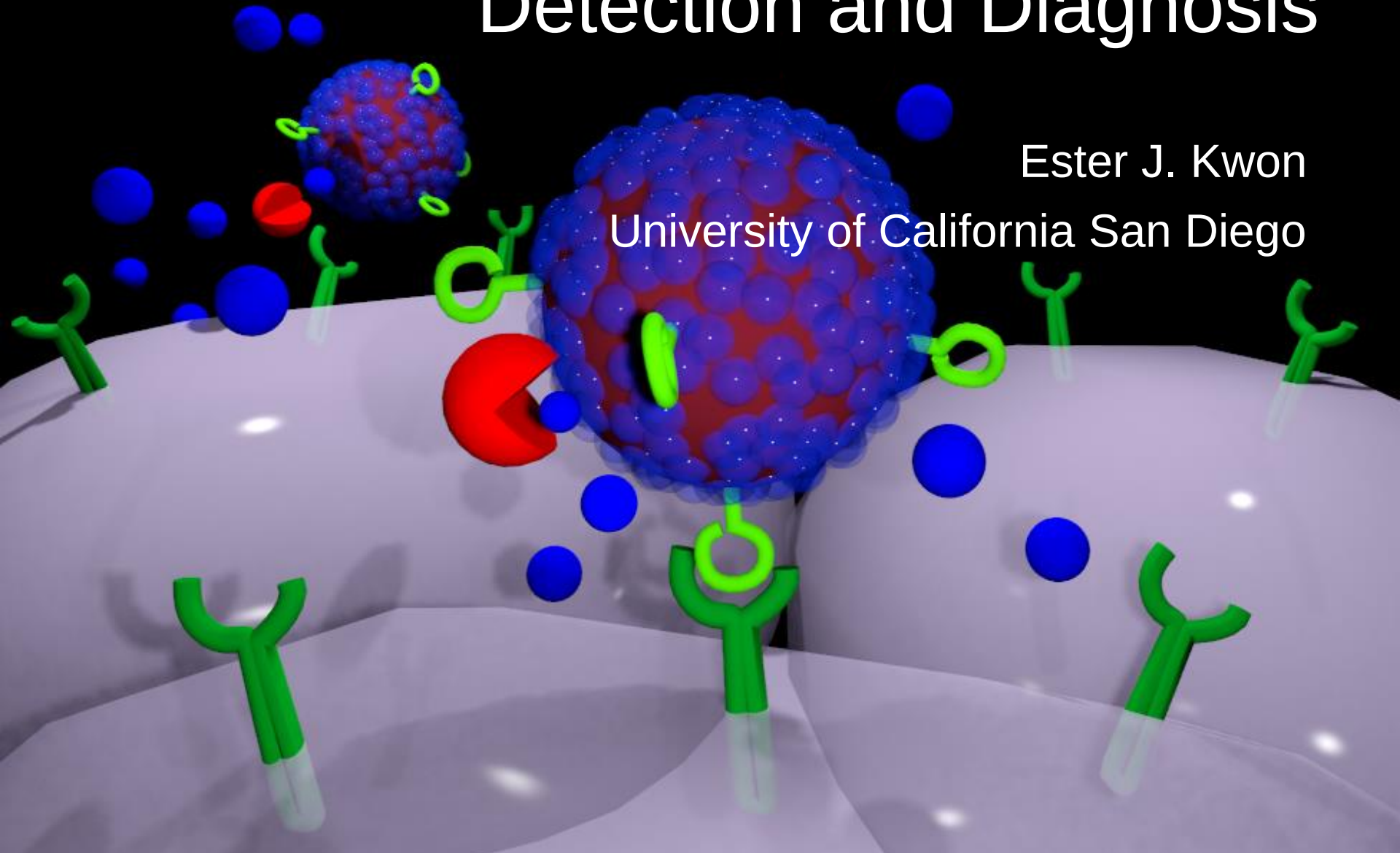
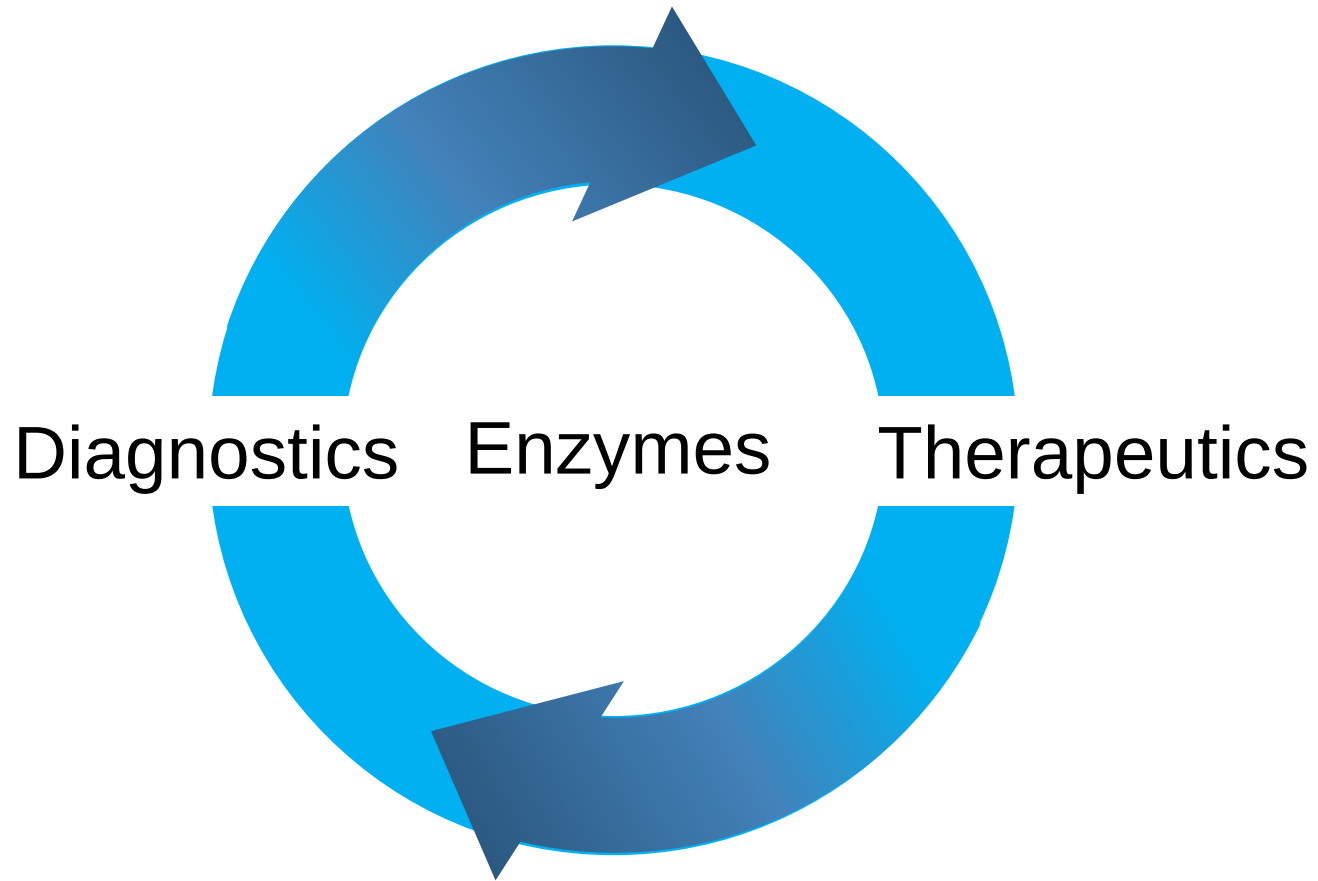


