Biomaterials for Targeted Drug Delivery

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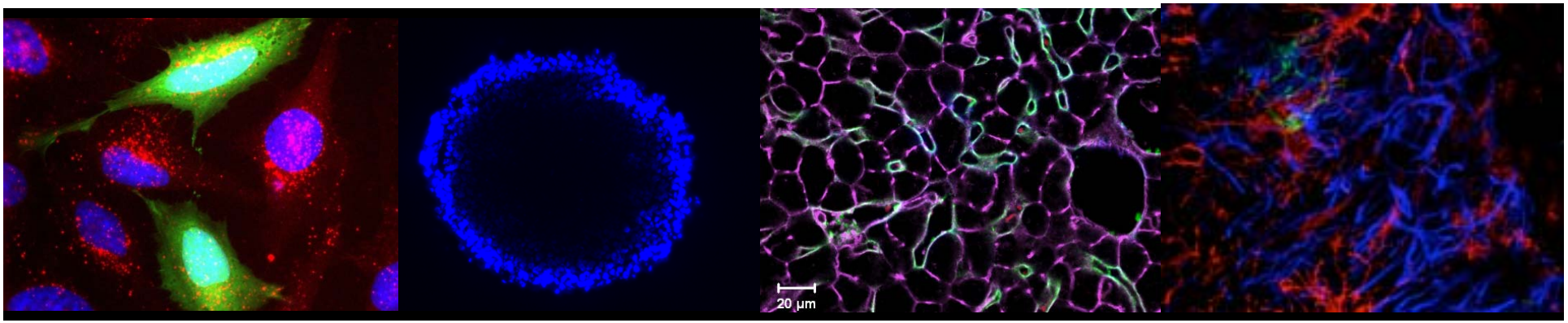


2014 Indo-American Frontiers of Engineering Symposium
May 19-21, 2014

Roadmap

Drug Targeting for Cancer

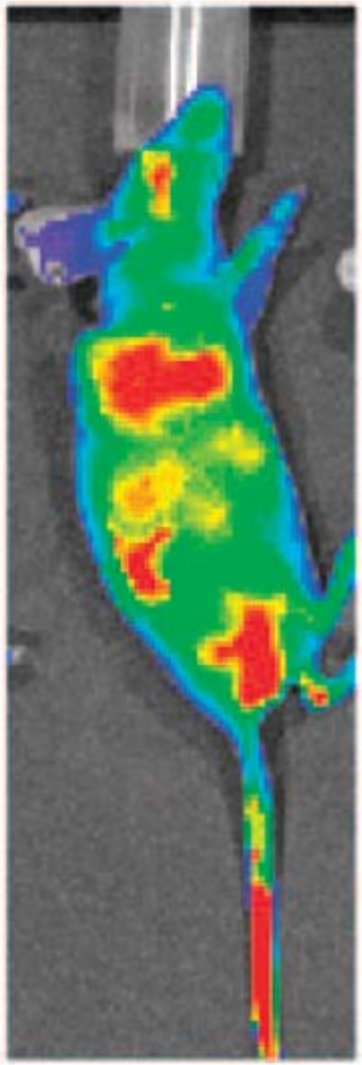
Passive Targeting Examples

Active Targeting Example

Looking ahead

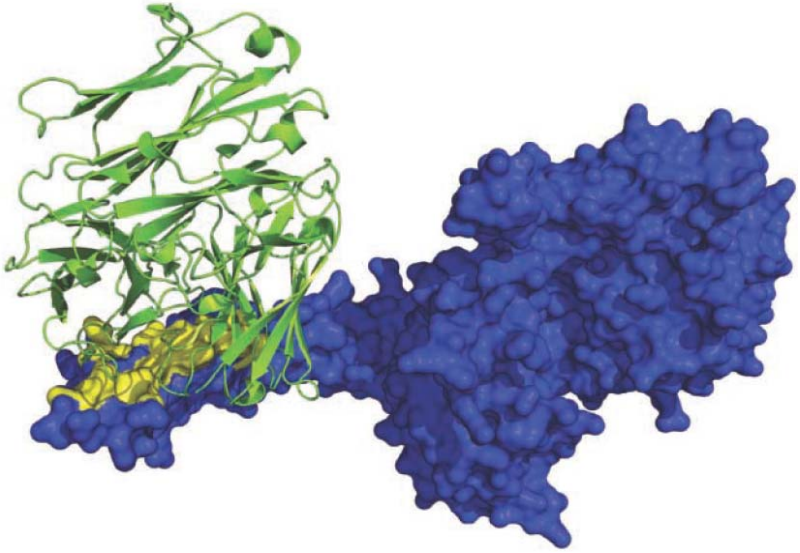
Introduction: Drugs

Pre-i.v.



15 min post i.v.

Protein therapeutics



<10% of all human proteins are cell surface or secreted.

… "disheartening revelation that the majority of all existing targets, as high as 75% to 80% are beyond the reach of these two established classes of drugs…"

Verdine and Walensky (2007)

Introduction: Drug Targeting for Cancer

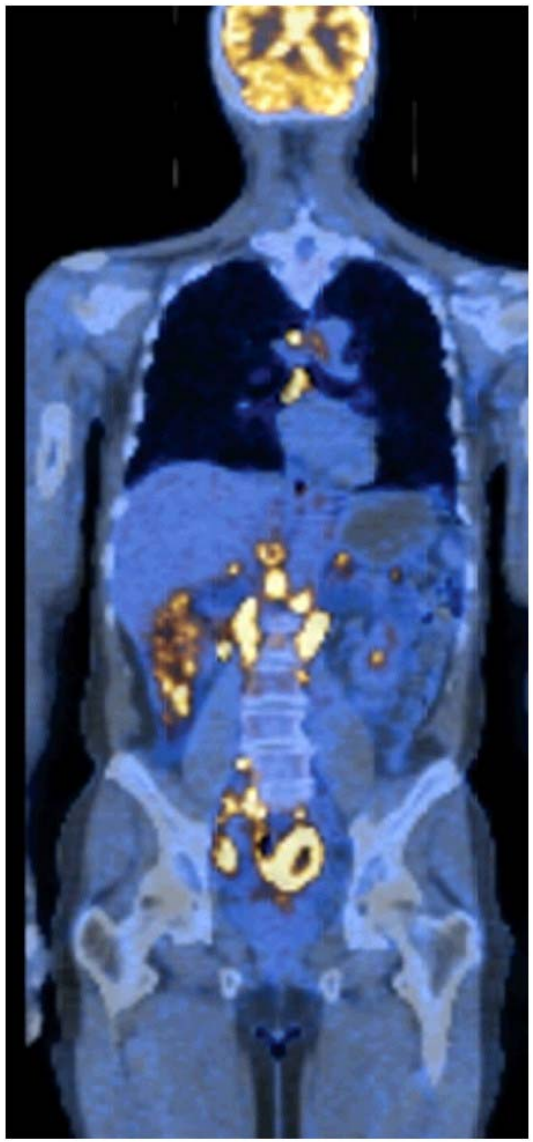


Figure 14.1 The Biology of Cancer (© Garland Science 2014)

Needs:

