



Report

2014 ELA Families - Scientists meeting

April 5 & 6, 2014
Paris, France

2014 ELA FAMILIES – SCIENTISTS MEETING

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The 2014 ELA Families/Scientists meeting gathered 360 participants in Paris, among them 27 international scientists with expertise in leukodystrophies and myelin diseases. During the 8 diseases' workshops and the plenary session organized, scientists presented the results of their research work in lay language and answered questions from patients and their families.

This special report compiles the information presented during the scientific workshops.

Summary

Diseases' workshops

- Workshop on ALD/AMN
- Workshop on Refsum disease
- Workshop on MLD
- Workshop on Krabbe disease
- Workshop on CACH/VWM syndrome, Alexander disease, MLC and Canavan disease
- Workshop on PMD and other hypomyelinating leukodystrophies
- Workshop on undetermined leukodystrophies
- Workshop on Aicardi-Goutières syndrome

**ALD: AdrenoLeukoDystrophy; AMN: AdrenoMyeloNeuropathy; MLD: Metachromatic Leukodystrophy; CACH/VWM: Childhood Ataxia with Central nervous system Hypomyelination / Vanishing White Matter; MLC: Megalencephalic Leukoencephalopathy with subcortical Cysts; PMD: Pelizaeus-Merzbacher Disease*

DISEASES' WORKSHOPS

WORKSHOP ON ALD/AMN

CLINICAL TRIALS



EVALUATING THE IMPORTANCE OF STRENGTH ON FUNCTION IN AMN

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X-linked adrenoleukodystrophy, a progressive neurodegenerative disease, is caused by a defect in the *ABCD1* gene. The disease has multiple subtypes, but the most common form is adrenomyeloneuropathy (AMN).

Our previous studies identified the symptoms of the disease in men as slowly progressive spasticity, weakness and sensory dysfunction. The worsening of these symptoms results in the progressive difficulty of walking and of balance problems. We have expanded this to include symptom characteristics of AMN in men and women and identify characteristics that have the greatest impact on function. We also evaluate how a home exercise program can affect the degree of symptoms or disability. In 60 men and 80 women with AMN in a single testing session in the Motion Analysis Laboratory at the Kennedy Krieger Institute we measured impairments of strength, vibration sensation and function. Our data show that the strength deficits are a primary factor affecting function. Weakness affects both men and women but varies among the sexes. Both the men and women were divided into three stages based on their level of strength. Each stage varied significantly for strength, vibration sensation, and functional walking measures. These findings indicate that the degree of weakness in people with neurodegenerative diseases such as AMN can be used for staging the severity of their disability.

Our other study evaluates the effects of a tailored exercise program and identifies outcome measures that best predict success with the program. Preliminary data show that strength is changeable with an individualized exercise program. Overall our findings indicate that the degree of weakness in subjects with neurodegenerative diseases such as AMN can be used for staging and to guide clinicians in selecting and evaluating therapeutic interventions.



RESULTS OF A CLINICAL TRIAL: VALIDATION OF OXIDATIVE STRESS BIOMARKERS IN ADRENOLEUKODYSTROPHY USING A COCKTAIL OF ANTIOXIDANTS

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X-linked adrenoleukodystrophy is a rare demyelinating neurodegenerative disease caused by the loss of function of the very long chain fatty acid transporter ABCD1. The most common form of the disease is adrenomyeloneuropathy (AMN), characterized by axonal degeneration of the spinal cord leading to spastic paresis and peripheral neuropathy. At present, there is no effective treatment for AMN. Our research work on adrenoleukodystrophy over the past 10 years has allowed us to demonstrate the crucial role played by oxidative stress in the axonal neurodegenerative process triggering the disease. We then discovered a cocktail of antioxidants could improve axonal degeneration and clinical symptoms in a mouse model of the disease. On this basis, we launched a clinical trial using a cocktail of antioxidants -N-acetylcysteine, vitamin E and lipoic acid- in order to test its safety and efficacy to correct the oxidative stress markers impaired in AMN patients. These data will serve as a first step towards the conduct of a randomized, double-blind, placebo-controlled clinical trial. Patients were also assessed for spasticity, timed walking tests, MRIs, electromyograms

and evoked potentials. Our preliminary results indicate normalization of oxidative stress markers with no modification of plasma very long chain fatty acids levels. The clinical data are currently being analysed.



GENE THERAPY FOR ADRENOLEUKODYSTROPHY

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Childhood cerebral adrenoleukodystrophy (CCALD) is a very rare genetic disease affecting young boys who are unable to metabolize very long chain fatty acids (VLCFA). The resulting accumulation of VLCFA leads to cerebral inflammation and progressive demyelination within the brain, which, if untreated, leads to severe loss of neurological function and death. The current standard of care for treatment of boys with CCALD is hematopoietic stem cell transplant (HSCT) optimally performed early in the course of the disease using an unaffected matched sibling donor. Given that a matched sibling donor is unavailable for a majority of the patients, alternative options include transplantation using an unrelated donor (*e.g.* umbilical cord blood). Unfortunately, this type of transplantation is associated with considerable risks of mortality. Therefore, there is a clear unmet clinical need for novel therapies. Gene therapy offers potential safety advantages over HSCT from a donor. Autologous therapy, using the patient's cells, lowers risk of graft failure, does not require long-term immunosuppression and the associated long-term risk of opportunistic infections.

The Starbeam study is designed to evaluate the efficacy and safety of the Lenti-D Drug Product, a novel gene therapy for the treatment of patients with CCALD. The Lenti-D Drug Product consists of autologous hematopoietic stem cells transduced with a viral vector containing the functioning *ABCD1* gene. This novel gene therapy is intended to restore normal function of the gene disrupted in patients with CCALD. The Starbeam study is open and enrolling.



MD1003 IN ADRENO-MYELONEUROPATHY: A RANDOMIZED DOUBLE BLIND PLACEBO-CONTROLLED STUDY

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Recently, preliminary data have shown that the MD1003 drug could halt disease progression and improve symptoms in patients suffering from primary or secondary progressive multiple sclerosis (MS). Among 23 consecutive patients with progressive MS treated with MD1003 for a mean duration of 9.2 months, 21/23 patients (91.3%) improved. It is hypothesized that the positive effects of MD1003 are linked to increased energy production in demyelinated neurons and stimulation of myelin repair. Two clinical trials are now running involving 250 patients with progressive MS with the goal of confirming the previous results.