Synthetic Biomarkers for Cancer Detection and Diagnosis

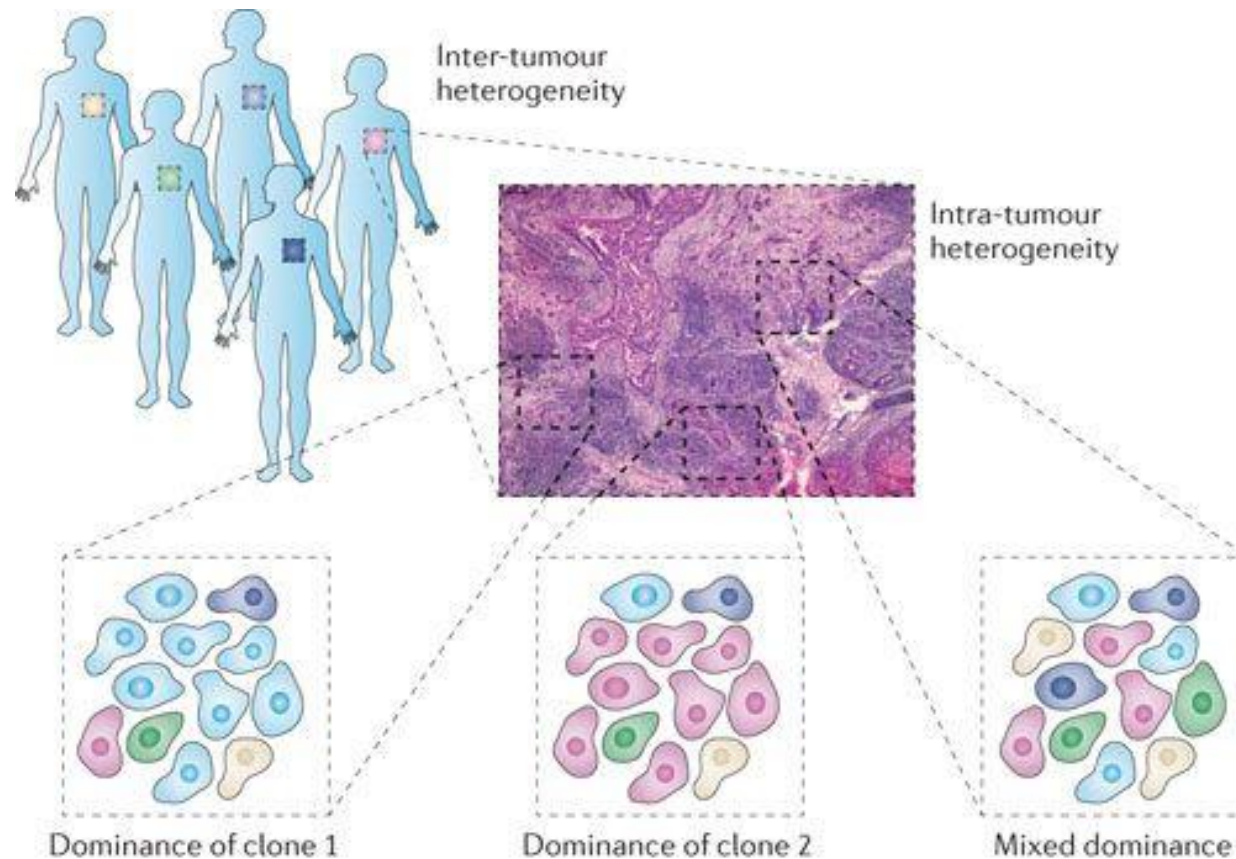
Ester J. Kwon

University of California San Diego

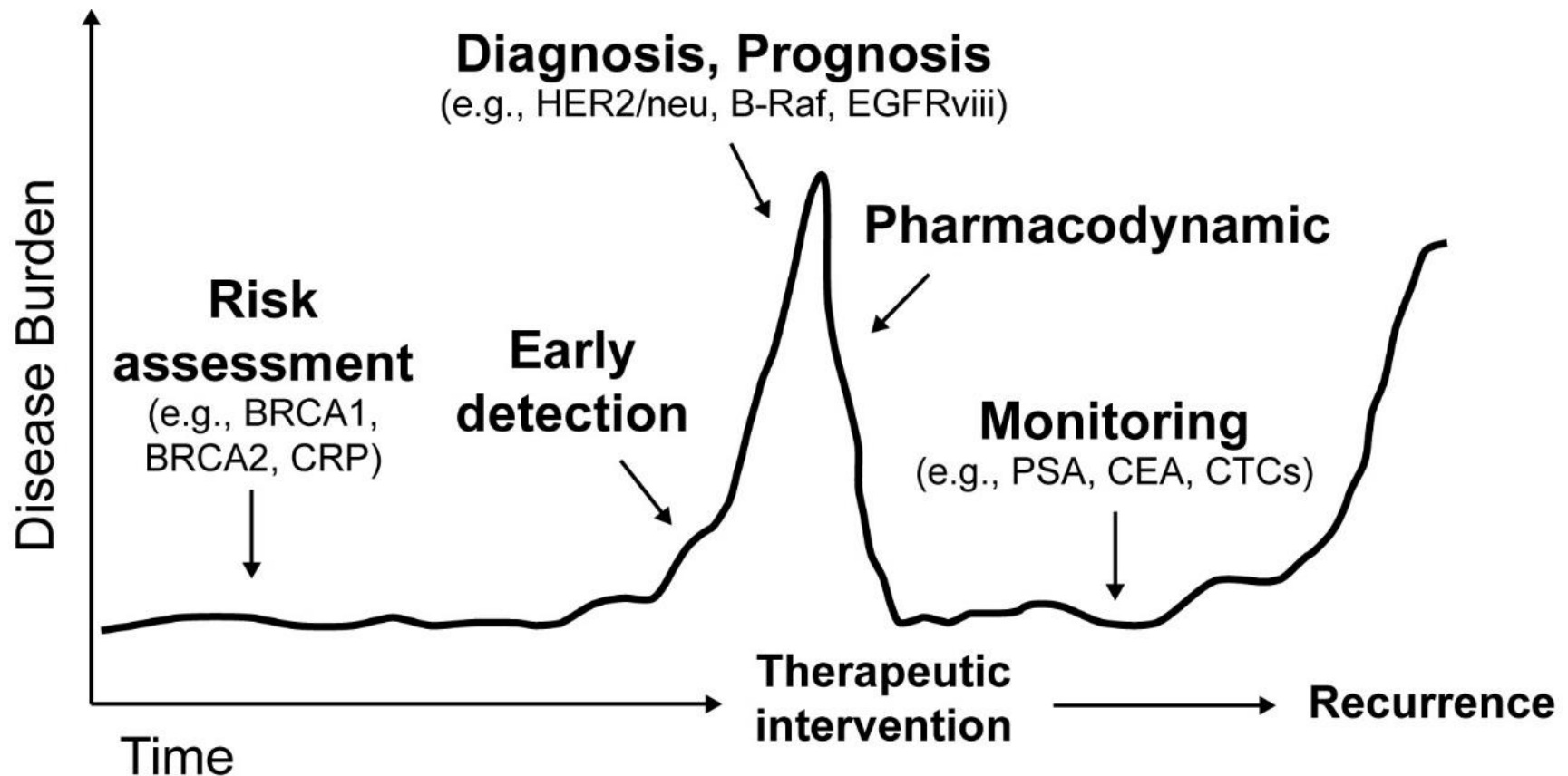




Cancer is a heterogeneous disease

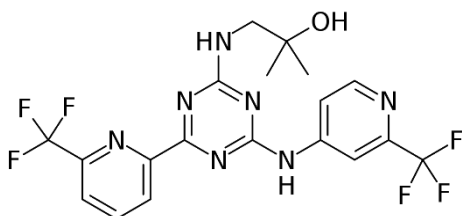


Cancer evolves over time and interventions

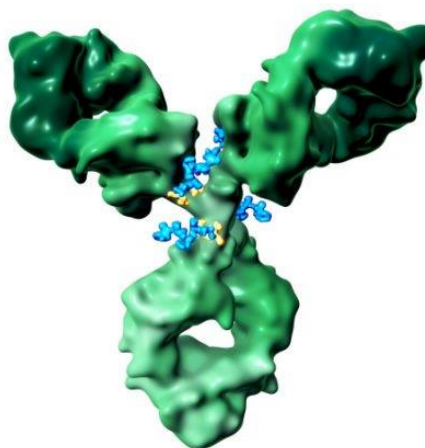


Cancer drugs are becoming more specific

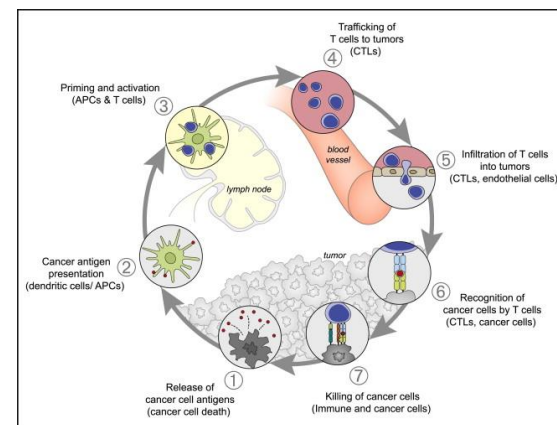
Small molecule therapies



Antibody-drug conjugates



Cancer immunotherapy



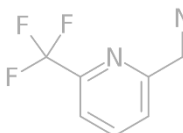
Chen & Mellman, Immunity 2013



KEYTRUDA®
(pembrolizumab) for Injection 50 mg

Cancer drugs are becoming more specific

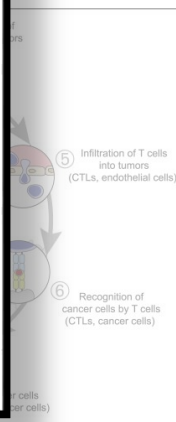
Small molecule



Theranostics

How do we decide which patient gets what treatment and at what time?

