Development of AU-011 for Choroidal Metastasis

Cadmus Rich, Anneli Savinainen, Rhonda Kines

Aura Biosciences, Cambridge , Massachusetts

Disclosures

- Cadmus Rich: Employee at Aura Biosciences
- Anneli Savinainen: Employee at Aura Biosciences
- Rhonda Kines: Employee at Aura Biosciences

Choroidal Metastases (C-Mets)

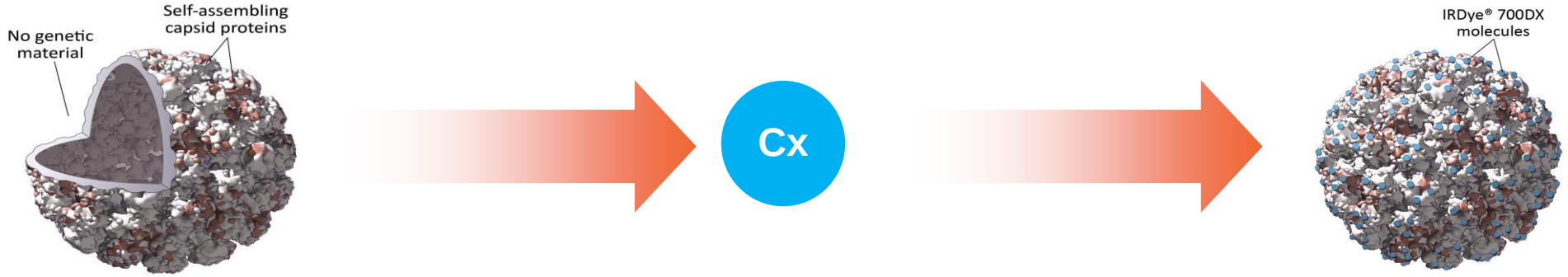
- Most common intraocular malignancy with global incidence ~ **22,000 patients/year**
  - Typical presentation – Solitary, yellow, plateau shaped lesion with subretinal fluid with less pigment than typical choroidal melanoma
  - 72% Unilateral and 72% are solitary lesions
  - Mean size: 3mm in thickness and 9mm in largest basal diameter
  - 66% diagnosed after primary cancer diagnosis
  - Primary cancer – breast 47%, lung 21%, Others (GI, kidney, skin, prostate) 14%, not established 17%

High Unmet Medical Need for A Vision Preserving Targeted Therapy

1. Shields, Ophthalmol, 1997, Survey of 520 Eyes with Uveal Metastases.

Novel Technology Platform: Virus-Like Drug Conjugates (VDCs)

Analogous to Antibody Drug Conjugates (ADCs)



Recombinant Virus- Like Particle (VLP)

Uses Virus Like Particle to Bind to Tumor Cell Surface Target

- Technology developed at NIH
- VLPs are empty modified viral capsid proteins derived from papillomaviruses
- VLPs have high specificity and multivalent binding to unique cell surface tumor target: modified HSPGs[1,2]
- Designed to spare normal tissues

Cytotoxic Drug (IRDye700Dx)

Cytotoxic Payload Delivered to Tumor Cell

- Drug activated with infrared light
- Light activation generates singlet oxygen that disrupts membrane of tumor cell leading to necrosis
- High potency with limited phototoxicity

Virus-Like Drug Conjugate (AU-011)

