INTERNATIONAL
PROGRESSIVE MS ALLIANCE

CONNECT TO END PROGRESSIVE MS

Collaborative Network Award Planning Grants – Project Summaries

PRIORITY AREA: Projects that will drive development of one or more pre-clinical drug candidates through identification and validation of molecular and cellular targets, which may be either repurposed or first-in-human drugs (within the 4-year funding period of the full network)

PROJECT #1

Project Principal Investigator: Francisco Quintana
Lead Institution: Brigham and Women's Hospital; Boston, MA (U.S.)
Project Title: Development of a drug discovery pipeline for Secondary Progressive MS

Project Summary:

MS often initially presents a relapsing-remitting clinical course (relapsing-remitting MS, RRMS) that is followed by a progressive phase (secondary progressive MS, SPMS) of continued and irreversible accumulation of disability. This project will address the lack of therapeutic options for the SPMS phase.

The goal of this project is to establish a multidisciplinary team with expertise from Genzyme Corporation (USA), research groups at Brigham and Women's Hospital (USA), the Montreal Neurological Institute (Canada), the University of Montreal (Canada) and The Weizmann Institute of Science (Israel), to screen for drug candidates that modulate the activity of immune cells in the central nervous system (astrocytes, microglia and infiltrating macrophages), which have been found to promote disease progression in SPMS. These studies will identify drug candidates, through innovative tools and experimental, multidisciplinary models, to be analyzed in SPMS clinical trials. As part of the studies, libraries of drugs already approved for human use in other diseases will be screened.

PROJECT #2

Project Principal Investigator: Steven Goldman
Lead Institution: University of Rochester Medical Center; Rochester, NY (U.S.)
Project Title: Stem cell-derived oligodendrocyte progenitor-based therapy of progressive MS

Project Summary:

Progressive demyelination of axons and the neuron from which they arise accounts for a substantial component of the disability of late-stage progressive MS, both primary and secondary. Because preclinical studies indicate that demyelinated axons may be remyelinated by the introduction of human oligodendrocyte progenitor cells, this project aims to develop a strategy that can both remyelinate axons before they are lost and to also restore function to already demyelinated brain and spinal cord tissue.

The project will compare oligodendrocyte progenitor cells obtained from three different sources (human induced pluripotential cells, directly induced neural stem cells, and human embryonic stem cells) for their effects upon transplantation into mouse models of chronic demyelination, identifying which is the most effective for treating progressive MS. Unlike most cell therapeutics for MS, which are targeted at non-brain cells to suppress inflammation, this project aims to begin clinical trials of stem cell-derived brain cells transplanted directly into the brain to achieve remyelination and structural repair of already injured, demyelinated brain.

PROJECT #3

Project Principal Investigator: Gianvito Martino
Lead Institution: Fondazione Centro San Raffaele-1; Milano (Italy)
Project Title: Bioinformatics and cell reprogramming to develop an in vitro platform to discover new drugs for progressive multiple sclerosis (BRAVEinMS)

Project Summary:

The goal of scientists working in the MS field is to speed up the understanding of nervous system degeneration occurring during the progressive and irreversible phase of the disease. This project will combine the bioinformatics and neuroscientific expertise of six laboratories (located in Europe, Canada and the U.S.) with the aim of identifying molecules that might have a therapeutic protective role on neurons and/or the capacity of favoring the proliferation of myelinating cells in order to save neurons left "naked" when the surrounding protective damaged myelin disappeared.

The collaborating laboratories will align protocols to generate controlled, stable and mature neural cells, while combining network-based analyses with *in-vitro* pharmacological testing, and functional and pharmacological databases in order to screen compounds with possible remyelinating and neuroprotective potential. The collaborative model, which benefits from from using novel bioinformatics and biological tools along with human neural cells (as opposed to rodent-derived cells) will more rapidly advance knowledge on the mechanisms underlying the progression of MS and more quickly identify new therapeutic drugs to enter human clinical trials.

PROJECT #4

Project Principal Investigator: Don Mahad
Lead Institution: University of Edinburgh; Edinburgh (U.K.)
Project Title: Mitochondria and progressive MS

Project Summary:

Developing potential drug candidates that preserve and protect neurons in progressive MS is dependent on the early identification of disease (prodromal phase). This project aims to leverage existing models for insight into pathological mechanisms of tissue damage, including neurodegeneration, inflammation and energy failure through damage to mitochondria, as well as the cellular mechanisms underlying the clinical presentation of progressive MS, while identifying the prodromal phase of progressive MS through performance related and reversible symptoms, such as exercise induced fatigue (motor fatigability). These reversible symptoms are frequently reported by individuals affected by MS and they become gradually more prominent over time, before the diagnosis of progressive MS. Preliminary findings indicate a role for mitochondria and cellular energy failure in the worsening of these exercise induced symptoms over a period of time, reflecting the dysfunction of vulnerable neurons before degeneration. By identifying such dysfunction earlier, neurodegeneration can be delayed and resulting symptoms improved through therapeutic targeting of mitochondria. A model of earlier identification of progressive MS will provide a clinical platform enabling future clinical trials to be performed more efficiently.

