INTERNATIONAL
PROGRESSIVE MS ALLIANCE
CONNECT TO END PROGRESSIVE MS

International Progressive MS Alliance Collaborative Network Awards

The International Progressive MS Alliance continues to fund the most promising and meritorious research that will find the solutions so urgently needed for people with progressive forms of MS. Each Alliance funding cycle has resulted in increased investment and focus on removing the barriers to developing treatments in progressive MS. The Collaborative Network Award initiative started with 52 original network applications. From these, 11 were selected to receive network planning awards. These planning awards were further developed over the past year and submitted for consideration of 3 multi-year €4.2 million Collaborative Network Awards. The proposals were submitted in one of three priority areas identified by the world's foremost experts in progressive MS:

- Drug Discovery
- Biological and Imaging Biomarker Development
- Faster and Smaller Treatment Trials

The Alliance Scientific Steering Committee, comprised of worldwide MS experts and members directly affected by MS, conducted a thorough review process. There were also comprehensive technical reviews and engagement of global Ad Hoc reviewers, as well as review by the Alliance Industry Forum. The strength of all eleven proposals is a direct reflection of the power in collaborative science with a shared goal of finding answers.

During the review process, there was thoughtful debate and provoking questions around the impact and potential of each proposal. Alliance members remain committed to decisions that consider the entire research landscape and the totality of research most critical to accelerate progress across the whole.

The Scientific Steering Committee provided a scientific recommendation to the Executive Committee, which approved funding in support of 3 Collaborative Network Awards. The quality, breadth, innovation, and focus of these awards has the potential to bring forth some of the most important and potentially transformative work in the area of progressive MS.

Learn more at www.ProgressiveMSAlliance.org

Project Title: An MRI biomarker for disability progression for use in clinical trials

Principal Investigator: Douglas Arnold, **M.D.,** McGill University (Canada)

Co-Investigators: Tal Arbel, **Ph.D.,** McGill University (Canada); **Fred Barkhof**, **M.D., Ph.D.,** VU University Medical Center (The Netherlands); **Declan Chard**, **Ph.D.,** University College London (U.K.); **Olga Ciccarelli**, **Ph.D.,** University College London (U.K.); **D. Louis Collins**, **Ph.D.,** McGill University (Canada); **Gary Cutter**, **Ph.D.,** University of Alabama (U.S.); **Charles Guttman, M.D.**, Brigham and Women's Hospital (U.S.); **Stephen Hauser, M.D.**, University of California, San Francisco (U.S.); **Roland Henry**, **Ph.D.,** University of California, San Francisco (U.S.); **Ludwig Kappos, M.D.**, University Hospital Basel (Switzerland); **Sridar Narayanan**, **Ph.D.,** McGill University (Canada); **Doina Precup**, **Ph.D.,** McGill University (Canada); **Jack Simon, M.D.**, Oregon Health & Sciences (U.S.); **Maria-Pia Sormani**, **Ph.D.,** University of Genoa (Italy); **Bernard Uitdehaag**, **M.D., Ph.D.,** VU University Medical Center (The Netherlands); **Jerry Wolinski, M.D.**, University of Texas Health Sciences Center (U.S.)

Identifying a biomarker of disability progression for use in clinical trials

Douglas Arnold, M.D., of McGill University is making remarkable headway in developing the next generation of tools for measuring disease progression in progressive MS. Dr. Arnold's team is pioneering the development of magnetic resonance imaging (MRI) markers that signal disease progression, and adapting these for use in early (phase 2) clinical trials of progressive MS treatments. Dr. Arnold's research examines the underlying idea that brain injury-associated disease progression in MS is detectable by MRI prior to its identification by physicians in a clinic visit, likely due the ability of the brain to compensate for injury, up to a point. The innovative tools being developed by Dr. Arnold and his team are essential for planning the larger scale phase 3 clinical trials required for approval of new treatments. The study also has extraordinary potential to inform proactive treatment for people with not-yet-evident progressive MS.

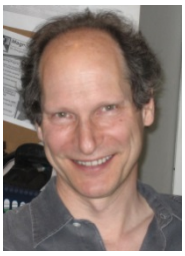
Dr. Arnold's novel research will investigate features of the MRI that i) Change measurably over the short time intervals used in phase 2 trials for progressive MS; ii) Relate to progression over the same period of time; and, iii) Are predictive of the effect of treatments on future progression. To identify MRI patterns with the above characteristics, Dr. Arnold and his multidisciplinary team will combine their expertise in computer science, image processing, and statistics to:

- Access existing data from more than 2,000 patients and 40,000 MRI scans to enable efficient, automated computer analysis and application of advanced information technology techniques.
- Apply cutting-edge computer science tools with demonstrated potential in other fields that have not yet been used in MS research.
- Use advanced imaging analysis tools to measure the size, shape, and appearance of the main structures of the brain, and statistical approaches to identify patterns of changes in the brain structures that have the required association with disease progression.