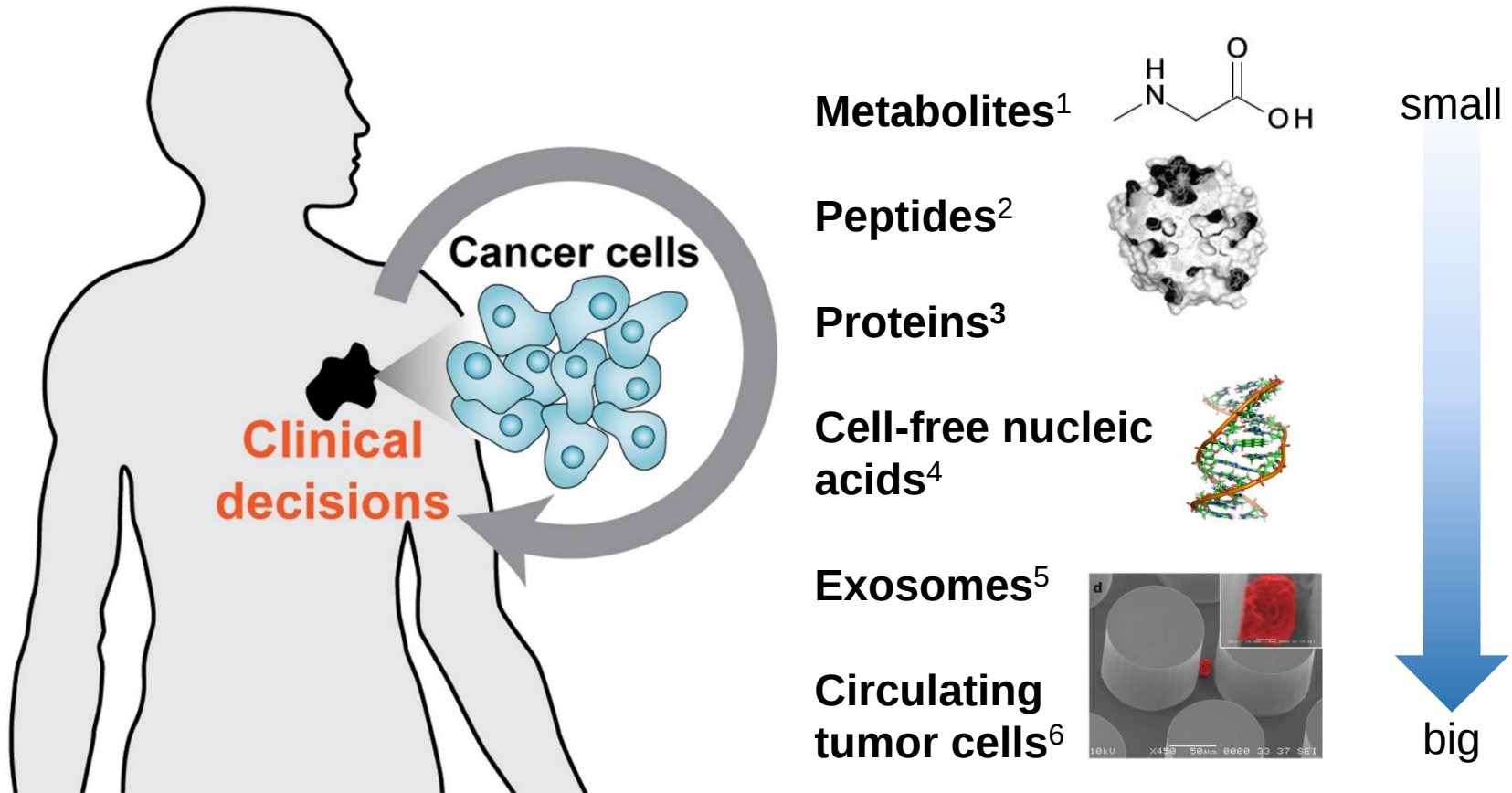
therapy



Chen & Mellman, Immunity 2013



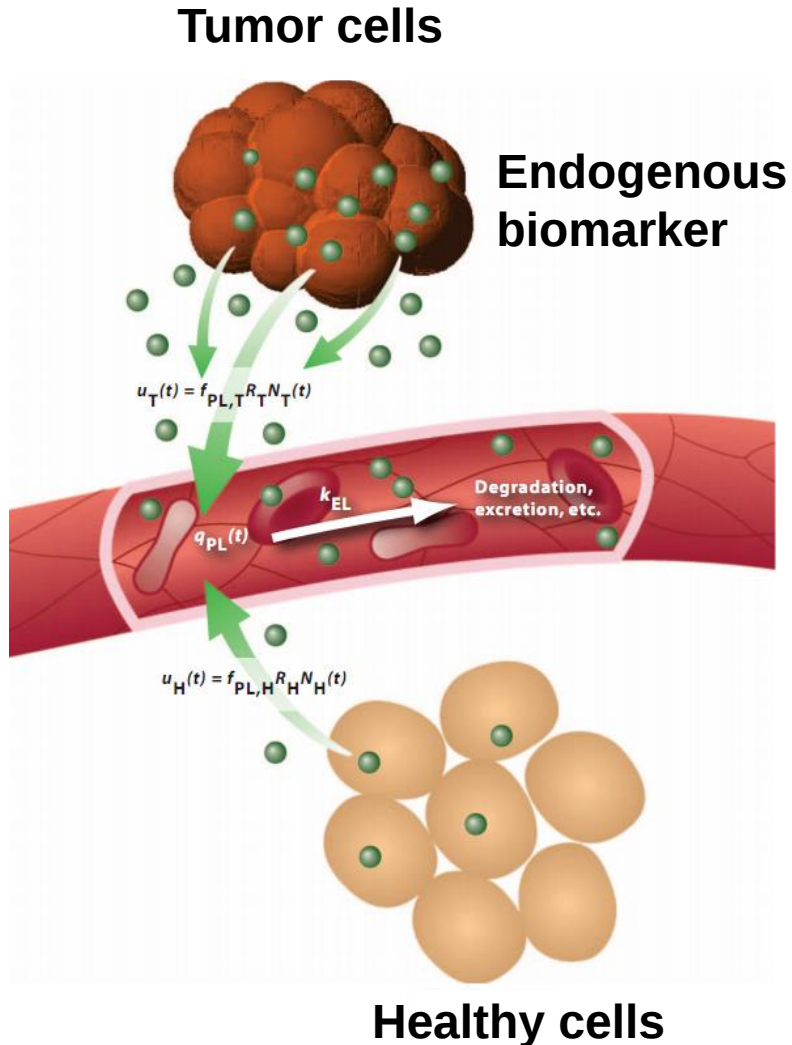
Cancer biomarker paradigm



¹ Sreekumar et al. *Nature* (2009), ² Findeisen et al. *Proteomics Clin Appl* (2012), ³ Surinova et al. *J Proteome Res* (2011),

⁴ Schwarzenback et al. *Nat Rev Cancer* (2011), ⁵ Moon et al. *Mass Spectrum Rev* (2011), ⁶ Nagrath et al. *Nature* (2007).

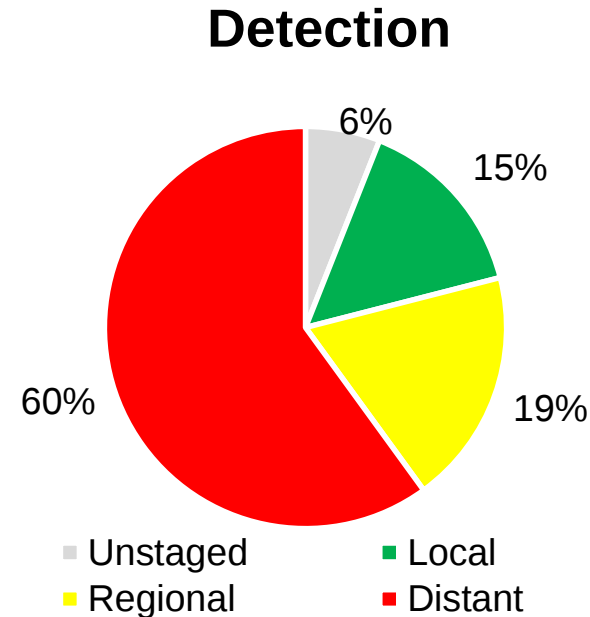
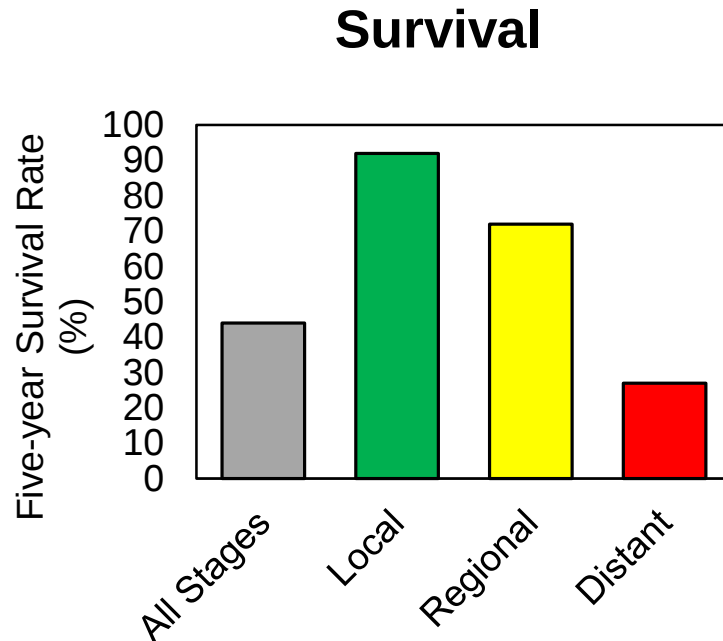
Detecting what nature gave us



Potential limitations of sensing endogenous biomarkers:

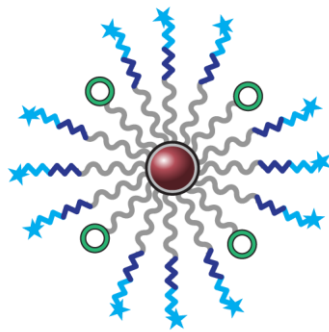
- Need to identify biomarkers shed by tumors.
- Endogenous biomarkers may not exist in measureable quantities in liquid biopsies
- Background secretion by healthy cells leads to high signal-to-noise
- Variable life time in biological samples (tissue, blood, urine)
- Difficult to measure biomarkers in complex biological fluids

Case study: Ovarian cancer

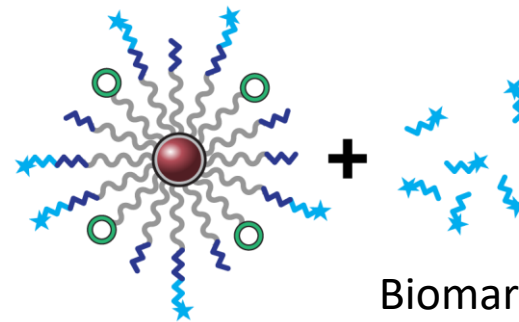
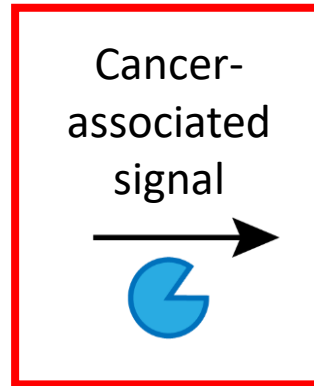


- Difficult to detect in early stages
 - CA125 and HE4
 - Transvaginal ultrasound
- High 70% relapse rate
- Little improvement in survival rate in the past 30 years

What if we could control the generation of biomarkers?



