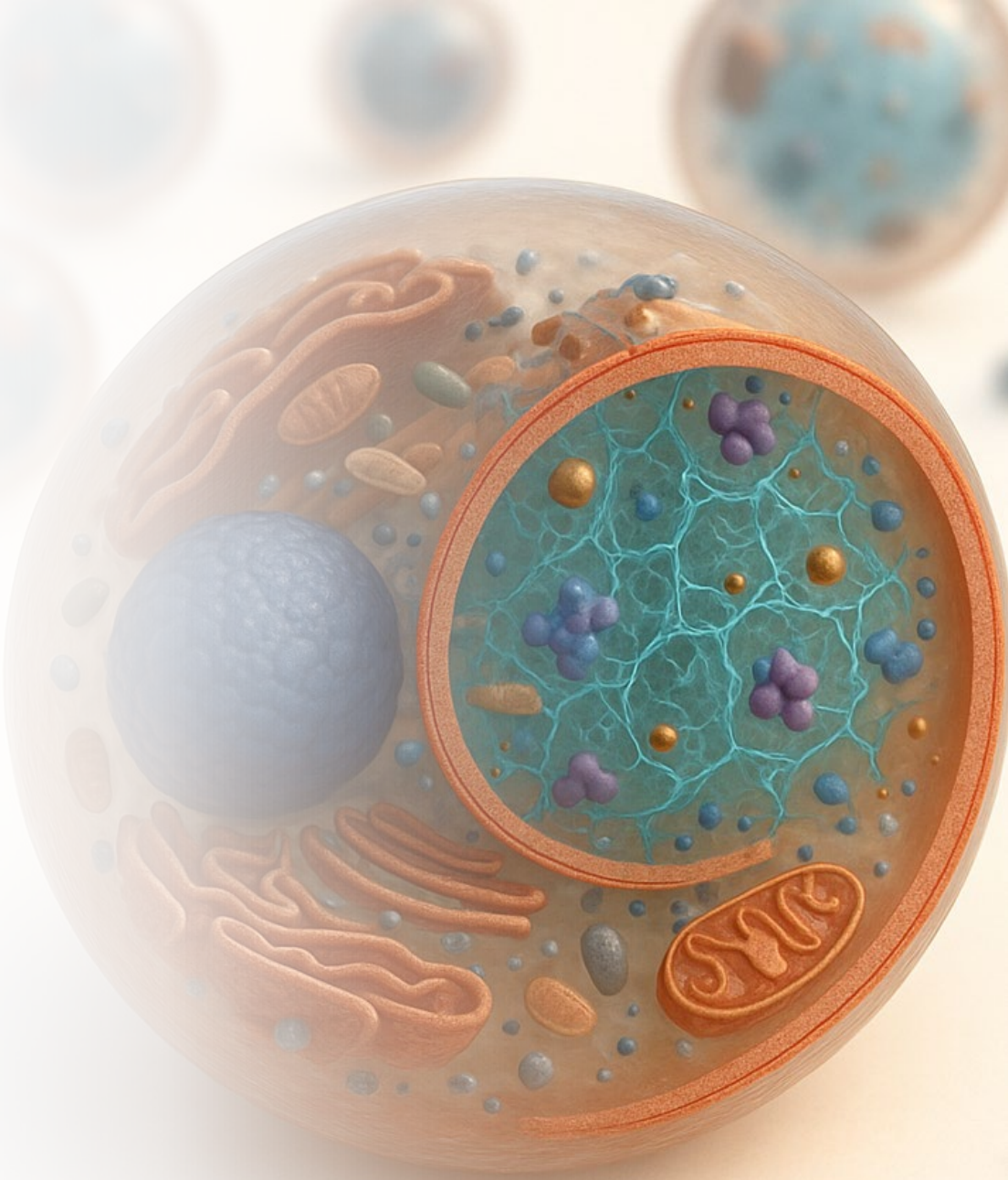
Crafting Synthetic Life against Diseases



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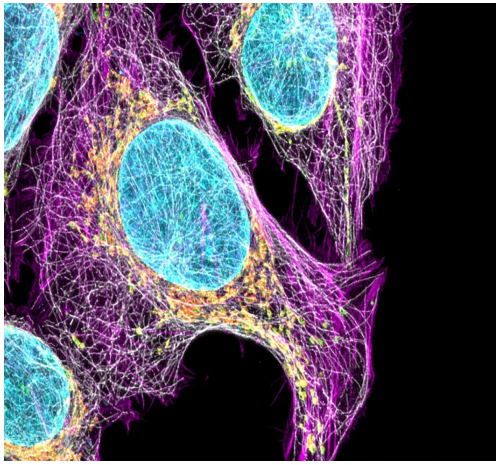
Current therapeutic paradigms have fundamental challenges for the treatment of many chronic diseases

