Trial in Progress: A Phase 1-2, First-in-Human, Open Label, Dose Escalation and Expansion Study of AU-007, A Monoclonal Antibody That Binds to IL-2 and Inhibits IL-2Rα Binding, in Patients with Advanced Solid Tumors

James Vasselli[1], Paul De Souza[2], Sophia Frentzas[3], Andrew Weickhardt[4], Tim Wyant[1,5], Jenny Tang[1], Aron Knickerbocker[1], Inbar Amit[1,5], Yanay Ofran[1,5]

[1]Aulos Bioscience, Larkspur, CA; [2]St. George Private Hospital, Sydney, Australia; [3]Monash Health; School of Medical and Health Sciences, Monash University, Melbourne, Australia; [4]Austin Health, Heidelberg, Australia; [5]Biolojic Design, Rehovot, Israel

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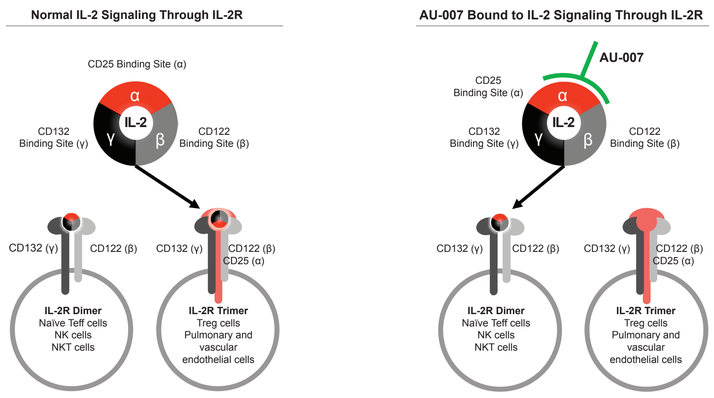
james@aulosbio.com

AU-007 Background

Redirects IL-2 to Teff / NK Cells and Away from Tregs and Vascular Endothelium

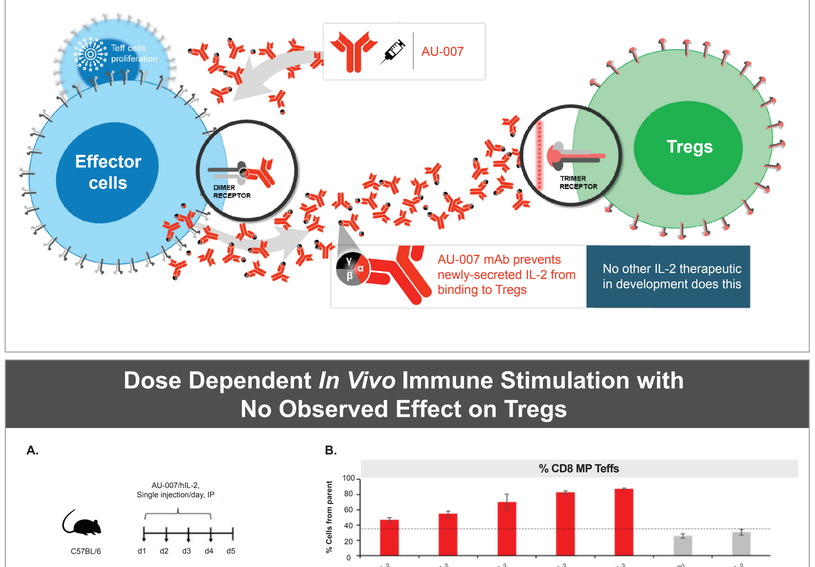
- AU-007 is a computationally designed (Biolojic Design), human IgG1 monoclonal antibody.
- AU-007 binds interleukin-2 (IL-2) with pM affinity and completely inhibits its binding to CD25, without hindering its binding to CD132/CD122.



