

Abstract

As a continuation of the NIH-funded "GO-grant" work on PD iPS cell genetic lines, our 6 research teams are now proposing a U24 grant consortium, according to the new RFA NS-11-011. The tool generation for public and scientific use of Parkinson's disease (PD) patient derived iPS cell lines will continue and new lines with mutations, isogenic genetically repaired iPS lines, and inserts of reporter systems for studying such lines will be established by the funds provided by the U grant. The PD iPS consortium director, Dr. Ole Isacson, and the Executive Science Committee consisting of Core leaders, the iPS resource representative and an NIH representative will carry out the work through the activity of: the (1) Clinical and Genetic Core led by Zbigniew Wszolek that will provide necessary patient fibroblast lines, including GBA, FTD and additional LRRK2 and alpha synuclein mutations, along with a mRNA sequencing and expression laboratory. These lines will be reprogrammed according to the priorities set by the RFA at (2) a contracting research organization (CRO) at the Harvard Stem Cell Institute, with their Directors Rossi and Cowan at the iPS Core facility providing the new lines in a timely manner. The (3) Reprogramming, Differentiation Reporter (and Isogenic Repair) Core is led by Lorenz Studer and Dimitri Krainc, who will provide a robust differentiation protocol for dopamine neurons and genetically repair PINK1 and LRRK2 G2019S into their isogenic forms and also add fluorescent reporter genes to these PD iPS cells. These tools and reagents will enable the assignments of the (4) Cell Function and Pathophysiology Core led by Ted Dawson, who will direct the teamwork around the phenotypes and etiobiology discovery of PD. The value provided by this U24 grant proposal is realized by the (a) new iPS lines provided, and (b) the engineered PD iPS lines as exceptionally useful human cellular tools for understanding PD, as well as (c) collaborative and shared use of cells lines for drug discovery.