Interluminescence for Trans-Cellular Modulation: Perspectives Beyond Neurons

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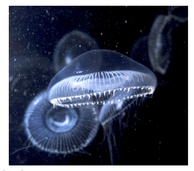
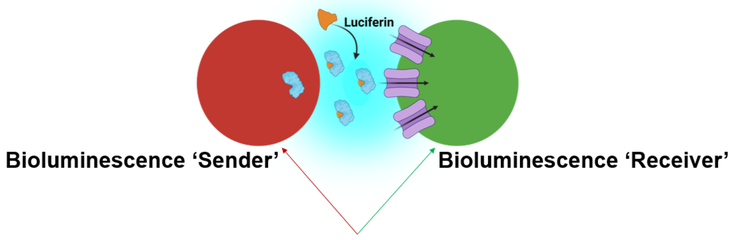


Interluminescence Driven Modulation

Interluminescence

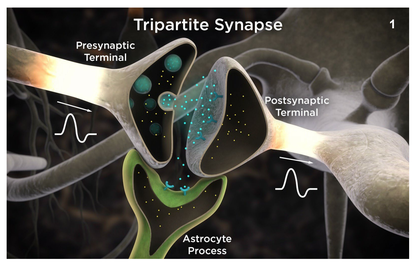
'Luminescence in-Between'



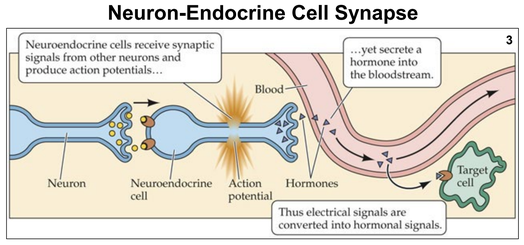
Interluminescence for selective control of genetically targeted synaptically connected circuit elements has broad applications in basic and translational research. It permits direct experimental control of the efficacy and form of synaptic transmission between specific partners, and is also a prospective strategy to strengthen desirable, and dampen undesirable, inter-cellular communication under various pathologic conditions. Interluminescence can be tailored and be extended from neuron-neuron communication to neuron-muscle, neuron-cancer cell, or to general cell-to-cell communication.

Examples of Possible Applications

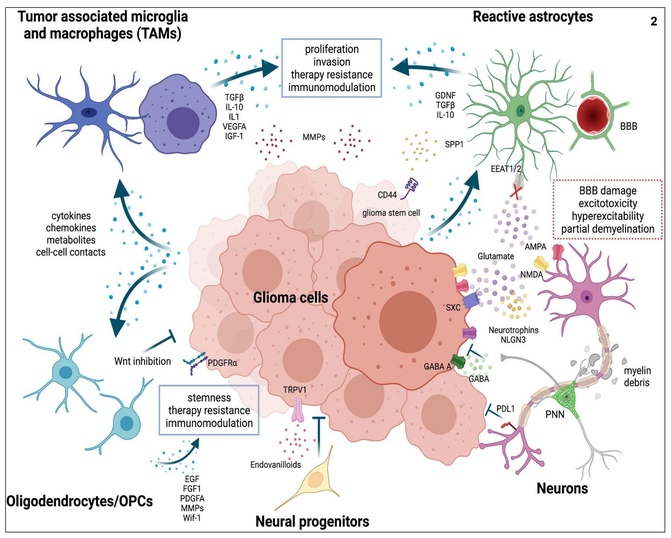
Neuron-Glia



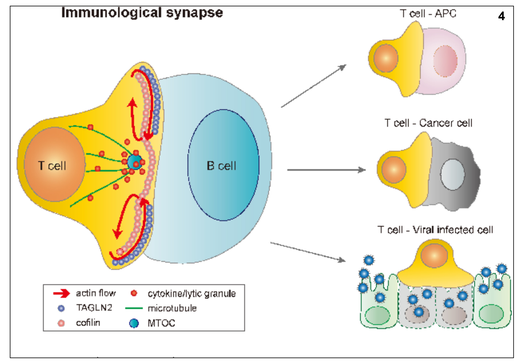
Neuron-Endocrine Cell Synapse



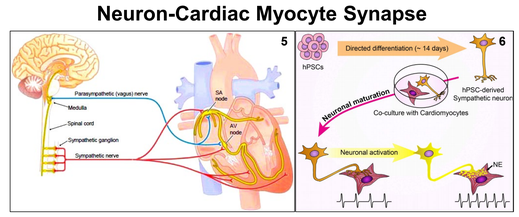
Neuron-Cancer cell Synapse & Tumor Microenvironment



