Weill Cornell Medicine

Inflammasome Agonist Proteins for Vaccine and Immunotherapy

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Inflammasome Agonist Proteins for Vaccine and Immunotherapy

Background & Unmet Need

- Immunity is driven by two types of adaptive immune responses: The cell-mediated immune response (activated T cells) and the humoral immune response (activated B cells and antibodies)
- The generation of adaptive immunity depends not only on exposure to an antigen, but also the context in which the antigen is encountered
- In cancer, the immunosuppressive tumor bed is a formidable barrier against cancer vaccines and immunotherapy like immune checkpoint blockade
- Adjuvants are used in conjunction with an antigen to enhance antigen-specific immune response
- However, traditional aluminum salt and oil-based adjuvants are often ineffective in boosting the immune response to therapeutic cancer vaccines or in immunocompromised individuals
- **Unmet Need:** Novel adjuvants that induce a strong adaptive immune response for both prophylactic vaccines and cancer immunotherapies

Technology Overview

- **The Technology:** Use of bacterial needle and rod proteins as adjuvants to activate the innate immune inflammasome pathway
- **The Discovery:** Bacterial needle proteins such as PrgI and CprI activate the inflammasome, a signaling complex that produces pro-inflammatory cytokines and mediates adaptive immunity
- **PoC Data:** Expression of Needle proteins activated the inflammasome and initiated an inflammatory form of cell death called pyroptosis in tumor cells
- Chimeric antibodies consisting of a single-chain variable fragment fused to a Needle protein, tumor antigen, and/or Flagellin activated the inflammasome and caused human dendritic cell maturation, proinflammatory cytokine production, and tumor antigen MHC-I presentation to T cells
- Expression of Needle proteins in established melanoma tumors in mice led to significant reduction of tumor volume and resolution over time

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Patents:
PCT Application Filed

Publications:
N/A

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Technology Applications

- Adjuvants to enhance the host immune response to both prophylactic and therapeutic vaccines
- Cancer therapy via the use of fusion proteins, chimeric target antibodies, or activated dendritic cells to trigger immune response to tumor cells

Technology Advantages

- Protein adjuvants are amenable to multiple delivery systems and to different cell types including tumors
- Protein adjuvants may be delivered in vaccine formulations or as chimeric antibodies *in-* or *ex-vivo*
- Adjuvants target inflammasome for stronger immunogenic effect than current adjuvants
- Controlled activation of inflammation by specifically targeting NLRC4 inflammasome

Supporting Data / Figures

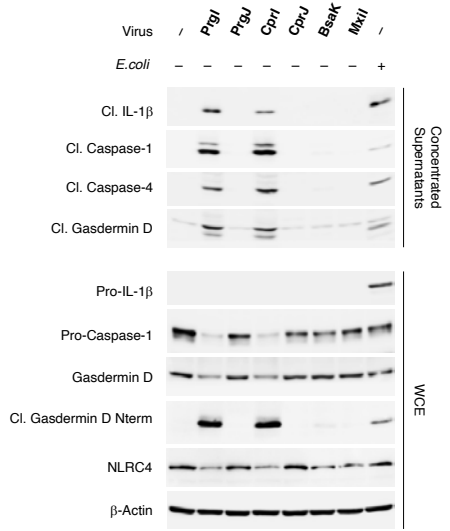

Figure 1: Transduction of human DCs with recombinant lentiviruses expressing Needle and Rod proteins induced inflammasome activation, indicated by cleavage of IL-1β, caspases 1 and 4, and Gasdermin D.

