NANO-GHOSTS: OPENING NEW FRONTIERS IN UNIVERSAL TARGETED DRUG AND GENE DELIVERY

The ultimate goal in targeted therapies is a 'magic-bullet' that can traverse *various* physiological barriers and target *multiple* pathologies at *different* stages while selectively delivering *diverse* therapeutics with minimal off-target effects. ***Here we present the prospects of a novel delivery platform that can do exactly that.*** This platform is based on nano-vesicles, termed *Nano-Ghosts* (NGs), which are technologically reconstructed from the cell membranes of naturally targeted *allogeneic* Mesenchymal Stem Cells (MSCs), after removing their cytoplasm and nuclei (Fig. 1).

The NGs' safety and targeting capabilities rely on their retention of the surface-associated mechanisms that govern MSCs' well-documented allogeneic tolerability and targeting of multiple inflamed and malignant tissues.

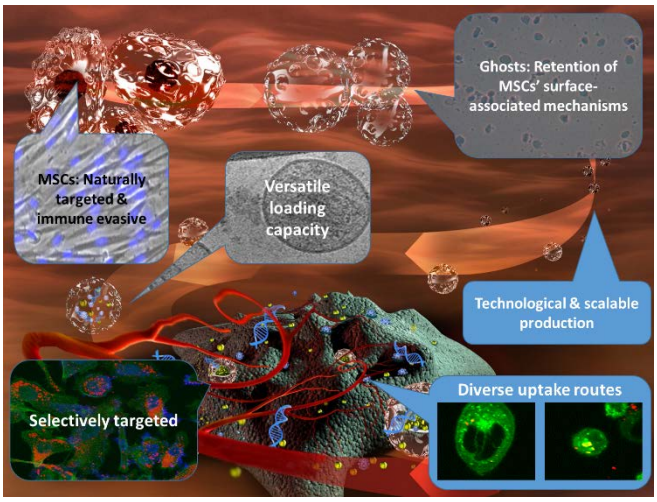

Figure 1. **Nano-Ghosts produced from naturally targeted MSCs retain the cells' targeting capabilities and selectively deliver diverse therapeutics attacking tumor cells and vasculature.**

The NGs represent a fundamental technological leap towards better treatment of cancer, neuroinflammatory diseases, and other MSC-targetable pathologies.

Versatility and promise of the Nano-Ghosts platform

- ✓ **Can target a wide range of pathologies at different stages including solid and hematological tumors, and inflammatory and degenerative diseases.**
- ✓ **Can traverse the Blood-Brain Barrier (BBB).**
- ✓ **May be loaded with diverse chemical and biological drugs, nucleic acids, and contrast agents for targeted therapeutic and theranostic applications.**
- ✓ **Wide potential immunotherapeutic applications.**
- ✓ **Non-autologous off-the-shelf product.**
- ✓ **Clear regulatory path: BMP (EU) or '*Biologics*' (USA).**
- ✓ **Potentially scalable & cGMP compliant manufacturing.**
- ✓ **Long shelf-life stability under various conditions.**

Building on pioneering achievements:

The NGs were shown to selectively target multiple cancer (prostate, breast, lung, and brain) and inflammatory cells. The NGs can deploy their payload into different compartments of the target cells (cytoplasm, nucleus etc.) through a variety of uptake routes (membrane fusion, endocytosis). The NGs' targeting capabilities were demonstrated *in vivo* using heterotopic prostate cancer xenograft and allograft models, and orthotopic metastatic xenograft lung cancer model, exhibiting wide accumulation in the tumor and rapid clearance from all blood-filtering organs (liver, lungs, spleen, and kidneys). **Systemic administration of NGs loaded with a biologic drug or a cancer-toxic gene led to almost complete tumor inhibition in mice bearing human prostate cancer (Fig. 2) and over 50% inhibition of *established* lung cancer metastases (Fig. 3), while dramatically prolonging the animals' survival.**

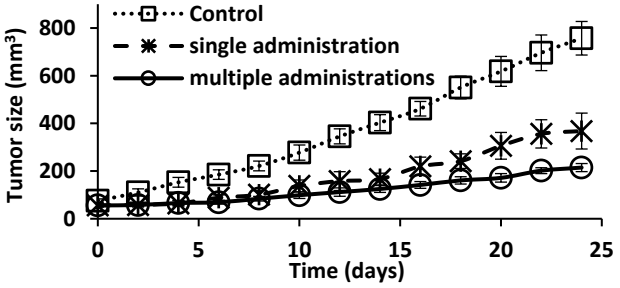

Figure 2. **Subcutaneous prostate tumors progression following single and repeated (Days 0, 7, and 14) *i.v.* administrations of NGs loaded with pDNA encoding for a cancer toxic protein.**

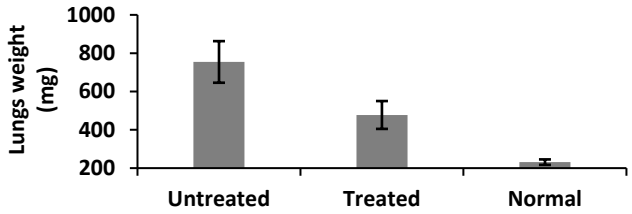

Figure 3. **The effect of repeated (X3) NG administrations (*i.v.*) on the progression of established orthotopic lung metastases.**

The NGs easily traversed an *in vitro* BBB model and when administered into a mouse model for multiple sclerosis they selectively accumulated in the brain and spinal cord (Fig. 4) and could be detected in and around MS lesions.

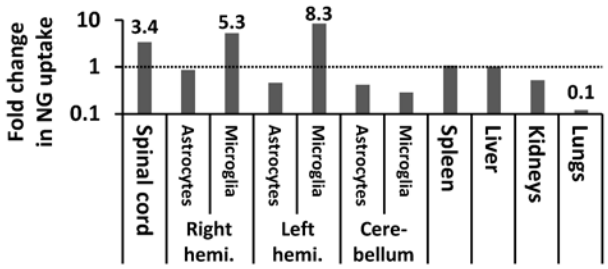

Figure 4. **Fold change in NG uptake by different cells and tissues due to EAE induction relative to control (healthy) animals.**

The NGs led to no organ or immune toxicity, and did not induce any immune response.

The NGs technology was recently selected by the Israel Ministry of Science and Technology (MOST) as one of the country's sixty most impactful developments.

IP Status: Patents pending in the US (US20120164214), EU (EP2470164), and China (CN102596179).

Publications (2): ●Nano Lett. 2016 Mar 9;16(3):1574-82 ●Nano Lett. 2013 Jul 10;13(7):3248-55.

This technology is being developed at the Laboratory for Cancer Drug Delivery & Cell Based Technologies at the Technion – Israel Institute of Technology under Prof. Marcelle Machluf and Dr. Tomer Bronshtein.
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