Weill Cornell Medicine

Microbiota-Derived Bile Acids Enhances T Cell-Mediated Anti-Tumor Immunity via the Androgen Receptor

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Background & Unmet Need

- Androgen receptor (AR) signaling plays a crucial role in tumor development, progression, and treatment response, particularly affecting immune checkpoint blockade efficacy
- Similarly, the gut microbiome significantly influences cancer outcomes and immunotherapy success, but the underlying molecular mechanisms remain poorly understood
- The gut microbiome produces numerous bile acids with diverse biological functions, with recent studies revealing their important immunomodulatory functions
- The relationship between microbiota-derived bile-acids and AR signaling remains unexplored
- **Unmet Need:** Novel AR antagonists are needed to overcome treatment resistance and improve cancer therapy outcomes

Technology Overview

- **The Technology:** Novel *E. coli* strains engineered to produce AR-antagonizing bile acids for treating androgen-dependent cancers
- **The Discovery:** Four previously uncharacterized microbiota-derived bile acids (including 3-oxo-Δ5-LCA, 3-oxo-Δ4-LCA, 3-oxo-Δ4,6-LCA and 3-oxo-LCA) act as potent AR antagonists
- **PoC Data:** The identified BA compounds specifically bind to AR ligand binding domain and suppress AR-dependent gene expression (Kd = 0.8-2.4 μM)
- Treatment with 3-oxo-Δ4,6-LCA reduced tumor volume by >80% and significantly decreased lung metastasis burden compared to no treatment
- 3-oxo-Δ4,6-LCA treatment increased tumor-infiltrating stem-like CD8+ T cells by 2.5-fold
- When combined with anti-PD-1 therapy, 3-oxo-Δ4,6-LCA enhanced therapeutic efficacy, leading to 90% reduction in tumor growth compared to anti-PD-1 alone

Inventors:
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Wen-Bing Jin

Patents:
PCT Application Filed

Publications:
Jin, Wen-Bing et al. *Cell.* 2025.

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Technology Applications

- Treatment of AR-dependent cancers (bladder, urothelial, prostate, kidney, or lung)
- As an adjuvants to enhance immunotherapy efficacy
- Manufacturing tool to produce bile acids with engineered *E. Coli* strains

Technology Advantages

- Naturally-derived compounds with novel mechanism of action
- Potential to overcome resistance to current AR antagonists
- Dual effect on both AR signaling and immune response

Supporting Data / Figures

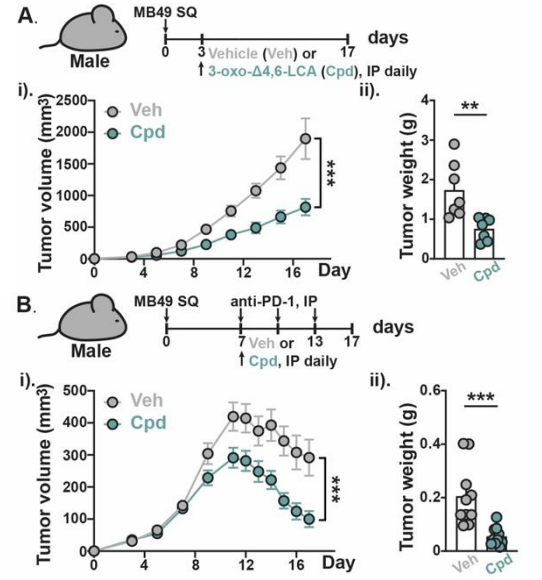

Figure 1: Microbiota-derived BA reduced bladder cancer tumor size alone (A) and with PD-1 inhibitor (B) *in vivo*.