PROJECT #5

Project Principal Investigator: David Hafler
Lead Institution: Yale University School of Medicine; New Haven, CT (U.S.)
Project Title: An International Network to Decipher Function and Impact of CNS-relevant Risk Variants for MS *will link with Gene discovery and lead compound identification for Progressive MS; Philip DeJager (Harvard University)– Lead Researcher (U.S.)*

Project Summary:

Understanding progression in MS requires identifying and understanding the cellular mechanisms responsible for progression, enabling ways to then identify patients at risk of developing progression. The project will leverage an integrated approach to identify genes that predispose to MS (risk genes) AND are at the same time important to the function of brain cells. These particular genes are likely to directly contribute to neurodegeneration and thereby to disease progression. Once identified, large patient cohorts from around the world will be tested for these genes to verify the higher likelihood of severe progression development. Ultimately, these genes can then be monitored for response to specific treatments that target that genetic dysfunction.

New technologies will be leveraged in the work, along with analysis of existing genetic studies and the known 150 genes associated with risk in developing MS. The groundbreaking approach of re-programming human skin cells into brain cells combined with the ability to study differences between individuals with and without risk genes,the project can result in a high-throughput system to test which preclinical drugs might help prevent progression in an individual.

Projects that will drive development of a meaningful outcome measure that could be integrated into early clinical development within the 4-year funding period

PROJECT #6

Project Principal Investigator: Douglas Arnold
Lead Institution: McGill University; Montreal, QC (Canada)
Project Title: An MRI biomarker for disability progression for use in clinical trials

Project Summary:

Outcome measures to assess drug efficacy in progressive disease are a significant contributor to the rising and extraordinary cost of clinical trials. The project aims to develop new MRI outcome measures that could result in more efficient preliminary assessment of drug efficacy, potentiallyresulting in smaller, shorter, less costly trials.

Large amounts of existing MRI and clinical follow-up data on patients with progressive MS will be collected from laboratories that have been in this field for many years and from large multicenter clinical trials that have been performed in the past. Advanced machine learning techniques, similar to those used for speech recognition, will be used to develop an MRI outcome measure that relates to and can predict clinical disability progression in far fewer subjects over shorter time. Such an approach will make it possible to study larger numbers of drugs, and lessen the investment and time required to conduct clinical trials.

PROJECT #7

Project Principal Investigator: Massimo Filippi
Lead Institution: Fondazione Centro San Raffaele-1; Milano (Italy)
Project Title: SPINE: Spinal cord imaging to Identify Novel biomarkers of disease Evolution and treatment monitoring in progressive MS

Project Summary:

The spinal cord is core to the central nervous system, whose damage is likely to be one of the major determinants of disability in MS. Abnormalities in the spinal cord, seen upon imaging, have been described in up to 90% of MS patients, and previous studies have consistently demonstrated that the cervical portion of the cord (near the neck) is more affected than lower segments This damage is with particularly pronounced in progressive MS and also significantly associated with clinical disability.

Spinal cord magnetic resonance imaging (MRI) is still suboptimal due to the many challenges, including those related to the standardization of cord MRI acquisition protocols across different centers. This project aims to establish an international neuroimaging network, involving centres with internationally recognized expertise (San Raffaele Scientific Institute, Milan, Italy; VU Medical Centre, Amsterdam, The Netherlands; Hospital Clinic of Barcelona, Barcelona, Spain; UCL Institute of Neurology, London, UK; Second University of Naples, Naples, Italy; Oxford University Hospitals NHS Trust, Oxford University, Oxford, UK), with the major goal to determine and validate novel cervical cord MRI biomarkers to be utilized as predictors and/or outcomes in future studies of progressive MS.

The cervical cord MRI protocol will be specifically designed for a comprehensive evaluation of cord damage, including lesions, normal-appearing cord tissue and atrophy of different cord compartments (i.e., white matter and gray matter). This approach will increase understanding of the mechanisms linking spinal cord damage to clinical disability and its progression over time, further enabling both pharmacological as well as rehabilitative strategies in progressive MS.

PROJECT #8

Project Principal Investigator: Fred Lublin
Lead Institution: Icahn School of Medicine; Mount Sinai, NY (U.S.)
Project Title: Prospectively Defining Secondary Progressive MS

Project Summary:

More accurate and earlier determination of the onset of secondary progressive MS is needed compared to current clinical determination, which is only made after an individual has entered the progressive phase. The project aims to identify a reliable predictor of secondary progressions, and will bring together an international consortium of MS Centers who have collected information on patients with MS over a long period of time and together develop strategies analyzing the information that could lead to new biomarkers.By studying clinical and MRI data on patients carefully followed for many years, early and reliable markers of transition into secondary transition will be developed, enabling better treatment strategy for this phase of MS.