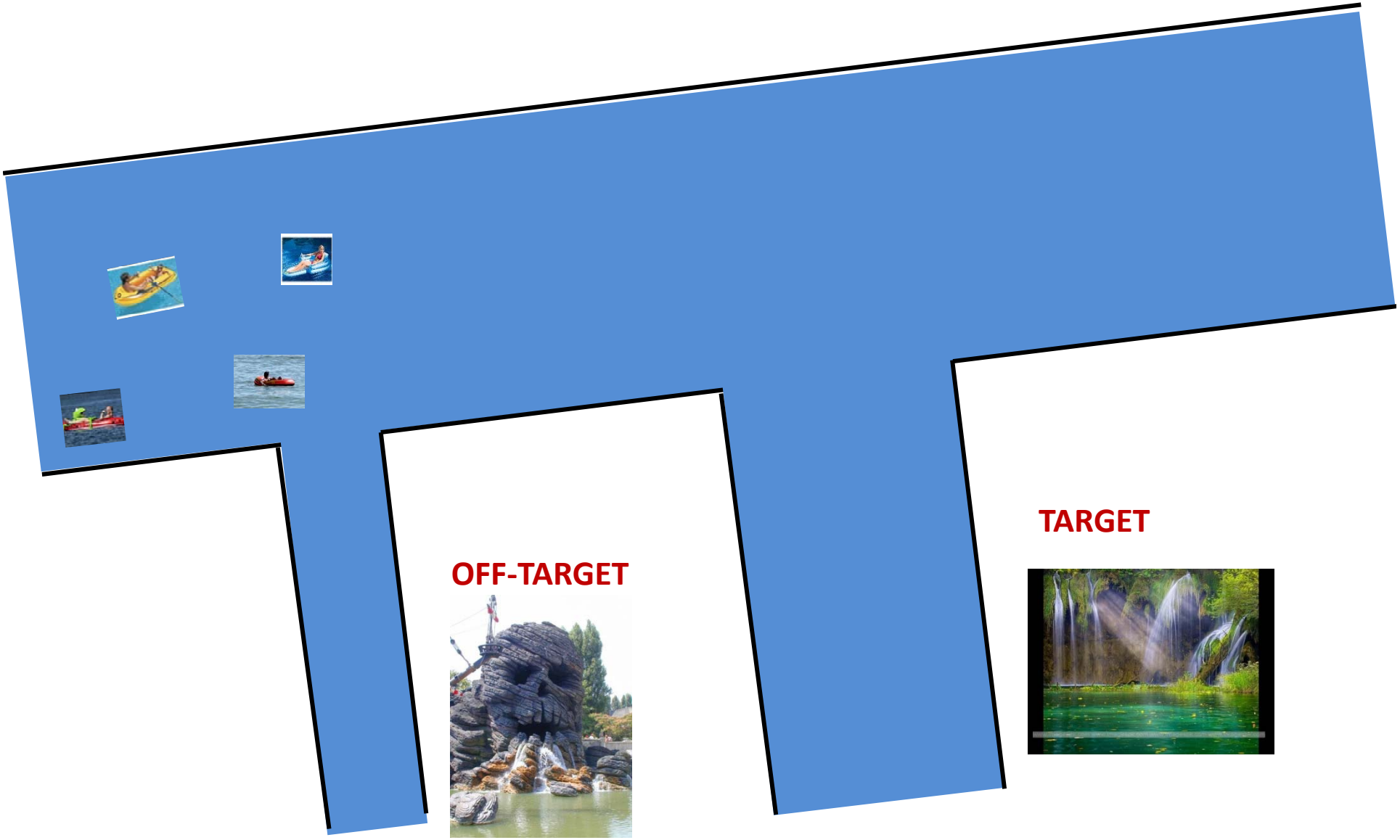
1. Delivery of drug via bloodstream

2. Minimize delivery to off-target tissues

3. Effectively reach cancerous cells

4. Facilitate drug transport into cells (for large molecular weight drugs)

Introduction: Passive vs. Active Targeting



OFF-TARGET

TARGET

Introduction: Passive vs. Active Targeting

Introduction: Passive vs. Active Targeting

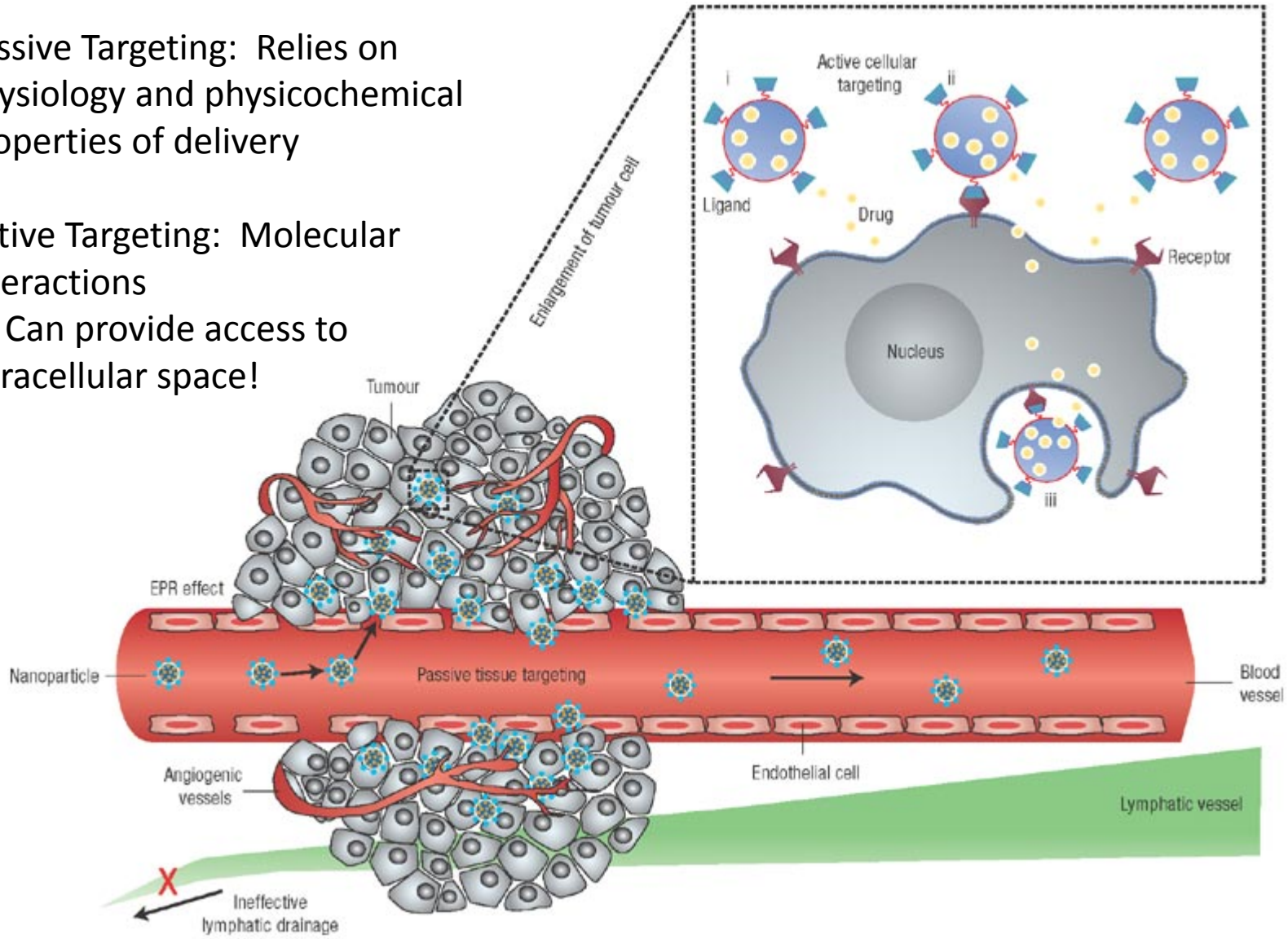
TARGET

OFF-TARGET

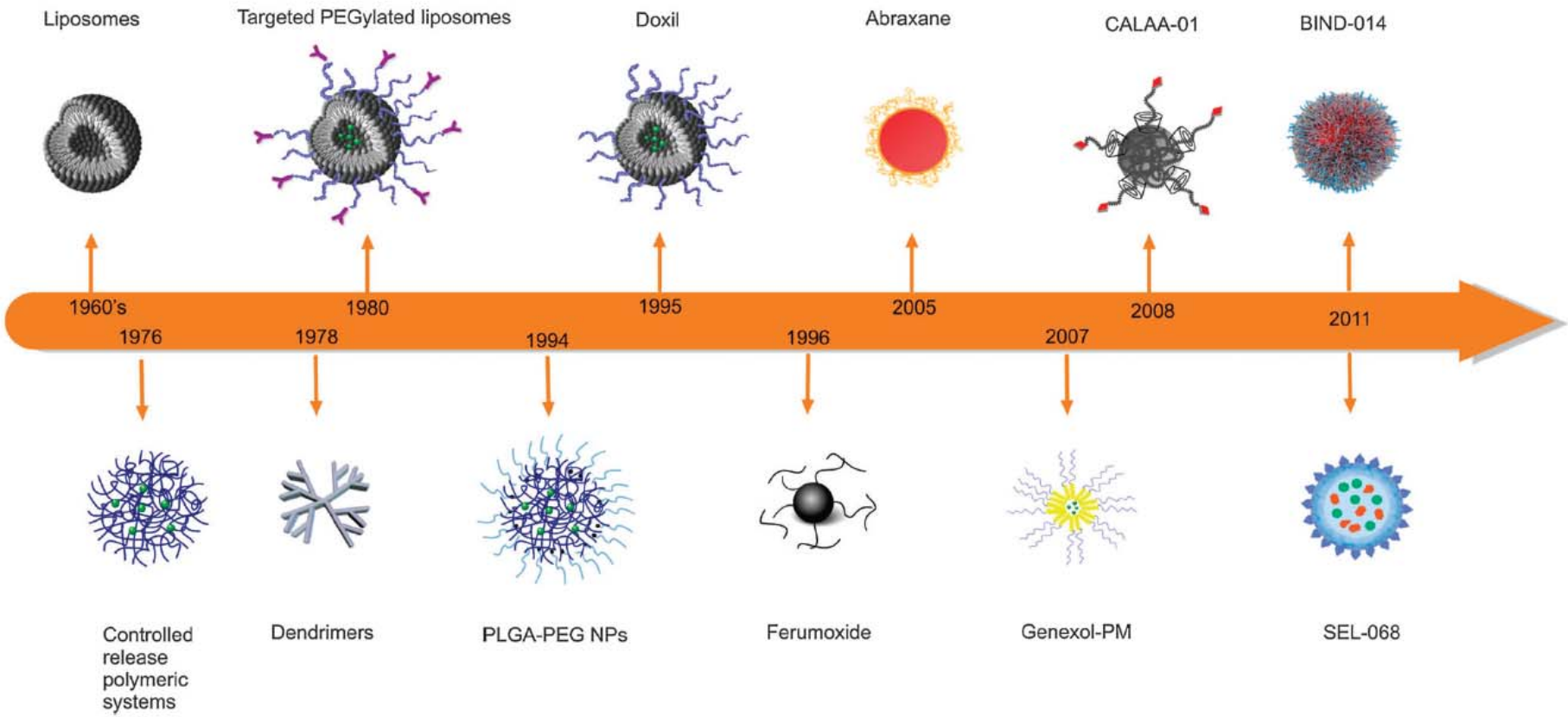
Introduction: Passive vs. Active Targeting

Passive Targeting: Relies on physiology and physicochemical properties of delivery

Active Targeting: Molecular Interactions
→ Can provide access to intracellular space!

