Overcoming Immunosuppressive Tumors by Stimulating the Adaptive and Innate Immune Systems

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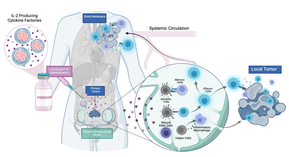
Introduction

Pro-inflammatory cytokines have been approved by the FDA for the treatment of metastatic melanoma and renal carcinoma. However, effective cytokine therapy is limited by its short half-life in circulation and the severe adverse effects associated with high systemic exposure. In an attempt to overcome the toxicities with systemic administration, intraperitoneal (IP) administration of IL-2 has been studied in multiple cancer types. Edwards et al. studied IP administration of IL-2 in platinum-resistant and platinum-refractory ovarian cancer (n=24) with an ORR of 25% (4 complete, 2 partial responses), however the use of in-dwelling peritoneal catheter led a significant number of patients having catheter obstruction or infusion pain. To overcome these limitations, we developed a clinically translatable localized cytokine delivery LOCOcyte™ platform composed of polymer encapsulated epithelial cells that produce potent immune effector molecules for local delivery with temporal regulation. AVB-001 is engineered to produce native hIL-2, for the treatment of peritoneal cancer including ovarian cancer.



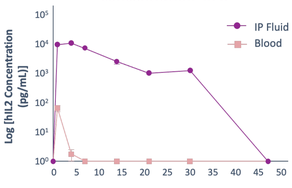
Potent **immune effector molecules** are continuously generated by synthetically engineering allogenic cells creating an **off the shelf therapy**

Therapy is localized in **proximity to the primary tumor site** and **generates innate and adaptive immune responses** treating the tumor **without systemic toxicity**

Immune cells travel through the lymphatic and systemic circulation **eradicating distal metastasis**

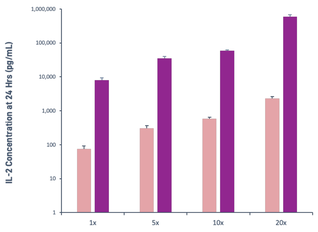
Results

Sustained hIL-2 production with high concentration in IP

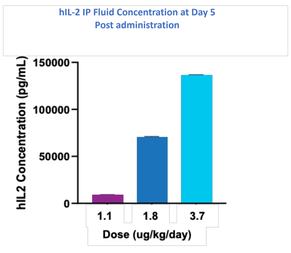


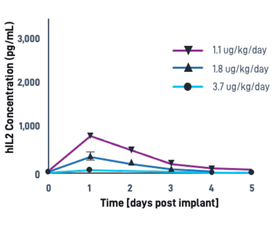
Development of programmed immune cell overgrowth correlates with drop in hIL-2 levels by AVB-001

AVB-001 demonstrates dose-dependent IL-2 concentration in IP fluid in mice

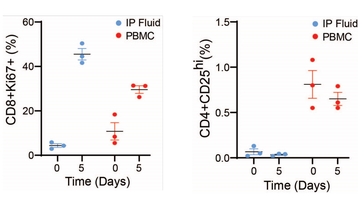


AVB-001 demonstrates dose-dependent IL-2 concentration in IP fluid in NHP



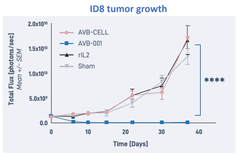


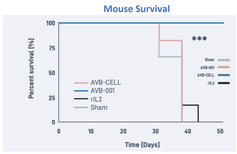
Local and systemic proliferation of CD4+ and CD8+ T cells in NHP



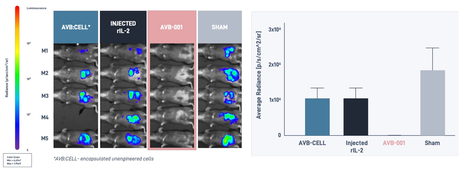
Results

Ovarian cancer model: AVB-001 completely eradicates tumor

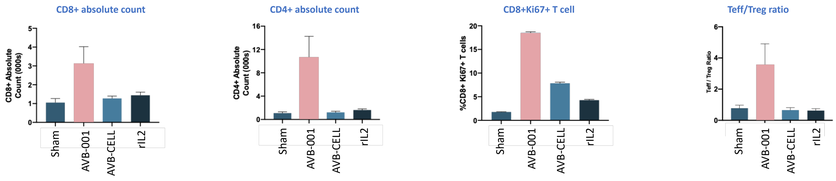




AVB-001 results in complete tumor suppression vs IP rIL-2 injection

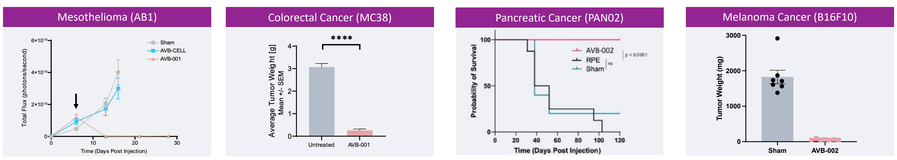


AVB-001 Increases local cytotoxic T cell proliferation in IP fluid of mice with ID8 tumors