Adrenomyeloneuropathy (AMN) and progressive MS share similarities including secondary energy failure leading to progressive axonal degeneration. One patient suffering from AMN was treated for 5 months with MD1003 and showed clinical improvement comparable to the effects observed in progressive MS.

The objectives of the trial are to evaluate the efficacy and safety of MD1003 in AMN patients. Sixty male patients from 4 different centers (France, Spain, Germany) will be initially divided into 2 groups: one group of 20 patients will receive a placebo while a second group of 40 patients will receive the MD1003 drug. The placebo-controlled study will last 12 months followed by a 12 months extension phase during which all patients will be treated with MD1003. The primary efficacy endpoint will be the mean change of the 2 minutes walking test (2MWT) between M12 and baseline. Secondary efficacy judgment criteria will include:

- the time to walk 25 feet test,
- the timed up and go test,
- the Euroqol ED-5D and MOS SF-36 quality of life questionnaires,
- the Qualiveen urinary function questionnaire.

In addition, exploratory analyses including MRI, nerve conduction velocities and evaluation of muscle strength will be performed in a subset of centers.

WORKSHOP ON REFSUM DISEASE



REFSUM'S DISEASE

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In 1945, Refsum described what would later be known as Refsum disease as the combination of night blindness, an absent sense of smell, deafness, poor coordination (ataxia), numbness and weakness in the legs (due to “peripheral neuropathy”) and dry scaly skin (ichthyosis). The first symptoms usually arise in the second decade of life, and then progress. Much later, it was discovered that Refsum disease is caused by a defect in the degradation (alpha oxidation) of phytanic acid. Phytanic acid subsequently accumulates in all tissues of the body. Phytanic acid is derived from phytol, present in green vegetables, plankton, and animals that eat (and can digest) these foods: meat from cows and other ruminating animals, many dairy products, fish. It was discovered in 1988 that green vegetables are safe to eat (because humans, unlike ruminating animals, cannot digest the chlorophyll that contains the phytol). The treatment for Refsum disease is primarily to adhere to a diet low in phytanic acid, since all phytanic acid is of exogenous origin (*i.e.*, from the food we eat). If phytanic acid levels are lowered, the disease is stabilized (at least the ichthyosis, ataxia and neuropathy). For patients with Refsum disease it is also important to not lose weight rapidly, because that can free large amounts of phytanic acid from the fat stores in the body. Weight loss should be gradual. Current research in Refsum disease is exploring the option of inducing an alternative degradation pathway for phytanic acid (*i.e.* omega-oxidation).



Infantile Refsum disease: a relatively mild Zellweger Spectrum Disorder

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Zellweger Spectrum Disorders (ZSDs) result from defects in the functions of cellular structures called peroxisomes, and are also called the peroxisome biogenesis disorders or generalized peroxisomal disorders. The peroxisome performs a number of important functions within the cell that are needed to help various organs work properly, including the nervous system, liver, and adrenal glands. Individuals with ZSDs can vary from relatively mild to severe in their clinical presentation, a continuum of at least three conditions: Zellweger syndrome, the most severe; neonatal adrenoleukodystrophy; and infantile Refsum disease (IRD), the least severe. The names of

the different conditions were originally named before the biochemical and molecular bases of these disorders had been determined.

The clinical course of IRD is variable and may include intellectual and motor development delays, hearing loss, visual impairment, liver dysfunction, and (mild) craniofacial abnormalities. Children may first come to attention because of a failed hearing test and/or visual problems. Liver dysfunction may be first observed in children with bleeding episodes caused by a vitamin K-responsive clotting defect. Children may also have adrenal insufficiency. The overall clinical course may be stable, but the condition is often slowly progressive and hearing, vision, and walking capacity worsen with time. Some individuals may develop a leukodystrophy, which may lead to loss of previous skills. Others may present as an adult with predominantly sensory deficits or only with ataxia (movement abnormality). Since ZSD individuals may well reach adulthood clinical manifestations should be followed-up and treated, such as:

- Feeding and nutrition;
- Hearing aids;
- Vision correction;
- Liver, supplementation of fat-soluble vitamins;
- Adrenal insufficiency, cortisol supplementation.

Experimental therapies are being studied, such as the administration of bile acids (cholic acid), docosahexaenoic acid, and a diet low in phytanic acid. Up to now the treatment of ZSDs is primarily symptomatic and supportive.

Recently, we started oral cholic acid supplementation in ZSDs. It is the purpose to reduce the levels of the toxic bile acids metabolites di- and tri-hydroxycholestanic acid. We expect the first results within one year.

The diagnosis of ZSDs can be definitively determined by biochemical investigations in blood and/or urine, followed by confirmation in cultured skin fibroblasts. Specialized biochemical testings are: very-long-chain fatty acids, phytanic acid and pristanic acid, bile acids, pipecolic acid in plasma; plasmalogens in erythrocyte membranes; pipecolic acid, bile acids, oxalate in urine.

Mutations in twelve different *PEX* genes have been identified in ZSDs. *PEX1* is the most common cause of ZSDs, associated with about 70% of all ZSDs individuals.

WORKSHOP ON MLD

CLINICAL TRIALS



PHASE I/II CLINICAL TRIAL OF HEMATOPOIETIC STEM CELL GENE THERAPY FOR THE TREATMENT OF METACHROMATIC LEUKODYSTROPHY

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Metachromatic Leukodystrophy (MLD) is an autosomal recessive lysosomal storage disorder caused by Arylsulfatase A (ARSA) deficiency leading to severe demyelination, neurodegeneration and premature death of affected patients. Currently, there is a need for new treatment options for this devastating disease. According to preclinical data demonstrating the safety and efficacy of hematopoietic stem cell gene therapy in the animal model of the disease, and based on the experience we acquired on the natural clinical course of the disease, on March 2010 a clinical trial based on transplantation of autologous hematopoietic stem cells transduced with a lentiviral vector (LV) encoding *ARSA* was approved by the Italian Regulatory Authorities. The clinical protocol enrolls late infantile (LI) and early juvenile (EJ) patients, in pre- and, in the case of EJ

patients, early-symptomatic stage, in order to provide them a reasonable expectation of clinical benefit. The study objectives are the evaluation of:

- i) the safety of the treatment, related to the myeloablative conditioning regimen employed and to the use of LVs, and
- ii) its efficacy by measuring patients' motor and cognitive abilities and demyelination occurring in the nervous system through the use of validated instrumental readouts.

