Synthetic Biomarkers for Cancer Detection and Diagnosis

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Diagnostics  Enzymes  Therapeutics
Cancer is a heterogeneous disease

Marusyk et al., Nat Rev Cancer 2012
Cancer evolves over time and interventions

Disease Burden

Risk assessment (e.g., BRCA1, BRCA2, CRP)

Diagnosis, Prognosis (e.g., HER2/neu, B-Raf, EGFRviii)

Early detection

Pharmacodynamic

Monitoring (e.g., PSA, CEA, CTCs)

Therapeutic intervention

Recurrence

Time
Cancer drugs are becoming more specific

Small molecule therapies

Antibody-drug conjugates

Cancer immunotherapy

Chen & Mellman, Immunity 2013
Cancer drugs are becoming more specific

Theranostics
How do we decide which patient gets what treatment and at what time?
Cancer biomarker paradigm

Detecting what nature gave us

Potential limitations of sensing endogenous biomarkers:

- Need to identify biomarkers shed by tumors.
- Endogenous biomarkers may not exist in measurable 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 → Cancer-associated signal → 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

Active kallikrein-specific antibody

Binding epitopes recognize only active kallikrein

Fc region drives cell internalization

Can attach cargo

Human kallikrein-related peptidase 2
An antibody specific to an active-protease as an imaging probe

Active kallikrein-specific antibody

Thorek et al. STM, 2016
An antibody specific to an active-protease as an imaging probe

Active kallikrein-specific antibody

Thorek et al. STM, 2016
Protease activity-guided surgery

Whitley et al. STM, 2016.
Probodies create a protease cleavage and target binding AND gate
Probodies create a protease cleavage and target binding AND gate

Desnoyers et al., STM 2013.
Probodies create a protease cleavage and target binding AND gate

Neutrophil count

(x10^3/μL)

Mean Tumor Volume (mm^3)

Study Day

Kwong et al. Nature Biotechnology; Kwon et al., Nature Biomedical Engineering.
An activity based nanosensor for sensitive cancer detection

- Iron oxide core
- Targeting ligand
- Protease sensitive linker
- Urinary reporter
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

Proteases in the disease management of cancer

Diagnostics

- Biomarkers
  - Screening (identify disease in high-risk population)
  - Diagnostic (differentiate potential diagnoses)
  - Prognostic (stratify disease based on clinical score)
  - Companion and pharmacodynamic (predict and track therapeutic efficacy)
  - Monitoring (identify disease recurrence)

Therapeutics

- Protease inhibitors
- Antibody-based drugs

Outlook

Diagnostics

Cancer
Traumatic brain injury
Liver fibrosis
Atherosclerosis
Infectious diseases

Therapeutics