Immunological Synapse



Neuro-Cardiac Junction: Neuron-Cardiac Myocyte Synapse



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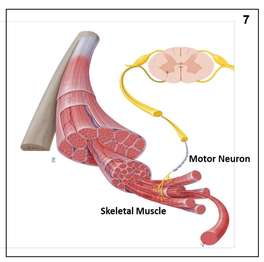
Interluminescence at Neuro-Muscular Junction: Trans-Cellular Modulation of Skeletal Muscle Activity



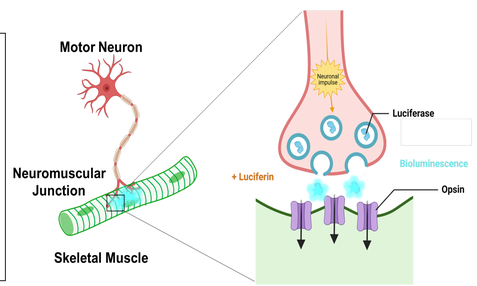


Fig. Illustration showing Interluminescence at NMJ. A pre-synaptic motor neuron (red) releases the luciferase into the synaptic cleft where it glows in the presence of externally added luciferin (CTZ), and opens light-sensitive channels in the post-synaptic skeletal muscle cell (green) at NMJ.

The junction between a motor neuron and a skeletal muscle fiber [neuro-muscular junction (NMJ)] is an ideal site for reinforcing trans-cellular communication using Interluminescence. NMJ is a specialized peripheral synapse that translates the action potential of the presynaptic motor neuron to the contraction of the postsynaptic muscle fiber through the release of the neurotransmitter acetylcholine (ACh).

Significance:

Deficits in NMJ formation and maintenance cause several NMJ disorders (NMJDs), including Myasthenia Gravis (MG). Broadly, Interluminescence carries the potential to rescue trans-synaptic neuro-muscular events when the traditional NMJ synaptic milieu is compromised under various circumstances including aging, disease and injury. Muscle properties can be rescued by using an excitatory opsin, and overexcitability can be dampened by using an inhibitory opsin.

Myasthenia Gravis

Autoantibodies Against Receptors Cause Disease by Blocking Receptor Function

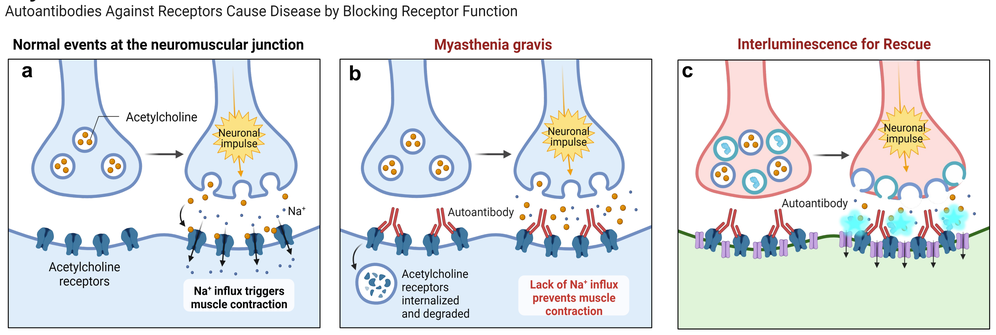


Fig. Possible therapeutic potential of Interluminescence at NMJ in Myasthenia Gravis (MG). Interluminescence to rescue the muscle contractility through trans-synaptic bioluminescence driven optogenetics **(c)** when traditional Acetylcholine receptor-mediated synaptic communication **(a)** is compromised in MG due to autoantibodies against acetylcholine receptors by blocking post-synaptic receptor function and muscle contraction **(b)**.