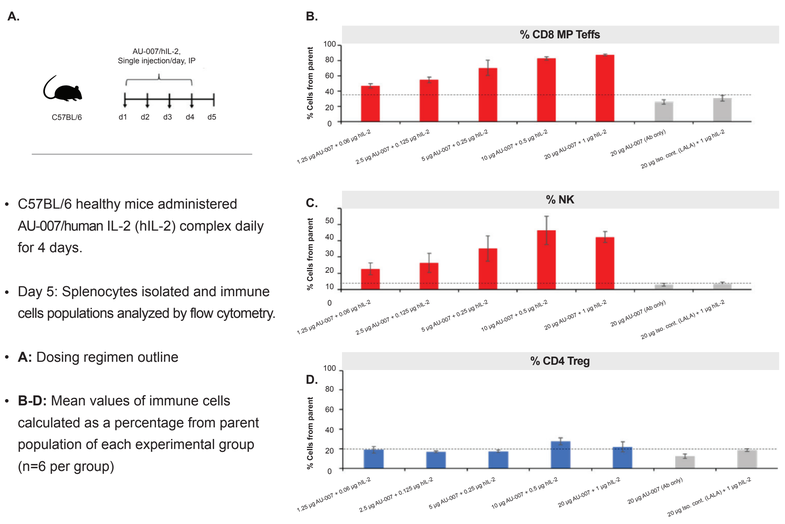
Unique MOA Addresses the IL-2 Negative Feedback Loop

- Treatments activating effector cells against tumors are undermined by an autoinhibitory loop caused by endogenous IL-2 secreted from activated T effector cells.
- AU-007 can transform the IL-2 negative feedback loop into a positive feedback loop.
- Re-engineered IL-2 therapeutics cannot address the negative feedback loop.

AU-007 Uniquely Tips the Balance Toward Immune Activation, Away from Immune Suppression



Dose Dependent *In Vivo* Immune Stimulation with No Observed Effect on Tregs



- C57BL/6 healthy mice administered AU-007/human IL-2 (hIL-2) complex daily for 4 days.
- Day 5: Splenocytes isolated and immune cells populations analyzed by flow cytometry.
- **A:** Dosing regimen outline
- **B-D:** Mean values of immune cells calculated as a percentage from parent population of each experimental group (n=6 per group)

Redirected IL-2 Signaling by AU-007 Leads to Tumor Growth Inhibition and Regressions

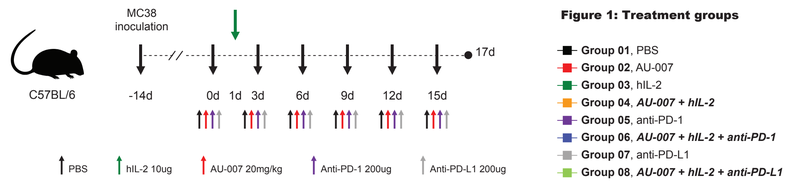
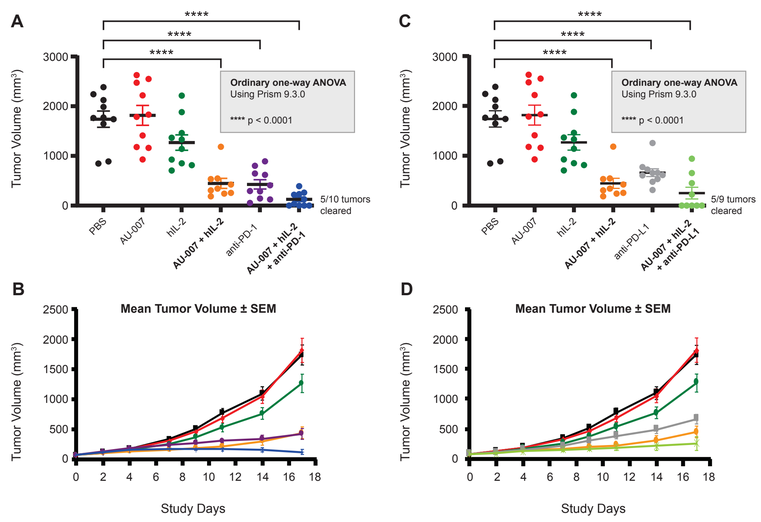