Pure materials-based approach (nanoparticles, gels)

Pros: Ease of manufacturing and control

Cons: Lack of sustained activity in vivo



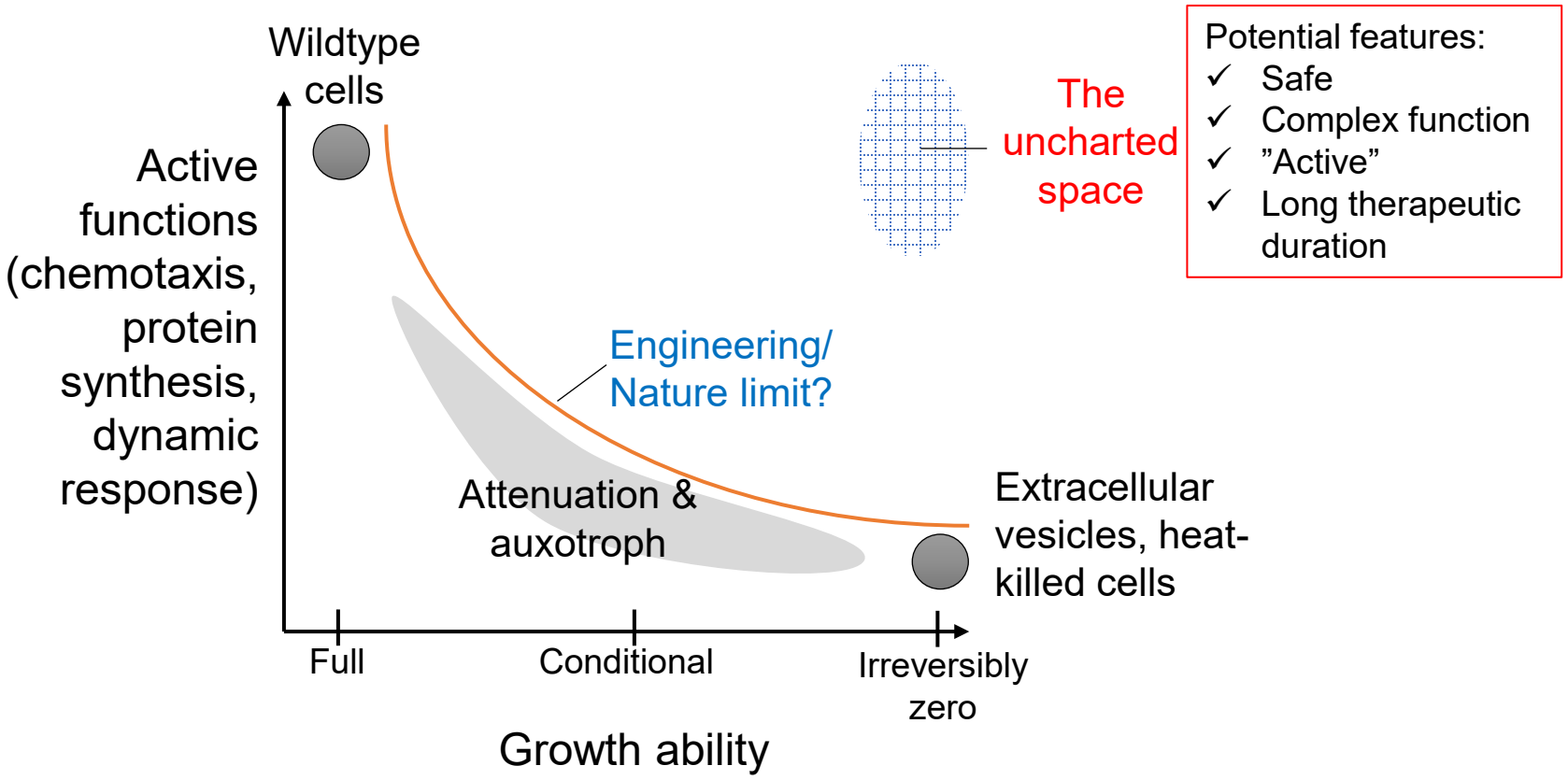
Cell-based approach

Pros: Sustained drug delivery in vivo

Cons: Lack of stability, risk of uncontrolled proliferation/differentiation