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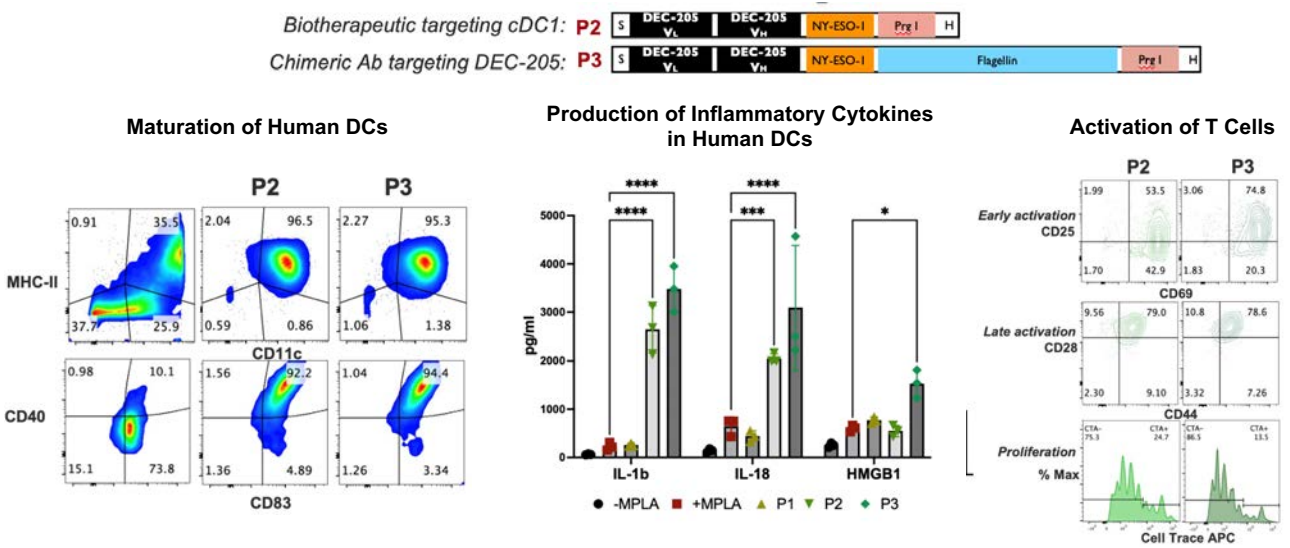

Figure 2: Top: Schematic of chimeric antibody-based biotherapeutic consisting of Needle Protein *PrgI*, tumor associated antigen *NY-ESO-1*, with or without *Flagellin* fused to the single-chain variable fragment. Treatment of DCs with chimeric antibodies induced **Left:** DC maturation, as indicated by increased MHC-II and T-cell costimulatory CD40 and CD86 **Middle:** DC production of inflammatory cytokines IL-1β and IL-18, and HMGB1 **Right:** DC activation of NY-ESO-1 tumor antigen-specific T cells.

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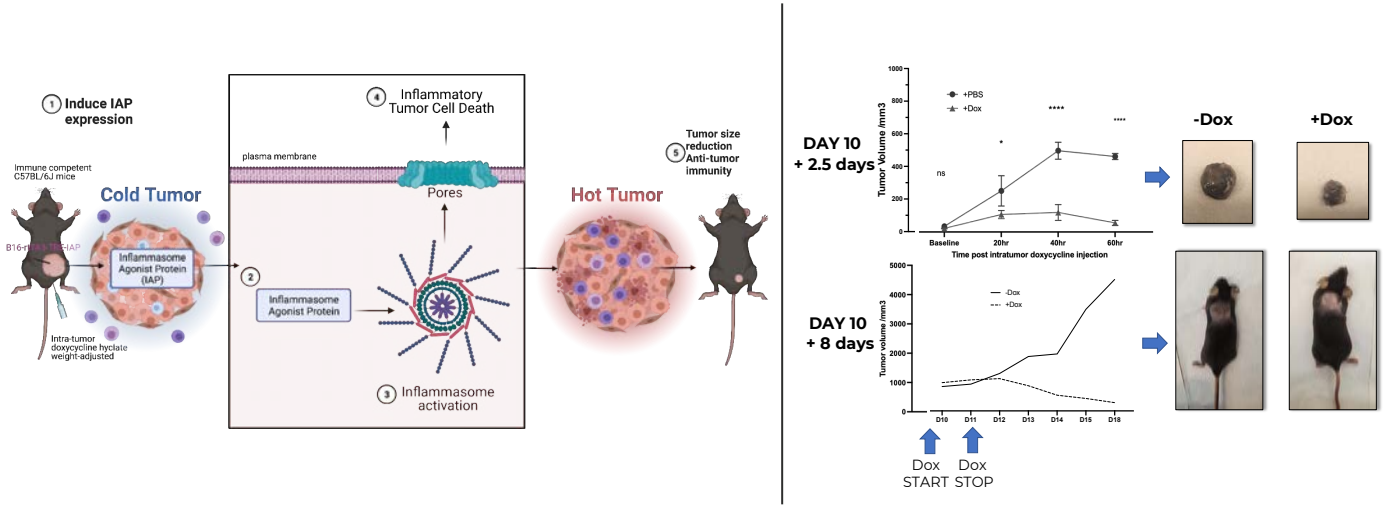

Figure 3: Left: Schematic of inflammasome agonists mediating anti-tumor immunity **Right:** Expression of Needle proteins reduced tumor volume in mice inoculated via subcutaneous injection of melanoma cells. Melanoma cells are transduced with a dox-inducible protein expression system to express Needle proteins. Doxycycline was administered through intratumoral injection.

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