A Review of Seed Investments at the Knight Cancer Institute For Early Detection Research

Bree Mitchell, Paul Spellman, Sadik Esener

March 6th, 2018

Cancer Early Detection Advanced Research (CEDAR) Center

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DISCLOSURE

Co-inventor on two patents on electrokinetic separation licensed to
Biological Dynamics
Co-founder and Co-inventor on two patents on nano-delivery particles licensed to
Devacell Inc.
Co-founder and Co-inventor on 5 patents on Optophoresis licensed to
Genoptix (A Novartis Co.)
Co-founder of endoscope manufacturer
Pensivision Inc.
Co-founder, SAB member and co-inventor of two patents licensed to
Nanomed Tracking
Co-founder of
Trogenex Inc.
Co-founder and SAB board member of
Cellics Therapeutics Inc
Co-founder of
Ziva corp.

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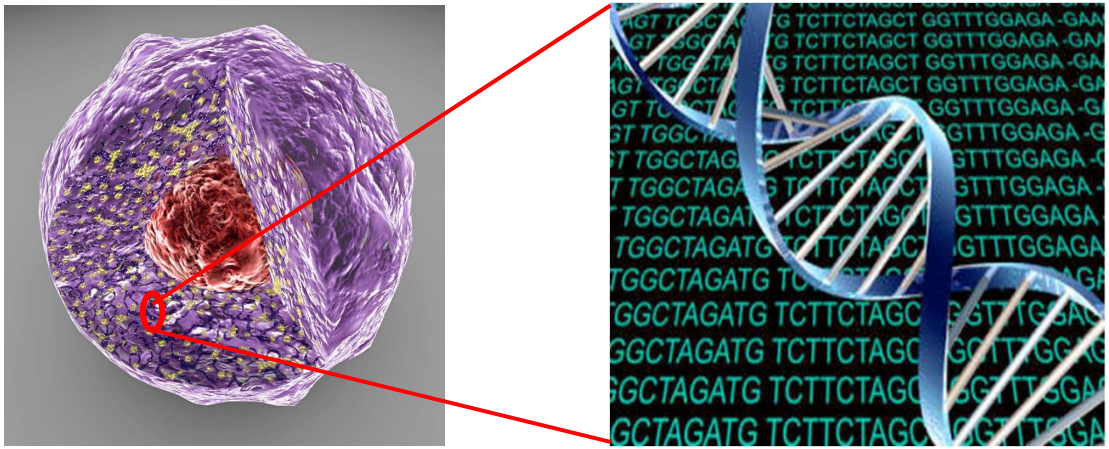
A Computer Engineer's Perspective on Cancer?

- **Biological Tissue: a network of *self-replicating* processors with a well defined instruction set to respond to a given stimulus to perform a related function**
- **The response results from the interaction of the input received with the stored instruction set**

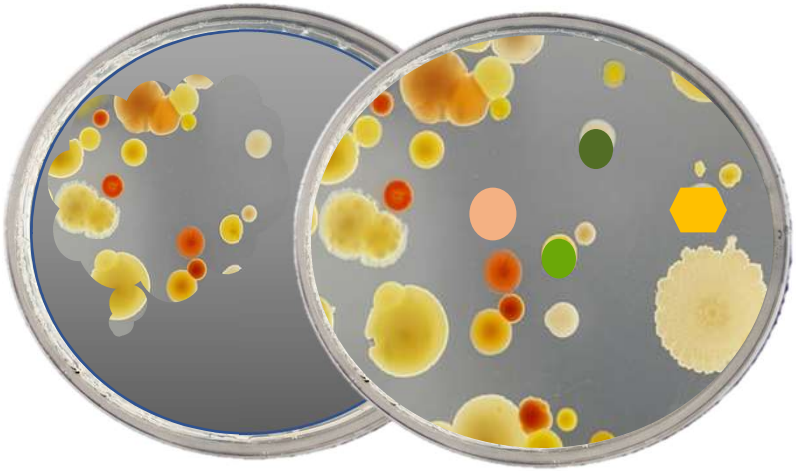


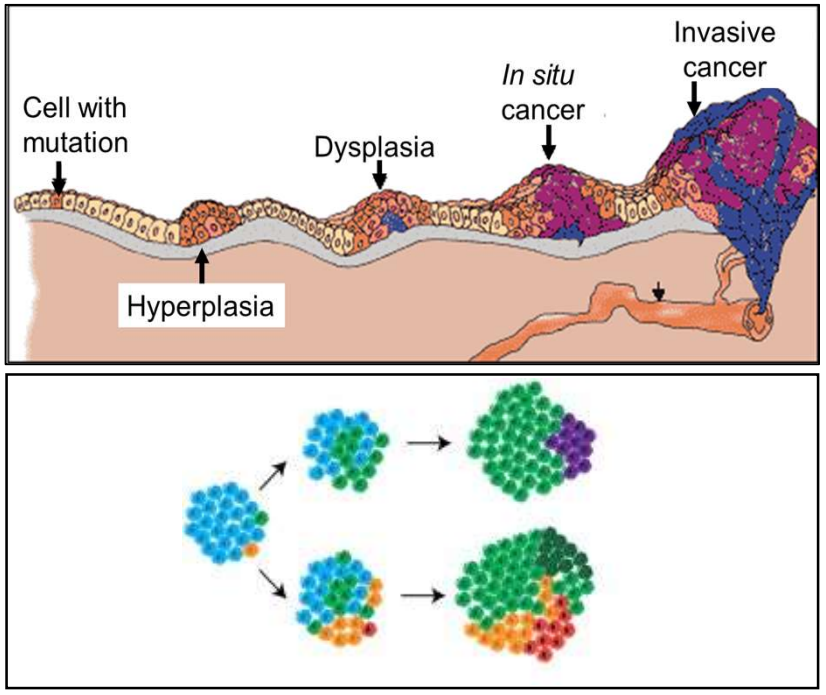
At its core, cancer originates from biological cells with a modified instruction set as a result of internal, extrinsic, and/or external factors

Late Stage Cancer: a combination of diseases

As the cell self-replicates alterations propagate and integrate and the diseased cell types grow leading to a heterogeneously populated network

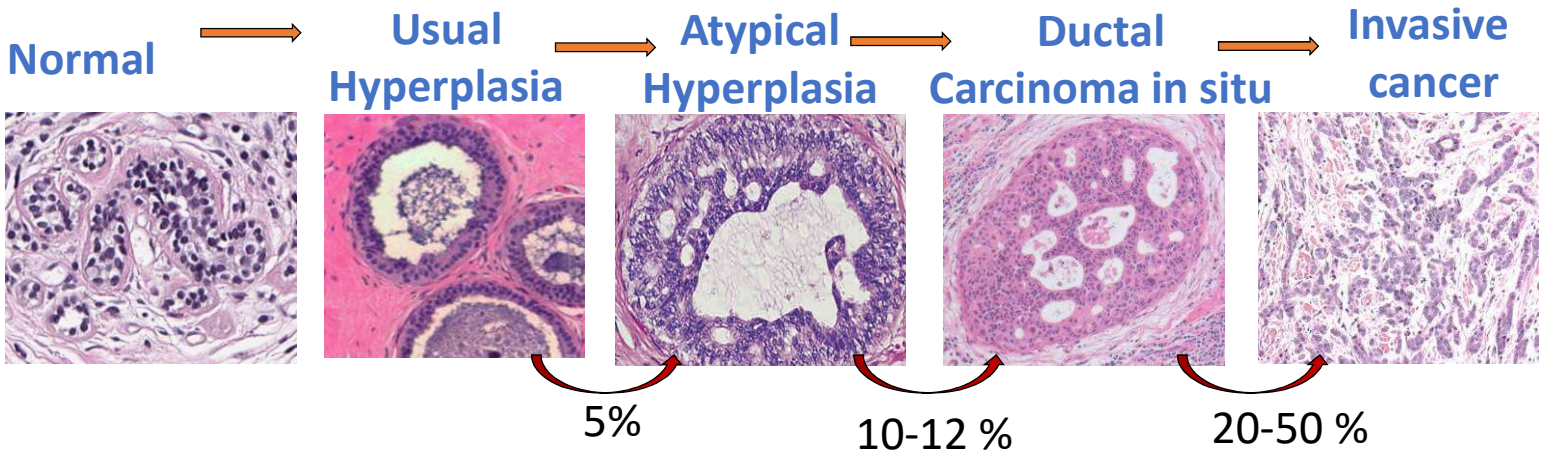
Cancer is not just one disease – it's many!