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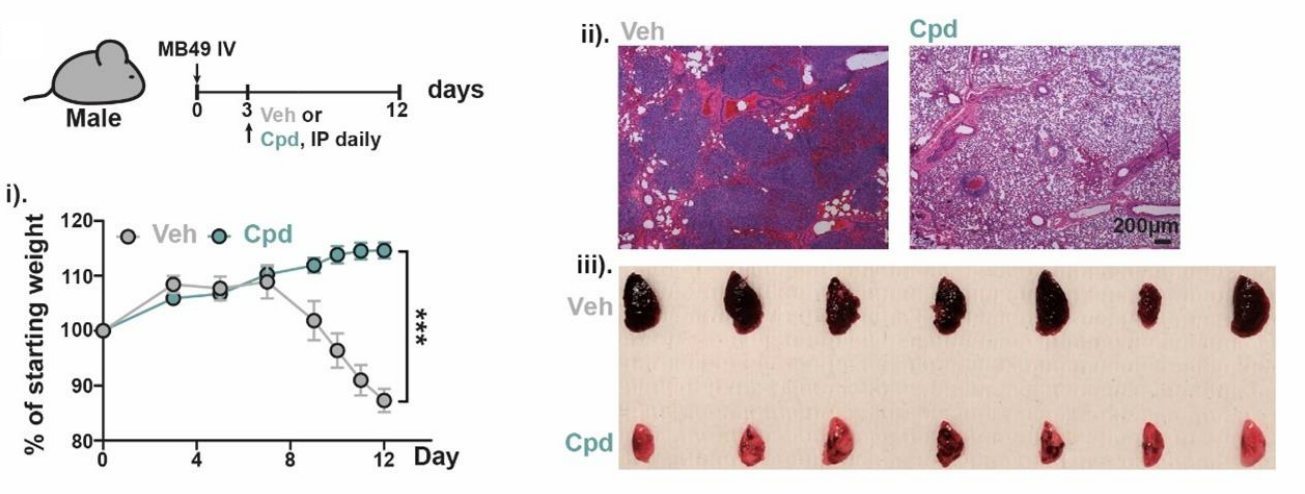

Figure 2: Novel BAs inhibits tumor metastasis as evidenced by: i) reduced weight loss, ii) decreased tumor burden in lung histology, and iii) improved lung lobe appearance

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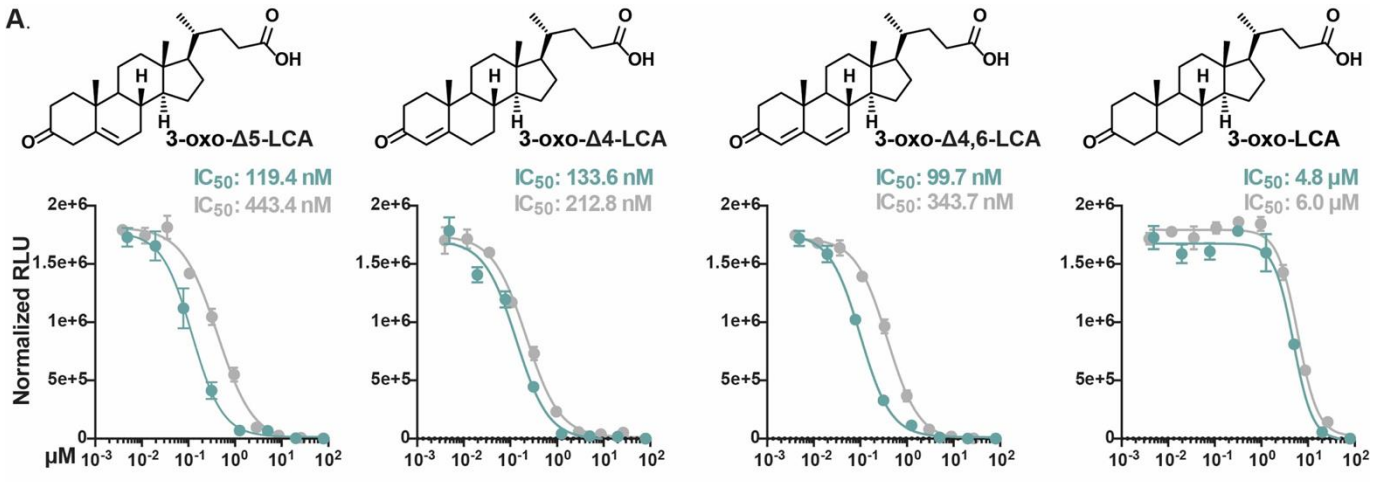

Figure 2: Microbiota-derived BAs are potent hAR antagonists.

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