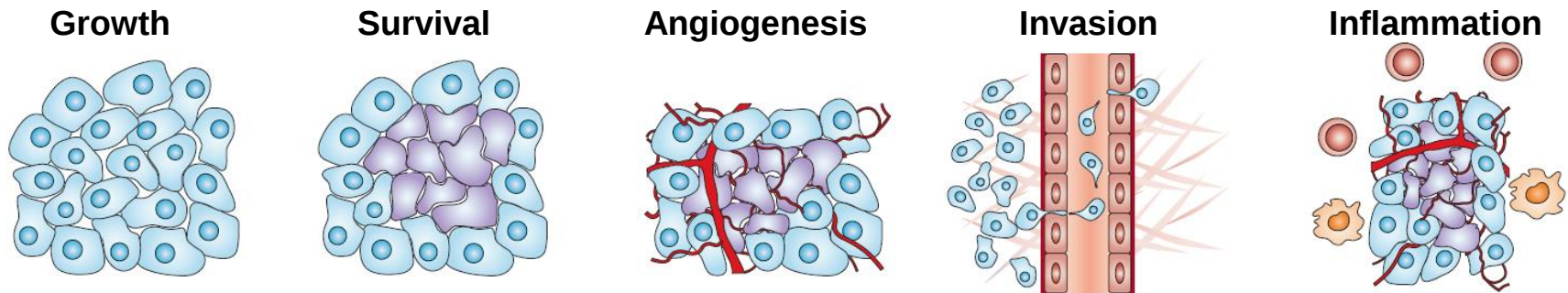
Engineered sensor



Biomarker generation



Proteases are enzymes that are central to cancer progression

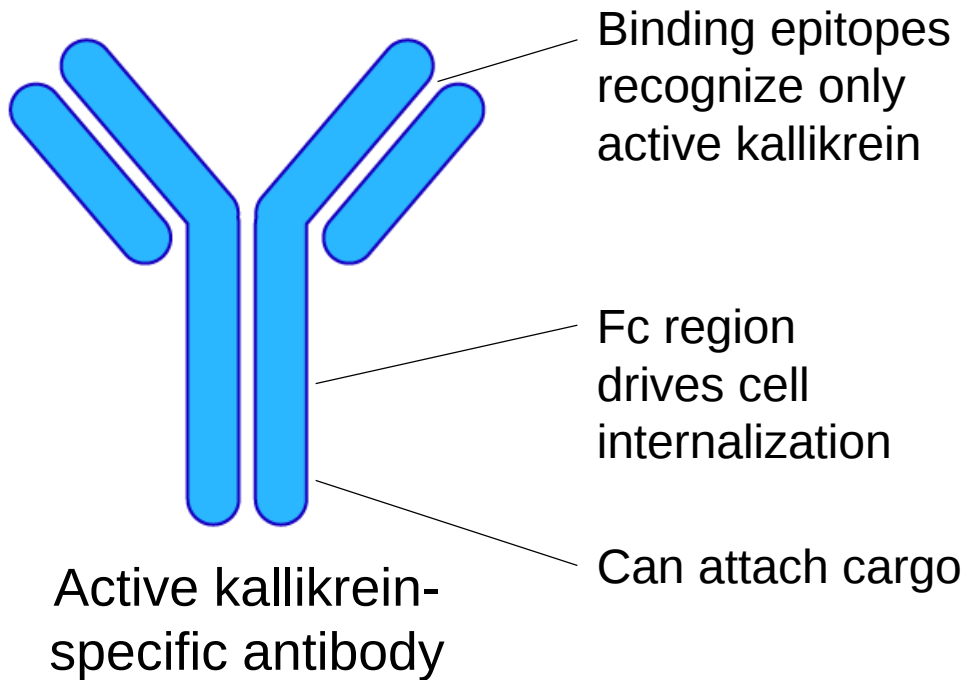


Therefore proteases are good targets for cancer theranostics:

Can we diagnose using proteases?

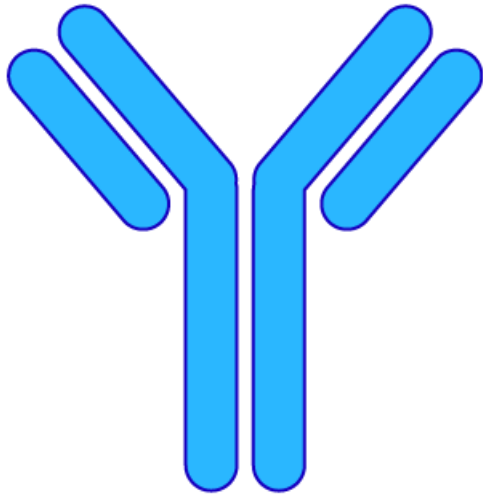
Can we drug proteases?

An antibody specific to an active-protease as an imaging probe

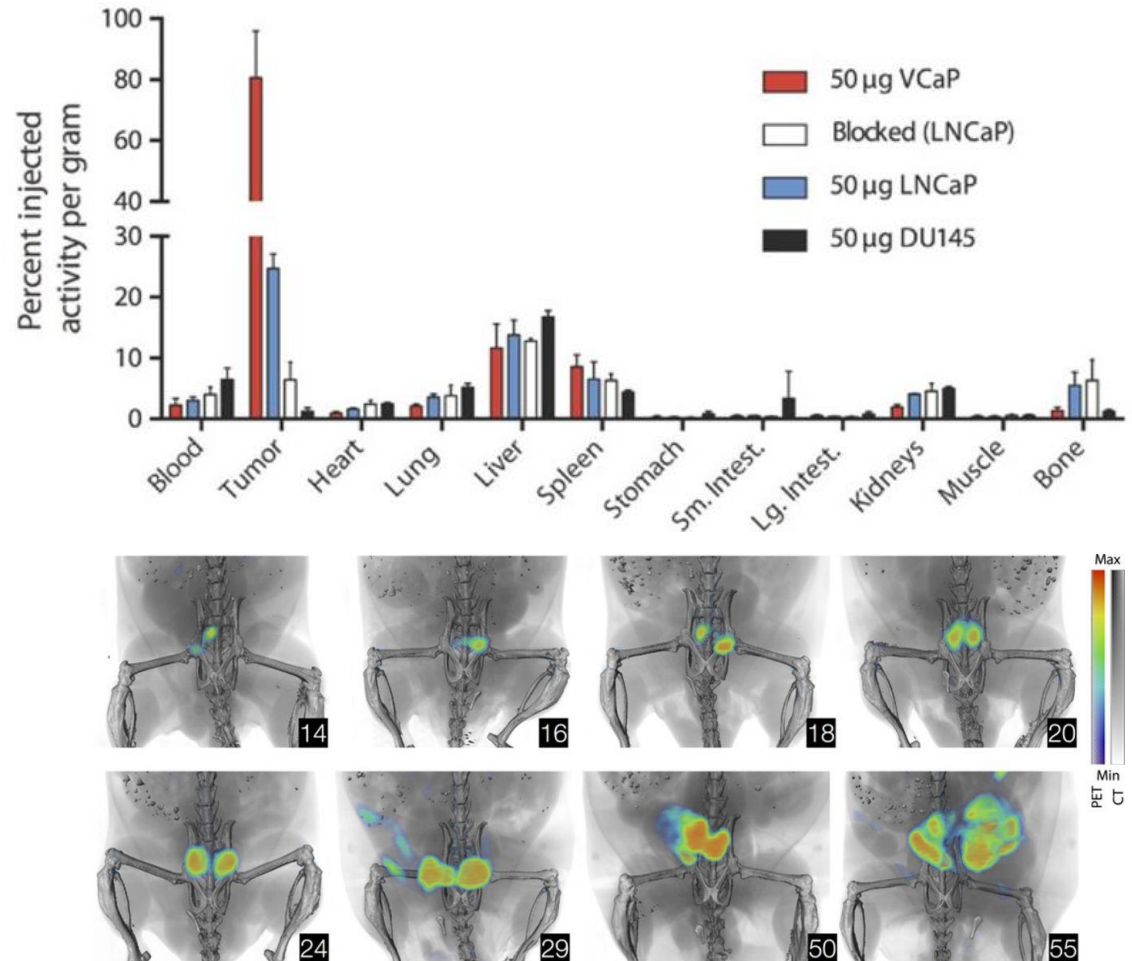


Human kallikrein-related peptidase 2

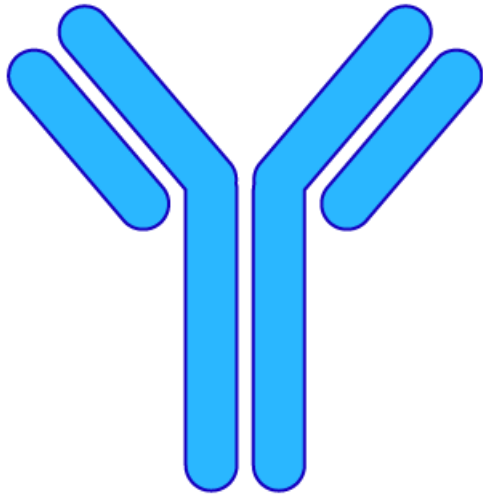
An antibody specific to an active-protease as an imaging probe