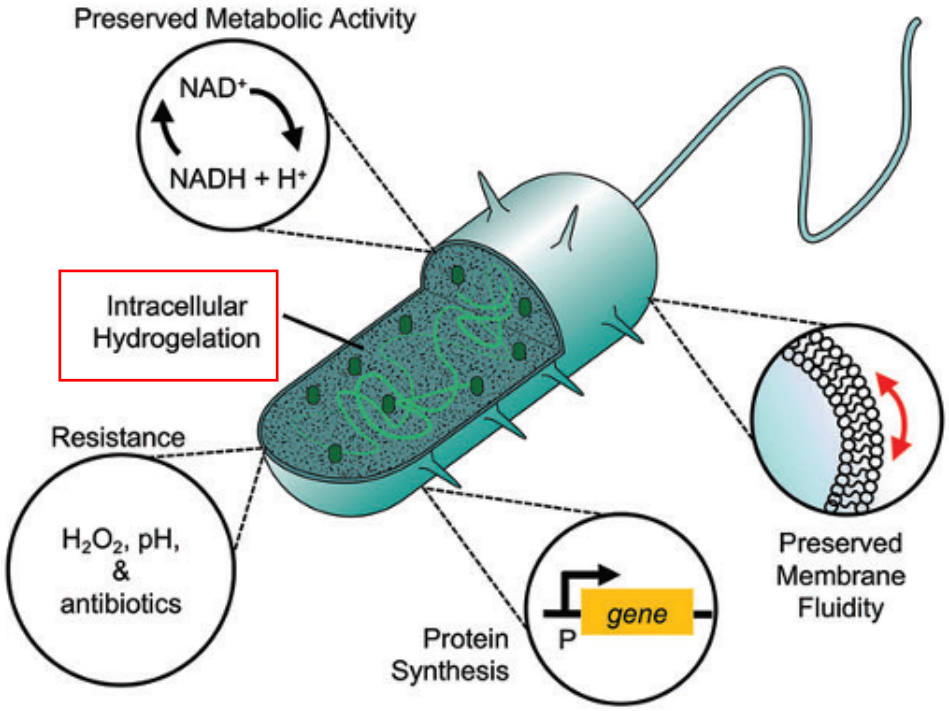
As a result, many chronic diseases lack effective therapy. Need for a new paradigm!

Exploring the nature limit using synthetic approaches



How do we reach the design space robustly and easily?

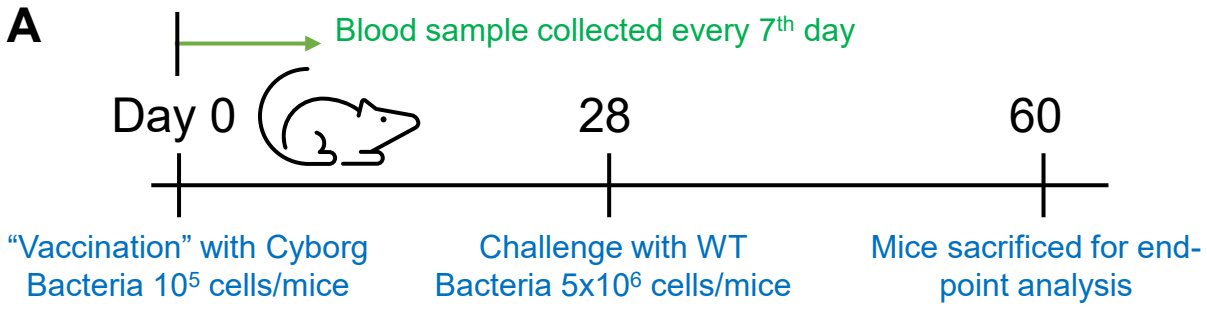
Meet synthetic non-replicating-but-active cells (Cyborg Cells)

