DEVELOPMENT OF A CATHETER-BASED APPLICATOR FOR IMMUNO-ONCOLOGY

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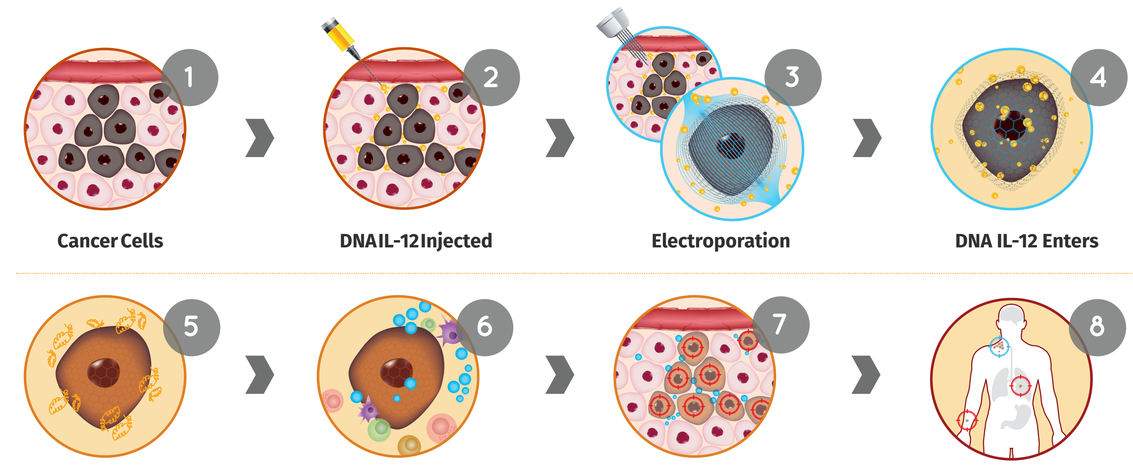
ABSTRACT

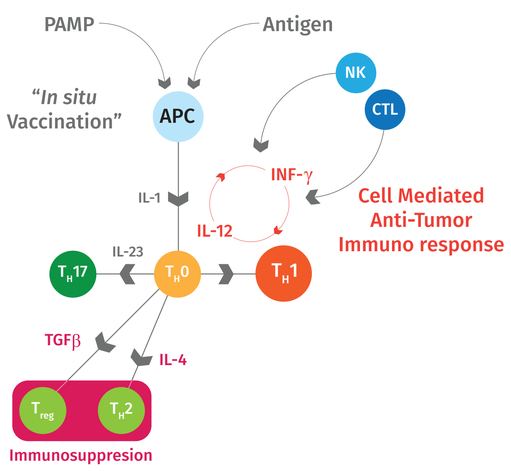
OncoSec Medical is an immuno-oncology company developing plasmid-based intratumoral immunotherapies for the treatment of advanced-stage cancers. Delivery of these therapeutic entities relies on the concomitant application of an electric field to transiently disrupt membrane integrity, allowing plasmid DNA access to the cytoplasm. In clinical trials, intratumoral delivery of cytokine encoding plasmids results in local and systemic tumor regression. Due to the size of traditional electroporation applicators this approach has been limited to cutaneous lesions, such as melanoma, Merkel cell carcinoma, and cutaneous T-cell lymphoma. As a majority of malignant tumors occur within the body, OncoSec Medical has begun developing catheter-based devices to perform minimally invasive intratumoral immunotherapy. These devices are guided by an endoscope to an internal tumor, where they are capable of anchoring to the neoplasm, injecting a plasmid DNA payload, and deploying electrodes to perform electroporation. Performing each of these steps with one catheter-based device increases the co-localization of exogenous therapeutic DNA with the electric field, improving the therapeutic outcome of the treatment. This catheter-based device will enable minimally invasive treatment of cancers of the lung, liver, stomach, oropharynx, pancreas and others.