Preliminary data will be presented for the first 9 patients enrolled in the study, three of whom have completed at least 30 months of follow up. Seven subjects had a biochemical, molecular and family history compatible with a diagnosis of LI MLD and have been treated in a pre-symptomatic stage of their disease. Two EJ MLD patients were treated in an early symptomatic stage. Thus far, the transplant procedure has resulted in good bone marrow recovery and evidence of short/medium-term safety of both the conditioning regimen and of the use of LVs in all the patients. Moreover, we report stable ARSA activity reconstitution often above normal levels both in the hematopoietic lineages and in the cerebrospinal fluid. These findings are associated with protection from marked disease progression in LI patients. Follow-up of these patients, performed up to 3.5 years after the expected symptoms onset (as defined according to disease onset in the affected older siblings), shows that disease had not significantly progressed. Most patients exhibit continuous motor and cognitive development, which is at odds with the natural disease course and the disease course of their siblings. The observation of the only two EJ patients treated thus far does not allow drawing conclusions in terms of therapeutic benefit due to their different disease stage at treatment and post-treatment course. Overall, these data are encouraging, but need validation with further long-term follow up.



ENZYME REPLACEMENT THERAPY USING HGT-1110

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Metachromatic leukodystrophy (MLD) is a type of lysosomal storage disease (LSD) which are a family of genetic disorders caused by missing or deficient enzymes. For some LSDs, many symptoms can be effectively treated by intravenous (iv) administration of recombinant enzymes. These enzymes are relatively large and cannot pass from the blood stream to the central nervous system when given intravenously and are not expected to significantly impact the central nervous system manifestations associated with some types of LSDs. Metachromatic leukodystrophy is one of the lysosomal storage disorders that primarily affects the central nervous system and Shire has a clinical development program to investigate direct delivery of investigational recombinant human arylsulfatase (rhASA) to the central nervous system.

Shire's development program for MLD is currently in early clinical development. In animal models, rhASA was detected in all areas of the brain, from the surface grey to the deep white matter tissues of the brain. It was also observed that the administered enzyme was deposited in the lysosomes of oligodendrocytes, the site of the pathologic sulfatide accumulation in MLD. Studies evaluating weekly intrathecal administrations of rhASA in another animal model of MLD showed a reduction in CNS sulfatides, both in the spine, near the site of injection as well as the deep tissues of the brain. Taken together, this series of experiments demonstrated that IT administration of rhASA reached the target central nervous system tissues. Data from these studies will be useful in supporting research in humans; however, results in animals do not necessarily correlate to experience in humans.

Shire currently has a phase I/II study to evaluate the safety of a recombinant form of ASA in patients with MLD. In addition to safety, this study will evaluate changes in gross and fine motor skills, swallowing, cognition, adaptive behavior, and changes in the peripheral nervous system. This study has an extension study that will allow for evaluation of longer term safety and effect on clinical outcome measures. Shire is also conducting a natural history study and the goals of this study are to better understand the natural course of MLD in pediatric and adult patients.



CLINICAL TRIAL: INTRACEREBRAL GENE THERAPY FOR METACHROMATIC LEUKODYSTROPHY

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Metachromatic leukodystrophy (MLD) is a neurodegenerative disease caused by a defect in arylsulfatase A (ARSA) enzyme activity, leading to a build-up of sulfatides in cells of the central and peripheral nervous system - especially myelin-producing cells - as well as in neurons. The late infantile form - the most severe and frequent form of the disease - begins around the age of 1 or 2. It is characterized by very rapid motor and cognitive deterioration, leading to early bedridden state and death. At present there is no treatment for this form of the disease once the children are symptomatic. Intracerebral gene therapy may enable rapid and sustained expression of the ARSA enzyme in the brain, a necessary condition to stop the neurodegenerative process in time. In the MLD mouse model, we demonstrated the efficacy and safety of intracerebral administration of a viral vector carrying the ARSA therapeutic gene and named AAVrh.10/ARSA.

In primates in which the brain volume is much closer to that of a child, we optimized and validated the neurosurgical procedure in order to allow simultaneous administration of the vector to 12 areas of the brain. We thus demonstrated the injection of the AAVrh.10/ARSA vector leads to significant over-expression of ARSA throughout the brain of primates, with no detrimental effects. The required toxicological studies were carried out and we obtained the necessary authorizations from the French National Medicine Agency and the ethics committee to start a phase I-II (safety and efficacy) clinical trial in children with MLD in March 2013. The trial, currently open for enrollment, will include five children (aged from 6 months to 5 years) suffering from early forms of MLD (late infantile, early juvenile), at the very beginning of the disease based on specific motor and cognitive inclusion criteria.

The viral vector will be administered to 12 brain sites, chosen using brain imaging (MRI). Safety and efficacy parameters will be assessed for 2 years, a period that should be sufficient to assess the safety and therapeutic efficacy of this gene therapy approach.