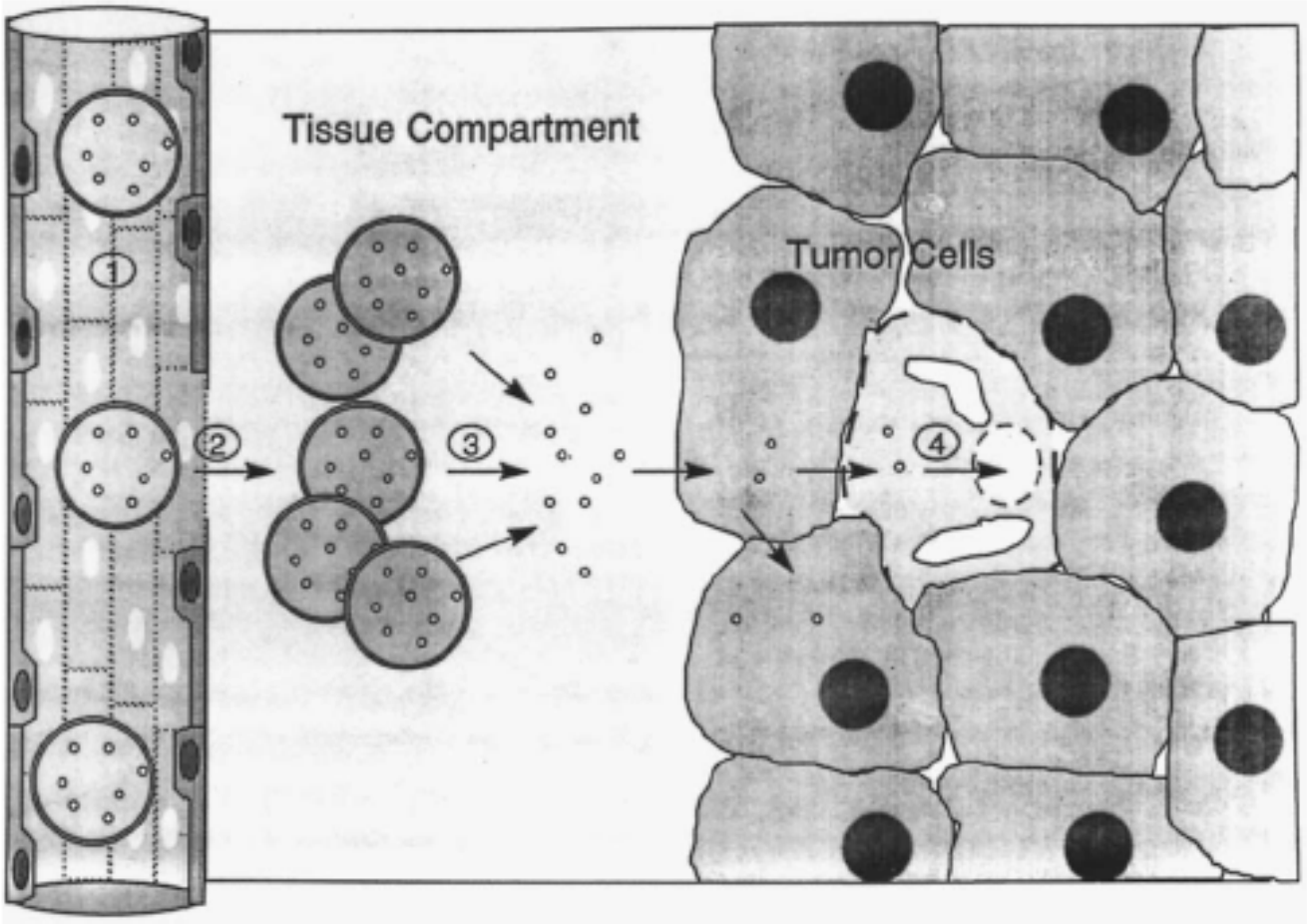


Passive Targeting: Nanoparticle Formulations



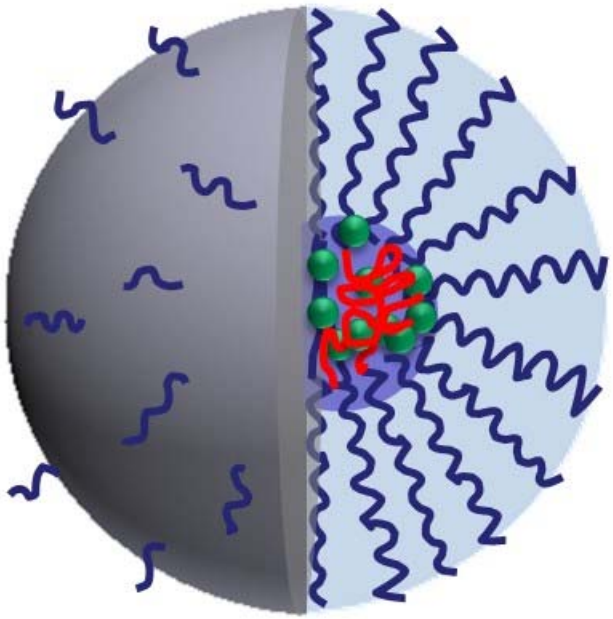
Kamaly et al. *Chem Soc Rev* 2012 v41:2971

Passive Targeting: DOXIL



Martin, F.J. Clinical Pharmacology and Anti-Tumor Efficacy of Doxil (Pegylated Liposomal Doxorubicin). In *Medical Applications of Liposomes*; Lasic, D.D., Papahadjopoulos, D., Eds.; Elsevier: New York, 1998; 638.

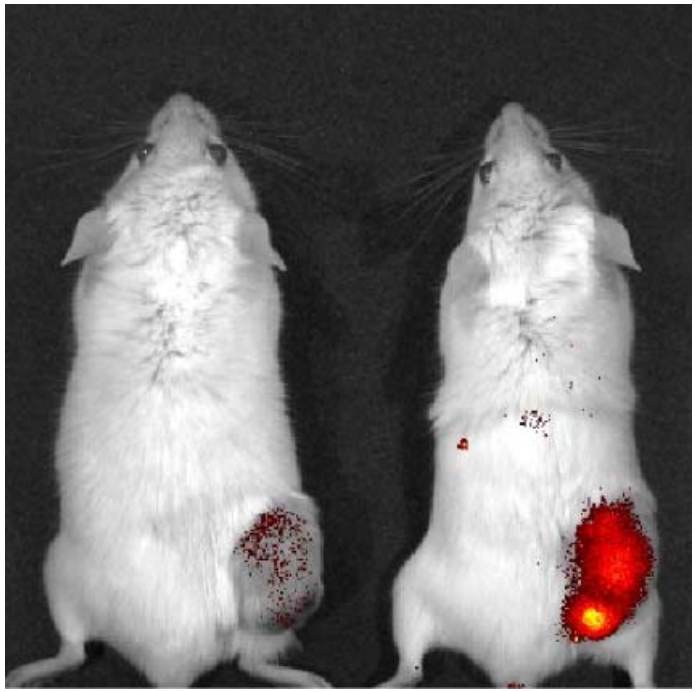
Passive Targeting: Polymer Micelles



ICG
(NIR dye)