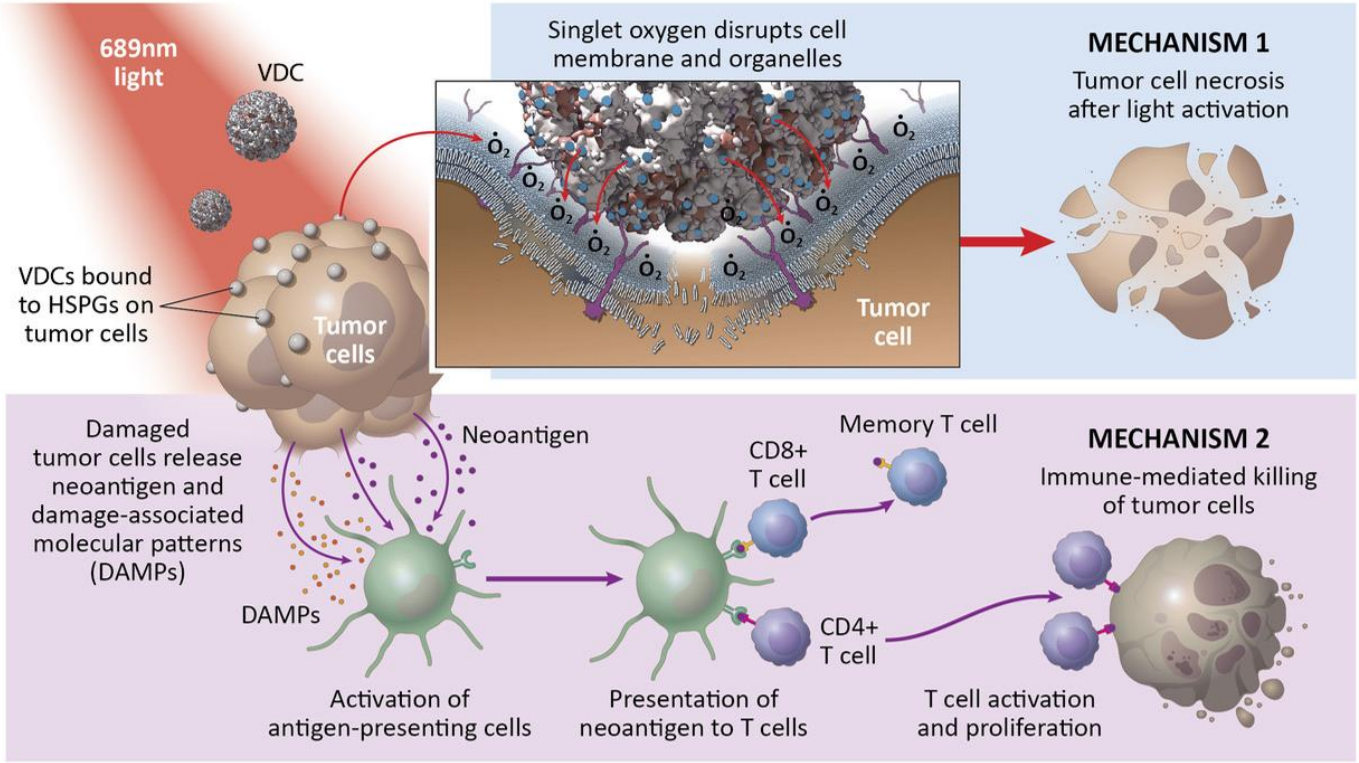
Activation of VDC with Light Selectively Kills Tumor Cell

- 200 cytotoxic molecules covalently linked to virus surface can be delivered with single VDC (vs ~4 linked to ADC)
- Activation of VDC with infrared light designed to cause acute tumor cell necrosis
- Necrosis causes a pro-immunogenic cell death that leads to T-cell activation (accpeted for publication in Cancer Immunology Research)

Technology Platform to Target Solid Tumors with Multiple Options for Cytotoxic Payloads

1. Kines et al; *International Journal of Cancer,*138;901–911, February 2016; Kines et al; *Molecular Cancer Therapeutics*, 17(2) February 2018
2. HSPGs: Heparan Sulphate Proteoglycans

AU-011 has a Novel Dual Mechanism of Action



AU-011 is designed to cause tumor cell necrosis by:

- Binding multivalently to the tumor cell surface and delivery of hundreds of cytotoxic drug molecules that upon light activation generate singlet oxygen that disrupts the membrane of the tumor cell