IN VIVO ELECTROPORATION

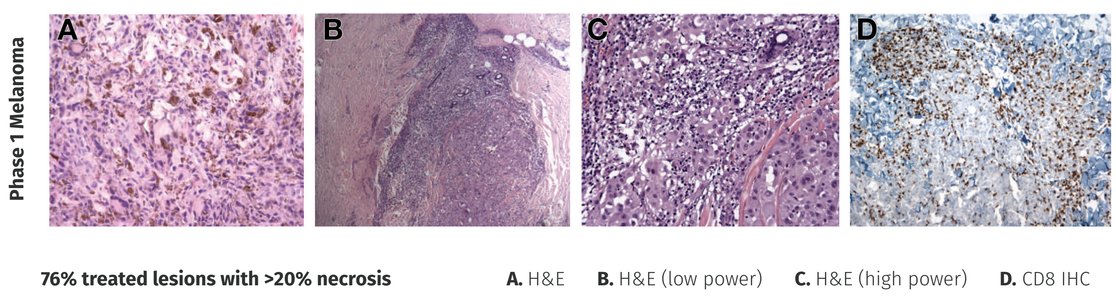


INTRATUMORAL "IN-SITU VACCINATION" CAN PROMOTE ANTI-TUMOR IMMUNE CD8 RESPONSES

- Effective adaptive immune responses: "good" antigen + "danger signal" › immunostimulatory APC
- TH1/cell-mediated response appears to be most effective type of anti-tumor immunity
- IL-12–IFNγ feed forward loop is critical to linking innate & adaptive responses and specifying TH1/cell-mediated response
- In-Situ Vaccination › Immunogenic cell death exposes all antigens (including mutation derived "private" neoantigens) obviating the need to choose "good antigens" a priori



INTRATUMORAL IL-12 EP RESULTS IN LOCAL NECROSIS AND CD8 INFILTRATION



76% treated lesions with >20% necrosis

A. H&E **B.** H&E (low power) **C.** H&E (high power) **D.** CD8 IHC

COMPLETE RESPONSE AND DISTANT LESION REGRESSION AFTER ONE CYCLE OF IT-pIL12-EP

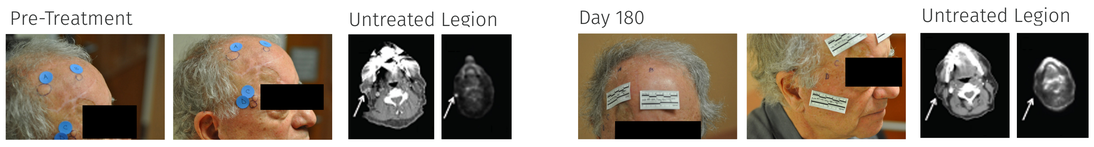
Cycle = 3 treatments (Day 1, 5, 8)

Daud-A, *et al*, J Clin Oncol. 2008 Dec 20;26(36):5896-903.

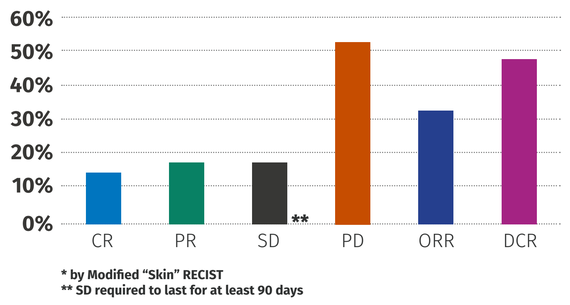
No measurable systemic IL-12 or IFNγ (ELISA)

COMPLETE RESPONSE AND DISTANT LESION REGRESSION AFTER ONE CYCLE OF IT-pIL12-EP

Case #1 (001-003)



PHASE II: PIL-12 EP MONOTHERAPY DEMONSTRATES ANTI-TUMOR ACTIVITY IN METASTATIC MELANOMA



* by Modified "Skin" RECIST
** SD required to last for at least 90 days

Response Category *	N (%)
Complete Response (CR)	4 (14%)
Partial Response (PR)	5 (17%)
** Stable Disease (SD)	5 (17%)
Progressive Disease (PD)	15 (52%)
Overall Response Rate (CR + PR)	9 (31%)
Disease Control Rate (CR + PR + SD)	14 (48%)