Early Detection:
Enable intervention before lethal disease gains significant heterogeneity preferably at the premalignant stage

Example: Breast Cancer "Progression"



- **Genomic instability occurs early** and DCIS have copy number alterations similar to IDC (Berman Cold Spring Harb. Symp. Quant. Biol 2005, K. Chin Nat. Genet. 2004)

=> the majority of gene changes occur between normal and DCIS

- Genomic studies comparing DCIS to IDC found
  - **Microenvironment affects gene expression changes that occur between DCIS and IDC** (Lee, Cancer Res 2012, X. J. Ma 2003, 2009, A.C. Vargas, 2012)

- **DCIS is lethal in a small subset of patients**, *irrespective of treatment received*

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CEDAR's MISSION

Similar progression characteristics have been reported for many other cancers

- Ductal Carcinoma In Situ (DCIS)
- Lobular Carcinoma In Situ (LCIS)
- MGUS (Multiple Myeloma)
- Diabetes (Pancreatic cancer)
- Cervical dysplasia
- Oral submucous fibrosis
- Actinic keratosis (Melanoma)
- Dyskeratosis congenita
- Leukoplakia erythroplakia
- Clonal hematopoiesis (AML)
- Prostatic intraepithelial neoplasia (PIN)
- Atypical small acinar proliferation (ASAP)
- Proliferative inflammatory atrophy (PIA)
- Sideropenic dysphagia (esophageal)
- Barrett's esophagus
- Atrophic gastritis
- Colorectal adenoma
- Chronic inflammatory bowel diseases
- Colon polyps
- Mucinous cystic neoplasm (pancreas)
- Intraductal papillary mucinous neoplasms (IPMN)
- …….

TO DETECT, PREDICT, AND PREVENT PROGRESSION OF PREMALIGNANT DISEASES TO AGGRESSIVE CANCERS

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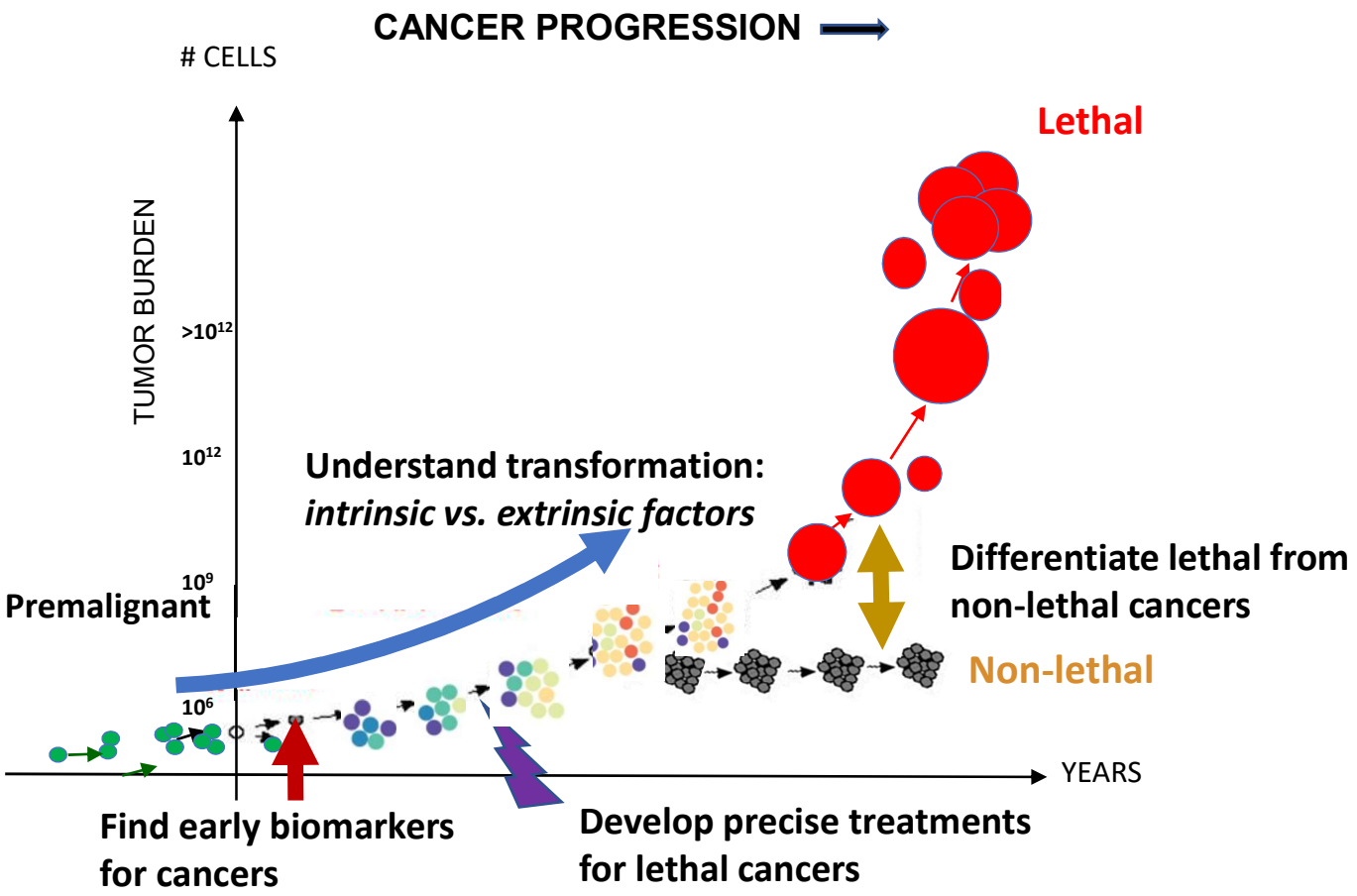
CEDAR's Early Detection Goals



COLLECT LONGITUDINAL DATA ON AS MANY BIOMARKERS AS POSSIBLE

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BARRIERS

CANCER: A multidimensional nonlinear time dynamics problem
Need longitudinal multi-parametric large amounts of measured data

- **ASSEMBLING A LONGITUDINAL HIGH RISK COHORT -> Very costly**
- **ESTABLISHING THE BIOMARKERS -> Biology and Technology complexity**
- **SCREENING FOR BIOMARKERS -> Regulations and technology**
- **UNDERSTANDING FACTORS INVOLVED IN EARLY DISEASE PROGRESSION**
  -> many confounding factors -> Big data overlay
- **DIFFERENTIATING LETHAL FROM NON LETHAL EARLY CANCERS**
  -> time dynamic multivariable nonlinear process -> Machine Learning
- **TREATING EARLY LETHAL CANCERS**
  -> Require less invasive treatments
- **BUSINESS MODEL**
  -> Convincing to Pharma and Insurance provider
  -> Global coordination & collaboration

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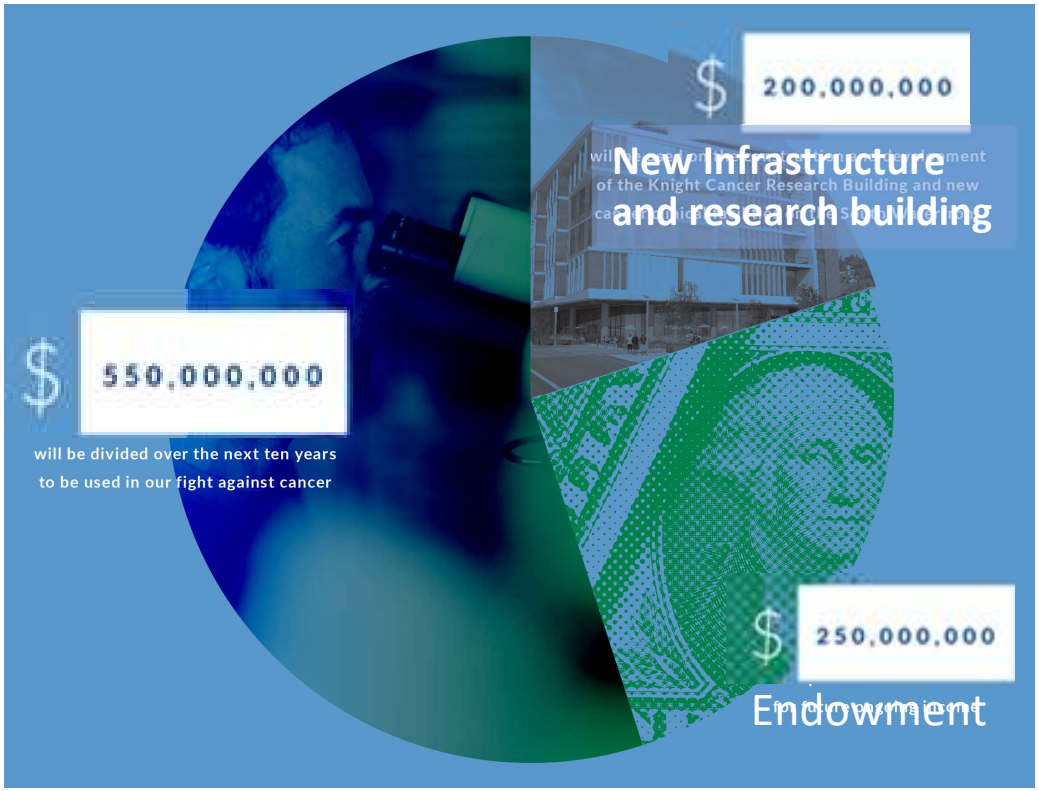
The Knight Cancer Challenge