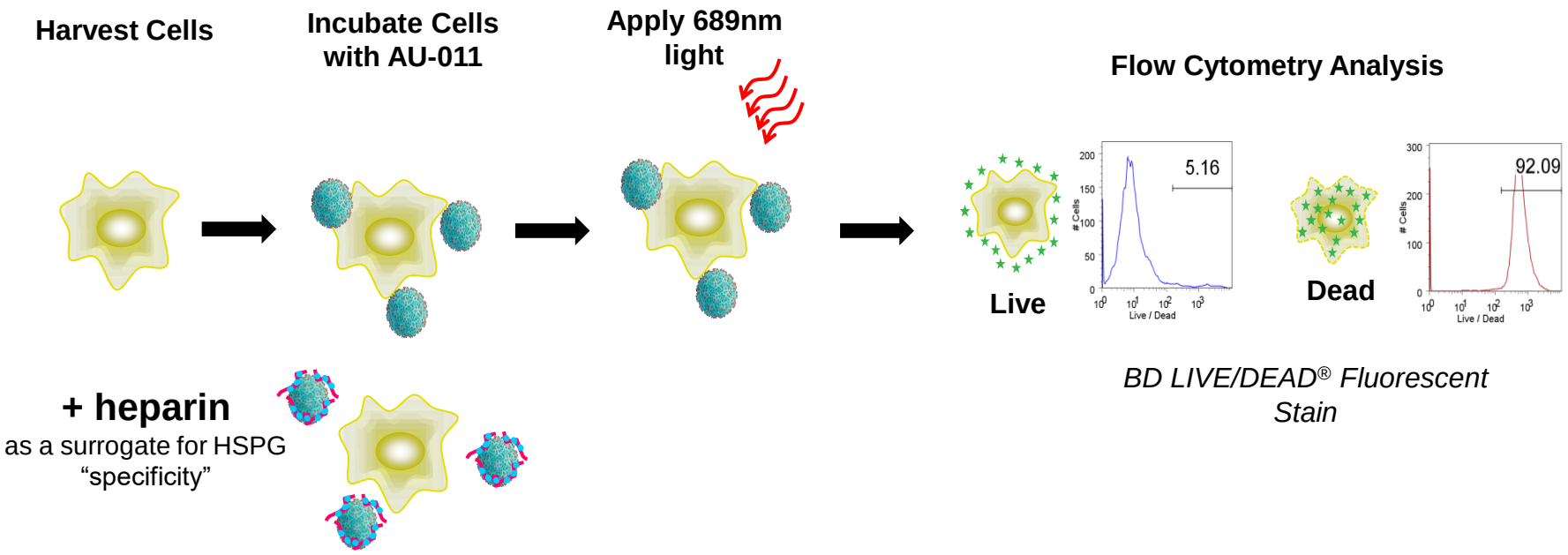
And then…

- Damaged tumor cells release neoantigens and DAMPs which communicate to the body's immune system that the cells should be removed
- T- cells are activated generating long-term anti-tumor immunity in preclinical studies

Disruption of Tumor Cell Membrane Leads to a Pro-Immunogenic, Acute Cellular Necrosis and can lead to T Cell Activation Generating a Long Term Anti-tumor Immunity*