WORKSHOP ON KRABBE DISEASE



KRABBE DISEASE: WHAT WE HAVE LEARNED FROM 10 YEARS OF NATURAL HISTORY AND TREATMENT OUTCOMES

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We have studied the natural history of early and late infantile Krabbe disease, and developed a staging system that evaluates disease burden. The transplant outcomes correlated well with the staging at the time of treatment in both early and late infantile. Other tests such as brain imaging and neurophysiological studies were found to reflect disease progression but are not predictive of outcomes after transplantation. In the early infantile onset, babies benefit from unrelated umbilical cord blood transplantation only if the patients are diagnosed before the onset of symptoms. Newborn screening is available in New York State since August of 2006 and more recently it is also available in Missouri. Several states have passed legislation and are considering adding Krabbe to the expanded newborn screening programs. Therefore, there is an urgent need to establish predictors of disease onset since it is not known whether babies who screen positive will develop disease as a baby or as an adult. Our group has studied and developed new methodologies to identify differences in the internal capsule using brain MRI tractography. We found that our new tool distinguishes between babies who have early-onset disease from those who will develop symptoms much later. The tool provides very consistent values that can detect small regional

differences and age-related changes in the first weeks of life. In addition to this methodology we have established a tissue repository and evaluated potential biomarkers of disease onset. Both tools may be key components of population-screening programs to help determine who should receive treatment before symptoms develop.

WORKSHOP ON CACH/VWM SYNDROME, ALEXANDER DISEASE, MLC AND CANAVAN DISEASE

MLC



DEVELOPMENT OF EXPERIMENTAL MODELS FOR MEGALENCEPHALIC LEUKOENCEPHALOPATHY WITH SUBCORTICAL CYSTS (MLC)

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Defects in the astrocytic membrane protein MLC1 or the adhesion molecule GlialCAM underlie MLC. GlialCAM binds MLC1, and this binding is required for MLC1 endoplasmatic reticulum exit and its targeting to cell junctions. Furthermore, GlialCAM also binds and targets the chloride channel CIC-2 to cell junctions, and modify CIC-2 currents. Recently, mutations in CLCN2 have been identify in a different type of leukodystrophy. Taking into account these biochemical relationships, it remains unclear why patients with recessive mutations in MLC1 (MLC1 patients) or GLIALCAM (MLC2A patients) show the same clinical phenotype. In this talk, I will present new results obtained from zebrafish and mice models of MLC disease and a brain biopsy from a human MLC patient. Our data points to a functional relationship between astrocytic MLC1 and oligodendrocytic CIC-2 mediated by GlialCAM trans-homophilic interactions. The work suggests that CIC-2 dysfunction in glial cells may contribute to the pathogenesis of MLC. Finally, we demonstrate an evolutionary activity-dependent conserved role of MLC1 in regulating glial surface levels of GlialCAM, and this relationship rationalize the undistinguishable symptomatology of MLC1 and MLC2A patients.

CACH/VWM syndrome



ESTABLISHING AN IN VITRO (IN THE DISH) MODEL OF VANISHING WHITE MATTER DISEASE

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Vanishing white matter disease (VWM) is one of the most common forms of childhood leukodystrophy, a type of inherited disease that affects the white appearing areas of the brain, resulting in increasing brain damage and death. This devastating disorder is usually detected in early childhood, although older children and adults can also be affected.

VWM disease is caused by abnormalities in proteins needed to make other proteins in a cell. These badly effect two types of cells, called oligodendrocytes and astrocytes, which are found in the brain. These cells provide support and protection for nerve cells. In particular, oligodendrocytes produce a fatty substance called myelin that wraps nerve cells, allowing fast signal transmission. We do not understand exactly what effect these abnormalities have on the oligodendrocytes and astrocytes and how this leads to the brain damage associated with the disease.

In order to understand the effects of these protein abnormalities it is essential to study the affected cells, but oligodendrocytes and astrocytes are difficult to obtain from the brains of patients with

VWM. To overcome this problem we have taken advantage of the ability of embryonic stem (ES) cells to be converted into any cell type in the body. Using the correct chemical signals we can turn ES cells into oligodendrocytes and astrocytes in a dish.

ES cells have another advantage- it is relatively easy to alter their DNA to insert changes, such as the ones that occur in VWM disease. We have chosen to study two abnormalities that cause VWM disease in patients and we have successfully altered ES cells to carry these changes. We can now convert these abnormal ES cells into astrocytes and oligodendrocytes and add them to nerve cells in a dish. Over time the oligodendrocytes wrap the nerve cells with myelin, just as they do in the brain. This simplified in the dish model of the brain will allow us to try to understand what effects the VWM abnormalities have on the oligodendrocytes and astrocytes and how these altered cells cause VWM disease in people.

Alexander disease



RESEARCH UPDATE ON ALEXANDER DISEASE

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Alexander disease is associated with dominant mutations of the *GFAP* gene encoding the structural protein bearing the same name, the major intermediary filament of mature astrocytes. In the vast majority, this genetic disease is sporadic, linked to the appearance of a new *GFAP* mutation in the patient without having any member of the family (either from current or past generations) affected. More rarely, the disease is familial. The age of onset, symptoms, progression and severity of the disease are very variable. Classically, the forms with an onset in newborns, called infantile, are more severe than the ones with a later onset (juvenile and adult).

Clinical research aiming at describing the natural history of the disease is essential in order to appreciate in the future the effects of potential treatments in the frame of clinical trials. As no biochemical marker of the disease is known, we are currently carrying out the study of the disease progression in 45 patients from a clinical, imaging and electrophysiological point of view. Our results show a large heterogeneity in the evolution and severity of the disease including for patients suffering from infantile forms.

So far studies conducted to understand the mechanisms of the disease have shown *GFAP* mutations lead to overexpression of this protein and formation of aggregates (called Rosenthal fibers) containing GFAP and cellular stress proteins in astrocytes. The GFAP accumulation triggers the increase in cellular stress favoring also GFAP overexpression. The goal of our research work is to identify drugs that could stop this vicious circle. Initial work performed by Dr. Danielle Pham-Dinh tested numerous drugs on mouse astrocytes expressing mutated *GFAP*. These studies allowed us to select two drugs leading to a decrease in aggregates without toxicity.

We currently have access to 2 mouse strains, each carrying two different *GFAP* mutations closer to the disease than the previous cellular model. We showed these mice overexpress GFAP and show Rosenthal fibers in the brain and in cultured astrocytes. The selected two drugs decrease the number of aggregates and the GFAP overexpression in cultured astrocytes from mutated mice. We are currently testing the effect of these drugs on other astrocytic impairment signs recently identified in cell cultures. These two drugs will also be tested in these mice.