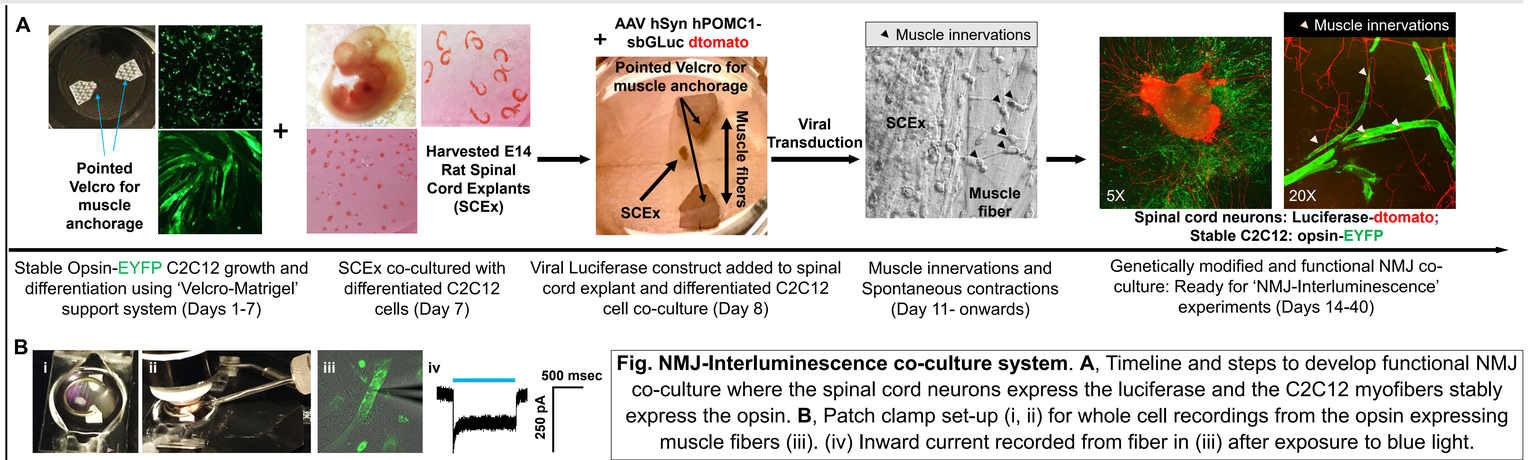
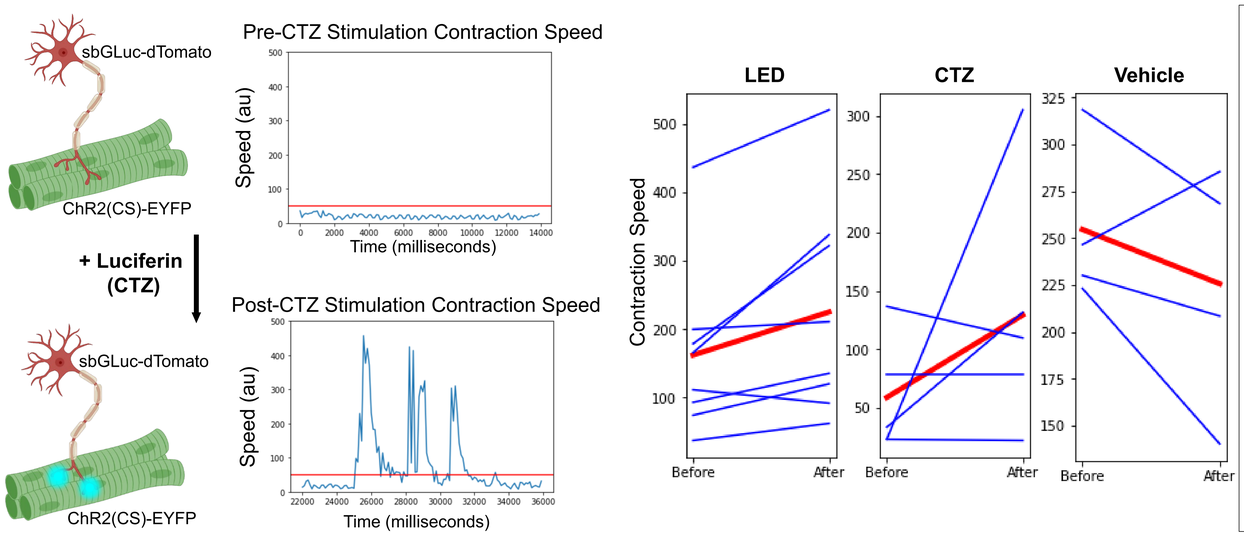


Fig. NMJ-Interluminescence co-culture system. **A**, Timeline and steps to develop functional NMJ co-culture where the spinal cord neurons express the luciferase and the C2C12 myofibers stably express the opsin. **B**, Patch clamp set-up (i, ii) for whole cell recordings from the opsin expressing muscle fibers (iii). (iv) Inward current recorded from fiber in (iii) after exposure to blue light.



Myotube contractions were analyzed before and after LED, CTZ, or vehicle application. The image analysis tool MUSCLEMOTION was used to analyze recordings in the open-source software Fiji. MUSCLEMOTION measured the speed of contractions based on changes in pixel intensity from a chosen reference frame to a frame of interest. The data regarding speed of contractions before and after treatment present promising findings and more research is needed to determine if results can be replicated *in vivo*.

Future directions & Acknowledgements

Future Directions:

- *In vivo* translational application of Interluminescence at Neuromuscular junction to modulate skeletal muscles.
- Targeting trans-cellular communication beyond neurons.

Acknowledgements:

- This work was supported by the National Science Foundation (NeuroNex-1707352), and National Institutes of Health (R01NS120832).
- The figures were created with BioRender.com.