Combination of IGF-1R Targeted Alpha Therapy with Immune Checkpoint Inhibitors Results in Synergistic Efficacy in a Syngeneic Colorectal Tumor Model.

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Abstract

Objective: In the last decade, immunotherapy has revolutionized cancer care and became a mainstream therapy along with surgery, chemotherapy and radiation. Unfortunately, only a limited number of cancers exhibit intrinsic sensitivity to immunotherapies and the overall response rate is only 20-25%. Therefore, there is a strong impetus to identify treatments which can sensitize patients to immunotherapies. Fusion utilizes targeted alpha therapy (TAT) which enables delivery of alpha particle emitting isotopes (actinium 225) to the targeted tumor cells. The rationale for the combination of TAT and immunotherapy stems from known immune stimulating properties of radiation, leading to release of tumor-associated antigens, maturation of antigen-presenting cells (APCs) and in turn activation and proliferation of CD8+ T cells. Therefore, we have hypothesized that combination of TAT with immunotherapy will lead to a robust therapeutic effect resulting in a synergistic response as compared to monotherapy alone.

Methods: The syngeneic CT26 colon cancer model was used to evaluate therapeutic efficacy of combination treatment with actinium 225-radiolabelled IGF-1R antibody (mAb), FPI-1792 (or [225Ac]-TAT), and checkpoint inhibitors. FPI-1792 was used as a surrogate therapeutic that cross-reacts with mouse IGF1-R. Mice with subcutaneous tumors (tumor volume ~175 mm^3) were treated with either vehicle, an anti-CTLA-4 mAb (5 mg/kg) or anti-PD-1 mAb alone (5 mg/kg), FPI-1792 alone (375 kBq/kg or 200nCi) or the respective combinations. CD8+ T cells infiltration was evaluated via flow cytometry and IHC staining. Granzyme B production was assessed by IHC.

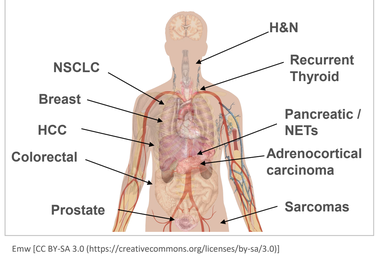
Results: While only transient tumor growth suppression was detected in animals treated with either checkpoint inhibitors or FPI-1792 alone, complete tumor regression was observed in 13 out of 15 mice treated with combination therapies, indicating development of potent synergy in the combination groups. To investigate whether animals with regressing tumors will be able to reject a secondary tumor, all surviving animals were re-challenged with CT26 cells on the contralateral flank. Rejection of the secondary tumors was detected in 87% of mice previously treated with either FPI-1792 alone or a combination therapy, while tumors grew in all control animals. To gain a better understanding of the mechanism responsible for tumor regression, tumors were collected 14 days post re-challenge and analyzed via flow cytometry. An increased frequency of CD8+ T cells was observed in mice treated with combination therapy as compared to untreated animals (5-20% vs 1-2%, respectively). Importantly, high frequency of AH1 antigen-specific T cells was detected using a tetramer staining - 30-70% in the treated animals as compared to 2-3% in the control mice.

Conclusions: The combination of targeted alpha therapy with checkpoint inhibitors led to tumor regression in a CT26 syngeneic model. Moreover, mice re-challenged with the same tumor on the contralateral flank were protected due to development of a strong immune response. Finally, increased frequency of antigen specific CD8+ T cells in re-challenged tumors suggests that combined treatment can break T cell tolerance and elicit a strong CD8+ T cell mediated immune response, culminating in tumor rejection.

Background

Type I insulin-like growth factor receptor (IGF-1R) is a transmembrane protein which is overexpressed in solid tumors including non–small cell lung, prostate, sarcomas, and breast cancers. FPI-1792 (or [225Ac]-TAT) is a radioimmunoconjugate consisting of a human monoclonal antibody that binds to IGF-1R, a proprietary bifunctional chelate, and the alpha-emitting radionuclide actinium-225 (Ac-225). Internalization of the radioimmunoconjugate and decay of Ac-225 causes tumor cell death primarily through induction of double stranded DNA breaks followed by CD8+ T cell mediated immune response.