Free ICG

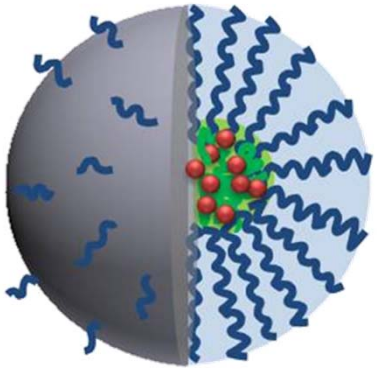
ICG-loaded micelles



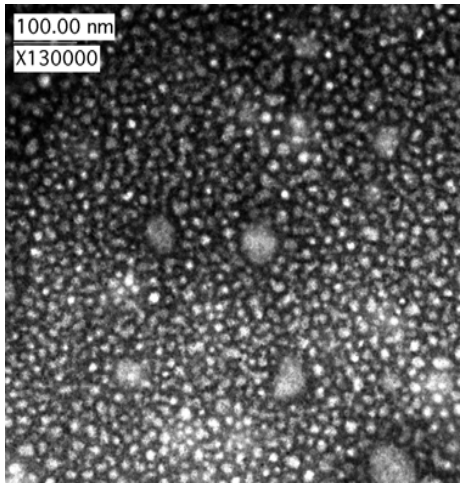
Fluorescence

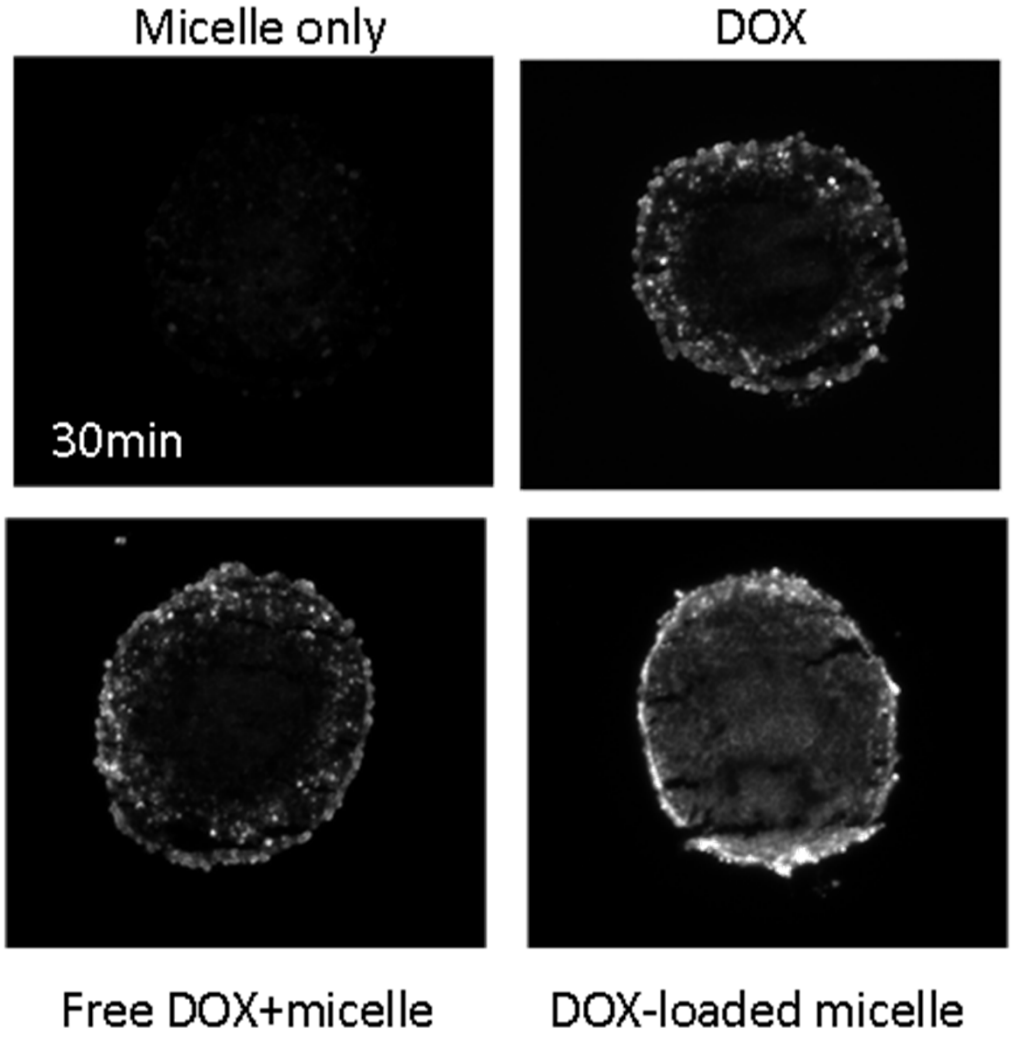
36 hrs after injection

Passive Targeting: Polymer Micelles



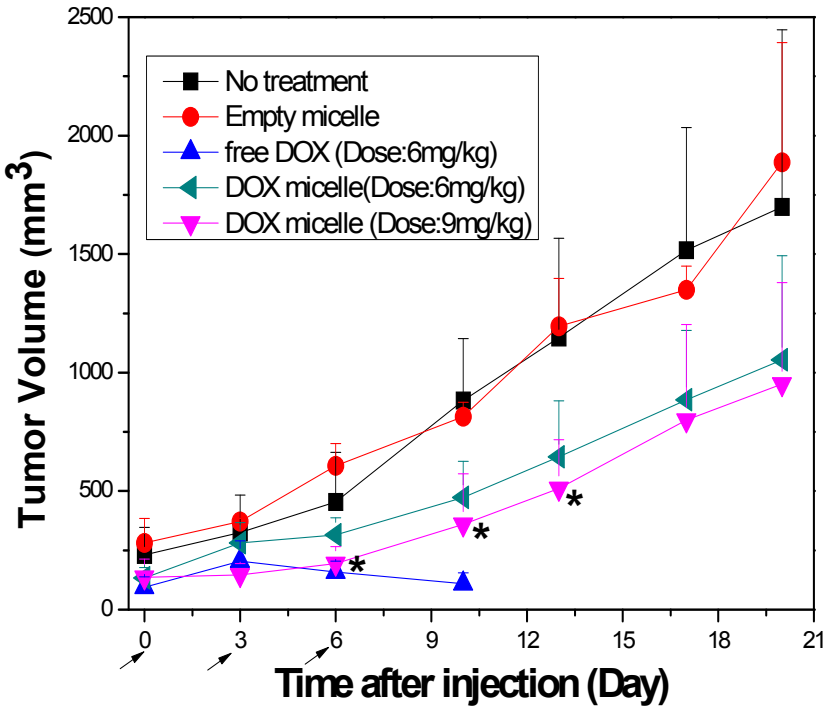
DOX encapsulated
PEO-PHB-PEO micelle
(~30-40 nm)



