# Translation: Screening for Novel Therapeutics Using Disease-Relevant Cell Types Derived from Human Stem Cell Models

***Supplemental Information***

## Additional Alternatives to Human iPSC Models for Chemical Neurobiology Studies

One potential solution to limited number of neurons is the creation of induced neural progenitor cells (iNPCs), rather than iNs, that can be expanded as self-renewing, progenitor cells (1-5). Successful examples of this approach for human cells include the demonstration that the transduction of foreskin fibroblast cells with *Zic3* along with *OCT4*, *SOX2*, and *KLF4* resulted in iNPCs that expressed progenitor markers and could be expanded for up to 40 passages as neurospheres while still retaining multipotency for different lineages (2). Using a different approach, Ring and colleagues demonstrated the formation of iNPCs after the transduction of human foreskin fibroblasts with *SOX2* alone, which produced NESTIN positive neurospheres after multiple rounds of re-plating (1). These iNPCs could be differentiated when cultured in a cocktail of WNT5A, retinoid acid, and forskolin into TuJ1 and MAP2 positive neurons (1). However, the degree to which these human iNPCs could be expanded and still give rise to more defined neural subtypes has not been well described. Nonetheless, continued improvement of the methodology for the direct reprogramming of somatic cells to iNPCs could greatly simplify the process of patient-specific disease modeling and the development of high-throughput phenotypic screens.

Another alternative may be the study of cells derived from olfactory neuroepithelial biopsy. This transnasal procedure allows culture of neuronal precursor cells and allows multiple passages (6); for example, one recent investigation demonstrated calcium signaling or cytoskeletal abnormalities in patient-derived cells from individuals with schizophrenia and bipolar disorder, respectively (7). Further details of this strategy are described elsewhere in this issue. While precursors cells must still be cultured to derive specific lineages, and heterogeneity of resulting cell types is still observed, this approach may provide an important complement to iPSC and iN-based studies. Indeed, an important question is the relative similarity and differences in neuronal cells derived by each of these methods and the capacity to ultimately derive disease-relevant subtypes.

## Supplemental References


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