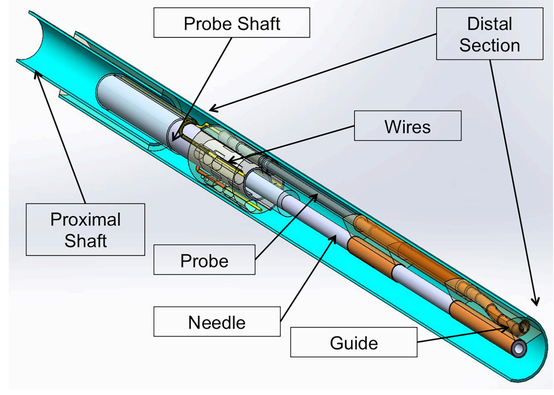
Evaluable for Objective Response
N=29

LIMITATIONS OF CURRENT TECHNOLOGY SUMMARY

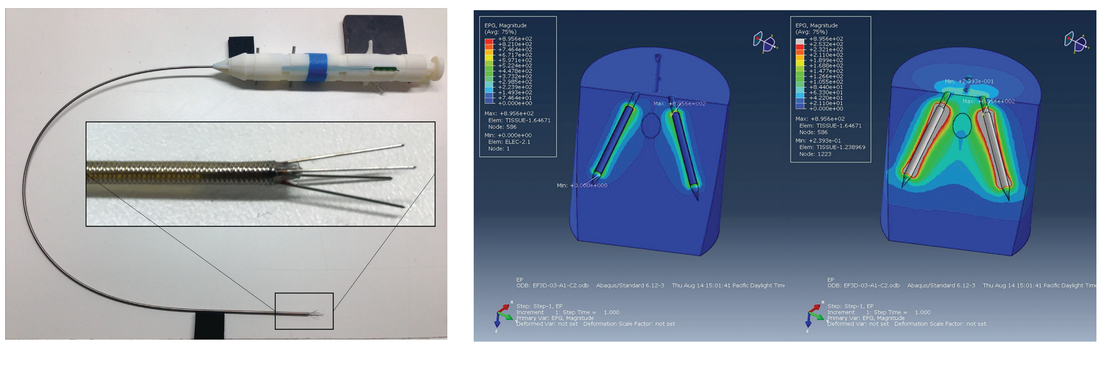
- Clinical evidence supports intratumoral delivery of IL-12 can induce local and systemic immune responses
- Without invasive procedure, current state of technology limited to superficial treatments due to applicator size:
  - 1.0 cm diameter applicator with 6-needle electrodes
  - Maximum penetration depth 1.5 cm
  - Good for targeting:
    - 1.0 cm diameter applicator with 6-needle electrodes
    - Maximum penetration depth 1.5 cm
    - Good for targeting:
- Treating more invasive tumors requires advancing technology forward to catheter-based solution

CATHETER DEVELOPMENT

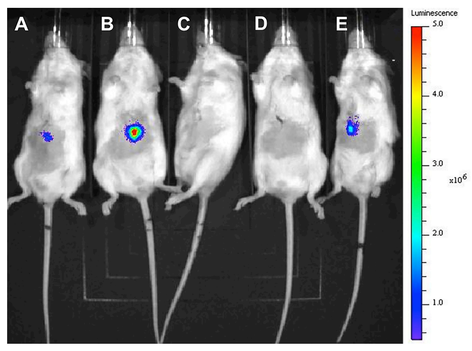
- Catheter being developed to treat cancers of the lung, liver, stomach, pancreas, oropharynx, and others
- Device deployed through lumen in endoscope, trocar, guide catheter, or sheath
- Distal catheter features:
  - Designed to fit 2.8 mm diameter lumen
  - Central needle allows local delivery of plasmid DNA encoding cytokines
  - Electrodes deploy around injection site to perform electroporation
- Proximal catheter features:
  - Control deployment of central needle and electrodes
  - Adjust penetration depth for needles and electrodes
  - Control rate and volume of injection
  - Remote control over electroporation process



E-FIELD GENERATED



CATHETER-BASED DELIVERY OF pDNA



Luminescent images acquired through the skin 24 hours after catheter-based delivery of a luciferase expressing plasmid. Imaged animals treated with: (A and B) 50 µg of plasmid DNA followed by electroporation; (C) no treatment; (D and E) injection of 50 µg of plasmid DNA only.

CONCLUSIONS

- Clinical evidence supports intratumoral delivery of IL-12 can produce local and systemic reduction in tumor burden
- Catheter-based technology will enable intratumoral gene electrotransfer to tumors that are inaccessible with current technology
- Fully adjustable needle and electrode penetration depth on catheter handle allows clinician to optimize treatment for tumors of varying dimensions
- Combining electrodes and needles improves co-localization of the therapeutic agent with electric field
- Combination therapy with other agents, such as anti-PD1 drugs, have the potential to improve response rates by increasing tumor infiltrating lymphocytes