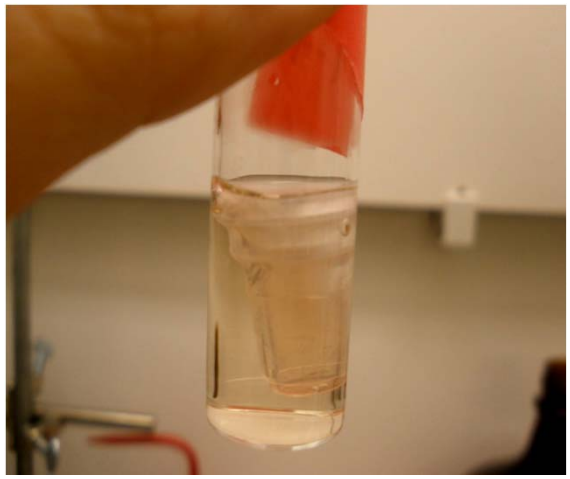


Kim TH et al., *Biomaterials* 2010, 31, 7386-97

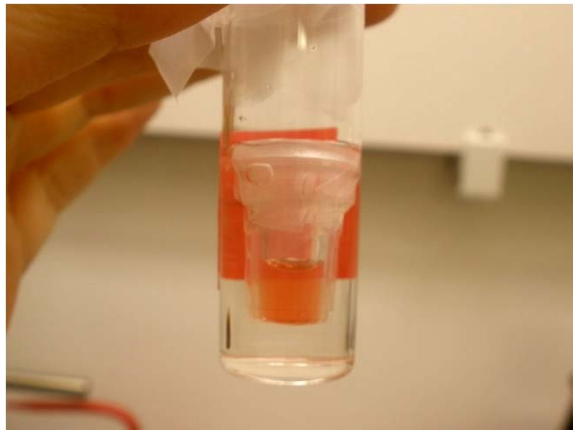
Passive Targeting: Polymer Micelles



Free DOX

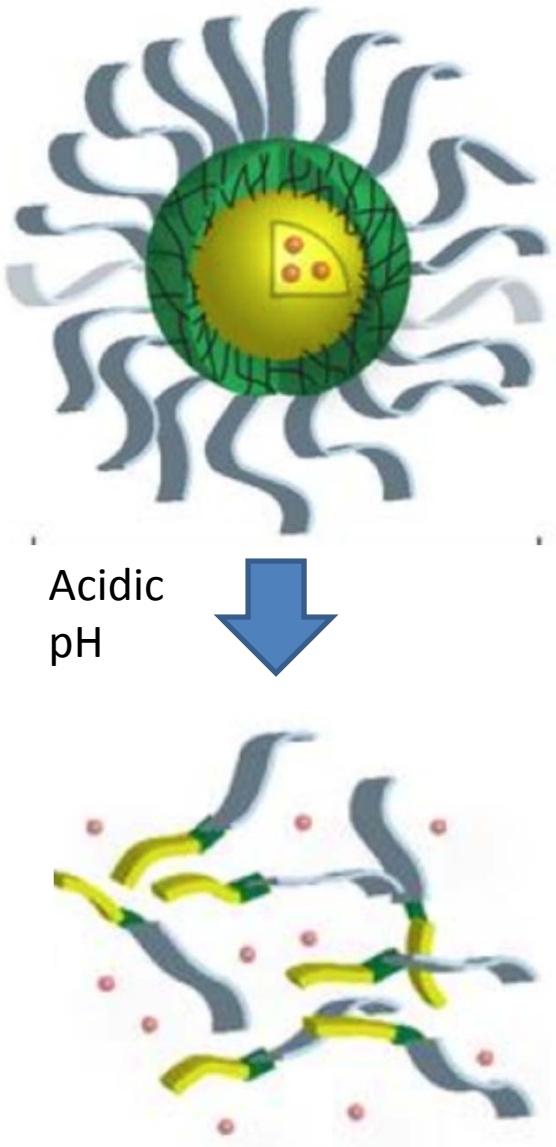


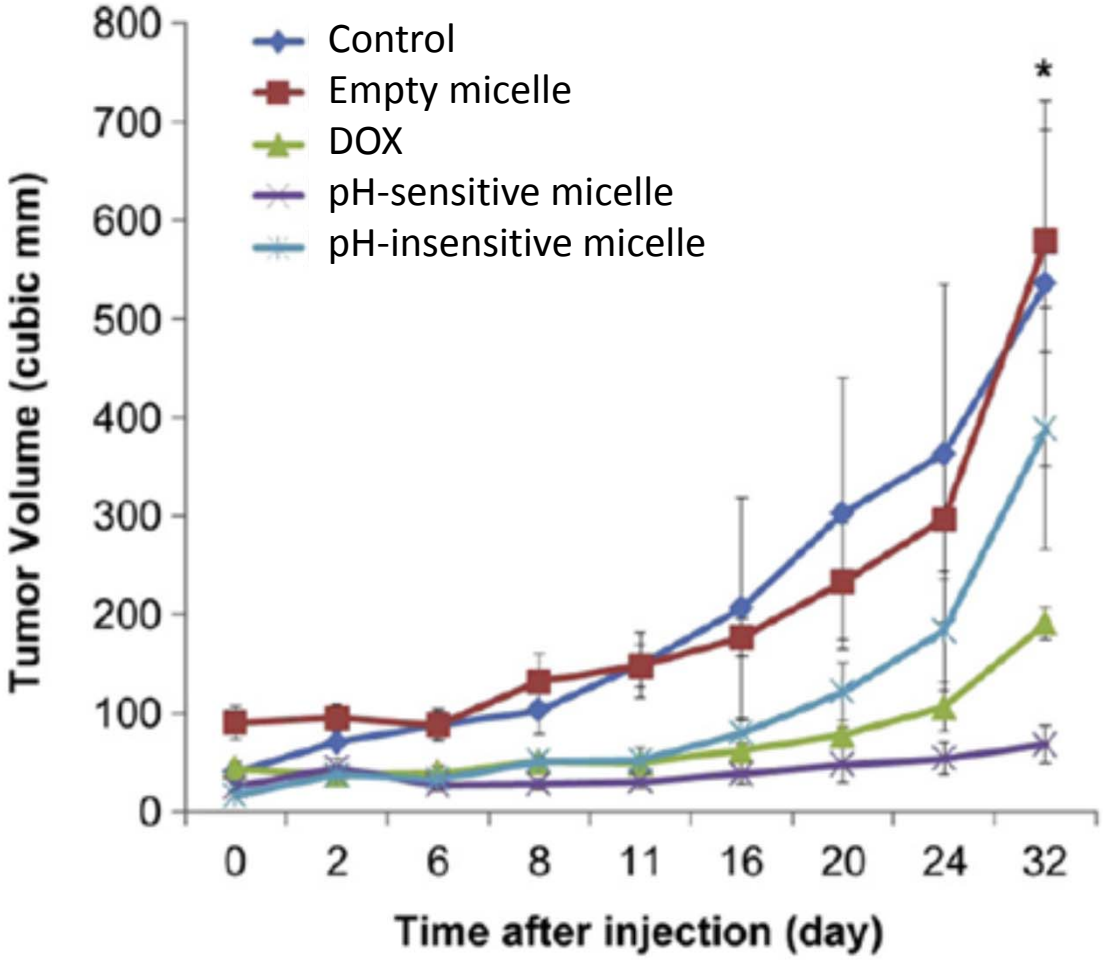
DOX-micelle



Kim TH et al., *Biomaterials* 2010, 31, 7386-97

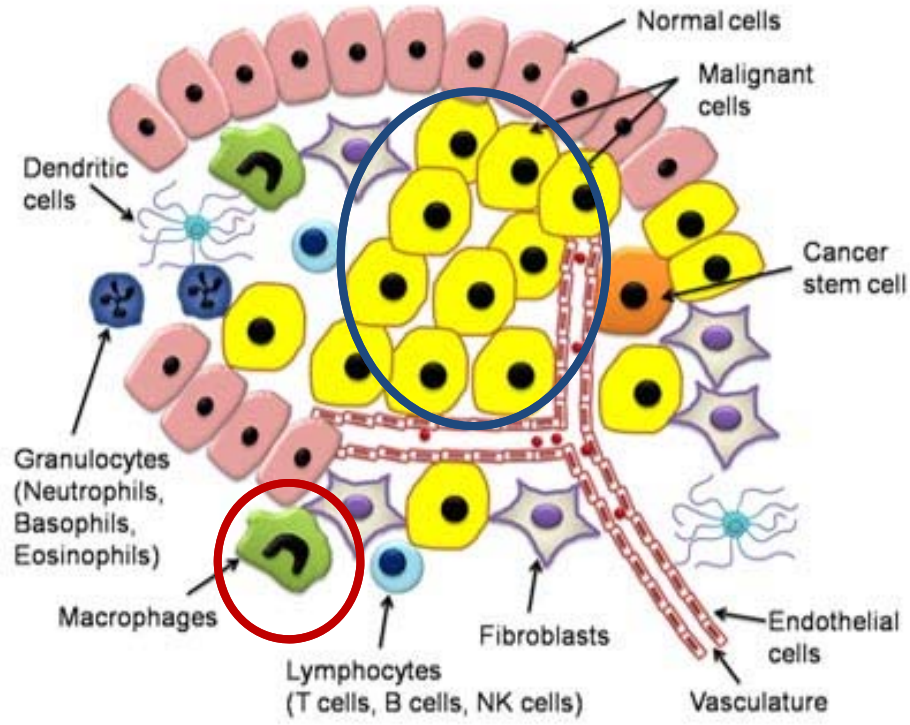
Passive Targeting: Polymer Micelles





Chen et al., *Biomaterials* 2013, 34, 3501;