- $500M donation
  - from Phil Knight (Nike co-founder) with a match requirement
- Matching funds came from:
  - 10,000 individual donors from across the country and world
  - State bond to build a new building



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CEDAR **focus areas**

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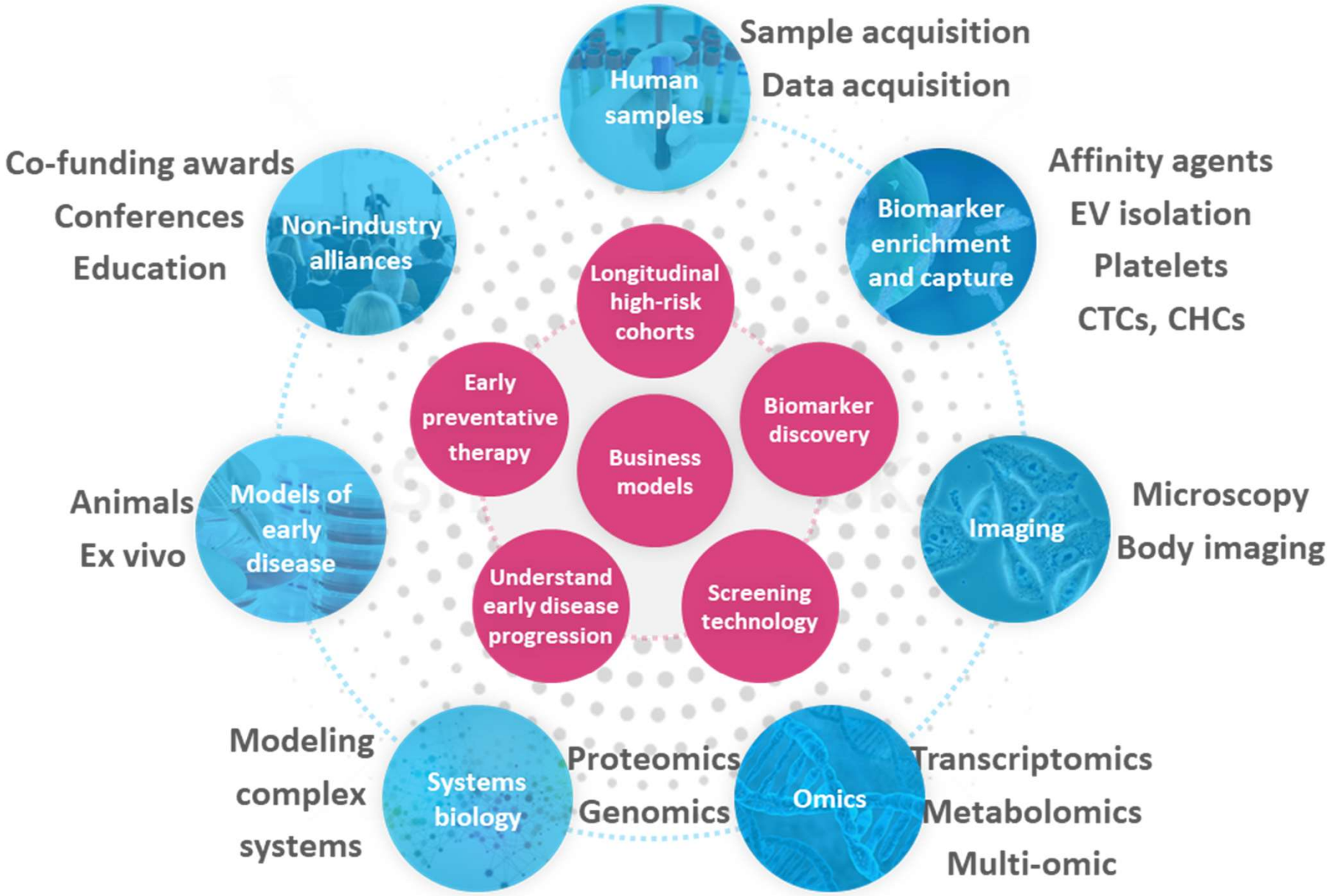
CEDAR **focus areas** and related **capability expertise**



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Pioneer Project Oregon


P. Spellman


J. Shannon

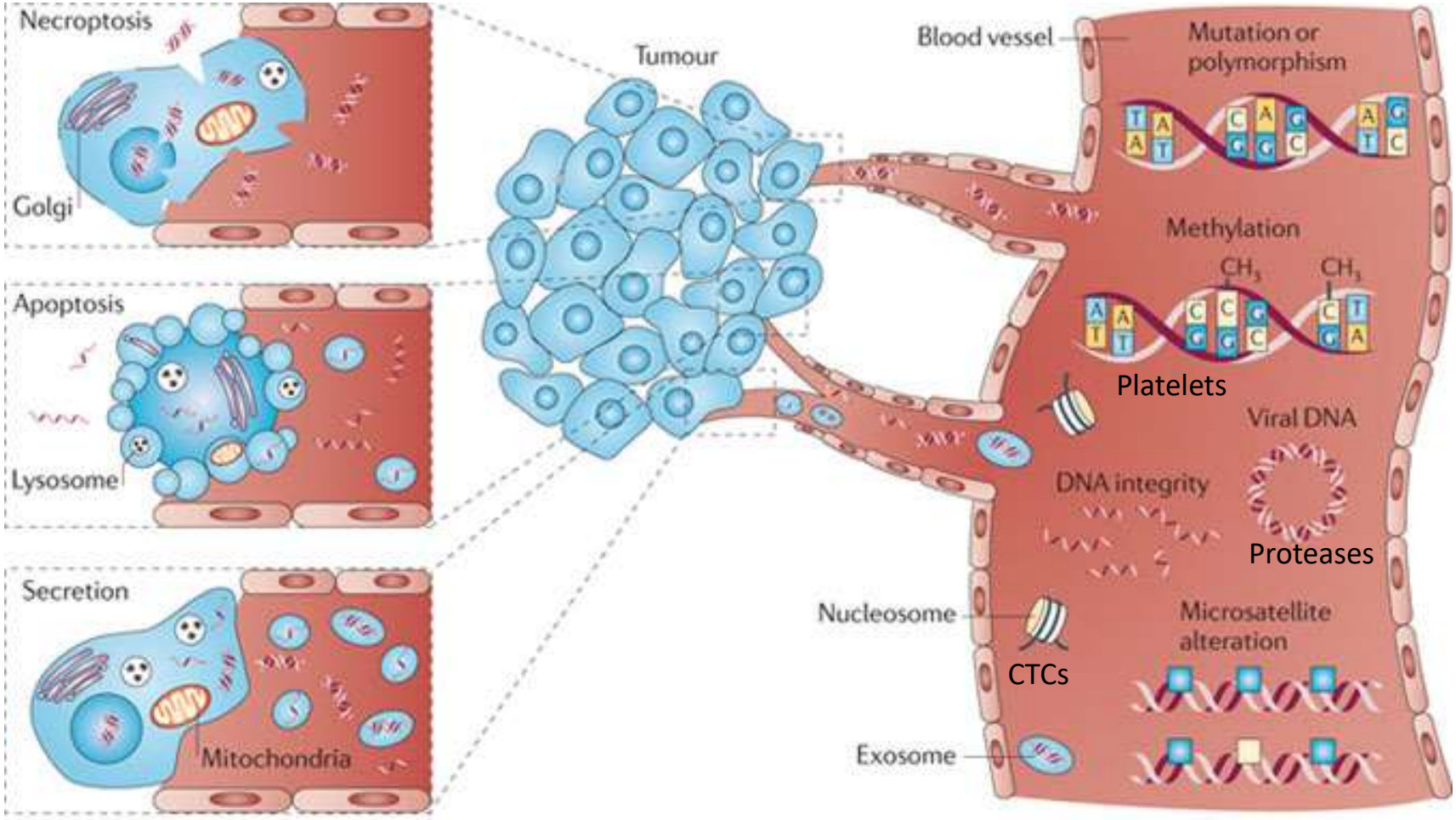
Bringing Oregon together to improve health and wellness

We will recruit up to a Million Oregonians…

Recruiting Partners

Triage a cancer high risk cohort to follow with longitudinal studies
So we can develop prevention and treatment approaches
that meet the needs of our state.