At the same time, we are continuing the characterization of the mutated mice that are not clearly showing clinical signs of the disease but rather some behavioral abnormalities. Nevertheless, the mice show important abnormalities in the brain similar to the ones described in patients.

Canavan disease



GENE THERAPY FOR CANAVAN'S DISEASE, A SEVERE INHERITED PEDIATRIC LEUKODYSTROPHY – ARE WE THERE YET?

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Leukodystrophies are a group of disorders that primarily affect the white matter of the central nervous system (CNS) (as opposed to the grey matter). However, the term can be misleading since many diseases can present with white matter dystrophy even if the primary cause is not within the brain, *e.g.* late stage of HIV infection. Using the term of leukodystrophy in the context of gene therapy, however, usually refers to a group of inherited disorders that present with dystrophy of the white matter. Unfortunately, disorders of that kind present with severe symptoms and substantially reduced life quality for affected individuals and their families.

Canavan Disease (CD) is such a disorder of the group of leukodystrophies. It is a recessively inherited disease (meaning a gene defect has to be inherited from both parents), that is caused by a mutation in the aspartoacylase gene (*AspA*). When mutated, this gene fails to metabolize its only substrate N-acetylaspartate (NAA), which leads to accumulation of very high levels of NAA in the brain and urine (NAA aciduria). Affected individuals become symptomatic very early in life (first months after birth) or years later (teenager). The symptoms can be very broad: poor feeding and irritability in infants, macrocephaly (increased head circumference), hypotonia (reduced tension of the muscles) and seizures at the age of one year and later. Furthermore, children become blind, lose weight, develop tremor and show severe developmental delay (*e.g.* cognitive function). On brain imaging (MRI), a common finding is water accumulation within the brain tissue (brain edema) that is also characteristic for leukodystrophies in general. Currently, only symptomatic treatment is available, *e.g.* medication to treat seizures or casts to support posture or joints.

A very promising strategy, however, to treat patients with inherited leukodystrophies, *e.g.* Canavan Disease, is gene therapy. For most of dystrophies, gene therapy follows a simple principle: replacement of the sick (mutated) gene with a healthy gene. In early attempts using gene therapy to treat Canavan disease, the healthy gene was either wrapped in lipid drops or put into a nonpathogenic residential virus in humans and nonhuman primates, called adeno-associated virus (AAV). Though, in these studies the healthy gene (encased in lipid drops or the first generation of AAV vector) was injected directly into the brain. Direct injection into the brain matter was necessary because the lipid drops or the first generation of AAV vectors was not able to cross the blood-brain barrier (BBB). The BBB is a barrier of cells and other material that is supposed to protect the brain from substances and organisms that might cause harm to the brain, *e.g.* viruses, bacteria, toxins. The first proof-of-concept studies in mice and humans could show some reduction in water accumulation around the injection area and such treatments are safe for the patients, when the healthy *AspA* gene was injected into the brain matter (either encased by lipids or AAV). These results were promising but could not significantly improve the disease phenotypes.

The next major step taken started several years ago, when it was discovered, that some AAVs discovered by our laboratory are capable of crossing the BBB. Our group started to inject those second generation of AAVs packed with the healthy *AspA* gene in the vein of one day old mice that carry a mutation in the *AspA* gene. These mice, called CD mice, have very severe symptoms as CD patients and uniformly die within 4 weeks of life (in contrast, the healthy siblings of this mouse model live up to 2 years). In order to assess whether our treatment is successful, we measured several parameters: body weight, life expectancy, motor function (coordination, strength and balance) and NAA in the brain and urine. We even obtained MRI (magnet resonance imaging) images from treated and untreated mice. Overall, treated mice performed similarly to healthy mice in all the categories mentioned above. Strikingly, the treated mice survived up to two years (the same as

healthy mice and in contrast to untreated mice that die within the first 4 weeks of life). In addition, we were wondering if we can still rescue the sick mice if we inject at later time points. Indeed, we were able to treat animals successfully until one week before they die when untreated. This means, that our treatment could extend the life expectancy of CD mice to that of healthy mice, even when treated late in the disease progression.

Very encouraged from these first results in CD mice, we are currently working on improving our treatment. One strategy is to inject our AAV that contains the healthy *AspA* gene, in the ventricular system of the brain. The ventricular system is comprised of a naturally occurring system of cavities that are interconnected; first results are very promising. This treatment will need 1/100th of the gene drug used in intravenous injection. Another strategy is, to increase the expression of the *AspA* gene. The idea is that a gene is read several times over time before it produces functional protein. If we can increase the number of times the gene is read, we might be able to increase the strength of the treatment (potency). On the other hand, a more efficient gene expression could help us to again reduce the dose we are using currently. This might be important to reduce the chance of potential side effects.

Besides these current studies, we are aiming to answer the following questions before we attempt transitioning to a clinical trial:

1. How late along the disease progression are we able to successfully treat Canavan Disease? There are several thoughts behind this question. The two most important ones are:
 - 1.1. there might be a time point where our current treatment strategy will not be therapeutic anymore, meaning will not improve the patient's condition. If we can determine that time point, we will be able to reconsider our strategy to eventually overcome underlying restrictions.
 - 1.2. the blood-brain barrier appears to be less tight at very young ages but more impermeable and fully developed in adults. Thus, it is important to find out if this change in the BBB will affect our treatment outcomes. Again, answering this question will help to improve gene therapy for Canavan Disease. Even more important, the findings from those studies will be certainly informative and helpful to treating other leukodystrophies as well since many of these principles also apply to other diseases of the brain.
2. Following the concept that no treatment is without side effects, we also want to know at what dose gene therapy for Canavan Disease will be most effective but causes the lowest side effects. This will help, to find a dose that can be up-scaled to the body size of human beings, which becomes very important for the first clinical trial.

To conclude, we are convinced that our strategy to use gene therapy for the treatment of inherited leukodystrophies, *e.g.* Canavan Disease, has the great potential to be successfully translated to the treatment of human patients. As outlined above, we aim to answer all remaining questions regarding gene therapy of Canavan Disease before moving gene therapy to clinical applications. For that reason, we have a strong team working on answering these crucial questions that will finally improve the life and even cure the devastating leukodystrophy diseases of many individuals.