With Jen group, UW Materials Science

Active Targeting:
Delivery to Tumor-associated macrophage



Cancer Cells

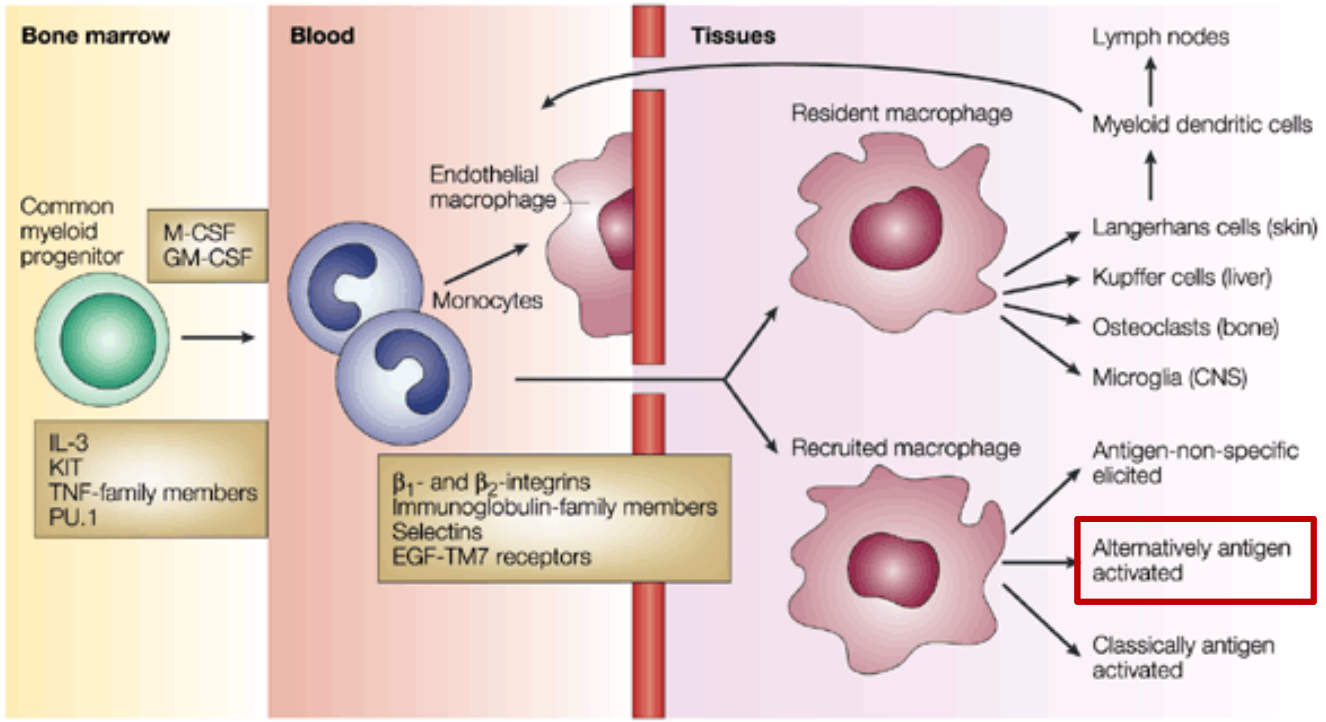
- Responsive to chemotherapy
- Changing and evolving

Tumor-associated Macrophage (TAM)

- Promote tumor growth and metastasis
- Help tumors evade immune system
- Aid chemotherapy resistance of tumors

Goal: To develop TAM-targeted therapies that potentiate chemotherapy

Active Targeting:
How to target TAMs?