Searching for early biomarkers in Fluids: Detecting CTC's, Tumor affected proteases, Platelets, ctDNA, RNA and EVs



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SORTING BIOMARKERS:
Electro-kinetics & Magneto-kinetics

DIELECTROPHORETIC FORCE

$$\langle F_{dep} \rangle = 2\pi r^3 \varepsilon_m Re\left\{\frac{\varepsilon_p - \varepsilon_m}{\varepsilon_p + 2\varepsilon_m}\right\} \nabla |E_{rms}|^2$$

size

Dielectric properties

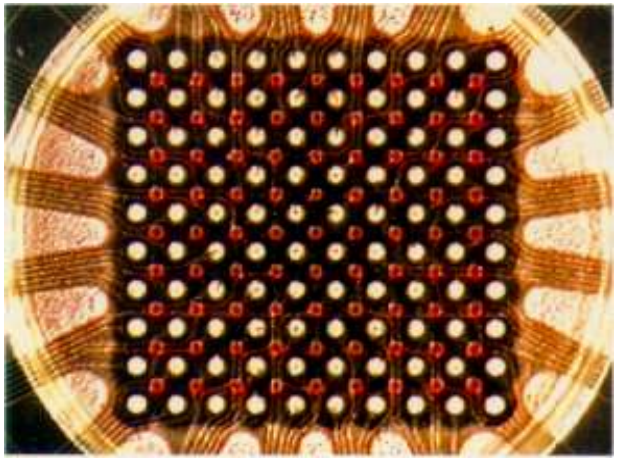
- High electric field gradients
- Heating
- Electro chemistry

MAGNETOPHORETIC FORCE

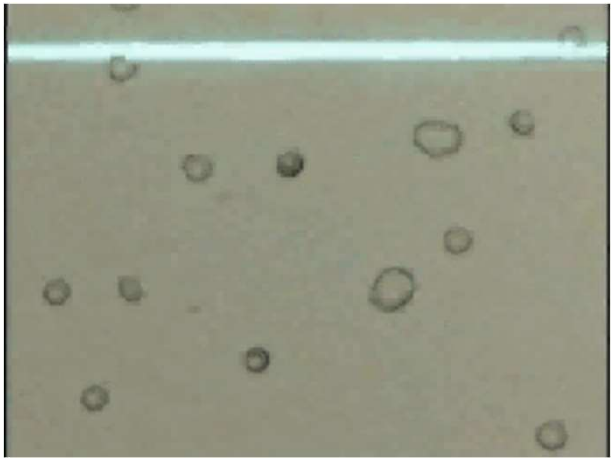
$$\langle F_{mep} \rangle = 2\pi r^3 \mu_m Re\left\{\frac{\mu_p - \mu_m}{\mu_p + 2\mu_m}\right\} \nabla |B_{rms}|^2$$

Magnetic properties

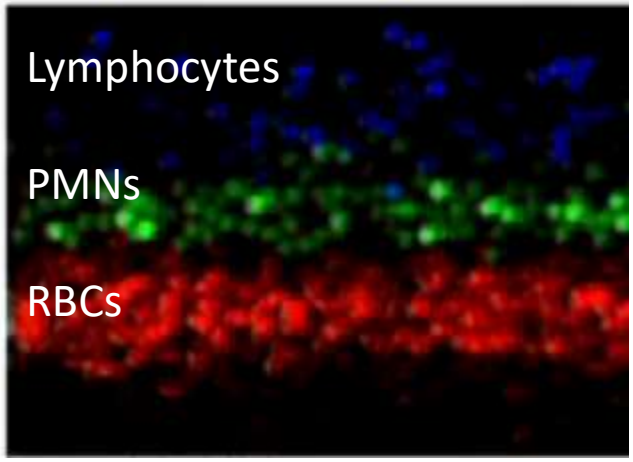
- Passive system
- Requires addition of Gd
- Lower gradients



Separation of RBC from WBC by Dielectrophoresis *(Nanogen)*



Separation of leukemic cells by Optophoresis (*Genoptix*)



Magnetic separation in blood *Durmus et. Al, PNAS, 2015*

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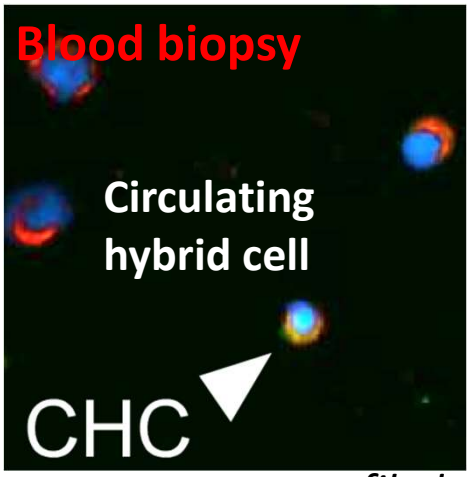
Circulating Hybrid Cell (CHC)

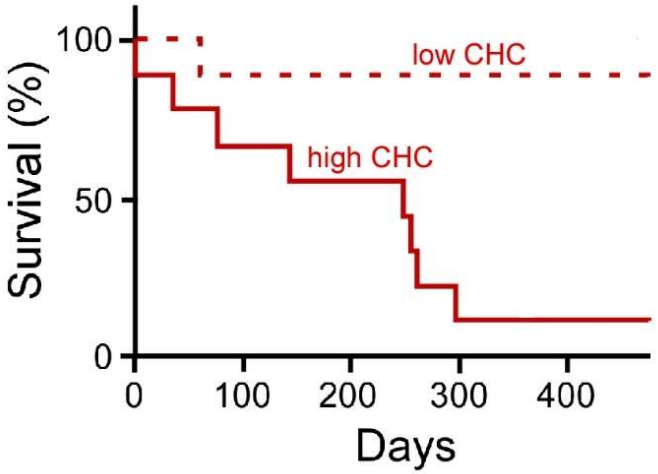
Prof. Melissa Wong Lab.

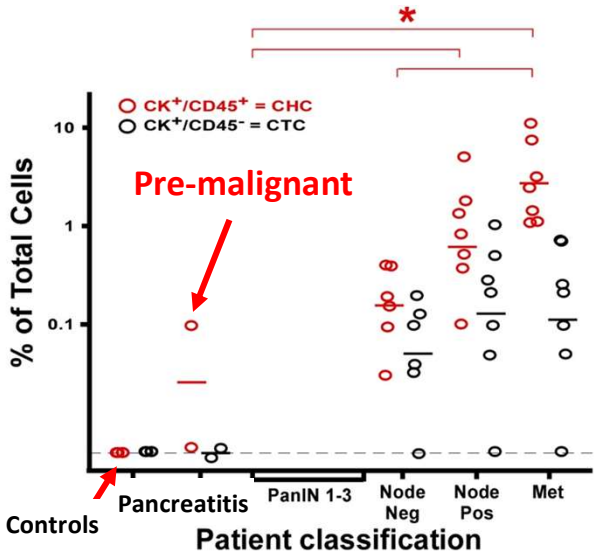
CHCs: Novel circulating cell biomarker in Early Disease