Figure 1: Treatment groups

- **Group 01**, PBS
- **Group 02**, AU-007
- **Group 03**, hIL-2
- **Group 04**, ***AU-007 + hIL-2***
- **Group 05**, anti-PD-1
- **Group 06**, ***AU-007 + hIL-2 + anti-PD-1***
- **Group 07**, anti-PD-L1
- **Group 08**, ***AU-007 + hIL-2 + anti-PD-L1***

- Day minus 14: C57BL/6 mice inoculated with 1x10^6 MC38 mouse colorectal tumor cells.
- Day 0: AU-007 treatment begun, dosing every 3 days (groups of 10 mice).
- IL-2 administered on day 1 only.
- **As AU-007 does NOT bind mouse IL-2, hIL-2 is required to be given in these studies.**
- Tumor volumes measured on days 0, 2, 4, 7, 9, 11,14, and at termination.
- Study terminated on day 17 as tumor volumes in the hIL-2 GEM mice control arms obtained ethical limits.



Efficacy of AU-007/IL-2 alone or in combination with immune checkpoint treatment of MC38 in C57BL/6 mice.
A: Terminal tumor volumes in anti-PD-1 cohorts
B: Growth curves for anti-PD-1 cohorts
C: Terminal tumor volumes in anti-PD-L1 cohorts
D: Growth curves for anti-PD-L1 cohorts. Note that the same control arms are in A/B as in C/D. Color coding matches color coding in methods above.

Safe and Well-Tolerated Preclinical Safety Profile

Repeat dose toxicity study in cynomolgus monkeys: 8 weeks of IV AU-007 dosing 2X per week followed by 4-week recovery

No significant clinical observations beyond very minor rash that persisted in some animals.

No unusual necropsy findings.

No cytokine storm.

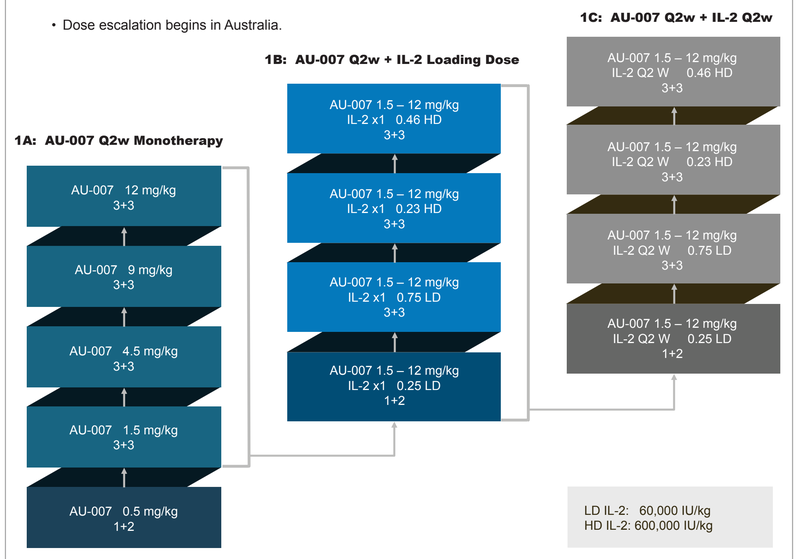
GLP immunohistochemistry assessment of tissue cross reactivity

No observed cross reactivity on any human tissues.