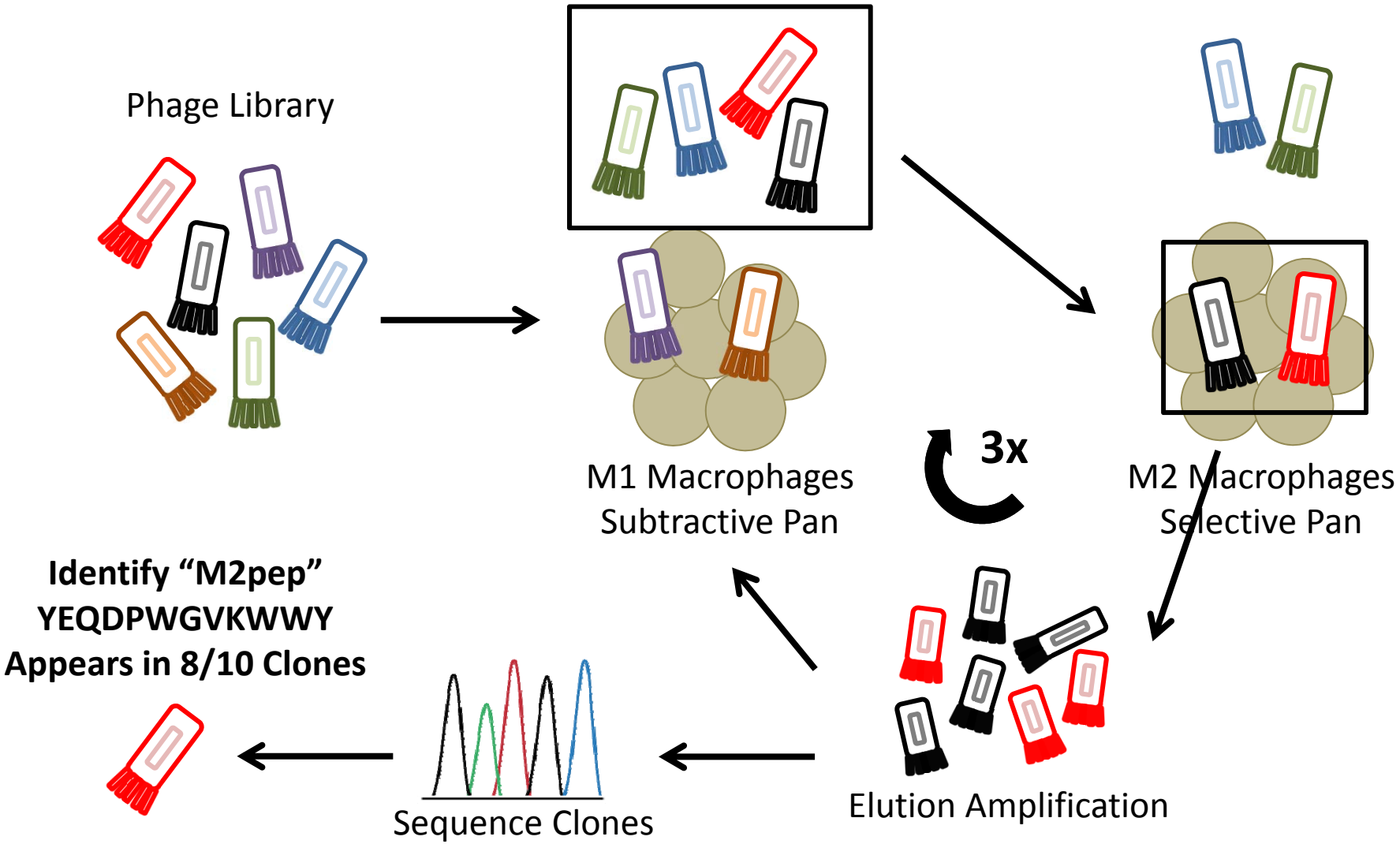


"M2"

"M1"

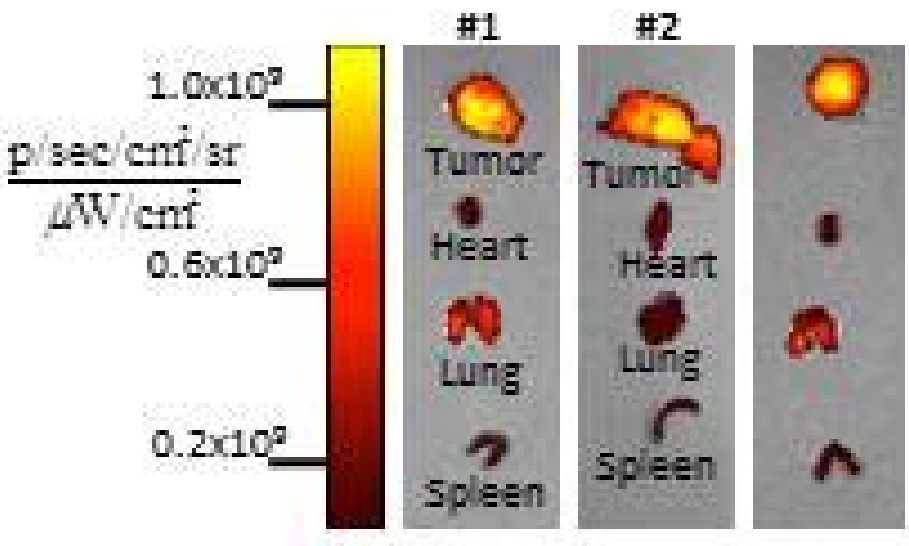
How can we engineer a system that selectively destroys a sub-population of macrophages?