- CHCs can be identified in the blood as a distinct cell population that co-expresses cytokeratin and a macrophage marker, CD45.
- Macrophage and cancer cell genetic materials may sometimes fuse together to create CHCs
- Early tumors produce 10x more CHCs than traditional CTCs



patent filed





Early detection of CHCs may provide opportunity for prognosis assessment

Novel Electrophoretic Assay for Detection of Protease Activity

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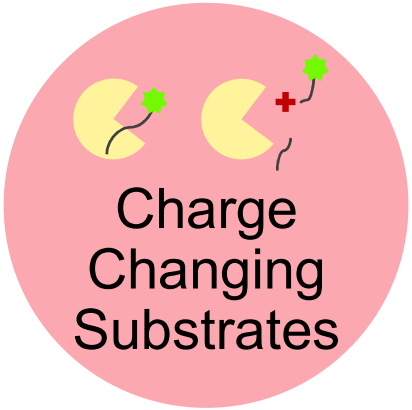
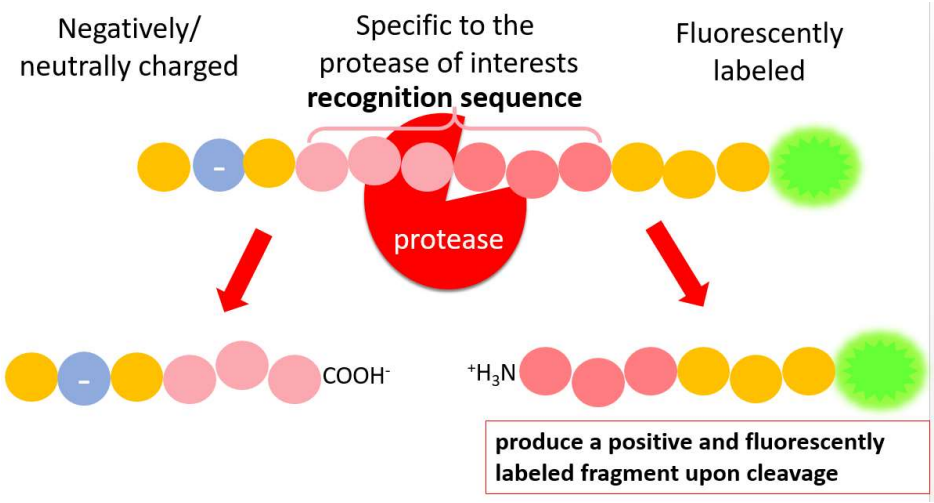
Augusta Modesto

Hypothesis: Proteases may drive the initiation and progression of cancers

To quantitatively detect proteases in whole blood we developed *charge-changing fluorescent peptide substrates* for a number of protease

- ✓Requires NO sample preparation
- ✓Small blood sample (~3-10 μL)
- ✓Simple electrophoretic formats
- ✓Rapid





Monitoring protease activity → opportunity to detect cancer at an early stage

Modestino, AE et al. Electrophoresis, 2015; Lefkowitz, R et al. Analytical Chemistry, 2010

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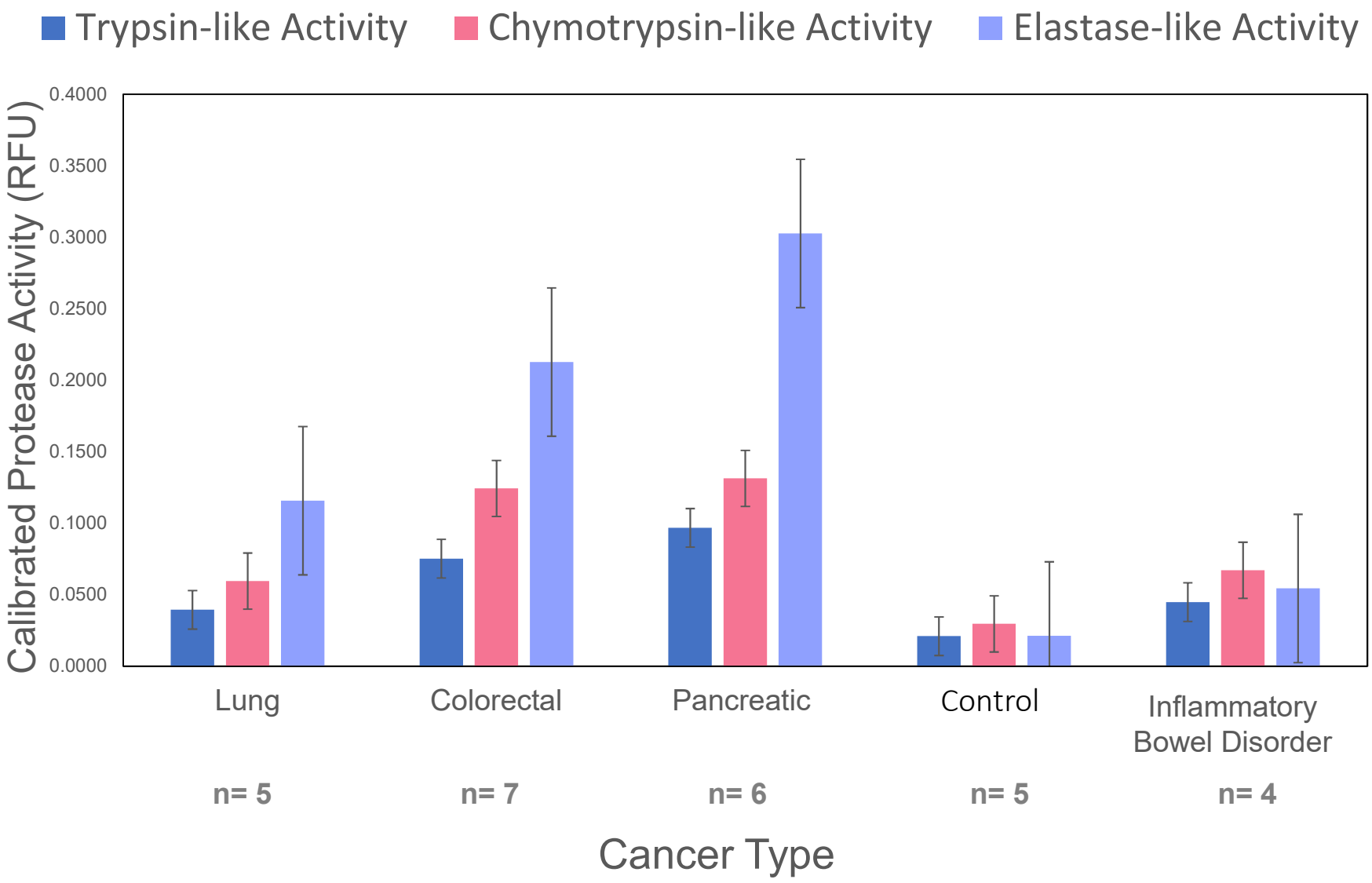
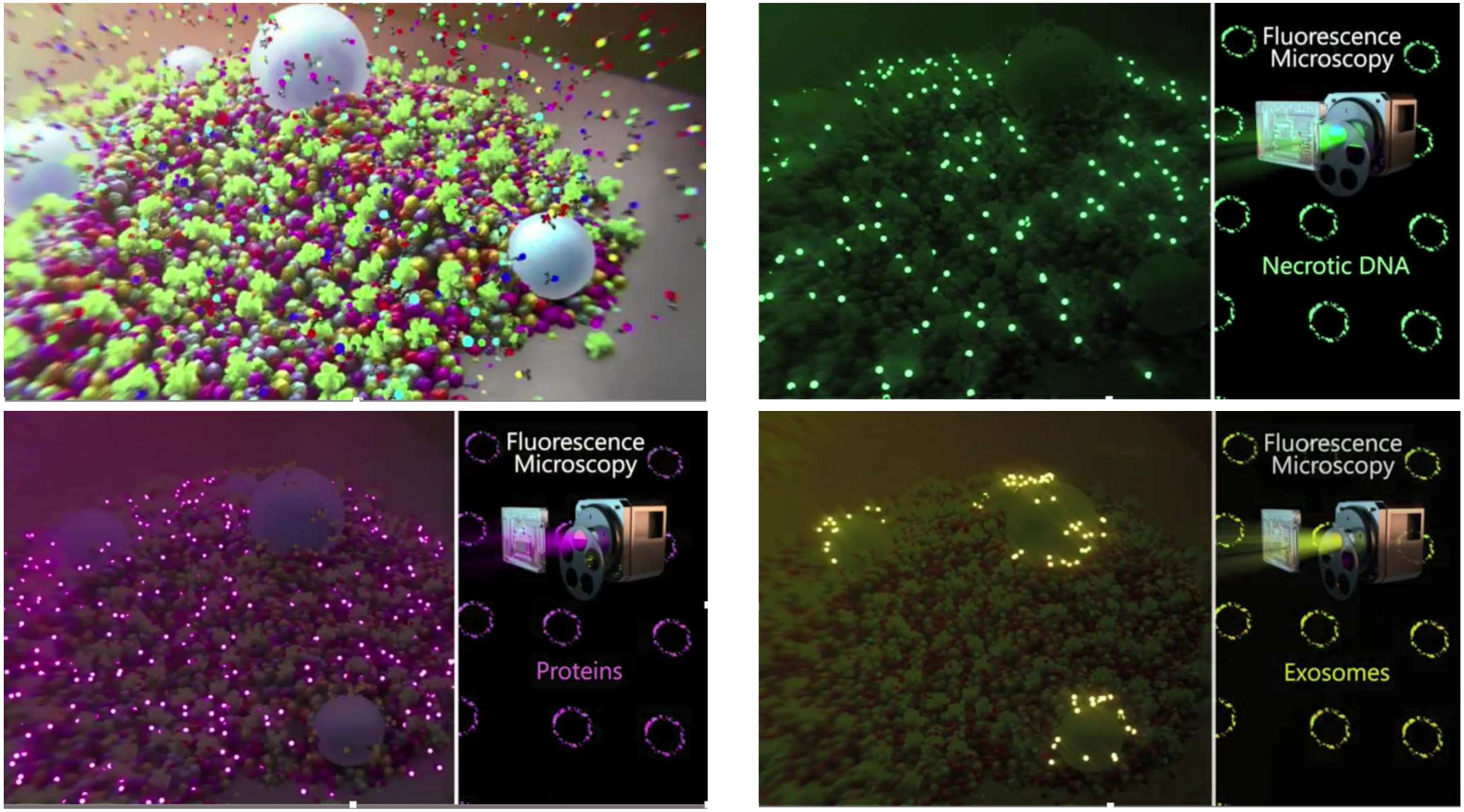
Pancreatic Proteases Activity
Preliminary Results