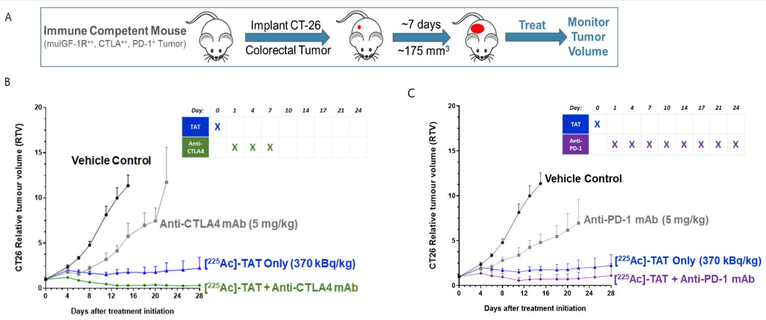
IGF-1R is expressed on nearly all tumor types



IGF-1R has been implicated in:

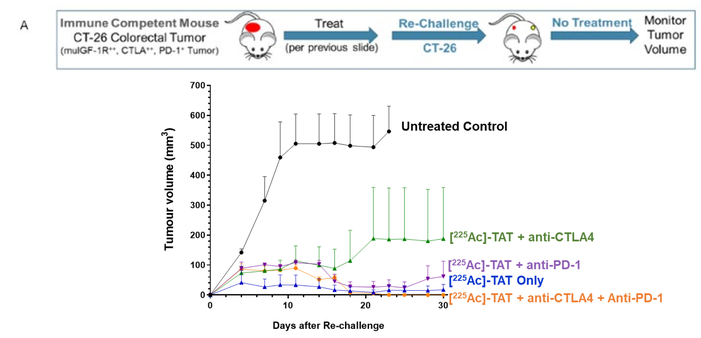
- Increased cellular proliferation
- Metastatic potential
- Cell survival
- Chemotherapy and radiotherapy resistance

[225Ac]-TAT (Single dose, 370 kBq/kg) + immune checkpoint inhibitors therapy: Combined efficacy demonstrated in colorectal cancer syngeneic mouse model



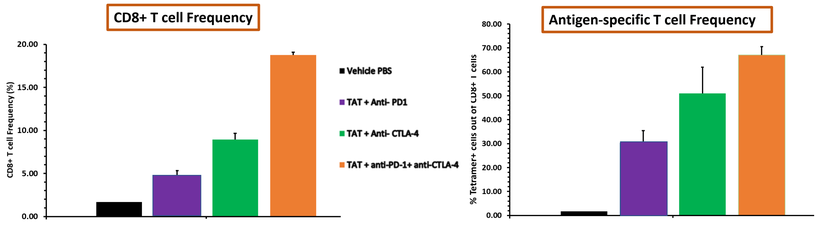
- CT26 primary tumors:
  - Partial tumor growth suppression was observed with [225Ac]-TAT alone treatment.
  - Complete regression was observed in 87% of mice in combination treatment groups.

[225Ac]-TAT (Single dose, 370 kBq/kg) + immune checkpoint inhibitors therapy: "Vaccine" Effect demonstrated in secondary tumors



- CT26 secondary tumors (post re-challenge):
  - Complete regression was observed in 87% of mice treated with either [225Ac]-TAT alone or combination treatments