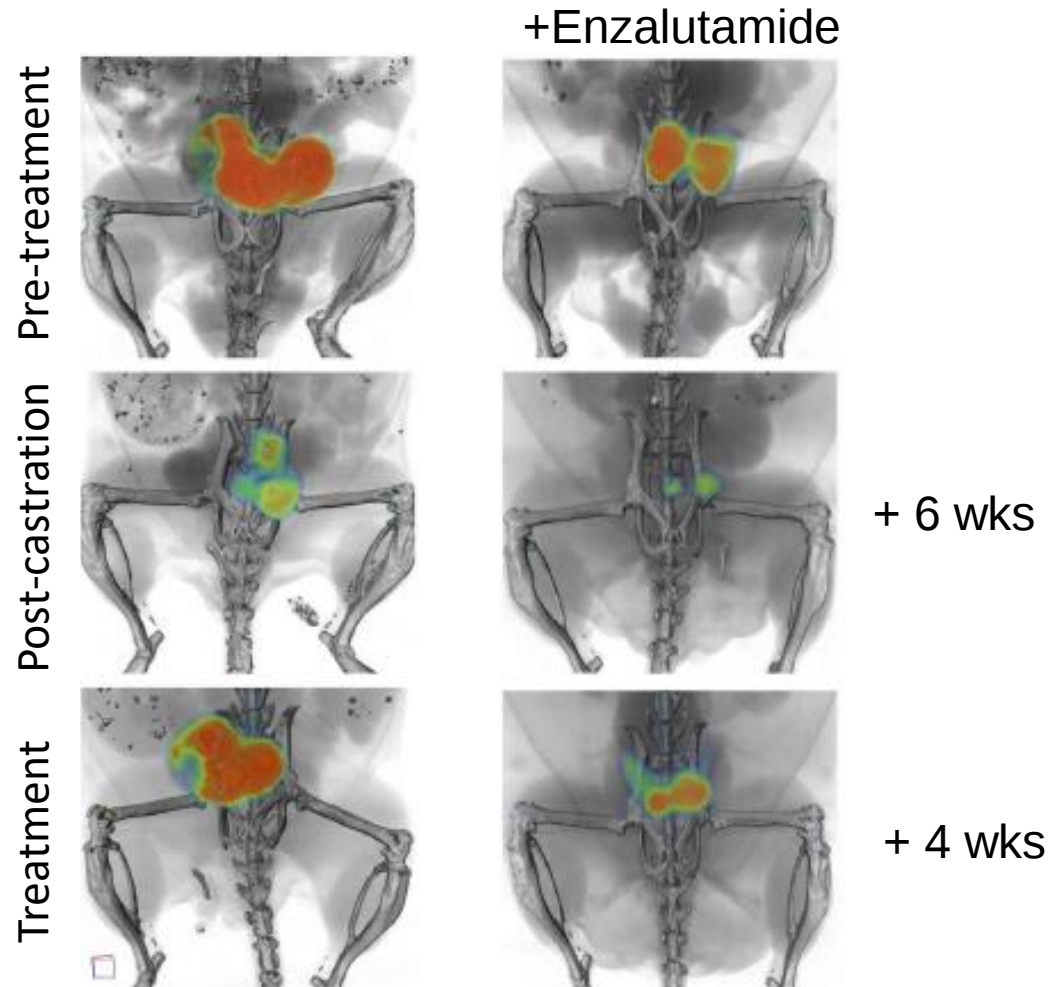
Active kallikrein-specific antibody



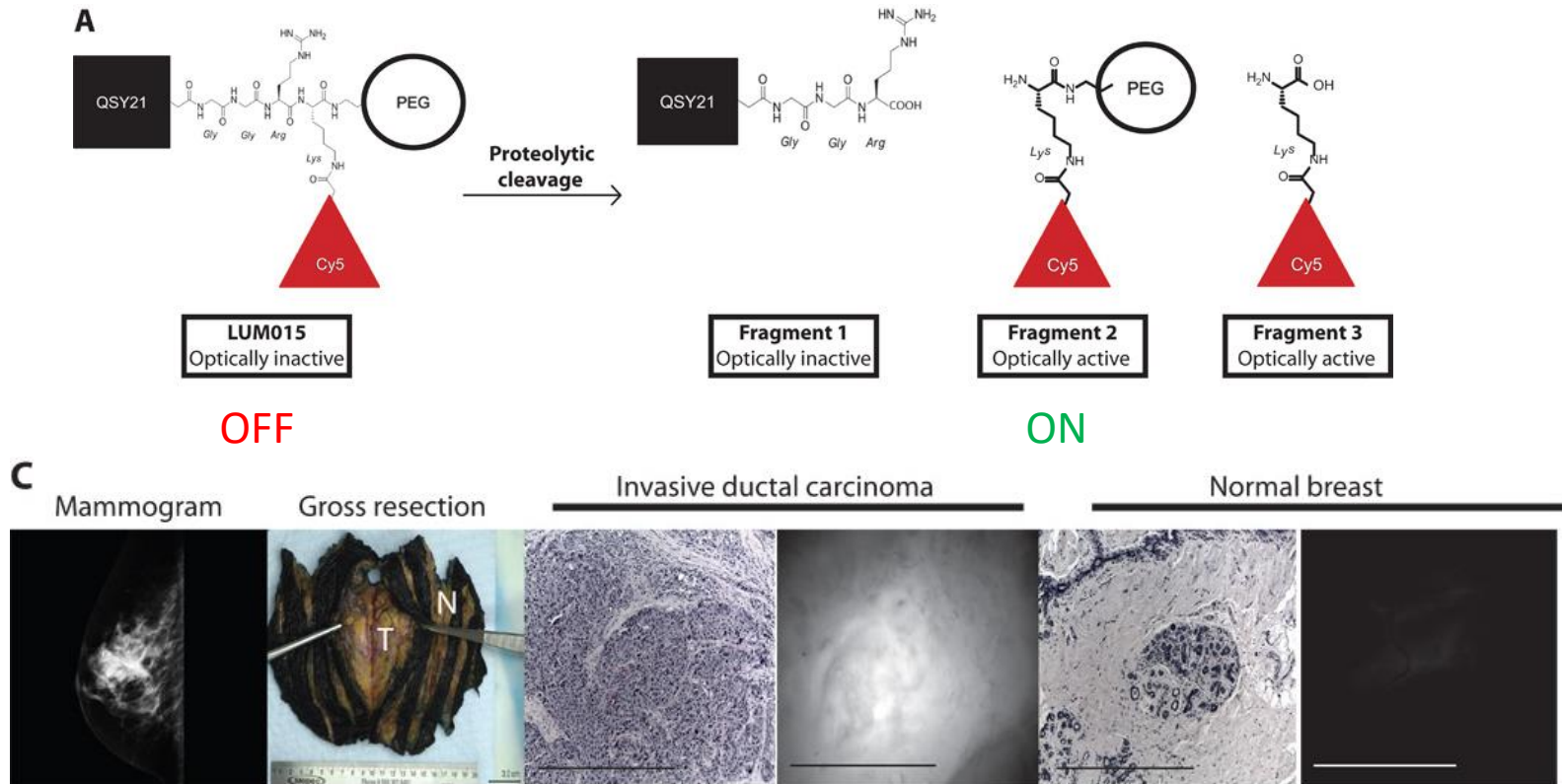
An antibody specific to an active-protease as an imaging probe



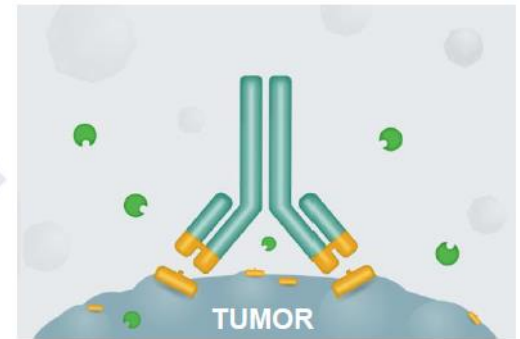
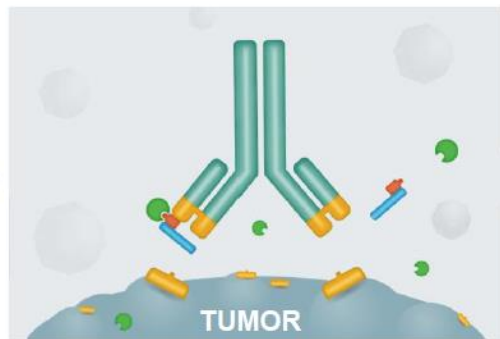
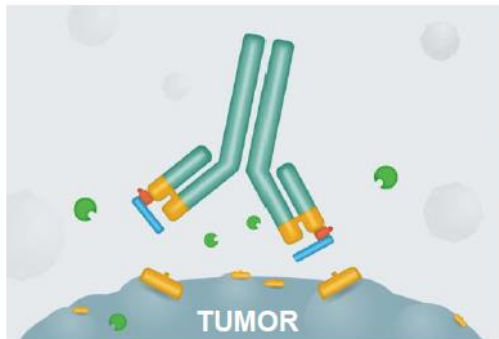
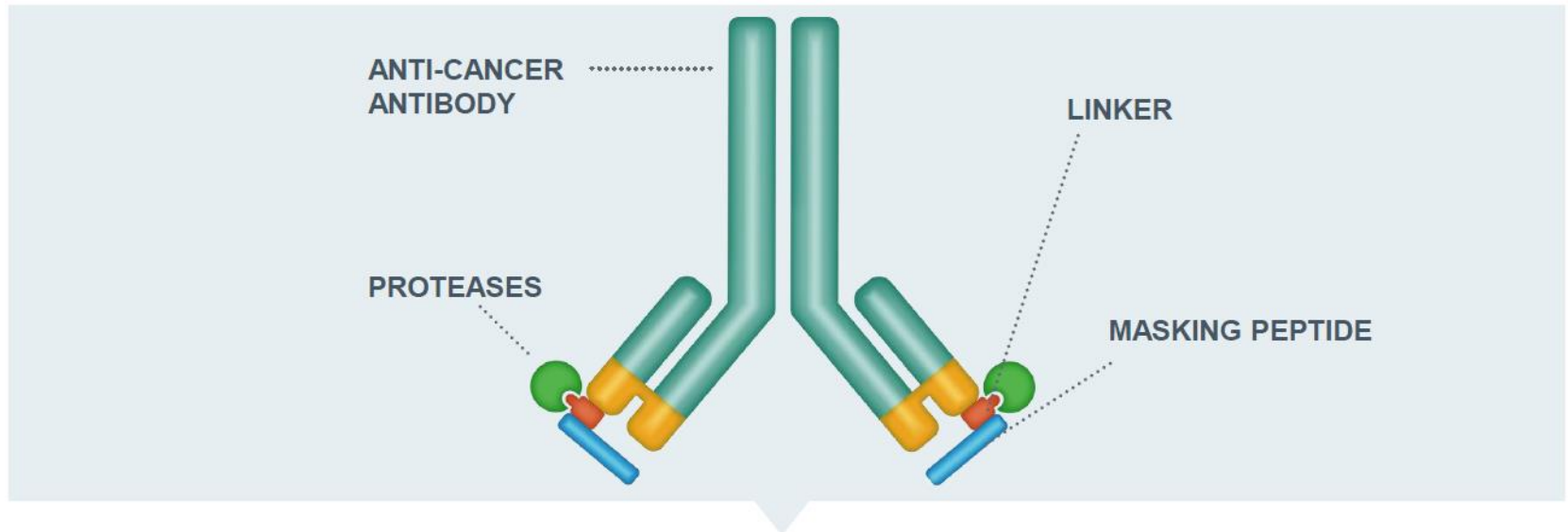
Active kallikrein-specific antibody