WORKSHOP ON PMD AND OTHER HYPOMYELINATING LEUKODYSTROPHIES



INTRODUCTION ON PELIZAEUS-MERZBACHER DISEASE (PMD)

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Leukodystrophies can be divided into two main groups depending of their brain MRI features: hypomyelinating leukodystrophies and non-hypomyelinating leukodystrophies. Pelizaeus-Merzbacher disease (PMD) is the prototype, and based on current data, the most common hypomyelinating disease. PMD is an X chromosome-linked disease caused by mutations in the *PLP1* gene. The clinical presentation of diseases linked to the *PLP1* gene is variable and includes several subtypes, depending on the age of disease onset and its severity. The connatal form is the most severe with an onset during the neonatal stage followed by the classic form, which starts in the first year of life, by the *PLP1*-null form and, finally, by the complicated and uncomplicated spastic paraplegia form (SPG2). The classic form usually appears during the infantile stage with hypotonia (reduced muscle tone) and nystagmus. The child develops spastic quadriplegia (arms and legs increased tone), ataxia (balance problems) and cognitive difficulties. PMD management requires a multidisciplinary team to offer physical therapy, treat problematic symptoms (*e.g.* spasticity) and prevent complications (*e.g.* use of gastrostomy to prevent aspiration pneumonia). A recent study on stem cell transplants was carried out in four patients with the most severe form of the disease, the connatal form. The study showed the treatment was safe over the observation period and stem cells engrafted in the brains of the patients. More studies will be required to determine the safety and efficacy of this therapy but current results are encouraging.



GENE THERAPY IN ANIMALS DEVELOPING PELIZAEUS-MERZBACHER DISEASE (PMD)

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Pelizaeus-Merzbacher disease (PMD) is linked to mutations in the myelin proteolipid protein (*PLP1*) gene. Proteolipids (PLP/DM20) make up around 50% of total myelin proteins. In the brain, myelin is synthesized by glial cells, the oligodendrocytes, to form an insulating sheath around the axon of neurons and thereby enable rapid conduction of nerve impulses. In the vast majority, PMD is caused by the acquisition of additional copies of the *PLP* gene (duplication) and, in a lower proportion of cases, gene sequence defects are found leading to the production of an abnormal protein (mutation). Since there are currently no treatments for PMD, the challenge is to find a treatment strategy using a gene therapy approach aimed at substituting or regulating the defective gene.

Transgenic mouse models of PMD expressing extra copies of the *Plp1* gene are used for our work. Mutations in mice trigger neurological disorders and nervous system anomalies similar to those observed in humans.

We are performing a preliminary study aimed at exploring the effect of antisense oligonucleotides, called Morpholino and marketed by Gene-tools®, on the PLP over-expression and on the mice phenotype. This product, selected since it is currently being assessed in gene therapy trials in children with Duchenne muscular dystrophy, does not seem to represent a pertinent tool in the treatment of PMD.

Our ongoing project aims at assessing the effect of antisense RNA in the same mouse model, delivered to the brain by an AAV-type viral vector, a vector infecting preferentially oligodendrocytes.



POLYMERASE III-RELATED LEUKODYSTROPHIES: A RESEARCH UPDATE

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Pol III-related leukodystrophies are a group of relatively common hypomyelinating leukodystrophies that include:

- 4H syndrome (Hypomyelination, Hypodontia and Hypogonadotropic Hypogonadism),
- ADDH (Ataxia, Delayed Dentition and Hypomyelination),
- TACH leukodystrophy (Tremor-Ataxia with Central Hypomyelination),
- Leukodystrophy with oligodontia (LO) and
- HCAHC syndrome (Hypomyelination with Cerebellar Atrophy and Hypoplasia of the Corpus Callosum).

This group of diseases is now considered to be a clinical continuum, *i.e.* some patients present certain features, while others do not, such as dental anomalies and delayed puberty (hypogonadotropic hypogonadism).

Pol III-related leukodystrophies are caused by recessive mutations in the *POLR3A* and *POLR3B* genes. To date, more than 40 patients with one of these diseases have been reported with mutations in one or the other gene. The *POLR3A* and *POLR3B* genes encode for the largest two subunits of an enzyme named RNA polymerase III, and, together, form the active or catalytic core of the complex composed of 17 subunits. No patient carries two null mutations, *i.e.* two mutations that would lead to the complete absence of the protein encoded by the gene. This is not actually surprising given the essential role of RNA polymerase III: transcription of DNA encoding small RNAs, such as transfer RNAs, 5S, U6 and 7SK.

Research is underway to discover why mutations in the *POLR3A* or *POLR3B* genes cause hypomyelinating leukodystrophy. These mutations may have an effect on the assembly of the enzyme subunits or on the DNA binding to the complex.

A comparative study of all small RNA produced by RNA polymerase III in patients and healthy subjects suggests the production of transfer RNAs may be more affected. The involvement of these small RNAs is also suspected in other hereditary diseases affecting the brain white matter, such as LBSL (Leukoencephalopathy with Brainstem and Spinal cord involvement and Lactate elevation) and in another hypomyelinating leukodystrophy called HBSL (Hypomyelination with Brainstem and Spinal cord involvement and Leg spasticity) caused by mutations in the *DARS* gene.

The discovery of the genes associated to leukodystrophies now known as Pol III-related leukodystrophies has allowed access to diagnosis and appropriate genetic advice for numerous patients and their families. Clinical, radiological and pathophysiological studies are still ongoing to gain a clearer understanding of the extent of the clinical and radiological manifestations, the genetic defects and, of course, the pathophysiology of this group of diseases in order to potentially develop therapeutic strategies.