Electrokinetic / Fluorescence Based Screening of Blood Components



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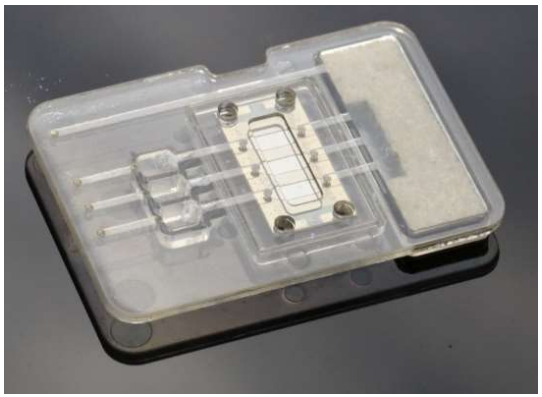
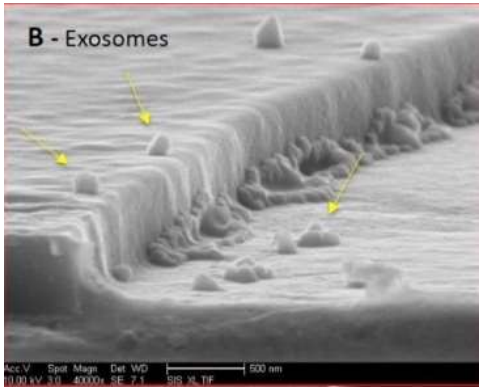
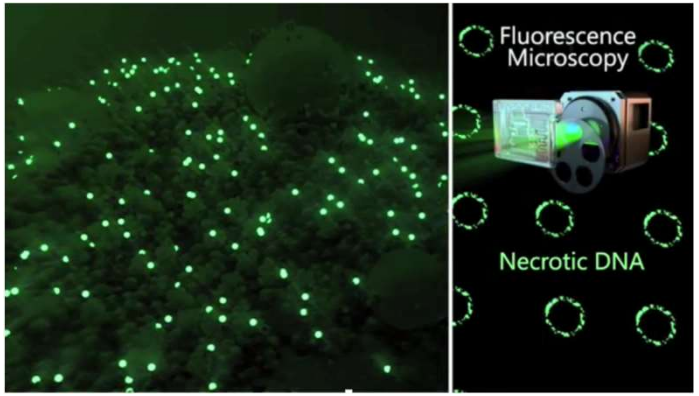
How can we use technology to screen cancers?

Need: minimally invasive, low cost, specific, and accurate strategy for low cost biomarker isolation and analysis for scalable cancer screening.

Approach:
Harness unique electrokinetic properties of biochips to isolate circulating nucleic acids and exosomes for early detection







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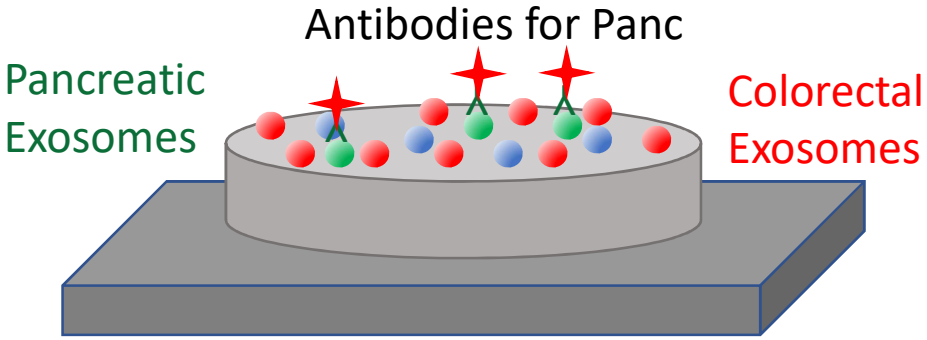
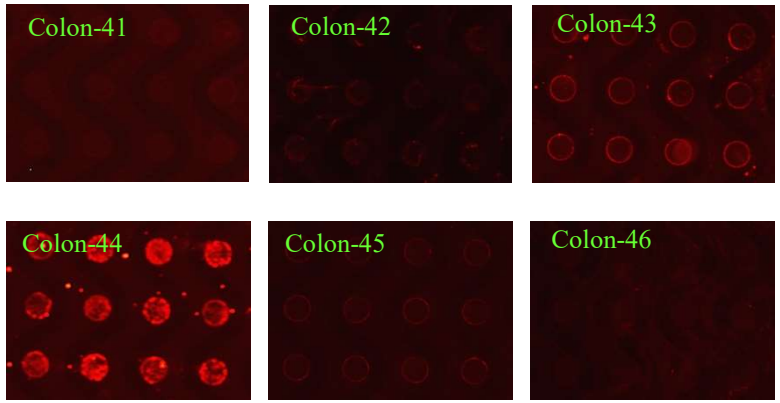
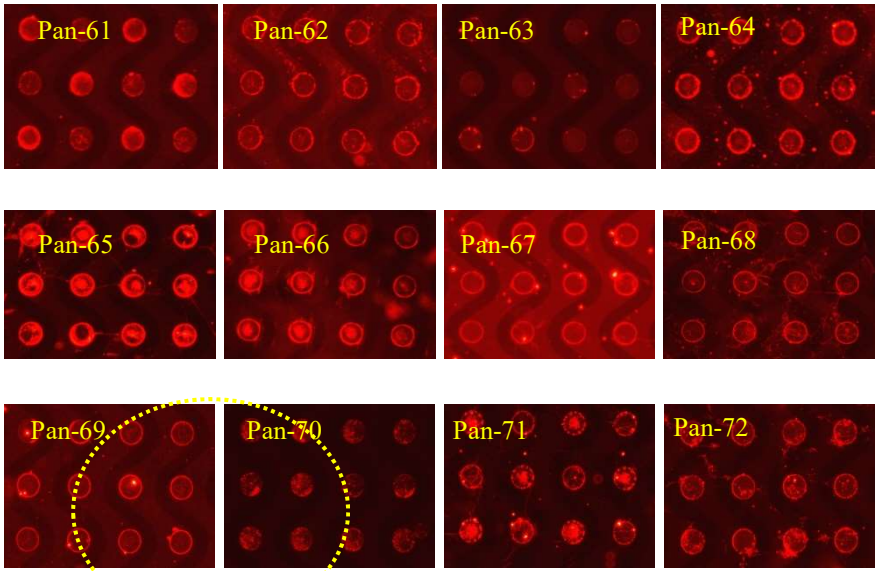
DEP Chip Isolation of Exosomes from Pancreatic and Colon Cancer Patient Plasma Samples

S. Ibsen, M. J. Heller and S. Esener Labs. UCSD



DEP 15-20 minutes, 50µl pancreatic or colon (control) cancer patient *archival* plasma sample On-Chip/In-Situ fluorescent double antibody assay Glypican-1 **(RED Fluorescence)**





