Designer genes: Developing optogenetic and chemogenetic therapies for neurological disorders

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Learning Objectives:

By the end of this presentation, the learner will:

- Understand the basic mechanisms of optogenetic light-activated channels and their regulation of neuronal excitability
- Understand the basic mechanisms of chemogenetic approaches to regulate neuronal function.
- Gain insight into the constructs by which designer genes can be inserted into animal models or humans to express optogenetic or chemogenetic modulators.
- Have an appreciation for preclinical studies in rodents and primates that suggest targeted neuromodulation through optogenetic and chemogenetic means can be used to treat neurological disorders, as well as the limitations of these approaches.
- Understand the opportunities for clinical translation and barriers to translation into humans.

Speaker disclosures:

None

Notes and links to literature:

Introduction to optogenetics and pharmacogenetics as gene therapy

The Tools: Optogenetics

- Channelrhodopsin and variants for neuronal excitation
- Halorhodopsin and variants for neuronal inhibition
- Stepwise excitation
- Modulating second messengers or protein-protein interactions
- Implantable optogenetics - https://www.ncbi.nlm.nih.gov/pubmed/26551059

The Tools: Chemogenetics

- Designer Receptors Exclusively Activated by Designer Drugs
- hM4Di to inhibit neurons
- hM3Dq to activate neurons
- CNO and other designer ligands

Advantages and disadvantages of optogenetics and chemogenetics

- Temporal resolution
- Targeted manipulations
- Physiological relevance
- Invasiveness and phototoxicity
- Drug effects

Expression systems

- Transgenics
- Viral Vectors (AAV, LV)

Considerations: Expression Systems

- Target specificity (promoter)
- Spatiotemporal profile
- Inflammation
- Serotype
- Inducible constructs

Use of Optogenetics and Chemogenetics in Rodents

- Modulating complex behavior and neural circuits
- Psychiatric Disorders
    - Anxiety (mouse) – https://www.ncbi.nlm.nih.gov/pubmed/26536109
    - Depression (mouse) - https://www.ncbi.nlm.nih.gov/pubmed/23235822

- Neurological Disorders
    - Stroke recovery (inducible) - http://science.sciencemag.org/content/344/6189/1250.long

    - Stroke recovery (mouse) - http://www.pnas.org/content/111/35/12913.long
    - Pain (mouse) - https://www.ncbi.nlm.nih.gov/pubmed/24531797
    - Epilepsy (chemo – mouse) - https://www.nature.com/articles/ncomms4847
    - Epilepsy (opto – mouse) - https://www.nature.com/articles/ncomms2376
    - Alzheimer's mouse - https://www.ncbi.nlm.nih.gov/pubmed/27929004

Use of optogenetics in primates

- Manipulating dopaminergic system - http://www.sciencedirect.com/science/article/pii/S0092867416310753
- Chemogenetic manipulation of reward value - https://www.nature.com/neuro/journal/v19/n1/full/nn.4192.html
- Manipulations in retina – mouse, primate, human (post mortem) - https://www.ncbi.nlm.nih.gov/pubmed/27679671

Clinical Translation to Humans

- Translation to humans http://www.nature.com/news/light-controlled-genes-and-neurons-poised-for-clinical-trials-1.19886
- Retrosense trial - http://retrosense.com/development.html#rst

Future Directions, Considerations, and Discussion

References

Stroke review - http://thejns.org/doi/full/10.3171/2016.2.FOCUS163

https://link.springer.com/article/10.1007%2Fs00702-017-1697-8
https://www.ncbi.nlm.nih.gov/pubmed/27610576