- Combine this approach with advanced machine learning techniques, such as those used for facial recognition, to detect features of the image that may not be recognized by humans, but are related to disease progression.

Dr. Arnold believes this research can directly facilitate testing new drugs for progressive MS in trials that are smaller and less expensive, and encourage pharmaceutical companies to develop new therapies for progressive MS. He and his team will create an interactive tool to share the methods they develop with the scientific community.

Douglas Arnold, M.D.



Dr. Arnold is a James McGill Professor at McGill University. He is also the Founder and President of NeuroRx Research, a company specializing in image analysis for clinical trials. Dr. Arnold is a neurologist with special expertise in advanced MRI acquisition and analysis, particularly as they relate to understanding the evolution of MS and neurodegeneration. He combines advanced image processing techniques with conventional and non-conventional MRI acquisition techniques, such as magnetization transfer imaging, magnetic resonance spectroscopy, and functional MRI to understand how inflammation in MS relates to injury to myelin, the insulation around nerves, and the nerves themselves. He also uses these techniques to understand how new therapies for MS work.

Project Title: Bioinformatics and cell reprogramming to develop an in vitro platform to discover new drugs for progressive multiple sclerosis (BRAVEinMS)

Principal Investigator: Gianvito Martino, San Raffaele Scientific Institute, Milan (Italy)

Co-Investigators: Maria Pia Abbracchio, CENTERS: University of Milan, Milan (Italy); **Cristina Agresti**, CENTERS: Italian Institute of Health (ISS), Rome (Italy); **Jack Antel**, McGill University (Canada); **Sergio Baranzini**, University of San Francisco (U.S.); **Anne Marie Baron Van Evercooren**, Université Pierre et Marie Curie, Hopital Pitié- Salpêtrière (France**); Ivano Eberini**, CENTERS: University of Milan, Milan (Italy); **Norbert Goebels**, University of Dusseldorf (Germany); **Tanja Kuhlmann**, University of Muenster (Germany); **Brahim Nait Oumesmar**, Université Pierre et Marie Curie, Hopital Pitié- Salpêtrière (France); **Stefania Olla**, CENTERS: Institute of Genetic and Biomedical Research (IRGB), National Research Council (CNR), Monserrato (Italy); **Marco Salvetti**, CENTERS: University La Sapienza, Rome (Italy); **Vincenzo Summa**, IRBM (Italy); **Frauke Zipp**, Johannes-Gutenberg University of Mainz (Germany)

Bioinformatics and cell reprogramming to develop an in vitro platform to discover new drugs for progressive multiple sclerosis (BRAVEinMS)

The BRAVEinMS team is working to identify molecules that may have a protective role in nerve cells or neurons and/or the capacity to promote myelin repair. They will focus their efforts in three phases: i) identifying potential drugs or compounds using sophisticated bioinformatics tools specifically developed to virtually reproduce pathogenic mechanisms of MS; ii) screening these compounds for their ability to protect nerve cells or promote myelin repair in laboratory tests using both rodent and human neurons and myelin forming cells; and, iii) evaluating in animal models of progressive MS the therapeutic potential of the 'candidate' compounds identified through the in vitro screening. In the first phase of the study, the researchers will leverage their world-class IT expertise to comb through large data sets of biological and chemical information. This data will help identify biological pathways and treatment targets, possibly useful chemical compounds, and drugs approved by the Food and Drug Administration or the European Medicines Agency that can be repurposed to promote remyelination and neuroprotection. In the study's second phase, the research team will test compounds for their neuroprotective and/or myelin repair potential in laboratory tests using rodent cells, and then reproduce the results using human neuro-glia cells. They will further validate their screening system by harnessing stem cell technology to generate neural cells from the skin cells of MS patients, the so called 'disease in a dish' technology. Compounds that will pass the different in vitro screenings in laboratory tests will be extensively evaluated in vivo in animal models, each representing a key aspect of the degenerative process occurring in MS.

The research team believes that BRAVEinMS will pinpoint a limited number of previously unidentified molecules with a high chance of therapeutic power in progressive MS patients. They expect that within four years from the start of the project they will identity one or two human grade compounds that can be used in Phase I/II clinical trials in patients with

progressive MS. As a result, the team aims to implement a clinical trial in the near future, by end of 2020.

Gianvito Martino, M.D.