CLINICAL AND MRI ENDPOINTS FOR CLINICAL TRIALS TARGETING HYPOMYELINATING LEUKODYSTROPHIES

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Hypomyelinating Leukodystrophies are a heterogeneous group of disorders unified by a paucity of development of myelin. These disorders include:

- hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC),
- Hypomyelination with Congenital Cataracts (HCC),
- Hypomyelination of Early Myelinated Structures,
- Hypomyelination with Brainstem and Spinal cord involvement and leg spasticity,

- Free sialic acid storage disease,
- Fucosidosis,
- Pelizaeus-Merzbacher disease (PMD),
- Pelizaeus-Merzbacher like disease (PMLD),
- Pol III-related leukodystrophies / Hypomyelination with Hypogonadotropic Hypogonadism and Hypodontia (4H),
- Oculodentodigital dysplasia (ODD),
- Trichothiodystrophy with hypersensitivity to sunlight, and
- *SOX10*-associated disorders.

Although there are specific clinical features to a number of disorders, such as absent puberty in 4H, skin sensitivity in trichothiodystrophy, cataracts in HCC, dental anomalies in 4H and ODD, among others, there are also a number of unifying features in hypomyelinating conditions.

This clinical overlap provides the opportunity to consider these disorders together in the development of outcome measures for future clinical trials. These include clinical outcomes, such as outcomes of gross motor function, dystonia scales and standardized neuropsychological scales. Unfortunately, these approaches may be difficult to apply in patients with severe motor deficits such as are seen in the hypomyelinating leukodystrophies. Natural history studies are therefore likely to be the most important clinical tool in future therapeutic trials. There are also no defined biochemical markers in hypomyelinating disorders to provide surrogate markers.

Therefore, we need to consider alternative surrogate biomarkers, including neuroimaging. Emerging MRI modalities may be helpful in identifying developing myelination. These include Proton MR spectroscopy (MRS), different quantitative approaches such as multicomponent relaxation approaches allowing fully three-dimensional acquisitions, such as through the use of rapid spiral imaging, or alternative non-spin echo based imaging methodologies (*i.e.*, GRASE or mcDESPOT), and Magnetization transfer (MT), Diffusion tensor imaging (DTI).

These approaches will become particularly relevant as emerging therapeutics in hypomyelinating leukodystrophies advance to clinical trials.

WORKSHOP ON UNDETERMINED LEUKODYSTROPHIES



PRESENTATION OF A NEW LEUKODYSTROPHY

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Background

Our studies are focused on patients with a leukodystrophy of unknown cause with the aim to define novel, homogeneous phenotypes suggestive of common genetic defects, based on clinical and MRI findings. Subsequently, our aim is to identify the causal genetic defect, shared by the patients with this phenotype.

Methods

We selected a group of thirteen patients with a similar MRI pattern suggesting a novel leukodystrophy. Independent next generation exome sequencing studies were performed in two unrelated patients. Clinical and MRI findings were investigated.

Results

In both patients next generation exome sequencing revealed compound heterozygous mutations in *AARS2* encoding mitochondrial alanine-tRNA synthetase. Functional studies in yeast confirmed the pathogenicity of the mutations in one patient. Sanger sequencing was performed in the remaining eleven patients and revealed *AARS2* mutations in four of them. The in total six patients with *AARS2*

mutations had childhood to adulthood onset signs of neurological deterioration consisting of ataxia, spasticity and cognitive decline with features of frontal lobe dysfunction. MRIs showed white matter abnormalities with striking involvement of left-right connections and ascending and descending tracts, and cerebellar atrophy. All female patients had ovarian failure. Signs of cardiomyopathy were not observed. Since we finished the study on this first group, we have identified several other patients.

Conclusions

Mutations in *AARS2* have been found in a severe form of infantile cardiomyopathy in two families. We present patients with a novel phenotype caused by *AARS2* mutations, characterized by a distinctive leukoencephalopathy and, in female patients, ovarian failure.



NEWS ON HYPOMYELINATING DISORDERS

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Hypomyelinating white matter disorders form together the largest group (about 20%) of inherited white matter disorders. As in other white matter disorders, a definitive diagnosis cannot be made in a substantial part of our patients, which used to be 50%. MRI pattern recognition approach, very useful in other white matter disorders and crucial for defining new disease entities, was traditionally thought to be not feasible in hypomyelination. During the last years, it became however evident that, at least for a part of patients with hypomyelination, MRI pattern recognition allows to define new disease entities. Together with the new genetic techniques, especially whole-exome sequencing (WES), it became possible to identify the responsible gene even in small groups of patients, as it was shown for the new hypomyelinating disease HBSL (hypomyelination with brain stem and spinal cord involvement and leg spasticity), which is caused by mutations in *DARS*. WES is also possible in single families, although the success rate is considerably lower than in groups of several unrelated patients with the same disease. Combination of MRI approach and WES made it possible to make a definitive diagnosis in two thirds of our patient cohort. Pelizaeus-Merzbacher disease and 4H syndrome are the two most common entities, all other entities are very rare.

It also became evident that clinical presentation is extremely variable in hypomyelination. We know adults with only mild symptoms and severely affected children, all with hypomyelination on MRI. With new MRI techniques, we try to quantify the small amount of myelin present in these patients in order to come to a better understanding of the clinical variation. This approach will also be important for future therapeutic studies.



NEW GENES IDENTIFIED FOR UNDETERMINED LEUKODYSTROPHIES

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Leukodystrophies (LDs) are inherited rare neurodegenerative diseases affecting the white matter and its main component, the myelin. Most of the disorders have onset in childhood. LDs are classified in two main conditions:

- 1) disorders that affect myelination and are characterized by a primary defect in myelination (hypomyelinating leukodystrophies-HLDs) and
- 2) disorders that are characterized by myelin destruction or myelin maintenance (demyelinating leukodystrophies-DLDs).

In the last 15 years MRI has emerged as a precious tool for the differential diagnosis of leukoencephalopathies.

In the last 5 years advances in genomic sequencing technology defined as next generation sequencing has allowed to accelerate the definition of new genes responsible for formerly undefined Leukodystrophies. The impression is that we now know most of the genes responsible for HLDs and of DLDs limited to the subgroup of megalencephalic leukodystrophies with subcortical cysts and the other subgroup of Vanishing White Matter leukodystrophies. However the prediction is that most of the new genes will be discovered in the DLD subgroup of mitochondrial leukodystrophies.



