1-mutations, kills off axons that connect the brain with motor cells in the spinal cord; the latter leads to random muscle movement. This causes the well-known symptoms of SPG2, including weakness, paralysis, and cramps. Our team was able to show that mice with comparable diseases display inflammatory reactions, which further aggravate the disease. Consequently, in the mouse models, the disease could be curbed through immunomodulatory drugs. Since it is known that physiotherapy can also curb inflammatory reactions in the nervous system, we conducted pioneer studies with mouse models, in which the mice had free access to a running wheel. This training actually curbed the inflammation, as well as the disease. This is why, in the project we have presented as a funding candidate, we would like to expand on this study, with the goal of establishing physiotherapy as a possible form of treatment for SPG2.

Rudolf Martini (rear left) and his team with Dennis Klein (rear, second left) Photo: University Hospital Würzburg

FUNDED RESEARCH PROJECTS 2019

REBECCA SCHÜLE/ ULRIKE ULMER | TÜBINGEN

From pathophysiology to therapeutic targets: Disturbed sphingolipid metabolism in HSP caused by GBA2 mutations

Hereditary spastic paraplegias (HSP) are characterized by extreme clinical and genetic heterogeneity. Disorders of the lipid metabolism, particularly the metabolism of sphingolipids, are an important reason for the dysfunction of motor neurons leading to HSP. Mutations of the GBA2 gene (SPG46) affect the degradation of the sphingolipid glycosylceramide. In our project, we want to examine the effects of GBA2-dysfunction on neurons and use a lab model to find out whether medication can reverse this metabolic disorder.

Using induced pluripotent stem cells generated from skin biopsies of patients with SPG46, we can examine the lipid composition of human neurons. By comparing patient-derived neurons with their isogenic controls created with CRISPR/Cas9, we will reveal the differences in the sphingolipid metabolism caused by the mutation in the GBA2 gene. We will also conduct mass-spectroscopic measurements of parallel plasma and CSF from SPG46 patients and compare the results with those in the changes seen in the neurons.

Dysregulated pathways will be evaluated with regard to possible interventions. Potential substances will be applied on the neuronal model system and analyzed regarding enzyme activity and/or their lipid composition. With these tests, we aim to see whether our treatment can reverse the defects caused by GBA2-dysfunction.

Ulrike Ulmer (back row, second left) and Rebecca Schüle (back row, second right) Personal photograph

FUNDED RESEARCH PROJECTS 2019

CHRISTEL DEPIENNE | ESSEN

Systematic identification of noncoding tandem repeat expansions in unresolved cases of spastic paraplegias and spinocerebellar ataxias using a combination of short- and long-read sequencing technologies

Genetic tests developed so far have mainly focused on the coding regions of the genome i.e. those parts of the genes that correspond with the sequence of protein(s) they encode. However, these tests only permit to find the cause of genetic disorders in less than half of the patients. An abundant source of variation in the human genome are unstable repeated DNA elements known as tandem repeats or microsatellites. The expansion of the number of repeated elements has been known to cause genetic disorders for more than 30 years, but since these repeats are so abundant and variable in the normal population, making their analysis extremely challenging, they are almost completely ignored in current genetic tests. In this project, using a combination of novel sequencing technologies we will search for novel repeat expansions in 16 patients with hereditary spastic paraplegia or cerebellar ataxia in whom current genetic tests have failed to identify a genetic cause.

Christel Depienne Personal photograph

FUNDED RESEARCH PROJECTS 2020

AMIR JAHIC | BERLIN

In vivo and ex vivo characterization of a novel spastic paraplegia knockout rescue mouse model to define the therapeutic potential of somatic gene repair in HSP

Hereditary spastic paraplegia (HSP) is a clinically and genetically heterogeneous group of monogenic disorders in which the main clinical feature is progressive lower limb spasticity. The pathological correlate of HSP is an isolated degeneration of upper motoneuron axons in the central nervous system (CNS). Many of the genes mutated in HSP are poorly characterized; even expressed in organ systems outside the CNS, their functional link to axon biology remains unknown. Currently, no causal treatment exists to prevent, curb, or reverse progressive disability in patients with HSP.

The main goal of this project is to examine the molecular requirements for therapeutic interventions in HSP. By combining genetic, phenotypical, histopathological, cell biological, and biochemical tools with imaging techniques, we attempt to elucidate the molecular mechanism of the disease before and after selective gene repair. Using a novel knockout rescue mouse model as an experimental tool, we will evaluate the potential subcellular abnormalities with the primary focus on endo-lysosomal structures and autophagosomes comparing pre- and postsymptomatic stages. As a whole, the expected results should define the therapeutic potential of somatic gene repair for HSP.

