

**2019 SOT *In Vitro* Toxicology Lecture and Luncheon
Host Discussion Guide**

Patient-Based Cellular Model Systems to Assess Individual Risk to Neurotoxicants

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Collectively, an individual's genetics, environmental exposure history, and the effects of aging can contribute to brain disease etiology. Each of these factors can be difficult to model using *in vivo* animal models. This lecture suggests that patient-based (individual-based) cellular model systems, such as human induced pluripotent stem cells (iPSCs), enable characterization of personalized toxicological susceptibility.

- A **gene-environment interaction** (GxE) is when two different genotypes respond differently to an environmental exposure. For example, individuals with mutations of the PARK2 gene are sensitive to copper exposure
- Human **induced pluripotent stem cells** (iPSCs) are reprogrammed cells from an adult individual that have the potential to become any other cell type in the body. For example, human skin cells can be “reprogrammed” into neurons.

General Discussion: Parkinson's and neurodegenerative diseases are not the only type of disease that could benefit from iPSCs models. As a group discuss different types of GxE that can underlie disease and how iPSCs could be leveraged for characterizing personalized susceptibility.

Examples below show a variety of genes and different types of environmental factors:

Disease/Toxic Outcome	Genetic Factors	Environmental Factors
Parkinson's Disease	PARK2	Copper Exposure (chemical)
Alzheimer's Disease	APOE	Organochlorine Pesticides (chemical)
Ischemic Stroke/Hypoxia	NOTCH3	Air Pollutants/Diet (chemical, lifestyle)
Tuberculosis	TLRs	<i>M. Tuberculosis</i> (bacterial)
Diabetes	SLC2A2	Dioxin/Diet (chemical, lifestyle)

Acknowledge that there are likely genetic and environmental factors for most diseases. iPSCs offer an in vitro model of complex diseases that are difficult to model in the lab. Clinically, iPSCs obtained from individuals with the disease and healthy individuals close

to them (family members, co-workers, etc.) could be used to provide personal toxicity susceptibility information.

Developing an effective iPSC model requires knowledge about the disease. Discuss the features of an appropriate iPSC disease model by considering the following:

1. Are there characteristics of individuals, populations, sub-populations, or risk groups that would be critical in the identifying whom to select for generation of a stem cell-based model system of the disease?
 - *Some characteristics of the disease must be identifiable to have a sense of the significance to human health and the experiments that would be most informative with the model system.*
 - *It is never easy to know how many different individuals need to be tested; is extrapolation possible or must everyone donate cells to be tested?*

2. Is there a target cell type primarily impacted or contributing to pathogenesis?
 - *Identification of a cell type that would be studied in vitro is important for studying susceptibility. But is studying only the “vulnerable” cell types of the disease sufficient to develop a good GxE model?*
 - *Identifying relevant endpoints in the given cell system for targeted in vitro assays is also critical. But undefined genetic factors that have not yet been characterized may also play a role (i.e., more than what is targeted upfront).*

Parkinson’s and Alzheimer’s Disease: neurons

Ischemic Stroke/Hypoxia: neurons, glia, cardiomyocytes

Tuberculosis: alveolar lung cells

Diabetes: adipocytes, beta islet pancreas cells

3. Are there known or suspected toxicants that contribute to disease risk?
 - *Refer to environmental factors listed in the table above (bacterial, chemical, lifestyle, etc.), and are these factors amenable to in vitro evaluation?*

4. Are there particular developmental stages or sequential time points that are important in the pathogenesis?
 - *Exposure during development or adulthood can have different outcomes.*

- *Some diseases show delayed effects which may require chronic exposures rather than an acute toxicity phenotype.*
- *Variance among individuals in the outcome of an acute exposure.*

Parkinson's and Alzheimer's Disease: chronic developmental
Ischemic Stroke/Hypoxia: acute, multiple events lead to different
pathologies (e.g., second stroke is less toxic in some people)
Tuberculosis: acute event
Diabetes: chronic

5. Are there genetic-based animal models that recapitulate human pathogenesis?

- *Many diseases do not have an animal model that fully recapitulate the human condition. Animal models are limited, and knock-out models may not be viable and are even further removed from the human condition.*
- *Validating iPSC models is difficult when animal models cannot be made, or the animal model doesn't elicit the expected pathobiology after introduction of homologous genetic and environmental risk factors. Being able to define benchmarks of human disease that can be translated between the cell-based model system and clinical/human-subject based or other in vivo data is important.*
- *The provided example diseases DO NOT have an animal model that fully recapitulates the human pathogenesis; however, "good" animal models do exist for some like the ischemic stroke and tuberculosis diseases.*