Multivalent dendritic cell vaccines designed to concurrently enhance class I mediated antigen presentation, dampen regulatory T cell activation, and modulate paracrine immune signaling

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Abstract: Dendritic Cells are commercially approved in multiple regions of the world for use as therapeutic cancer vaccines. The efficacy profile of these first generation products provides impetus for development of enhanced potency DC vaccines that exhibit robust, reproducible, and stronger clinical benefit.

Development of safe and effective cell-based therapeutic products that may lead to objective clinical benefit requires synergistic modulation of multiple independent pathways within the cell that may control the hypothesized sub-set of biological activities of cell intended for therapeutic use. Driven by this vision, we have sequentially evaluated multiple pathways within dendritic cells that specifically result in (a) skewing of antigen-up take, processing and presentation toward HLA class I mediated activation of CD8 T cells, (b) dampening the ability of the cell to activate Treg cells, and (c) examining the ability of dendritic cells, when transfected with plasmid DNA or messenger RNA, to serve as in vivo bioreactors to transiently synthesize and secrete pharmacological levels of immune-effector proteins into the local microenvironment to modulate the symmetry of immune activation elicited by antigen presentation.

The knowledge from these studies has been incorporated into development of (1) a cGMP compliant closed-system manufacturing process, and (2) regulatory-compliant characterization assays, and (3) scale-up for clinical manufacture and delivery of enhanced potency dendritic cell vaccines that permits robust, reproducible and controlled ability to concurrently modulates multiple biological pathways within each dendritic cell. We are currently evaluating safety and biological activity of these ‘enhanced’ potency dendritic cell vaccines in human clinical studies.

Key Attributes of MaxCyte-enabled DC Vaccines (1 of 2)

- More antigen loaded per DC (viz. improved antigen-utilization efficiency)
  - Stronger immune stimulation
  - ‘Better’ activity/function
  - More patients treatable
  - Treatment not limited by access to patient tumors
  - Broader market coverage
  - Lower COGS
  - Reduced vaccine DC
  - Single manufacturing lot is sufficient for 6-12 injections

Antigen-loading characterization

MaxCyte enables development of enhanced potency human DC vaccines

- More DC take up Ag & There is more Ag per DC
- hMSC loading efficacy

MaxCyte-loading has no negative impact on maturation of DC

- Loaded-antigen is preferentially expressed & presented via HLA class I pathway (viz. enhanced potency)
- Better antigen presentation via HLA class I processing
- Enhanced tumor-antigen-specific cytokine DC activation
- "ENHANCED" anti-tumor activity

DC vaccine (in vitro & in vivo results)

- Tumor Challenge Model
- In vitro function (tumor [effector:infiltrated DC]
- Therapeutic Vaccination Model

Potency of human DC Vaccine

MaxCyte-loading results in 3-5 fold higher potency

Enhancement of Effector Function

Engineering co-stimulatory capacity

Summary

- ~ 20 fold higher biological activity (under CD8 T cell activation in vivo co-culture)
- Efficient antigen delivery requires ~20 fold lower amount of antigen per patient dose
- Ability to upregulate antigen-loaded cells permits flexibility in manufacturing operations
- Single manufacturing lot supports multiple vial product lots in (3) batches
- Used in the buildup of pharmacokinetics may be satisfactorily in such environment of treatment
- Consent, Robust, scalable process and product manufacture
- Safe, Rapid, Automated, scale up, processing, amenability to delivery in outpatient setting
- Significant impact on COGS for manufacturers of potential scale
- Molecules in addition to antigens can be loaded into DC to enhance tumor antigen specific effective T cell function while concurrently inhibiting pathways involved in T cell dysfunction

- Enhanced potency no additional risk (compared to scale of art)