Richard Westlund
October 4, 2019

CReATe Consortium Aims for ALS Breakthroughs with NIH Renewal Grant

An international research consortium led by investigators at the University of Miami Miller School of Medicine has made significant progress in understanding amyotrophic lateral sclerosis (ALS) and related diseases since its founding in 2014. Now the Clinical Research in ALS and Related Disorders for Therapeutic Development (CReATe) Consortium is aiming for new breakthroughs after receiving a five-year, $7.9 million renewal grant from the National Institute of Neurological Disorders and Stroke and the National Center for Advancing Translational Sciences, part of the National Institutes of Health.

Richard Westlund
October 4, 2019

Dr. Michael Benatar

“We plan to build on the research, training and patient engagement accomplishments of the past five years,” said Michael Benatar, M.D., Ph.D., professor of neurology, the Walter Bradley Chair in ALS Research and executive director of the ALS Center at the Miller School.

Amyotrophic lateral sclerosis, also known as Lou Gehrig’s disease, is a neurodegenerative disease that attacks the motor nerves, leading to progressive muscle weakness. There is no effective therapy for ALS and the lifespan for those affected is typically only three to five years.

Advancing therapeutic development

The goal of the consortium, which is under the direction of Dr. Benatar, is to advance therapeutic development for ALS,

ALS-frontotemporal dementia (FTD), progressive muscular atrophy (PMA), primary lateral sclerosis (PLS), hereditary spastic paraplegia (HSP), and multisystem proteinopathy (MSP). These disorders are linked by their shared degenerative nature, as well as genetic and biological factors.

“Our multidisciplinary international scientific community brings together expertise from different clinical and research perspectives, with the support of patients and their families,” said Dr. Benatar. “We are constantly trying to keep the field moving forward by engaging innovative ideas. Every year, we issue a public request for applications to support a pilot project relevant to the mission of therapy development for this group of disorders. We also maintain an extensive repository of body fluids that is paired with phenotypic and genomic data, that is available for use by consortium members and the broader scientific community.”

Identifying biomarkers

One of the consortium’s major initiatives focuses on the discovery and validation of ALS biomarkers that are relevant to therapy development. “Our focus has been on prognostic, disease progression and pharmacodynamic biomarkers as they are expected to help facilitate efficiency of clinical trials,” said Dr. Benatar. “The biomarker development work that CReATe is doing is expected to significantly accelerate the evaluation of the new ALS drugs that are currently in the development pipeline.”

In a groundbreaking 2017 study published in the journal *Neurology*, CReATe researchers at Flinders University in Australia and at the Miller School identified concentrations

of p75ECD, the extracellular domain on the common neurotrophin receptor p75, as the first biological fluid-based biomarker for ALS progression. They found that the urinary concentration of p75ECD increases as disease progresses in ALS, and the level of p75ECD at the time of initial study assessment appears to predict the future course of disease.

Neurotrophin receptor p75 is a growth factor receptor that promotes the survival of nerve cells. Under normal circumstances, it is highly expressed on motor neurons during development but decreases after birth. Following nerve injury, however, the expression of p75 is increased and higher concentrations of the extracellular domain of p75 are detectable in urine.

Understanding the relationship between genotype and phenotype

CReATe investigators are also studying the genetic underpinnings of ALS and related disorders to better understand why the disease affects patients in different ways.

Dr. Benatar said the consortium will carefully evaluate the relationship between phenotype – the observable characteristics – and genotype – the genetic constitution – in this group of motor neuron and related disorders, and search for novel genetic modifiers of disease.

For example, some ALS patients have more upper motor neuron pathology while others have a greater burden of lower motor neuron pathology. Some develop signs of frontotemporal lobe dysfunction, but others do not. In some, the disease progresses very quickly, but in others, the disease may extend over many years.

“By deconstructing the complex phenotype that is ALS, CReATe investigators seek to better understand the genetic basis for these different aspects of the phenotype,” said Dr. Benatar.

Supporting training and education

The CReATe Consortium also supports a clinical investigator training program, providing funding for highly promising young clinician investigators and Ph.D.s who wish to focus their careers on clinical research in ALS and related disorders, or on some aspect of basic biology relevant to therapy development. “We hope to continue our work with the pharmaceutical partners to support this training program, and also to forge new partnerships through professional societies and organizations,” said Dr. Benatar.

CReATe has also built strong partnerships with organizations that represent patients afflicted with this group of rare diseases. These include the ALS Association, the Muscular Dystrophy Association, the Spastic Paraplegia Foundation, and the Association for Frontotemporal Degeneration.

“We have developed CReATe Connect – a contact registry accessible at www.rdcrn.org/createconnect – that allows patients and family members to learn about educational opportunities, CReATe research studies, and research initiatives ongoing in the ALS community,” said Dr. Benatar. “Participation is free, completely voluntary, and can be revoked at any time.”

Collaborative partners

The CReATe Consortium is part of the Rare Diseases Clinical

Research Network (RDCRN), an initiative of the Office of Rare Diseases Research. It includes clinical sites at the University of Miami; the University of Kansas Medical Center; the University of California at San Diego; California Pacific Medical Center; the University of Tübingen, Germany; the University of Pennsylvania; the University of Texas Southwestern Medical Center; the University of Texas Health Sciences Center San Antonio; the University of Iowa; the University of Virginia; Wake Forest University; Cleveland Clinic, Ohio; Twin Cities ALS Research Consortium, Minnesota; Stanford University; and University of Cape Town, South Africa. Key partners include St. Jude Children's Research Hospital, Duke University and Harvard University.