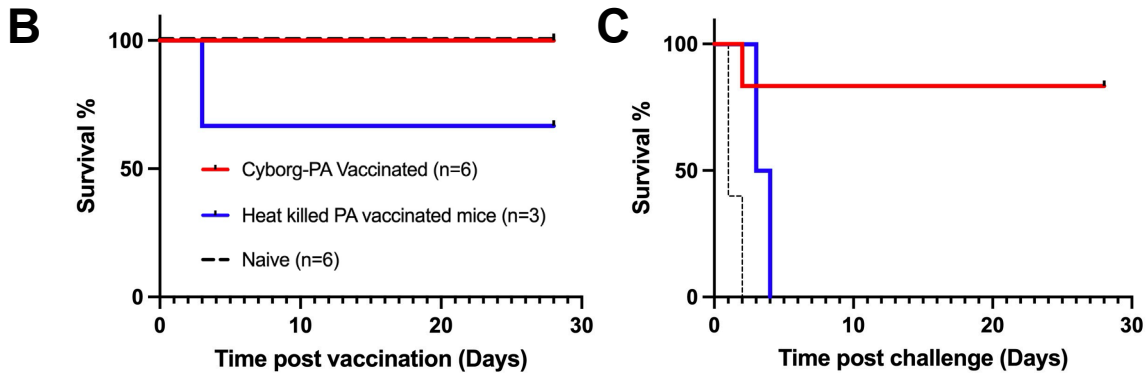


- Intracellular hydrogelation
- Maintain core features (size, functions, proteome, genome) of bacteria
- Semi living (non-dividing but active)
- Maintain metabolism and protein synthesis
- Resist high pH, hydrogen peroxide, antimicrobial agents
- Various bacterial pathogens

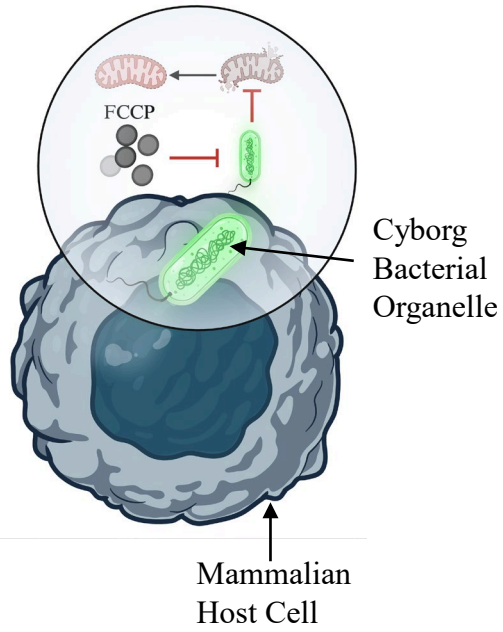
Contreras-Llano et al., Advanced Science, 2023
Baghdasaryan et al., Trends in Biotech, 2024
Contreras-Llano et al., Nature Protocol, 2024
Khan et al., ACS Syn Bio 2024.
Patent filed.

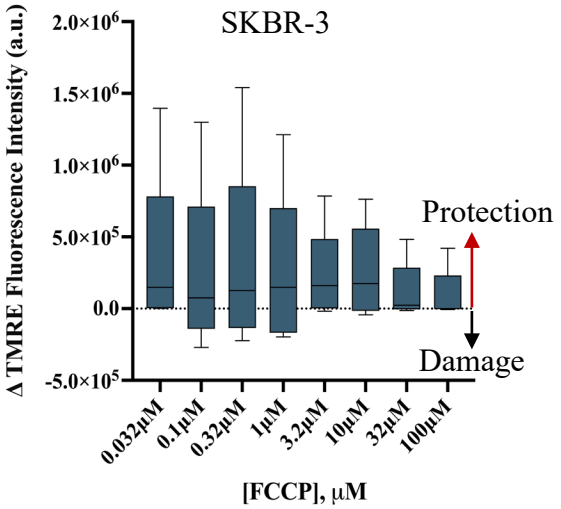
Cyborg Bacteria as cell or immune programming tools





Khan et al., in prep., patent filed
Baghdasaryan, in prep.