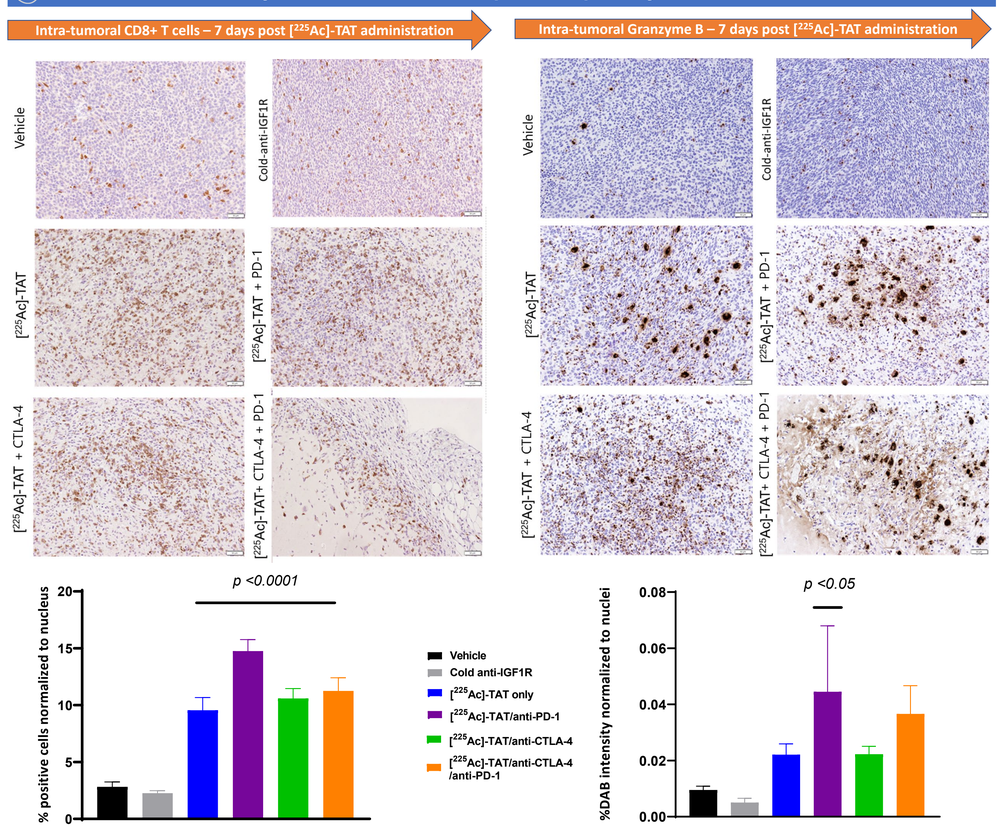
[225Ac]-TAT (Single dose, 370 kBq/kg) + immune checkpoint inhibitors therapy: Antigen-specific CD8+ T cell response elicited in secondary tumors



Immune checkpoint inhibition co-therapy is a rational approach to potentiate the CD8+ T cell immune response elicited by treatment with [225Ac]-TAT.

- Combination of [225Ac]-TAT with immune checkpoint inhibitors leads to increased frequency of CD8+T cells in tumors:
  - Decreased frequency of CD8+ T cells was observed in the spleens in the combination treatment groups as compared to the controls (data not shown), suggesting migration of T cells from the spleen to the tumors.
  - Antigen-specific CD8+ T cells induction was also observed in spleens, albeit with a lesser frequency than in the tumors (data not shown).

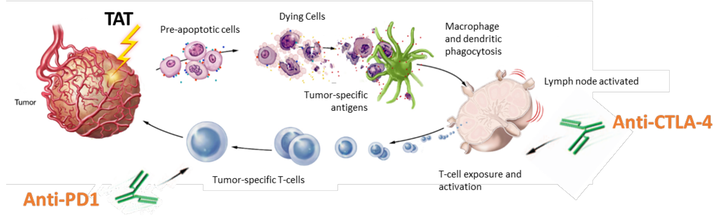
[225Ac]-TAT (Single dose, 370 kBq/kg) alone or in combination with immune checkpoint inhibitors elicits a cytotoxic CD8+ T cell response in primary CT26 tumors



- Treatment with [225Ac]-TAT alone and in combination with immune checkpoint inhibitors increased percentage of cytotoxic CD8+ T cells and granzyme B production in the primary tumors, as visualized by IHC staining in FFPE tumors samples.

CD8+ T cells are involved in both primary and secondary tumor immune response driven by [225Ac]-TAT treatment.

Summary and Conclusions



- Treatment with [225Ac]-TAT in combination with immune checkpoint inhibitors resulted in complete tumor eradication.
- Strong "vaccine" effect was observed with a combination of [225Ac]-TAT and immune checkpoint inhibitors, leading to regression of secondary tumors.
- Combination of [225Ac]-TAT with immune checkpoint inhibitors induced CD8+ T cell immune response that contributed to the regression of primary CT26 tumors and was solely responsible for the eradication of secondary tumors.
- Overall, enhanced therapeutic efficacy observed with immune checkpoint inhibitors and [225Ac]-TAT combination supports the consideration of this combination for clinical use.