*Accepted for Publication by *Cancer Immunology Research*

In Vitro Evaluation of AU-011 Tumor Binding and Cytotoxicity

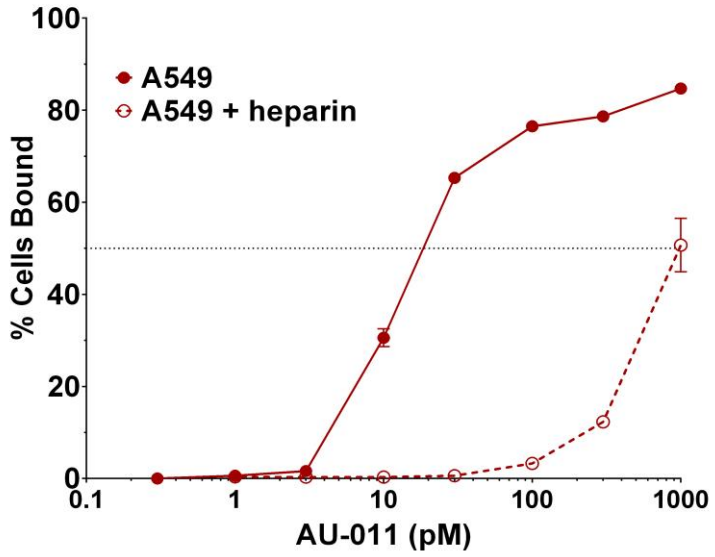


BD LIVE/DEAD® Fluorescent Stain

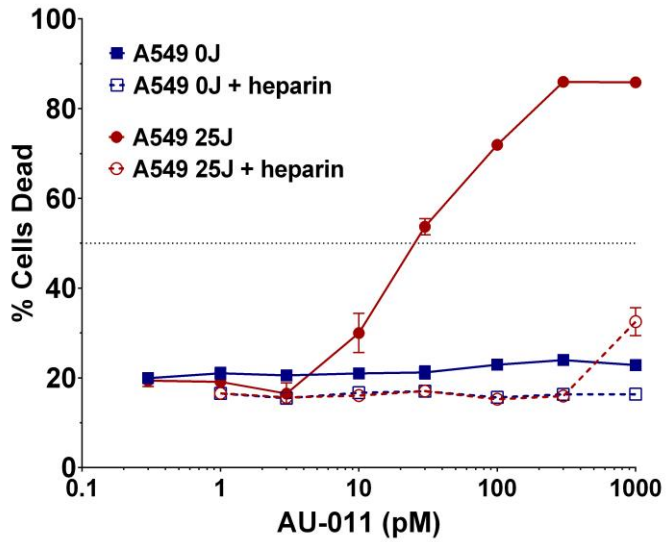
- In vitro binding and cytotoxicity was evaluated by Flow Cytometry
- Specificity was evaluated by adding heparin
  - Binding is inhibited by heparin which validates the requirement for interactions with HSPGs on the tumor cell surface which is conserved across multiple solid tumors

AU-011 has Demonstrated Binding and Potent Cytotoxicity in vitro in Lung Cancer Cell Lines

Cell Binding (A549)



Laser-induced Cellular Cytotoxicity (A549)



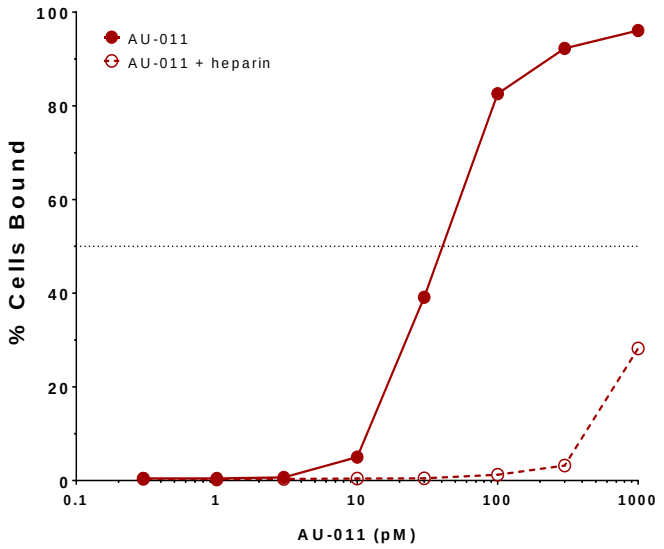
Lung Panel Summary

Cell Line	Binding EC^{50} (pM)	Killing EC^{50} (pM)
A549	13.3	30.51
NCI-H460	32.66	20.02
NCI-H23	38.29	35.81
NCI-H332M	39.29	39.93
MCI-H522	24.21	23.23