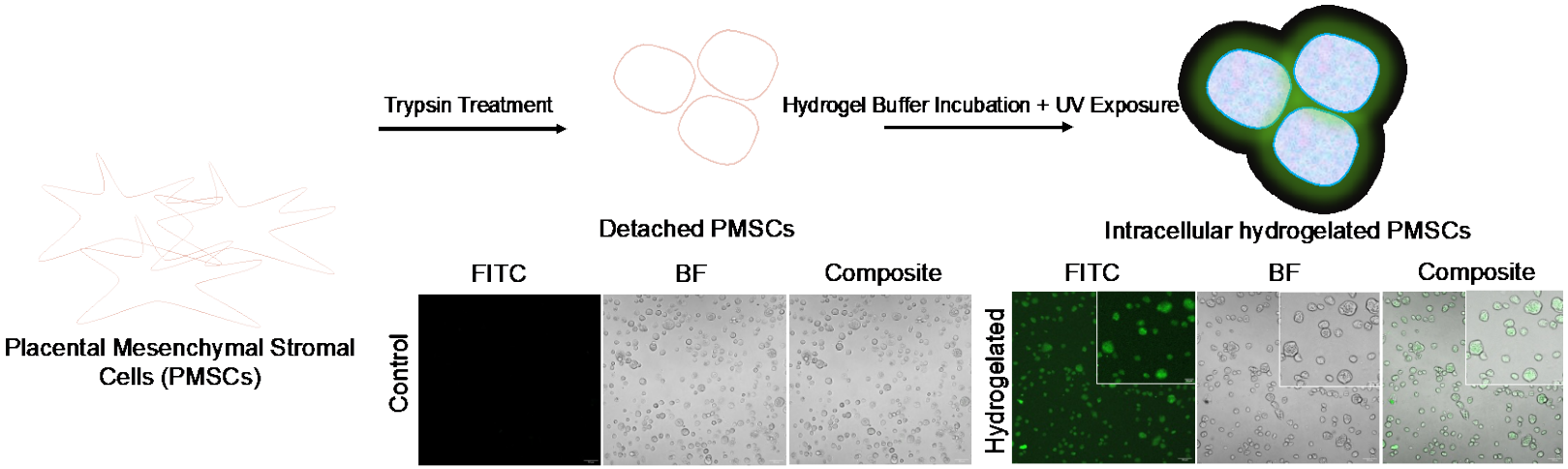




Moving toward antibacterial (S. aureus, M. tuberculosis), anti-aging, and anticancer

Can we create Cyborg Human Cells?

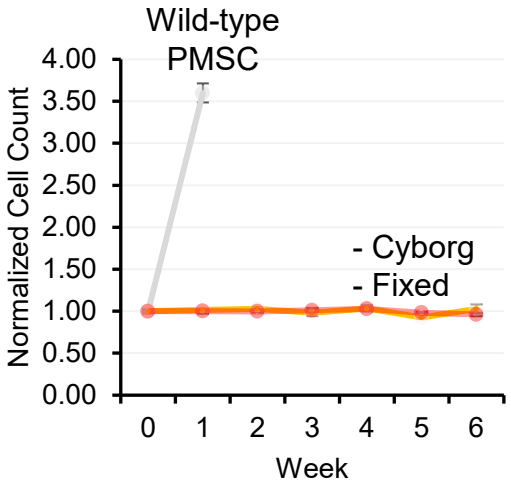
"Tan and Adamala agree that turning other cell types into cyborgs could be useful; yeast, for instance, is a fungus that can make proteins bacteria can't." – Scientific American



Contreras-Llano et al., in preparation, patent filed

Successfully created Cyborg Placental MSC, T-cell, HEK293, Primary GBM, 4T1 – non-replicating but metabolically active. With Aijun Wang and Russ Hovey lab

