Frank Soldner, M.D.

Positions:
Assistant Professor, Departments of Neuroscience and Genetics
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Research interests:

Our laboratory focuses on modeling human brain development and function in a cell culture dish to understand the molecular and cellular basis of complex disorders such as Parkinson's and Alzheimer's disease. A significant challenge of studying complex human diseases is the lack of relevant model systems that combine know genetic elements with disease-associated phenotypic readouts. This is particularly problematic for sporadic neurodegenerative diseases that have no well-defined genetic etiology and do not follow Mendelian inheritance patterns. Epidemiology and population genetics suggest that such diseases result from a complex interaction between multiple risk factors, both genetic and non-genetic (lifestyle and environmental). Although genome wide association studies (GWAS) have identified genomic variations, such as single nucleotide polymorphisms (SNPs), deletions, and insertions associated with a higher risk to develop specific neurological disorders, the vast majority of such sequence variants have no established biological relevance to disease or clinical utility to prognosis or treatment.

Three major recent innovations have fundamentally changed our ability to study human neurological disorders in a cell culture dish: (i) Reprogramming of somatic cells into human induced pluripotent stem cells (hiPSCs) to generate patient-derived disease-relevant neuronal cells, (ii) the development of genome engineering technologies such as the CRISPR/Cas9 system to modify the genome in human cells, and (iii) the availability of tissue-type and disease-specific genome-scale genetic and epigenetic information. Our previous work demonstrated that an interdisciplinary approach, integrating these technologies, enables us to study neurological disorders in a genetically controlled and systematic manner in human neuronal cells. Using these previously unavailable molecular and cellular tools, we were able to dissect the functional role of diseases-associated sequence variations in non-coding regulatory elements such as distal enhancer sequences in the pathogenesis of Parkinson's disease. My lab is extending this novel experimental framework in human pluripotent stem cell (hPSC)-derived two-dimensional (2D) monolayer and three-dimensional (3D) organoid neuronal culture systems to systematically investigate the genetic, cellular, and molecular basis of neurodegenerative disorders. We are establishing robust disease-relevant phenotypic readouts to perform unbiased compound and CRISPR/Cas9-based genome-scale genetic screens and will exploit these approaches to understand how genetic, epigenetic, and environmental factors contribute to the development and progression of neurological diseases.

Current grant funding:

ASAP-000486 (M.J. Fox Foundation for Parkinson's Research) 10/01/20 – 09/30/23
Title: Dissecting Genetic Interactions of Parkinson's Disease associated Risk loci

Recent publications (selected):

1. Li, H., Busquets, O., Verma, Y., Syed, K.M., Kutnowski, N., Pangilinan, G.R., Gilbert, L., Bateup, H., Rio, D.C., Hockemeyer, D., and **Soldner, F**. (2022). Highly efficient generation of isogenic pluripotent stem cell models using prime editing. ***bioRxiv,*** 2022.2002.2015.480601. 10.1101/2022.02.15.480601.

2. **Soldner, F.** & Jaenisch, R. Stem Cells, Genome Editing, and the Path to Translational Medicine. ***Cell***, 175, 615-632 (2018)

3. **Soldner, F**., Stelzer, Y., Shivalila, C. S., Abraham, B. J., Latourelle, J. C., Barrasa, M. I., Goldmann, J., Myers, R. H., Young, R. A. & Jaenisch, R. Parkinson-associated risk variant in distal enhancer of α-synuclein modulates target gene expression. ***Nature*** 533, 95–99 (2016).

4. **Soldner, F.**, Laganière, J., Cheng, A. W., Hockemeyer, D., Gao, Q., Alagappan, R., Khurana, V., Golbe, L. I., Myers, R. H., Lindquist, S., Zhang, L., Guschin, D., Fong, L. K., Vu, B. J., Meng, X., Urnov, F. D., Rebar, E. J., Gregory, P. D., Zhang, H. S. & Jaenisch, R. Generation of Isogenic Pluripotent Stem Cells Differing Exclusively at Two Early Onset Parkinson Point Mutations. ***Cell*** 146, 318–331 (2011).

5. **Soldner, F**.*, Hockemeyer, D.*, Beard, C., Gao, Q., Bell, G. W., Cook, E. G., Hargus, G., Blak, A., Cooper, O., Mitalipova, M., Isacson, O. & Jaenisch, R. Parkinson's disease patient-derived induced pluripotent stem cells free of viral reprogramming factors. ***Cell*** 136, 964–977 (2009).

6. Hockemeyer, D.*, **Soldner, F**.*, Beard, C., Gao, Q., Mitalipova, M., Dekelver, R. C., Katibah, G. E., Amora, R., Boydston, E. A., Zeitler, B., Meng, X., Miller, J. C., Zhang, L., Rebar, E. J., Gregory, P. D., Urnov, F. D. & Jaenisch, R. Efficient targeting of expressed and silent genes in human ESCs and iPSCs using zinc-finger nucleases. ***Nat Biotechnol*** 27, 851–857 (2009).

(* Equally contributing authors)