PROJECT #9

Project Principal Investigator: Bruno Stankoff
Lead Institution: INSERM - Institut National de la Santé et de la Recherche Médicale; Paris (France)
Project Title: Novel molecular imaging probes to predict disability progression and evaluate therapies in MS: The PROBIMS network *will link with Targeting microglia in progressive MS; Richard Nicholas (Imperial College London) – Lead Researcher (U.K.*)

Project Summary:

Available therapies in multiple sclerosis all target the auto-immune component of the disease, making them effective in reducing relapse rate, but generally failing to reduce long term disability and disease progression. New therapeutic strategies able to reduce the inflammation that resides within the central nervous system, called compartmentalized inflammation, or to promote myelin repair, are the most promising approaches that could succeed in preventing disability progression. New imaging technology to measure these mechanisms *in vivo* (in a living organism), which cannot be accomplished with classical magnetic resonance imaging techniques, must be developed to evaluate such new treatments.

Positron emission tomography (PET) is a nuclear imaging technology where a chemical probe that specifically binds to a target of interest is labelled with a radioactive positron emitting radionuclide and injected into individuals. This method provides quantitative imaging of the target in the brain, and opens up the perspective to visualize and quantify the cells involved in compartmentalized inflammation and remyelination. This project will bring together partners with complementary expertise in the molecular imaging field, with the objective to develop and apply in clinical studies new imaging probes that will allow to a better understanding of the mechanisms involved in inflammation and myelin repair. Additionally, the project will utilize PET scans to study changes in microglia which could indicate whether MS disease activity is being reduced, and further enable testing of potential treatments on small numbers of people over short periods of time before having to go forward to a large study.

PROJECT #10

Project Principal Investigators: Peter Calabresi & Peter Fuhr
Lead Institutions: The Johns Hopkins University; Baltimore, MD (U.S.) & University Hospital Basel; Basel, CH (Switzerland)
Project Title: New Tools to better understand test therapies in progressive MS

Project Summary:

The neurological problems that people with MS experience are related to both inflammation and neurodegeneration.

Working together, two teams will combine expertise to develop and validate the utility of four different methods to measure disease progression, including inflammation and neurodegeneration, in MS - ocular coherence tomography (OCT), evoked potentials (EP), neurofilaments in serum (Nf) and magnetic resonance imaging (MRI).

The visual system is an ideal model for monitoring neurodegeneration, neuroprotection, and remyelination in multiple sclerosis (MS). The retina, in the back of the eye, can be examined by OCT using a light beam, which allows one to measure the thickness of the retinal nerve fiber layer, and to monitor changes over time. OCT is inexpensive, reproducible, well tolerated, non-invasive, and easily repeatable .The goal of this part of the project is to establish the visual system as a model within which to monitor neurodegeneration, disease progression, neuroregeneration and neuroplasticity in PMS, both for tracking patients, as well as outcome measures in clinical trials.

The second tool that will be used, evoked potentials, measure the latency (delay) of the reponse to a stimulus, which can be applied as a checkerboard to the eye, as a small current to the wrist or ankle or as a magnetic impulse to the skull. In this way, the functional integrity of the visual, sensory and/or motor systems can be measured.

The third tool, the measurement of neurofilament in the blood, is possible due to the fact that when nerve cells and fibers decompose certain proteins are secreted, and Nf can be measured when this occurs.

Finally, MRI can show lesions and with that the integrity of the tissue and the volume of the brain and grey matter can be measured.

Each of these methods has been shown to correlate to clinical disability, and some also predict disease progression. Furthermore, they are used in routine clinical examinations with a very low risk of side-effects. In sum, more precise tools to quantify disease progression may allow investigators to perform clinical studies more efficiently.

Project that will drive initiate clinical trials of new interventions for progressive MS within the 4-year funding period

PROJECT #11

Project Principal Investigator: Anthony Feinstein
Lead Institution: Sunnybrook Research Institute; Toronto, ON (Canada)
Project Title: Cognitive rehabilitation and exercise for people with progressive MS: a multicenter, multidisciplinarary study *will link with Targeting nervous plasticity in progressive MS - a translational approach; Letizia Leocani (San Raffaele University) – Lead Researcher (Italy)*

Project Summary:

With significantly more knowledge around disease modifying treatment in relapsing MS compared to progressive MS, clinicians rely, or 'borrow' conclusions from current studies and apply them in progressive MS, raising questions about effectiveness. This project aims to undertake rehabilitation studies in people with progressive MS and address some of the questions about what might represent the most effective approach to symptom management. To date, there are preliminary findings suggesting that certain interventions, such as cognitive rehabilitation and exercise, that may lead to improvements in cognitive functioning, where impairment is present in up to 70% of people with secondary progressive MS. There is also evidence highlighting the beneficial effects of exercise on physical functioning in people with progressive MS, and treatment efficacy needs to be explored further in order to replicate the positive results. To achieve the best results, a multinational effort will be utilized, focusing on cognitive rehabilitation and exercise, and other novel interventions that deserve attention and which can be explored in a series of complementary, smaller studies. The project will also work to identify the most promising approaches toward promoting and customizing brain plasticity interventions.

Across multiple treatment centers, this novel study will measure the effectiveness of a specific cognitive rehabilitation program and specific exercise intervention for people with progressive MS. The ability to demonstrate effectiveness is essential to completing a successful trial and thereby determine a correlating standard of care – both singularly and when used in combination. By improving cognition, fitness and the ability to walk, people's quality of life will be improved and the efficacy of other treatments may also be increased.