Study Design

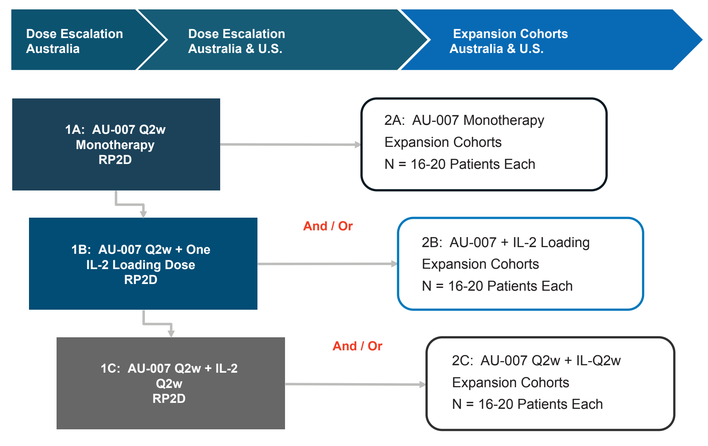
Dose Escalation

- AU-007 evaluated as 1A) monotherapy, 1B) in combination with a single loading dose of aldesleukin, or 1C) with both AU-007 and aldesleukin given every 2 weeks (Q2w).
- AU-007 monotherapy evaluates doses sufficiently high to ensure enough AU-007 is available to bind all IL-2 molecules: both exogenously administered (aldesleukin) and endogenous IL-2.
- 19 solid tumor histologies.
- Adverse events graded by the Common Terminology Criteria for Adverse Events.
- Efficacy based on PD markers of immune stimulation, total IL-2 (bound to AU-007 + free IL-2) and objective responses.
- Optional paired pre / on-treatment biopsies.
- Dose escalation begins in Australia.



Cohort Expansion

- Design enables further evaluation of the dosing regimen or regimens from Dose Escalation RP2D or MTD.
- Tumor histologies focus on melanoma and RCC before opening to other cancers.
- Mandatory paired pre / on-treatment biopsies.
- Utilize Simon's 2 stage design for decisions on efficacy.



Rationale

- IL-2 (aldesleukin): Approved for melanoma and renal cell carcinoma (RCC), but its therapeutic value is limited by frequent administration of high doses, short half-life and severe toxicity.
  - AU-007 MOA addresses the challenges associated with aldesleukin treatment by:
    - Reducing Treg activation and enhancing immune effector cell activation
    - Preventing IL-2 from binding CD25+ vascular endothelium, diminishing vascular leak syndrome
    - Prolonging IL-2 T1/2 nearer to a monoclonal antibody's T1/2 through binding to AU-007
    - Converting the IL-2 negative feedback loop to a positive feedback loop
- Therefore, AU-007 may substantially increase the therapeutic window of IL-2 potentially allowing the use of far lower amounts of IL-2 to achieve the anti-tumor activity observed with high-dose IL-2, and possibly enhanced efficacy.
- This may be accomplished with the patient's endogenous IL-2, or possibly exogenous IL-2 at doses that are tolerable and easily manageable in an outpatient setting.

Key Study Objectives

Primary Objective

- Safety, tolerability, dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of AU-007 alone or in combination with IL-2 (aldesleukin).

Secondary Objectives

- Pharmacokinetics (PK), pharmacodynamic (PD) activity and immunogenicity of AU-007 alone or in combination with IL-2 (aldesleukin).
- Preliminary anti-tumor activity evaluated conventional / modified RECIST 1.1.

Exploratory Objectives

- Relationships between PK, PD, patient safety and anti-tumor activity of AU-007 alone or in combination with IL-2 (aldesleukin).
- Relationship of serum biomarkers including serum cytokines, soluble CD25 and measures of T-cell activation in peripheral blood and/or tumor biopsy specimens with response to AU-007.

Entry Criteria

Key Inclusion Criteria

- Age ≥ 18 years old
- Histologically / cytologically proven unresectable locally advanced or metastatic cancer for which there is no approved therapy available, or patients ineligible or intolerant of standard therapy
- Measurable or non-measurable disease per RECIST 1.1 criteria
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Previous checkpoint inhibitor therapy allowed
- Symptomatic central nervous system (CNS) metastases (excluding leptomeningeal disease or cord compression) must have been treated and be asymptomatic for ≥ 14 days prior to treatment

Key Exclusion Criteria

- Second primary invasive malignancy not in remission for ≥ 1 year with exceptions
- Clinically significant history of autoimmune disease with exceptions
- Clinically significant pulmonary or cardiovascular compromise
- History of allogeneic bone marrow, stem cell or solid organ transplant
- Treatment with systemic cancer therapy within 4 weeks; radiation within 2 weeks; corticosteroids (greater than or equal to 10 mg prednisone or equivalent per day) or other immune suppressive drugs within 2 weeks

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