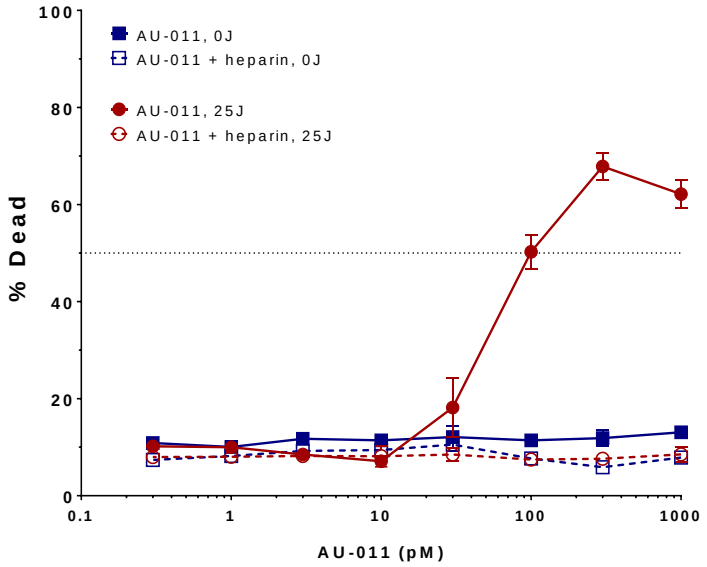
AU-011 Binds to HSPGs on the Cell Membrane of Lung Cancer Cell Lines and Induces a Potent Cell Killing Upon Light Activation

AU-011 has Demonstrated Binding and Potent Cytotoxicity in vitro in Breast Cancer Cell Lines

Cell Binding (T47D)



Laser-induced Cellular Cytotoxicity (T47D)



Breast Panel Summary

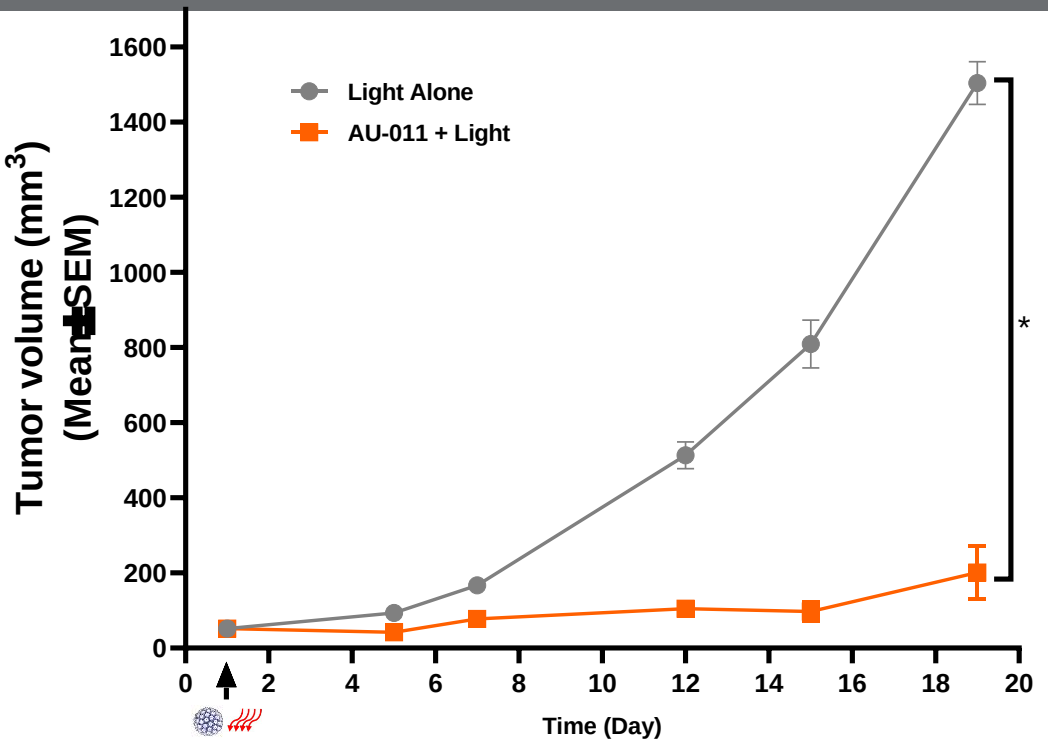
Cell Line	Binding EC^{50} (pM)	Killing EC^{50} (pM)
T47D	36.49	63.13
BT549	245.9	93.32
HS578T	50.13	57.61
MCF-7	56.08	117.9
MDA-MB-231	17.8	58.08
Mouse Cell line: EMT-6	14.0	33.27
Mouse Cell line: 4T1	36.1	39.44