Active Targeting:
Identification of targeting ligand

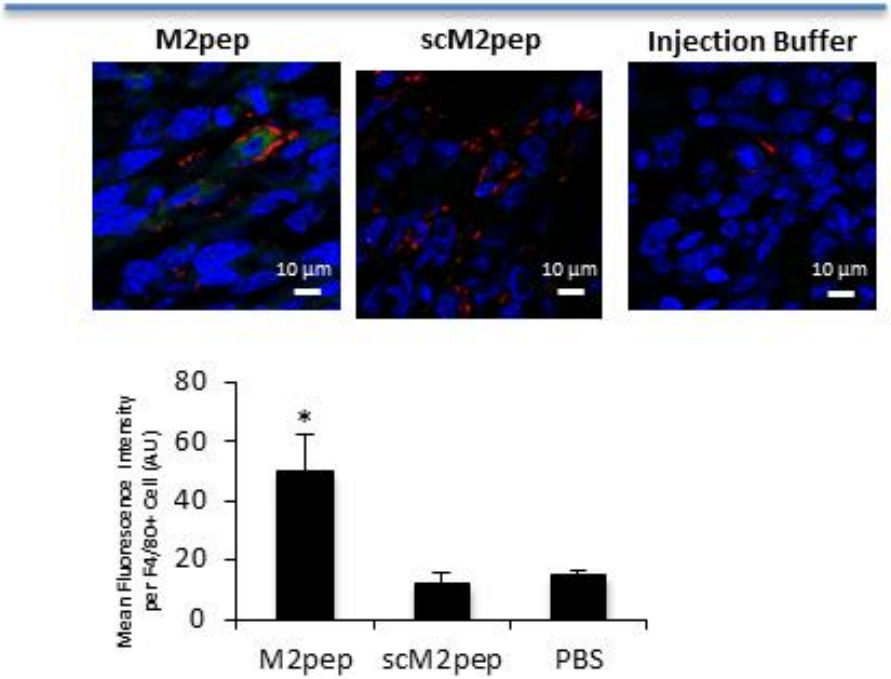


Active Targeting:
Delivery to Tumor-associated macrophage

Xenogen imaging of organs from injected mice



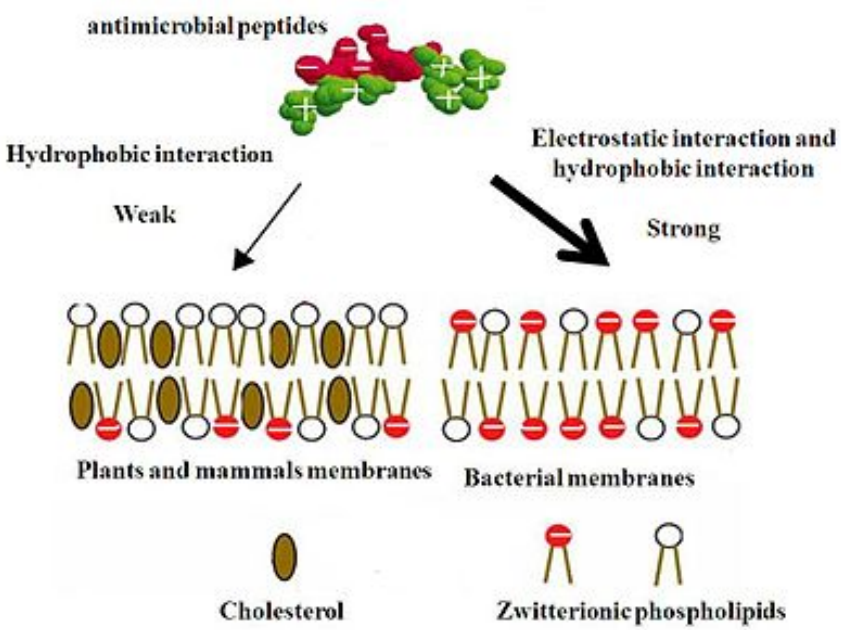
Confocal Microscopy of tumors from injected animals

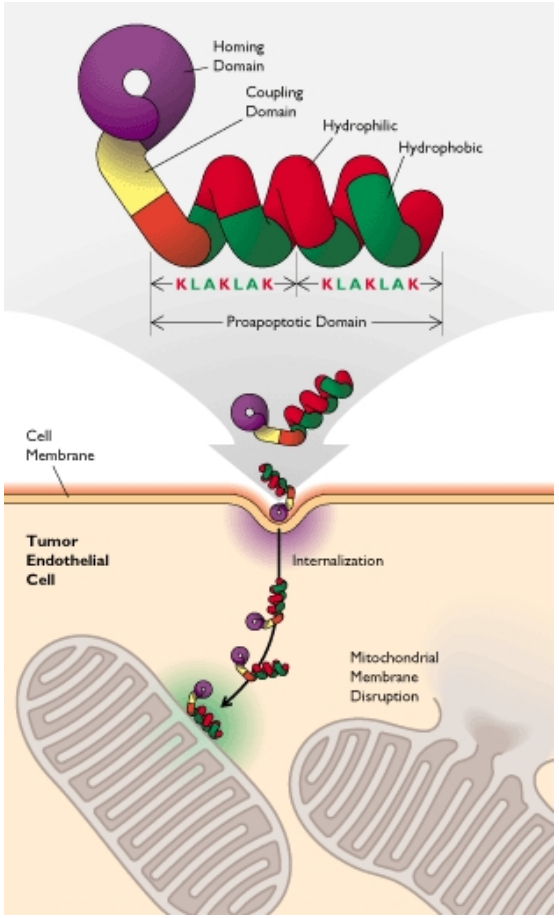


Cieslewicz, et al. (2013) *PNAS* v110:15919-24

Active Targeting:
Delivery to Tumor-associated macrophage

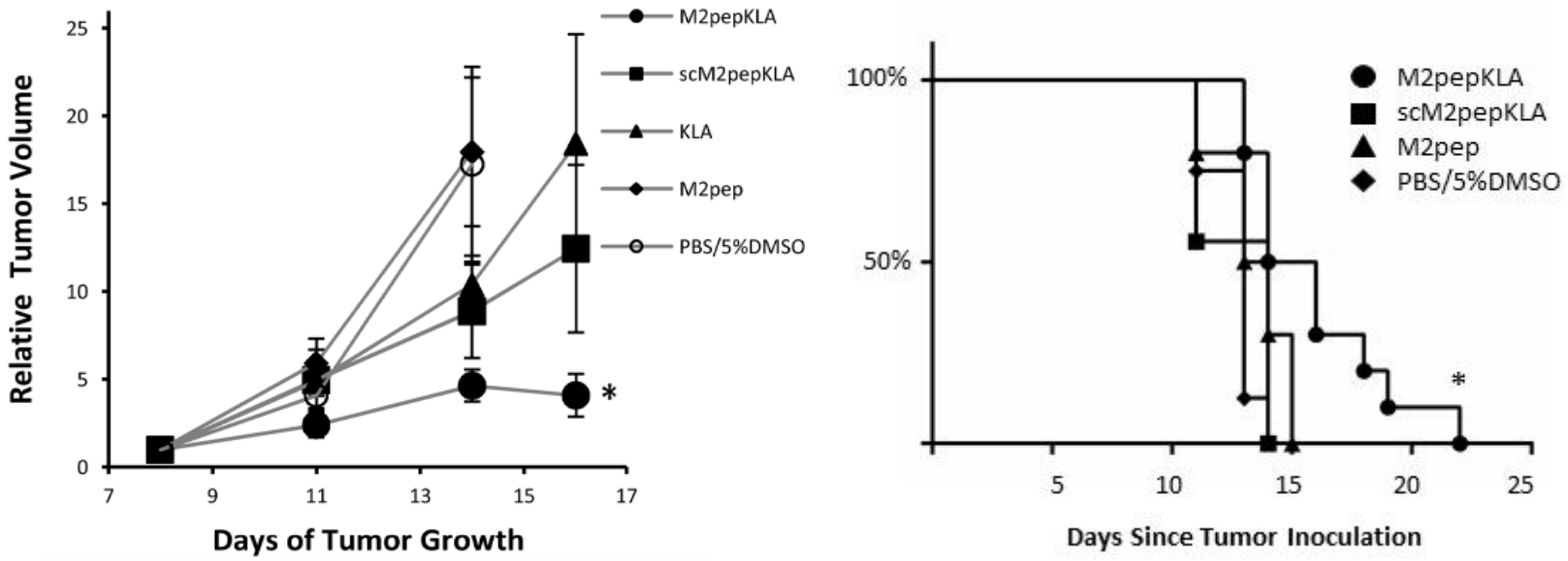
Cytotoxic peptides





Ellerby (1999) Nat Med v5:1032

Active Targeting:
Tumor reduction studies



Three intravenous injections of peptide

Cieslewicz, et al. (2013) *PNAS* v110:15919-24

Future Opportunities and Challenges

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Andre Lieber (Med Genetics)
Elaine Raines (Pathology)
Pat Stayton(BioE)
Tony Convertine (BioE)

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