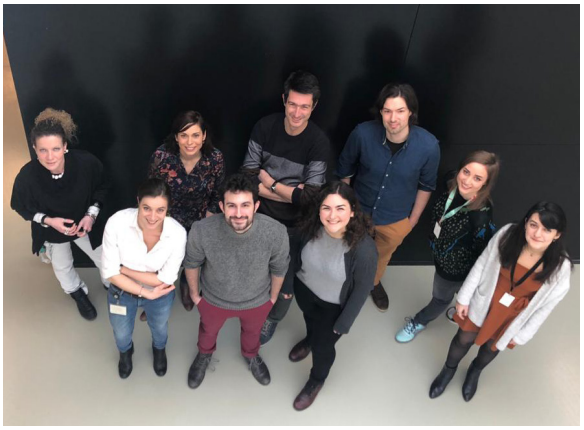
Amir Jahic Personal photograph

FUNDED RESEARCH PROJECTS 2020

CORALIE FASSIER | PARIS AND **MARIA MAGIERA** | ORSAY

Boosting spastin microtubule-severing activity through TTLL-mediated tubulin polyglutamylation: a novel therapeutic strategy in SPG4-linked hereditary spastic paraplegia.

Mutations in the SPG4 gene are responsible for the most common form of autosomal dominant hereditary spastic paraplegia, a neurological disorder characterized by the degeneration of axonal tracts controlling voluntary movements. The SPG4 gene encodes spastin, a protein essential for remodeling microtubules, one of the main components of our cell skeleton. Microtubule remodeling is vital for many cellular processes needed for neuronal homeostasis and survival. To circumvent the dysfunction of the cellular processes associated with spastin losing its functionality, our project aims to decipher the mechanisms that regulate spastin activity. In this context, studies have shown that enzymes called glutamylases deposit specific marks on the microtubule surface which establish a code that regulates the activity of several proteins involved in microtubule remodeling. Thus, using a combination of experimental approaches ranging from in vitro systems to mouse and zebrafish animal models, our project aims to: (i) identify the glutamylases that specifically stimulate spastin activity and (ii) test whether modulation of their activities attenuates or prevents axonal degeneration associated with lack of spastin, which could represent a new therapeutic approach for hereditary spastic paraplegia.



Coralie Fassier and Maria Magiera's research team

Personal photograph

FUNDED RESEARCH PROJECTS 2020

IVANA RICCA | PISA

Scouting biological effects of Miglustat in subjects with spastic paraplegia type 11

Hereditary spastic paraplegia type 11 (HSP-SPG11) is a rare, uncurable neurodegenerative disease characterized by weak and stiff legs, ataxia, and dementia resulting in the progressive loss of autonomy. SPG11 is caused by mutations in the gene encoding spatacsin (SPG11). Studies performed in skin cells (fibroblasts) from SPG11 individuals and in models of the disease have shown that spatacsin dysfunction determines the accumulation of lipids called glycosphingolipids (GSL) within cells, causing the death of neurons. Miglustat is a drug that inhibits an enzyme called glucosylceramide synthetase (GCS) used for the production of GSL. Miglustat therefore helps delay the production of GSL to help mutated cells degrade them. It has been shown that Miglustat reduces the accumulation of GSL both in neurons from Spg11-mutated mice and in fibroblast-derived cells of individuals with SPG11. This study aims to collect preliminary data on the safety of Miglustat for patients with HSP-SPG11 disease and assess plasma GSL modifications during treatment. We will enroll 5 patients aged 12 years or older with HSP-SPG11 confirmed by genetic analysis. The study will last 10 months, treatment will be applied over a period of 12 weeks. Participants will be treated with Miglustat taken orally at a dose of 100 mg three times a day during the first 4 weeks, then the dose of Miglustat will be increased to 200 mg three times a day for 8 weeks.

Ivana Ricca Personal photograph

Award winner Ivana Ricca, and research team working under Dr. Filippo Santorelli, Head of Molecular Medicine at IRCCS Stella Foundation, Pisa
Personal photograph

NEW PACEMAKER FROM BADEN-WÜRTTEMBERG

Jürgen Keck is a new prominent TWS supporter, helping us raise awareness and promote research of HSP.

Jürgen Keck, member of the Landtag and social policy spokesman of the FDP/DVP fraction in the district of Konstanz explains:

„For many years now, I have been looking at the issue of accessibility, and we urgently need to make improvements on this front – after all, it is about the right to take part in public like. To improve patients' quality of life, what we need most of all is support from the scientific community. This is where we often lack financial means. As a new PaceMaker I am proud to support the Tom Wahlig Foundation and the Wahlig family, which are making tremendous efforts to fund and promote HSP research, and offer a forum to HSP patients."

Jürgen Keck *Photo: FDP / DVP-Fraktion*

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100% of every donation goes toward research on and information for patients suffering from HSP.

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