UNDETERMINED LEUKODYSTROPHIES: STUDY OF A 80 PATIENTS COHORT USING EXOME ANALYSIS

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Exome technology makes it possible to sequence all the exons of the genome. The exon represents the part of the gene used for the synthesis of proteins. The human genome contains around 180,000 exons, which represent approximately 1% of the whole genome. Exons are involved in 85% of monogenic diseases.

Leukodystrophies are a group of genetic diseases affecting the white matter and primarily its major component: myelin. The diversity of genetic defects explains the broad heterogeneity observed in these diseases. Over the past decade, in collaboration with Europe and the LeukoFrance network, we gathered 1182 families with leukodystrophies of unknown cause. Despite the advances made for gene identification, the genetic defects involved in 60% of our families have not yet been identified. We performed exome sequencing in a cohort of 80 patients with leukodystrophies of unknown cause. This analysis allowed us to divide our cohort into three subgroups:

- the 1st group had mutations in genes known to be involved in leukodystrophies but with a highly atypical clinical presentation,
- the 2nd group had mutations in genes already implicated in another genetic disease. However, the mutation identified is different from the ones known for this disease,
- the 3rd group had mutations in possible candidate genes. None of these mutations were found in controls. They are described as detrimental by prediction sites. However, in order to prove that the defect found in a gene really is truly causal, it is essential to carry out functional tests.



USING TARGETED HIGH-THROUGHPUT SEQUENCING ON 70 LEUKODYSTROPHIES / LEUKOENCEPHALOPATHIES GENES FOR THE DIAGNOSIS OF UNDETERMINED LEUKODYSTROPHIES: AN EFFICIENT APPROACH?

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The leukodystrophy family is a vast and heterogeneous group of monogenic diseases resulting from primary defects in the myelination process in the central nervous system. To date, mutations in almost 50 different genes have been reported and identified as causing different forms of leukodystrophy.

In some cases, patient data (MRI, phenotype, biomarkers, etc.) help the clinician to think about a candidate gene, leading to diagnosis for around 35% of them. However, incomplete or atypical forms can make this approach relatively unsuccessful. This molecular heterogeneity significantly limits the diagnostic possibilities for patients and their families, making the search for mutations in these 50 genes impossible in terms of cost and time with "conventional" sequencing strategies, such as Sanger sequencing.

We have thus developed a molecular screening approach using targeted high-throughput sequencing, allowing to simultaneously capture and sequence all the coding parts of 70 genes involved in forms of leukodystrophies and leukoencephalopathies, in a large number of patients concomitantly.

In a cohort of 122 patients with undetermined leukodystrophies, we have managed to identify the disease-causing mutation in 17% of the cases (*i.e.* for 21 patients). Other potentially causal variants have been identified in another 10 patients, the pathogenic nature of which remains to be confirmed.

In several patients in the cohort, mutations have been found in the following genes:

- *EIFB2* and *EIF2B5* (CACH/VWM syndrome),
- *PLP1* (Pelizaeus-Merzbacher disease),
- *POLR3A* and *POLR3B* (pol III-related leukodystrophies, or 4H syndrome),
- *RNASEH2B* (Acairdi-Goutières syndrome),
- *SLC16A2* (Allan-Herndon-Dudley syndrome),

and in a single patient for the following genes:

- *ABCD1* (adrenoleukodystrophy),
- *ALDH3A2* (Sjögren-Larsson syndrome),
- *DARS2* (Leukoencephalopathy with Brain Stem and Spinal Cord Involvement and Lactate Elevation, or LBSL syndrome),
- *GFAP* (Alexander disease),
- *MLC1* (megalencephalic leukoencephalopathy with subcortical cysts) and
- *POMGNT1* (Muscular dystrophy/ α -dystroglycanopathy).

Of the 83% of patients left without any positive diagnosis, it can be imagined that the mutations are located either in currently unidentified genes or that, for some patients, the white matter abnormalities detected by MRI are, in reality, not specific to a primary white matter defect (*i.e.* to a leukodystrophy) but a secondary one (*i.e.* to a leukoencephalopathy, certain forms of epilepsy or intellectual deficit with white matter involvement, etc.).

WORKSHOP ON AICARDI-GOUTIÈRES SYNDROME



UPDATE ON AICARDI-GOUTIERES SYNDROME

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Aicardi-Goutières syndrome (AGS) is a genetic disorder of inappropriate immune system activation. Growing evidence suggests that an accumulation of nucleic acid (RNA and DNA), perhaps derived from 'ancient viruses' embedded in our own cells, provokes an immune response orchestrated by so-called type I interferon. AGS is a serious disease that warrants treatments, and designing effective therapeutic approaches will be enhanced by an improved understanding of disease mechanisms. Following proof-of-principle studies in the *Trex1*-null mouse and new knowledge relating to the AGS-associated proteins, strategies of immediate interest include blocking of type I interferon and other components of the associated inflammation pathways, interruption of the generation of the products of 'reverse transcription', and a depletion of B and T cells. Therapies already exist relating to some of these possibilities.

The difficulties of randomization and controlled studies in rare disorders with small populations are relevant to AGS. It may be useful to consider using an historical cohort as a control population in a treatment trial; to that end, careful attention to natural history remains crucial. Additionally, outcome measures to determine the effectiveness of treatments need to be established, and their best use carefully considered. Disease manifestations, *e.g.* radiologic findings and clinical outcomes, are frequently difficult to measure objectively. Thus, the relevance and specificity of so-called biomarkers needs to be established in anticipation of clinical trials. In this regard, we are particularly interested in the finding of an 'interferon signature' in almost all cases of AGS so-far analysed.

Therapy is most likely to be beneficial in the early stages of the disease, making rapid diagnosis of crucial importance. However, ongoing disease and later onset disease features (*e.g.* chilblains in some patients) mean that treatment will also likely have a role in, at least some, older patients. Unanswered questions as to whether one therapy will be appropriate for disease due to any 'genetic type' of AGS will become clearer as our understanding of AGS-related protein function improves.



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