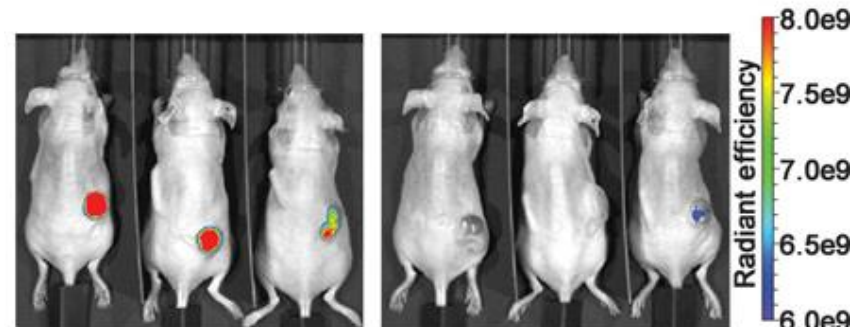
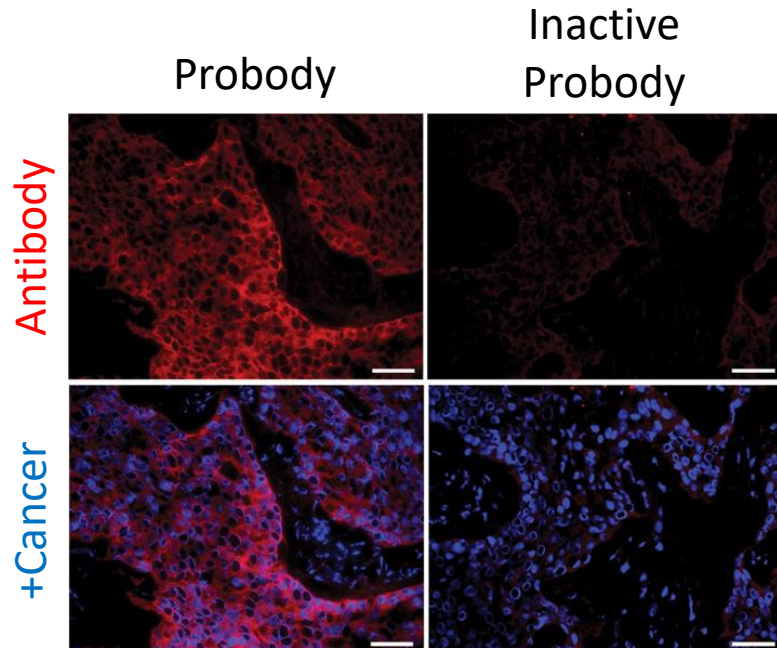
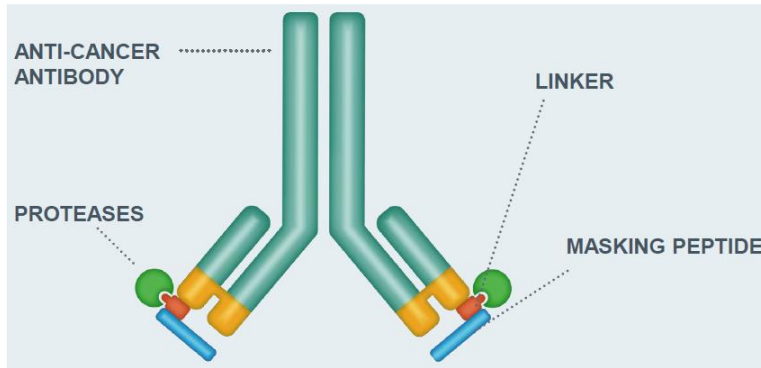
Protease activity-guided surgery



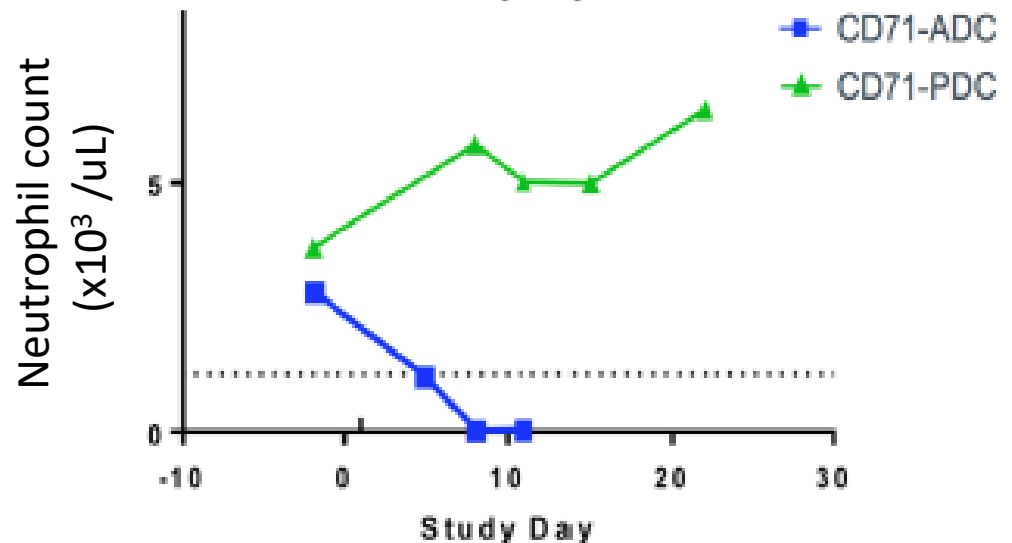
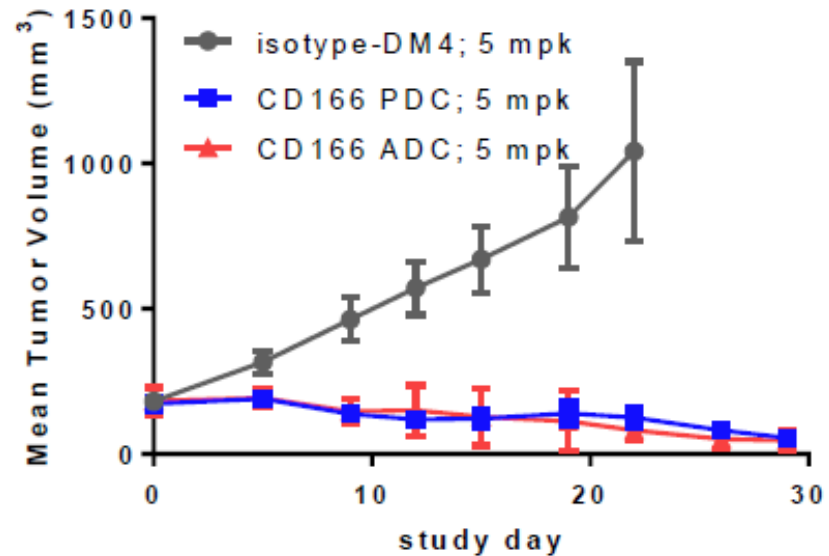
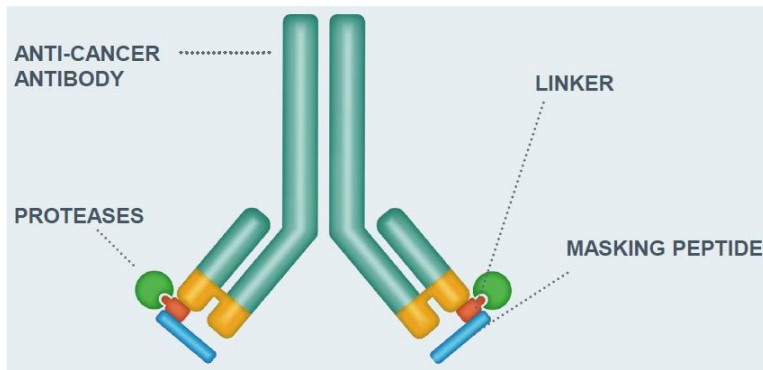
Probodyes create a protease cleavage and target binding AND gate