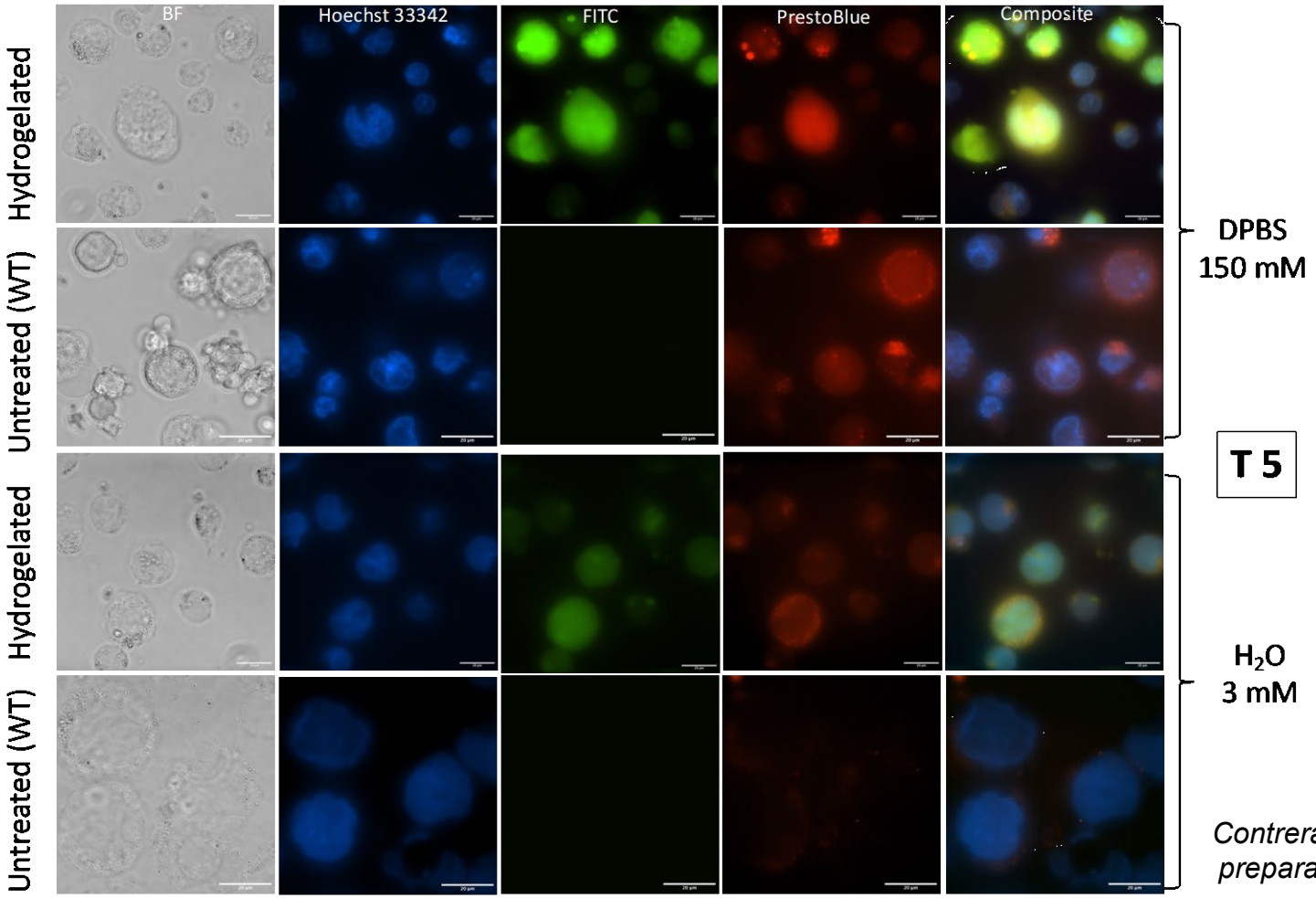
Cyborg PMSC preserve metabolic, protein synthesis, secretion activity, while not replicating, >5 weeks



Contreras-Llano et al., in preparation, patent filed

Also performed high-resolution imaging, tracking of molecular movement, organelle studies, metabolic activity studies, long term activity tracking, RNAseq, and large gene insert at precise landing pads.

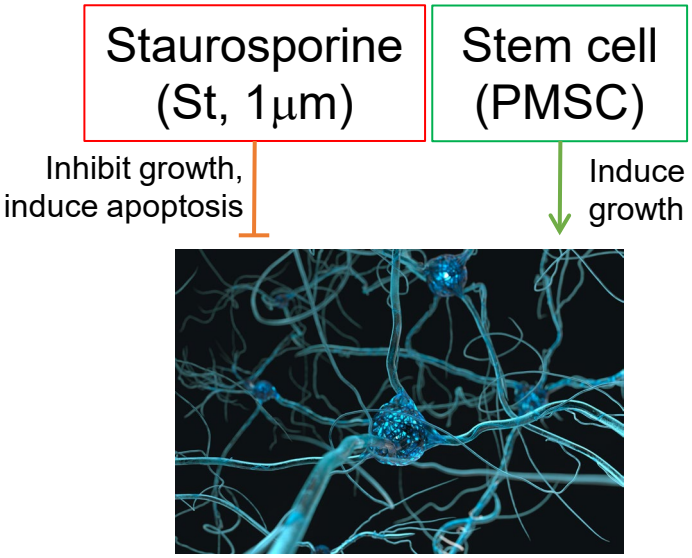
Cyborg PMSC are resistant to osmotic stress (ROS, hypoxia, H_2O_2, Staurosporine)