Dr. Gianvito Martino received his Medical Degree in 1987 from the University of Pavia (Italy) where he completed his residency in Neurology in 1991. In 1990, he was a Visiting Scientist at the Department of Neurology of the Karolinska Institute (Stockholm, Sweden) and, from 1991 to 1992; he held the position of Research Associate at the Department of Neurology of the University of Chicago (Chicago, IL, U.S). From 1992 to 2008, he worked first as Senior Scientist and then as Director of the Neuroimmunology Unit of the San Raffaele Scientific Institute in Milan (Italy) where, from 2008, he acts as Director of the Division of Neuroscience. He is a full professor of experimental biology at the University Vita-Salute San Raffaele in Milan (Italy) and honorary professor at the School of Medicine and Dentistry at Queen Mary University of London (U.K.). From 2009 to 2012, he served as President of the Italian Neuroimmunology Society (AINI). From 2010 to 2012, he was appointed Vice President and from 2012 to 2014, President of the International Society of Neuroimmunology (ISNI). In 2000, he founded The European School of Neuroimmunology (ESNI) and in 2012, The Global Schools of Neuroimmunology (GSNI); since then, he has been acting as scientific coordinator of the schools. He serves as member of the scientific committee of several national and international scientific societies and has received numerous scientific awards including the Rita Levi-Montalcini Award. He is co-author of more than 250 original articles and book chapters. His scientific interests range from the elucidation of the pathogenic mechanisms of immune-mediated central nervous system disorders to the development of gene and stem cell-based therapies for the treatment of these disorders.

Project Title: Development of a drug discovery pipeline for progressive MS

Principal Investigator: Francisco Quintana, Ph.D., Brigham and Women's Hospital (U.S.)

Co-Investigators:
Ido Amit, Ph.D., Weizmann Institute of Science (Israel); **Jack Antel, M.D.**, McGill University (Canada); **Kevin Hodgetts, Ph. D.**, Brigham and Women's Hospital (U.S.); **Adrian Ivinson, Ph.D.**, Brigham and Women's Hospital (U.S.); **Steffen Jung, Ph.D.,** Weizmann Institute of Science (Israel); **Nathalie Pochet, Ph.D.**, Brigham and Women's Hospital (U.S.); **Alexandre Prat, M.D.**, McGill University (Canada); **William Siders, Ph.D.**, Sanofi Genzyme

Development of a drug discovery pipeline for progressive MS

The goal of Dr. Quintana's project is to identify drug candidates that may be effective therapies for progressive MS, and that will be ready for evaluation in patients within four years of the initiation of this research. The project's central idea is that targeting the innate immune system in the central nervous system will uncover effective therapeutic approaches for progressive MS. The innate immune system normally functions to protect the body from infections. Dr. Quintana and others have found that innate immune cells in the central nervous system promote disease activity in MS and other diseases. Dr. Quintana's team recently identified the biological pathways that control the innate immune response. They also found that genetic manipulation of the pathways can arrest nerve damage and alter disease progression in pre-clinical MS animal models; however no candidate drugs are available to modulate the activity of innate immune cells.

Dr. Quintana's study will: i) Identify the biological processes that control the innate immune response in the central nervous system; ii) Evaluate the activity of candidate drugs on the innate immune system in experimental models of progressive MS; iii) Analyze how the candidate drugs exert their beneficial effect; and, iv) Identify additional candidate targets and therapeutic drugs that impact the innate immune system in progressive MS. The project uses cutting-edge tools and approaches to understand how the brain is damaged in progressive MS and to identify targets for treatment. The research team has access to unique collections of central nervous system-active compounds including FDA-approved drugs for human use in other diseases, patient sample collections, genetically-engineered mice, and advanced methods for conducting detailed genetic analysis of individual cells.

Dr. Quintana has assembled a novel multidisciplinary team that integrates the expertise of Sanofi Genzyme Corporation with top research groups focused on basic and clinical MS research and drug development that includes Brigham and Women's Hospital, The Broad Institute, The Montreal Neurological Institute, Universite de Montreal, and The Weizmann Institute of Science. The project's innovative hypotheses, use of the latest tools and technology, and multidisciplinary approach, including the partnering of industry with top researchers from across continents, offers new hope to families struggling with this unrelenting and devastating disease.

Francisco Quintana, Ph.D.

Francisco Quintana, is an Associate Professor at the Ann Romney Center for Neurologic Diseases at Brigham and Women's Hospital (BWH), Harvard Medical School, Boston. He is also an Associate Member at the Broad Institute of Harvard and MIT. Dr. Quintana's major research interests focus on the regulation of the adaptive and innate immune system in multiple sclerosis. At the Center for Neurologic Diseases, Dr. Quintana developed tools for the identification of biological pathways that control the adaptive and the innate immune response. Dr. Quintana earned his Diploma in Biology from the University of Buenos Aires and his Ph.D. in Immunology from the Weizmann Institute of Science in Rehovot, Israel. He completed his postdoctoral training with a focus on Neuroimmunology at the Weizmann Institute and at BWH. Dr. Quintana's work in immunology has earned recognition from the Weizmann Institute, the National Institutes of Health, Harvard Medical School, and *Nature Biotechnology* – a prestigious scientific publication. In 2014, he received the Harry Weaver Neuroscience Scholar Award from the National MS Society.

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