Ibsen et.al. ACS Nano 2017

Smart Phone Enabled Portable Screening

Biological Dynamics (San Diego)

Courtesy of Biological Dynamics

Signs of Early Cancer: Liver Cirrhosis

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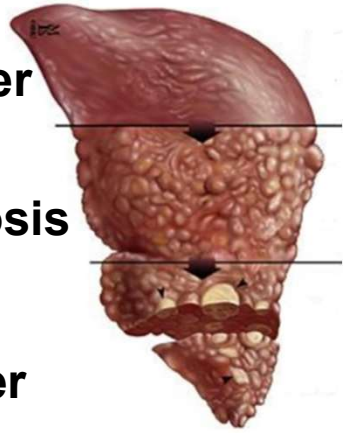
Healthy Liver

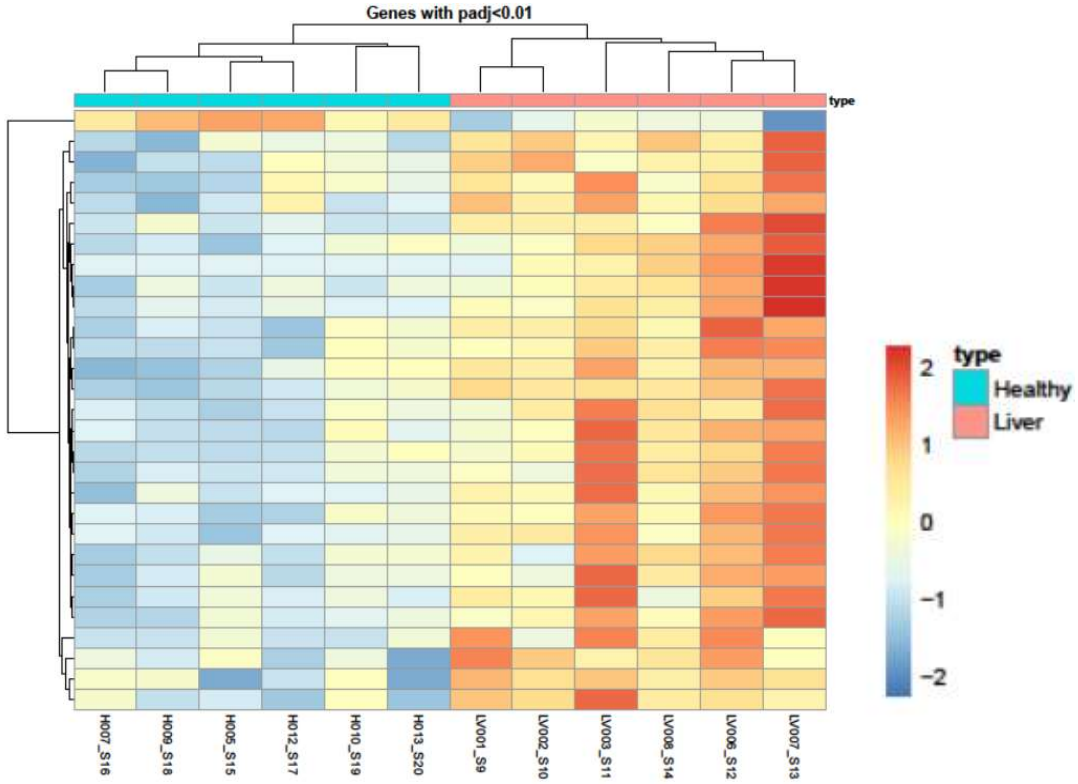
↓

Liver Cirrhosis

3-5%/y ↓

Liver Cancer





Identified a panel of **messenger RNA** from cell-free RNA sequencing that differentiates liver cirrhosis patients from healthy controls

This mRNA panel can now be used to follow patients at risk and their progression to liver cancer

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Global changes in the epigenetics: hallmark for cancer

Adapted from the Human Protein Atlas

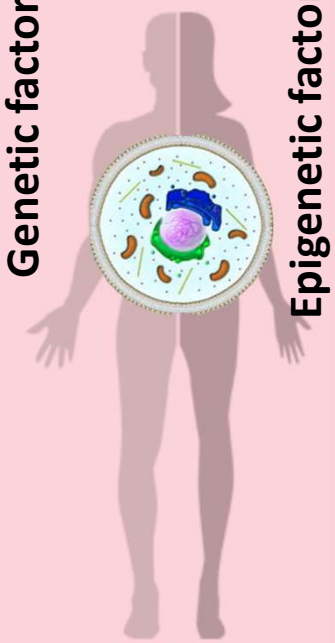
Intrinsic Factors:
Constitutive Genetics

Inheritance
Genetic alterations

External Factors:
Exposure to

Carcinogen: e.g., smoking
Radiation: e.g., UV light
Pathogens such as virus

Genetic factors



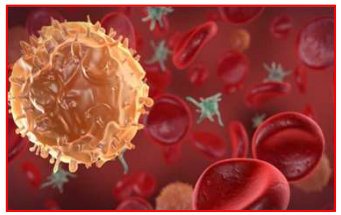
Epigenetic factors

Extrinsic Factors:
Systemic Regulators

Immune system
Hormones
Chronic disease

Local Regulators:

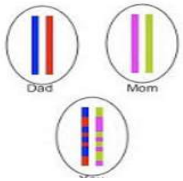
O2/Metabolism
Cell Cell Matrix
Physical Compartments



Disease

Carcinogen

Chemical



Diurnal patterns

Microbiome

Therapeutics

Exercise

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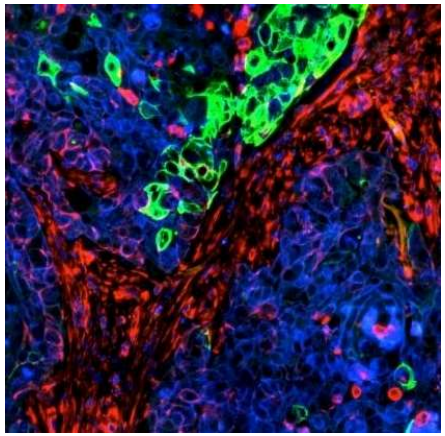
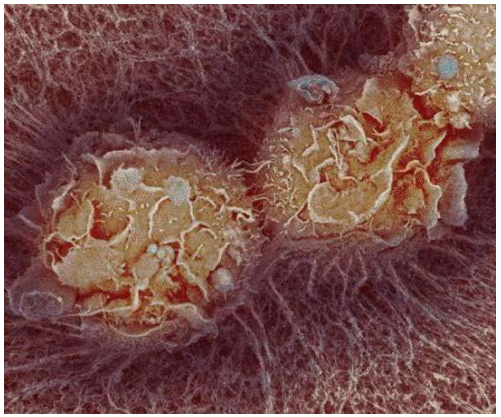
Multi-scale imaging: useful biomarkers may involve features across several length scales

Tissue Joe Gray



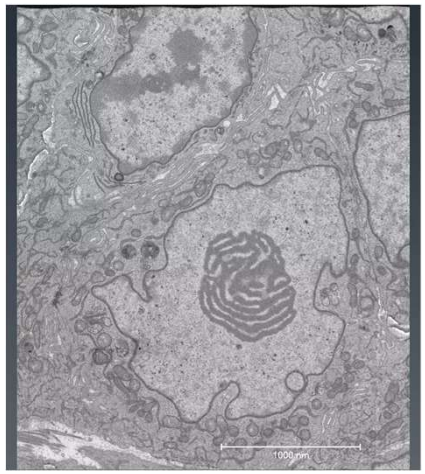
IHC Microcopy

Cell



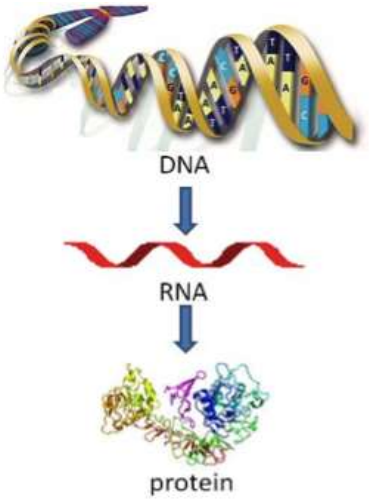
Nanoscale cell-cell interactions

Sub-Cell

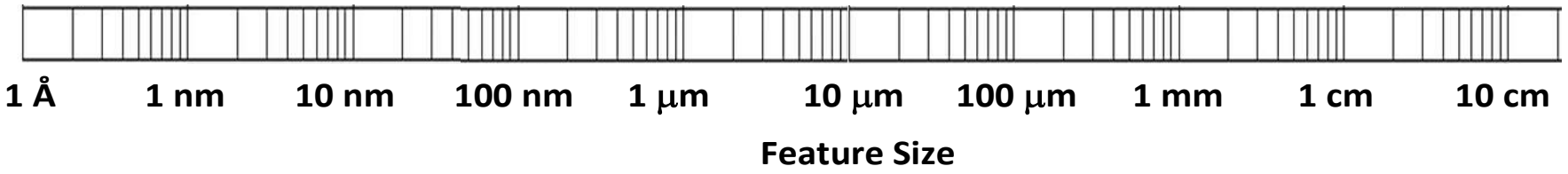


Chromatin & Nucleolus

Molecule



Knight Cancer Institute is developing tools to study cell-microenvironment interactions at many scales



