Intratumoral Activation of STING with a Synthetic Cyclic Dinucleotide Elicits Anti-Tumor CD8+ T-Cell Immunity that Effectively Combines with Checkpoint Inhibitors

Abstract

Activation of the STING pathway by intratumoral (IT) injection of synthetic cyclic dinucleotides (CDNs) induces stable tumor regression in preclinical models; yet the underlying immune correlates are not fully understood. ADU-S100, a CDN under clinical evaluation, was administered IT with an optimized dosing regimen to explore the immune requirements for anti-tumor efficacy in mouse syngeneic tumor models. We show that CD8+ T cells are necessary and sufficient for durable anti-tumor immunity elicited by ADU-S100 and that activation of STING in hematopoietic cells mediates CD8+ T cell induction. Both type I IFN and TNFα, which are induced by STING pathway activation, influence the anti-tumor immune response. The combination of ADU-S100 and anti-PD1 treatment enhances CD8+ T cell-dependent, non-injected tumor control that correlates with an enhanced effector profile of CD8+ T cells in the tumor. Combination of ADU-S100 with checkpoint inhibition (CPI) also enhances durable immunity in a poorly immunogenic tumor model. Together, these results elucidate the immune correlates to STING-mediated anti-tumor efficacy and highlight the potential of combining STING agonists with check point inhibition in the clinic.

Development of clinical compound ADU-S100/MW815

- Phosphorothioate increases resistance to phosphodiesterase to enhance potency
- Phosphorothioate increases resistance to phosphodiesterase to enhance potency
- Phosphorothioate increases resistance to phosphodiesterase to enhance potency

Therapeutic administration of ADU-S100 elicits durable CD8+ T-cell-dependent anti-tumor immunity

- T cell infiltrated tumors in humans are correlated with an IFN-γ transcriptional signature in the tumor microenvironment (TME)
- STING plays a critical role in activating immune cells, including dendritic cells, in the TME
- Intratumoral injection of CDNs induces IFN-γ, activating tumor-resident DCs which stimulates priming of tumor specific CD8+ T cells in mice
- Novel approach to stimulate priming of CD8+ T cells for specific individuals with nanoscale nanoparticles

Dose level impacts induction of ADU-S100 tumor-specific T cell response

ADU-S100 elicits durable CD8+ T-cell dependent anti-tumor immunity

- Type I IFN is required for optimal anti-tumor immune response
- Rationally designed STING agonist, ADU-S100, elicits durable CD8+ T cell immunity that is driven by STING signaling in the hematopoietic compartment in mice
- Immune defective mice of ADU-S100 in induce both innate immune activation in injected tumors and activate naive CD8+ T cells in tumor draining lymph node

Conclusions

- ADU-S100 is an effective combination treatment with checkpoint inhibition to enhance anti-tumor efficacy and durability in immune mice
- ADU-S100 is a first-in-human STING agonist being evaluated in cutaneously disseminated, advanced/metastatic, solid tumors or lymphomas in a single agent, with checkpoint inhibitor (PD1-ligand) and anti-CTLA4 (planned)

Intratumoral Activation of STING with a Synthetic Cyclic Dinucleotide Ellicits Anti-Tumor CD8+ T-Cell Immunity that Effectively Combines with Checkpoint Inhibitors

631

Leticia Corder1, Kelsey Smock Gauthier1, Anthony L. Deaklin2, Gabriela Reis3, Laura Hos Goodrick4, Thomas E. Hudson1, Uyen Vu1, Natalie H. Bush1, Brian Faccinetti1, George E. Kothavala1, Weisong Deng1, David B. Kanne1, Justin J. Leong1, Ken Melchett1, Chudi Ndubaku1, Jeffrey M. McKenney1, Steven L. Bender1, Marcellin L. Leong1, Thomas W. Dubensky Jr.1,5, Andrea van Elsas1, and Sarah M. McWhirter1

1Aduro Biotech Inc., Berkeley CA; 2Novartis Institutes for BioMedical Research, Cambridge MA; 3Genomics Institute of the Novartis Research Foundation, San Diego, CA; 4currently Actym Therapeutics; 5currently Tempest Therapeutics

Page dimensions: 2592.0x1296.0

Credit: Aduro Biotech/Christian Lee, Genomics Institute of the Novartis Research Foundation, 2022