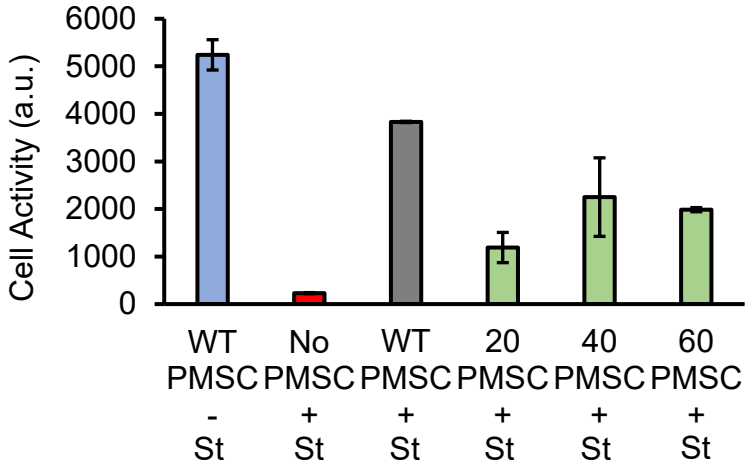
Contreras-Llano et al., in preparation, patent filed

Are they useful as therapeutics?

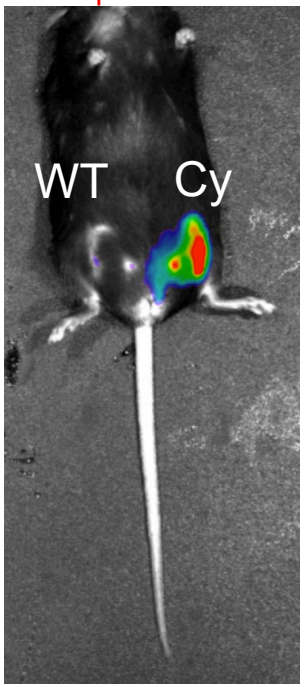
Cyborg PMSC boosts the recovery of "stressed" neuro cells



SH-Sy5y, neuroblastoma cell line; Primary rat neuron-astrocyte-microglia triculture



>3 weeks of stable transplant in immune-competent mice!

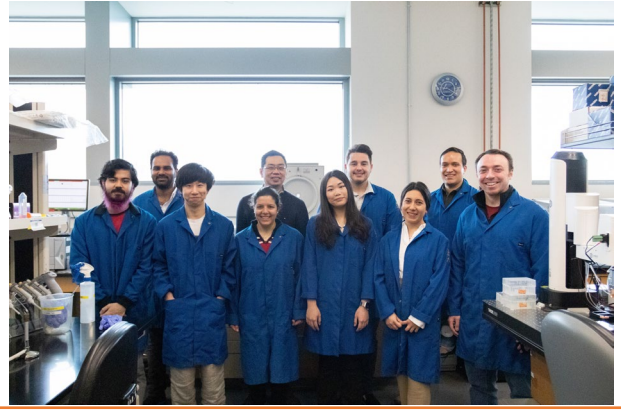


Contreras-Llano et al., in preparation, patent filed

On-going tests of various Cyborg Cells for ON-immune (anti-infection, anti-cancer), OFF-immune (anti-IBD, anti-aging), and regeneration applications

Conclusion

- Towards semi-living micro machines for biomedical applications
  - Cyborg cells: potentially safe and effective for chronic disease treatment
- Spirit of Asilomar Entreaty 2025: Synthetic Human Chromosomes - a call for global discussion.



- Lab members:
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  - Dr. Luis Contreras-Llano
  - Ofelya Baghdasaryan
  - Tanner Henson
  - Alessandra Arizzi
  - Jared Lee-Kin
  - Mariam El-Karim
  - Brianna Vargas, Nhu Bui, Desiree Poon, Sin-Chi Liu
- Collaborators: [UC Davis] Marjorie Longo, Aijun Wang, Russ Hovey, Randy Carney, Steven George, Sharon Aviran, Erkin Seker, Scott Simon, Roger Sciammas, Gant Luxton, Sean Collins, Yuanpei Li. [Mayo Clinic] Alex Revzin, Jim Wilkins. [Academia Sinica] Jack Hu. [UMN] Beau R Webber and Branden Moriarity.
- eMCB T32, NDSEG