AU-011 Binds to HSPGs on the Cell Membrane of Breast Cancer Cell Lines and Induces Potent Cell Killing Upon Light Activation

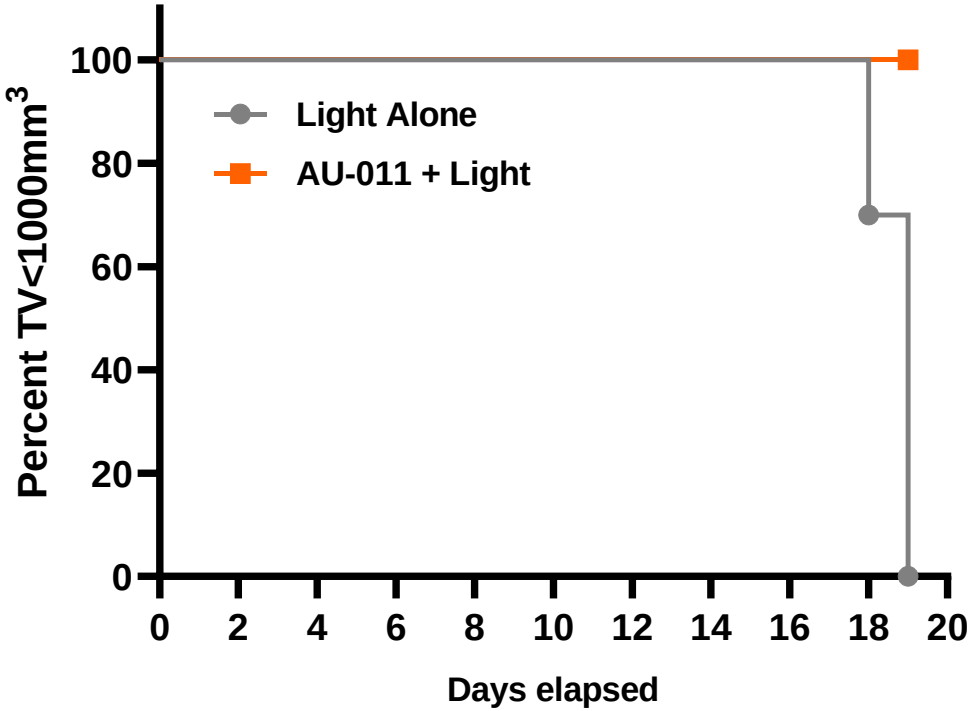
Single Administration of AU-011 Inhibited Tumor Growth and Prolonged Survival in Breast Cancer Mouse Model

Breast Cancer In-Vivo (Syngeneic Mouse Model, EMT-6)

Reduced Tumor Growth



Prolonged Survival (Endpoint: TV>1000mm^3)



- Similar qualitative results were seen in the 4T1 breast cancer cell line

Tumor cells were implanted subcutaneously. AU-011 treatment was initiated when tumors reached approximately 50 mm^3. Treatment consisted of a single intravenous administration of AU-011 (100 ug/mouse) followed 12 hours later by external exposure to near-IR light. Tumor volumes were measured over time.

Conclusion

- AU-011 shows binding and potent cytotoxicity in cell lines derived from the most common cancer types known to metastasize to the choroid: Breast and Lung
  - Potency values in the picomolar range (EC50: 17-250pM).
- AU-011 showed robust anti-tumoral activity in vivo as a single agent using cognate mouse tumor models for breast cancer (EMT-6 and 4T1)

Results Support Further Evaluation of AU-011 as a First in Class Targeted Therapy for the Treatment of Choroidal Metastasis

Contact Information

Cadmus Rich, MD, MBA

Chief Medical Officer and Head of R&D

Aura Biosciences

crich@aurabiosciences.com