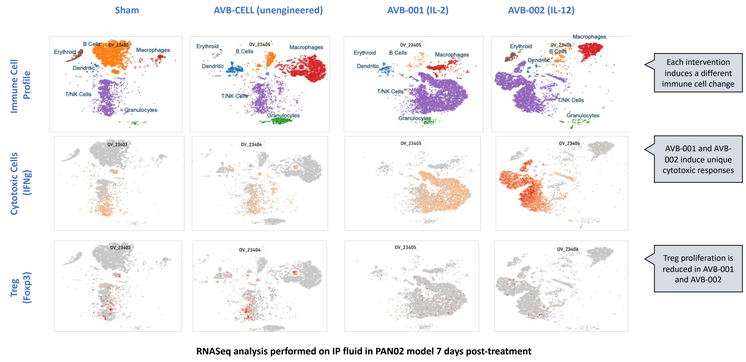


LOCOcyte™ achieves tumor eradication in multiple tumor models

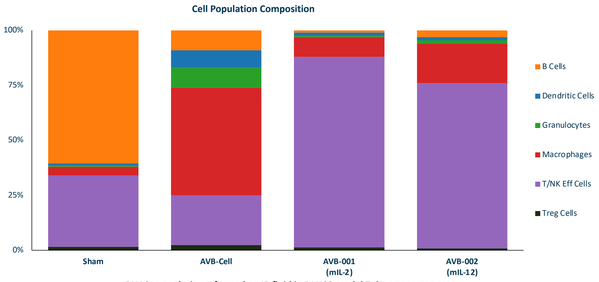
AVB-001 (IL-2) | AVB-002 (IL-12)



IP administration of RPE-mIL12 or RPE-mIL2 cause a local innate and adaptive immune response

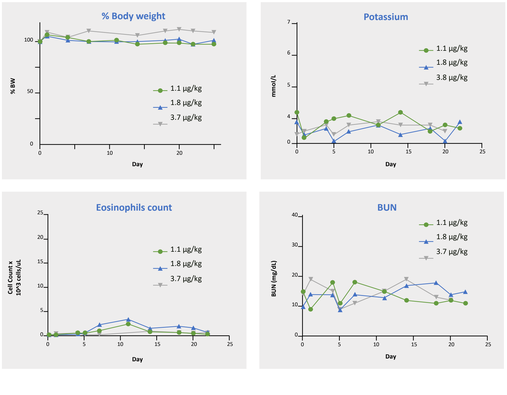


RNASeq analysis performed on IP fluid in PAN02 model 7 days post-treatment



RNASeq analysis performed on IP fluid in PAN02 model 7 days post-treatment

AVB-001 well tolerated in NHP: no signs of local or systemic toxicities



Minimal changes in body or organ weights

Minimal changes in blood chemistry and eosinophils

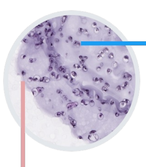
No abnormal findings in gross necropsy or histopathology of major organs

No signs of vascular leak syndrome

Additional studies demonstrate **no toxicity** at doses up to 12.8 µg/kg

Conclusions

Local regional delivery of LOCOcyte™ harnesses both innate and adaptive Immunity



hIL-2 Impact	Biomaterial Impact
Cell engineered to produce native IL-2	Alginate as immune-activating biomaterial
Regulates T_{EFF} differentiation	Promotes CD8 T cell memory
Activates proliferation of CD4/CD8 T cells, B cell, NK cells and DCs	CXCL13 production involved in TLS structure
Stimulates TIL activity	Promotes macrophage M2 to M1 transition
Ig production stimulated	Attracts immune-cell infiltration including Macrophages and DCs
Promotes activation-induced Cell Death	
3 times the T cell activation compared to recombinant IL-2	

- **Allogeneic cells engineered to produce native cytokines with higher T-cell proliferation potency than recombinant or engineered cytokines**
- **Sustained hIL-2 production with high concentration in IP cavity**
- **AVB-001 tumor adjacent delivery initiates local and systemic immune response with low systemic exposure to IL-2**
- **AVB-001 and AVB-002 monotherapy eradicates multiple tumor types in mice**
- **AVB-001 and AVB-002 modulate innate and adaptive immune responses**
- **AVB-001 well tolerated in NHP and has a favorable safety/tolerability profile**
- **FIH clinical trial in ovarian cancer patients with AVB-001 to is ongoing (NCT05538624)**