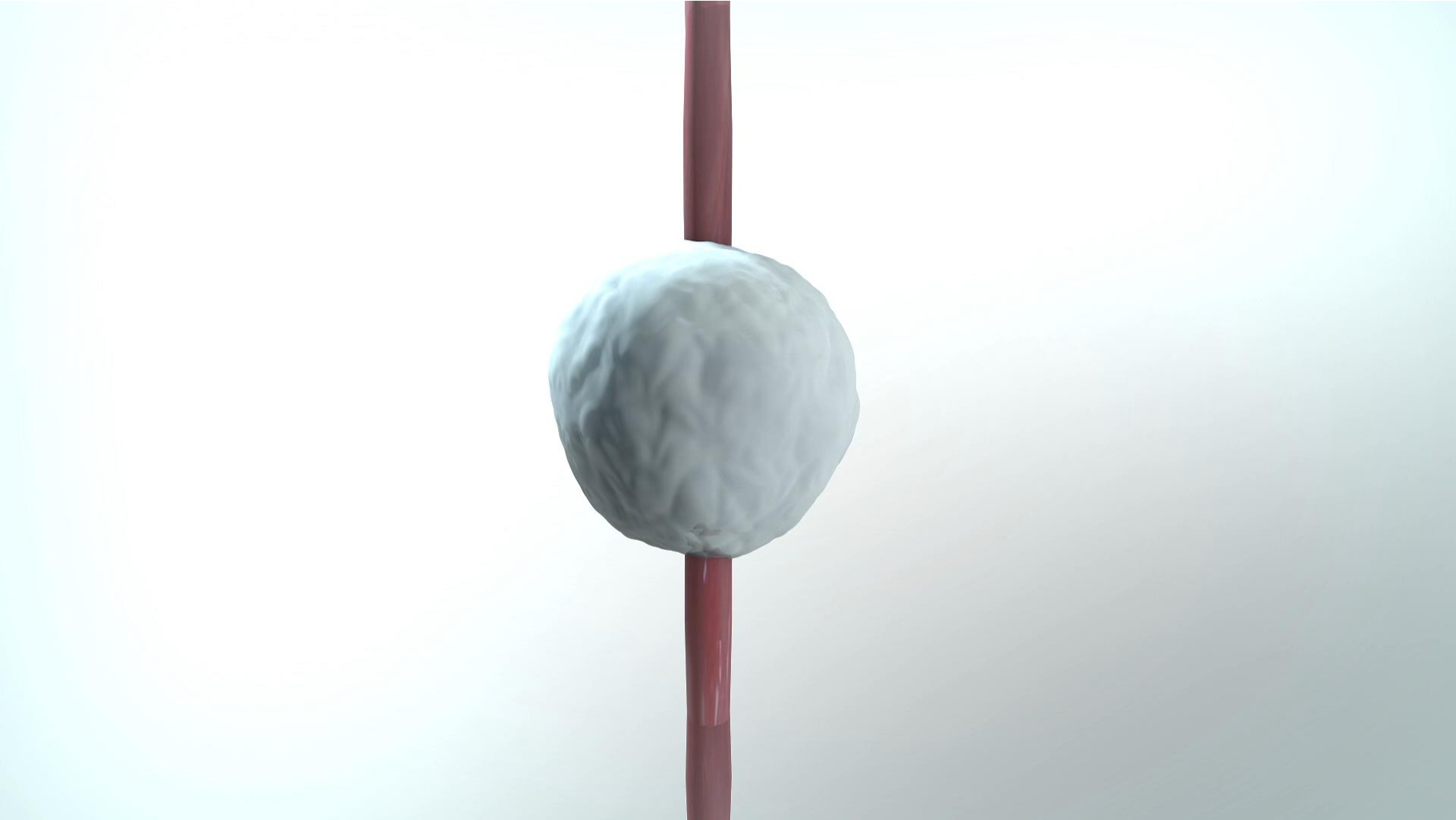


Probodyes create a protease cleavage and target binding AND gate

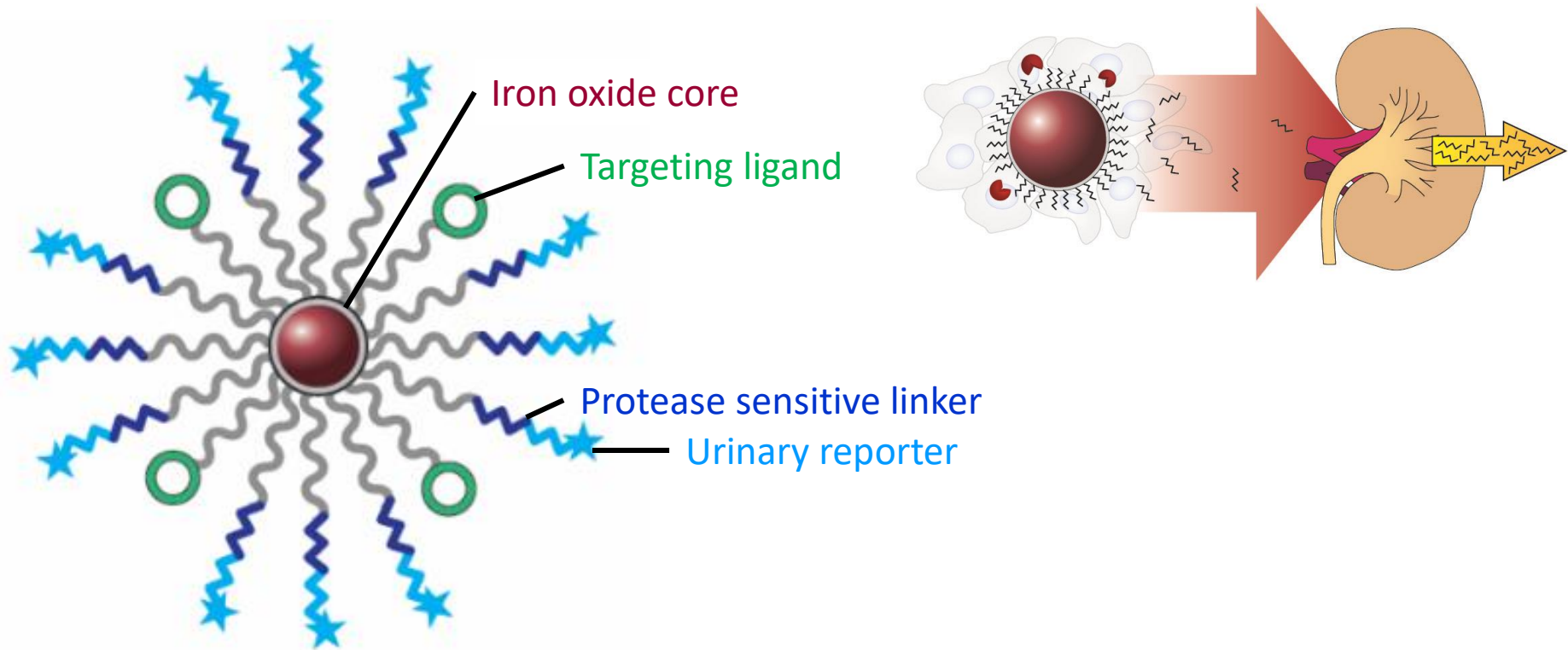


Probodyes create a protease cleavage and target binding AND gate

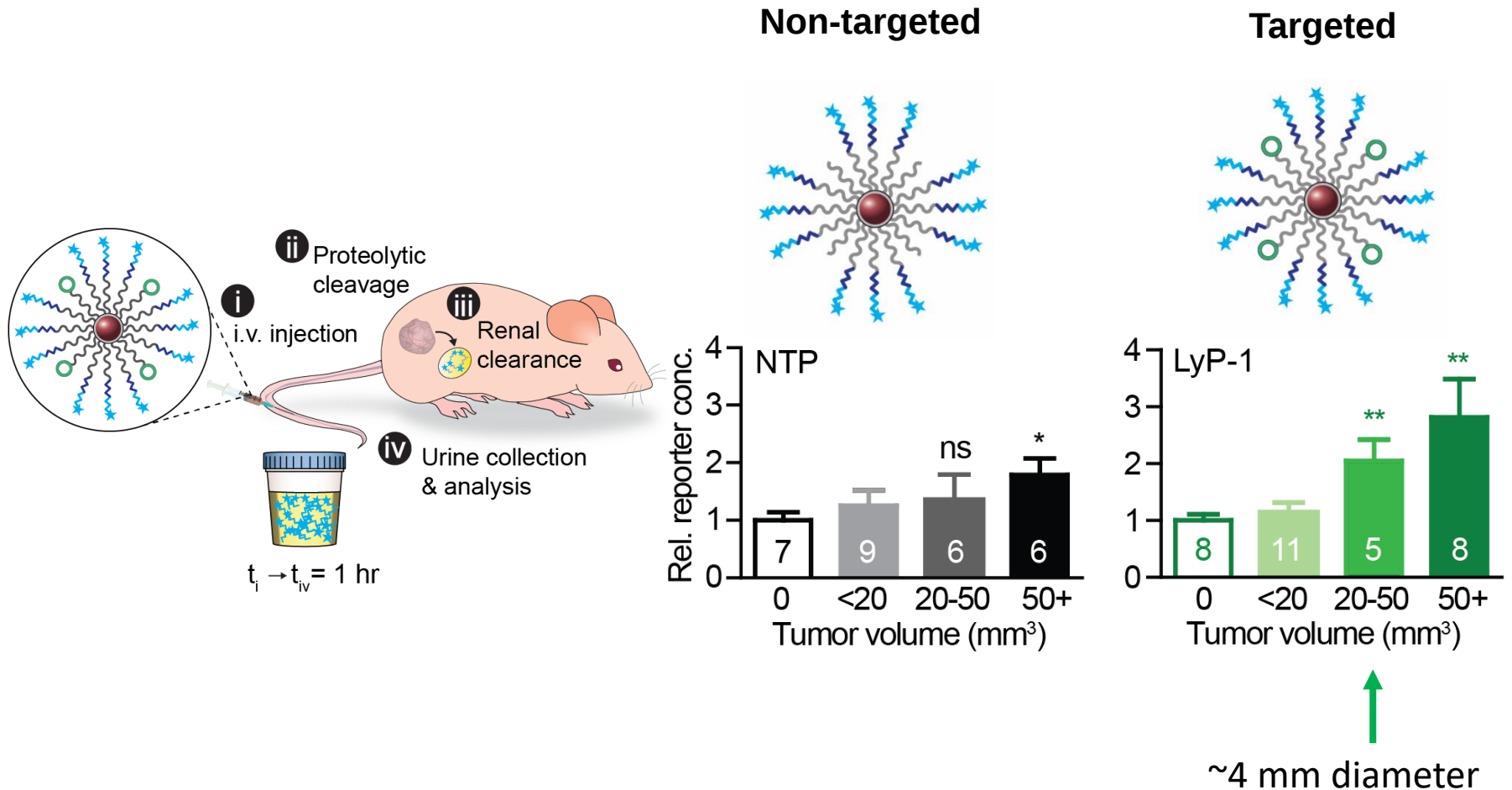




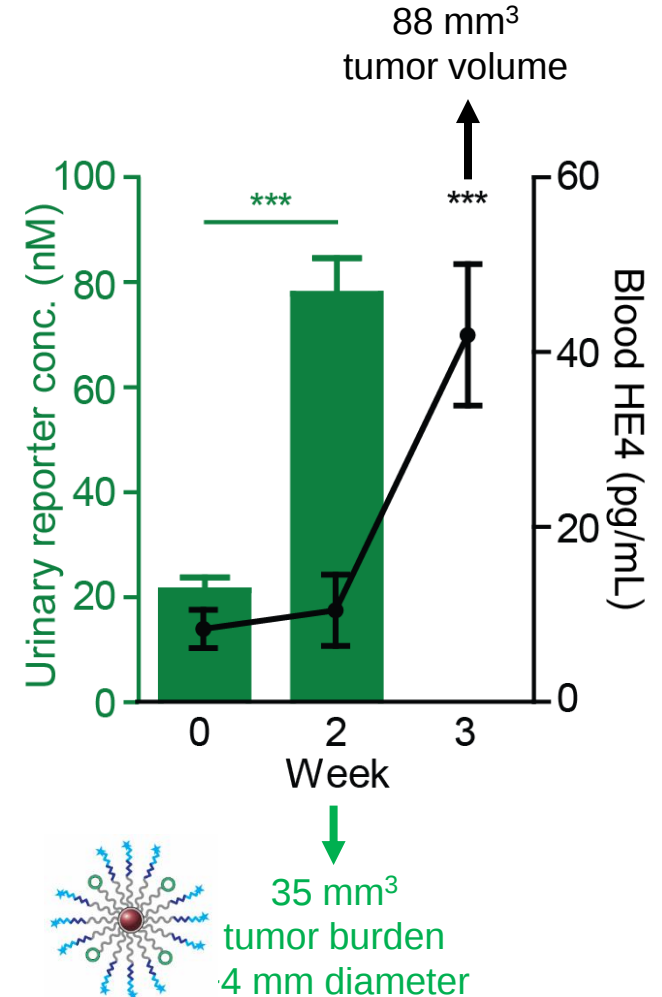
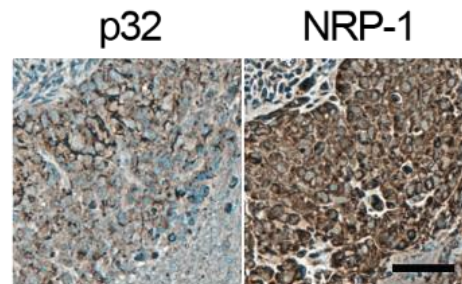
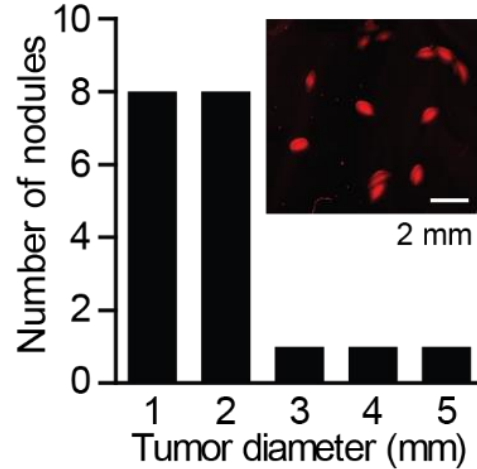
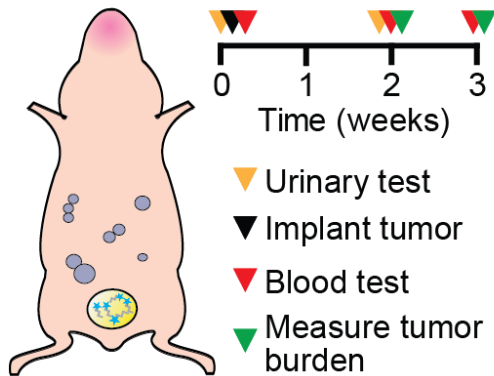
An activity based nanosensor for sensitive cancer detection



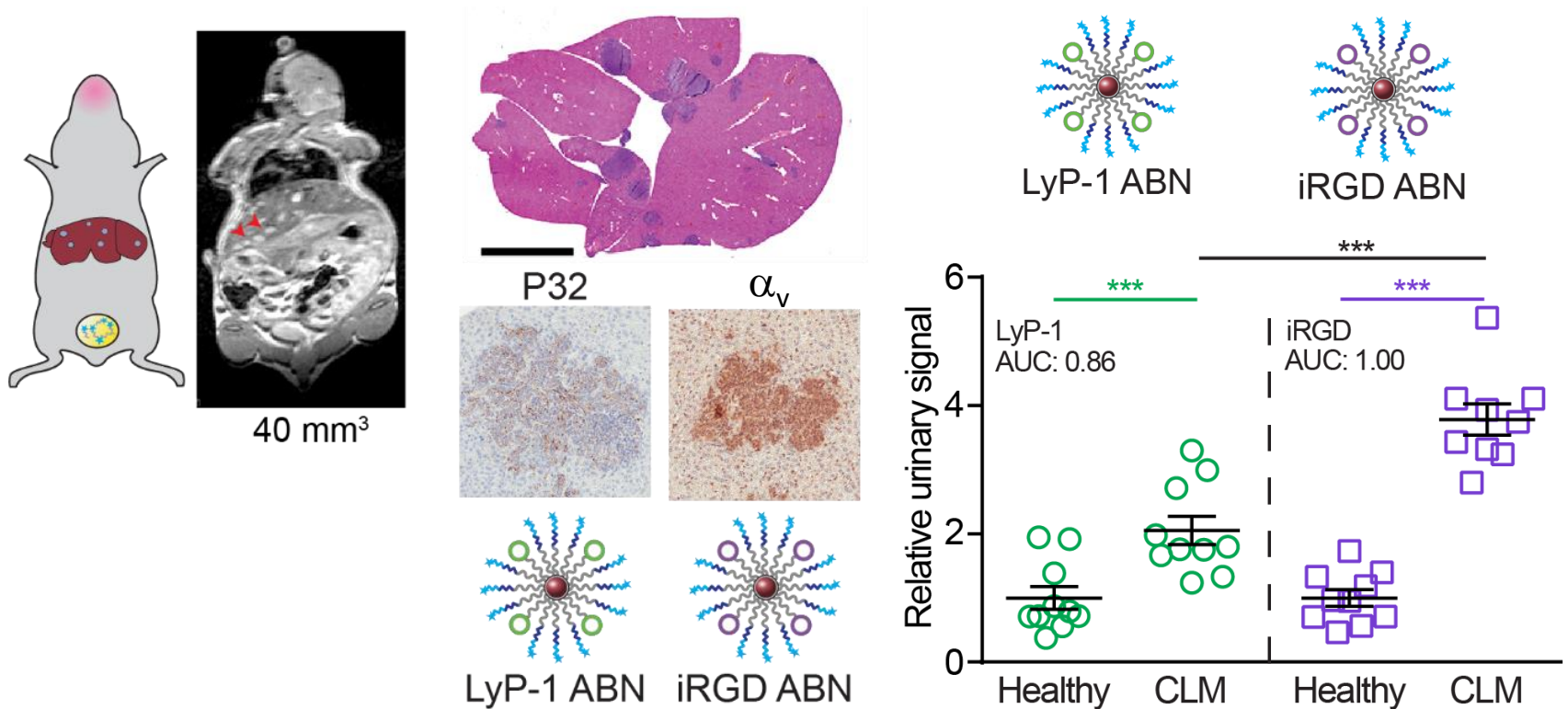
Targeting allows detection of <5 mm diameter tumors



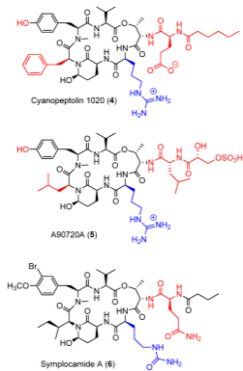
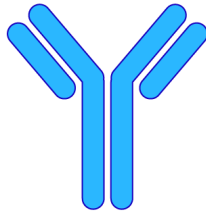
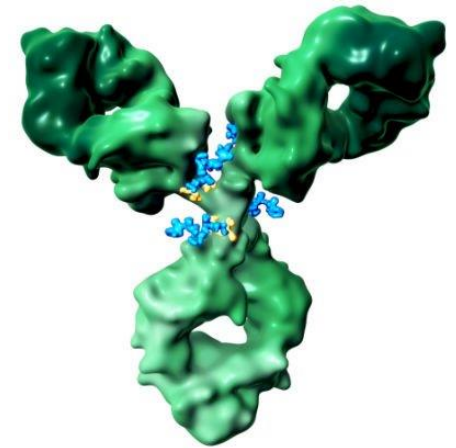
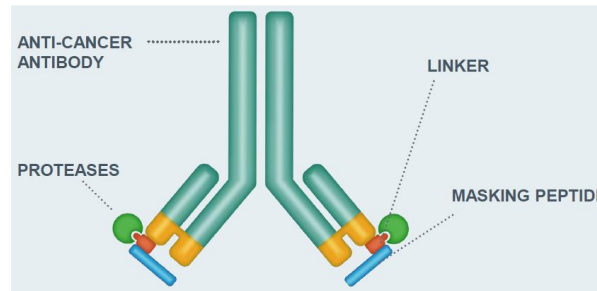
Nanosensor detects low burden in a model of ovarian cancer



Ligand matching can predict tumor receptor expression



Outlook



Diagnostics

Cancer
Traumatic brain injury
Liver fibrosis
Atherosclerosis
Infectious diseases

Therapeutics