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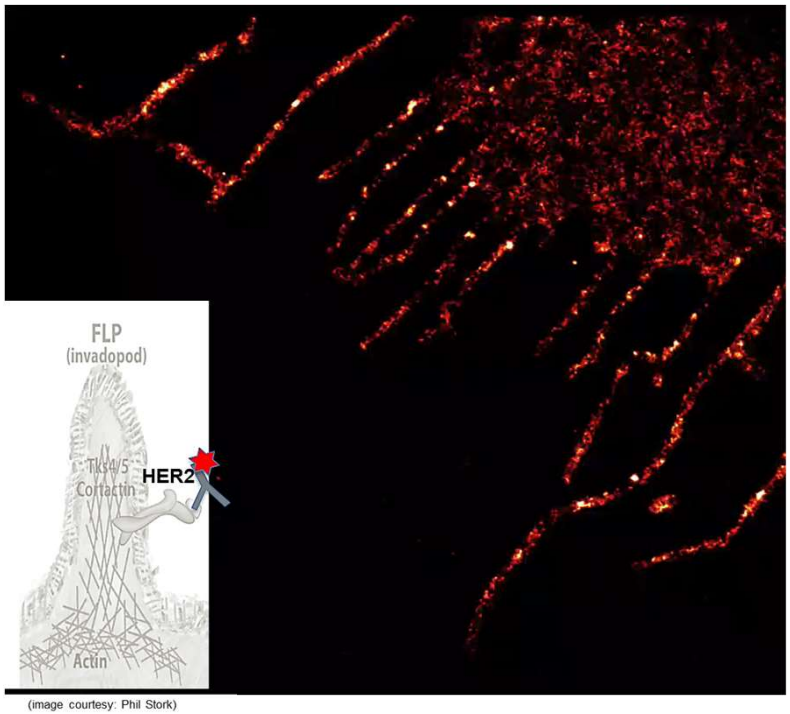
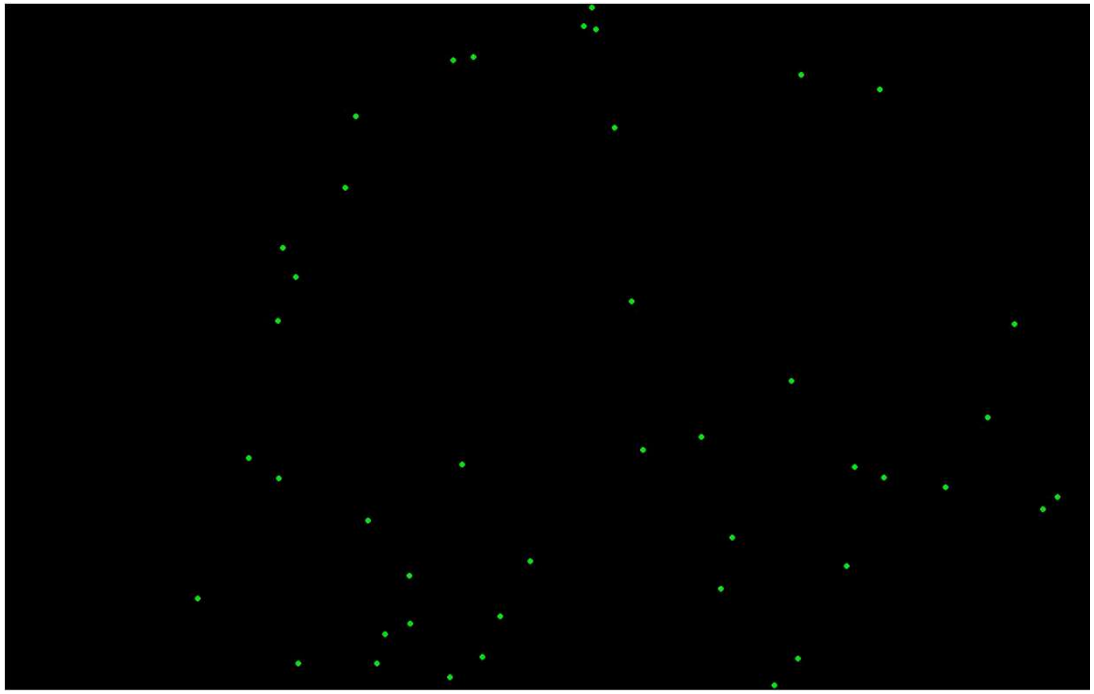
Nanoscale Biology:

Xiaolin Nan
<Nan@ohsu.edu>

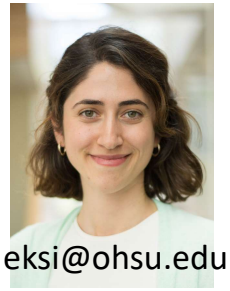
Visualization of: cell-cell interactions
cell inner workings





- **Filipodia-like structures** – Potential indicators of dynamic, cancer-microenvironment interactions that influence proliferation, invasion, ….

Spatial distribution of various proteins within a cell

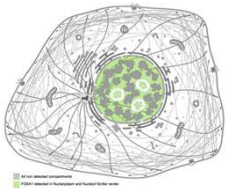


eksi@ohsu.edu

EPIGENETICS AND IMMUNE μ-ENVIRONMENT

aday@ohsu.edu

Biomarkers to distinguish indolent from aggressive disease

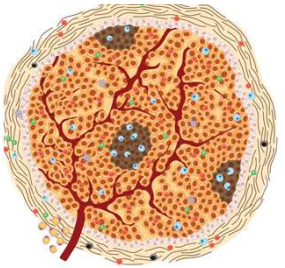


Human Protein Atlas

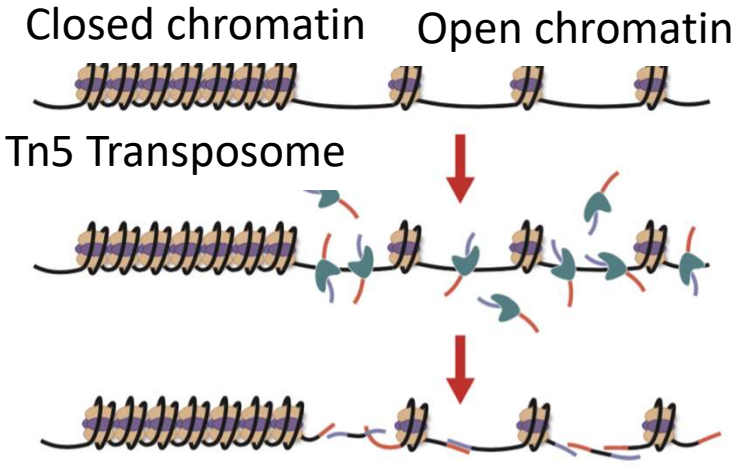
Capture cell identity based on
open and closed chromatin regions

Tumor heterogeneity

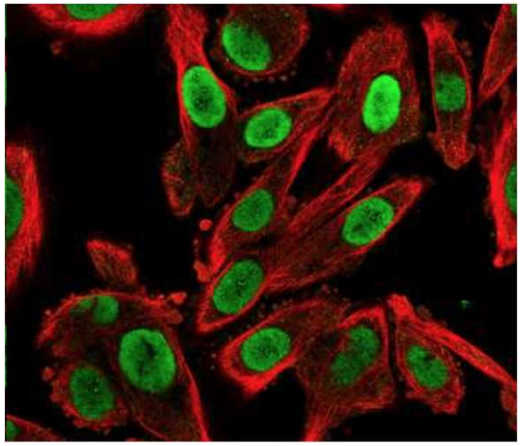
Tumor μ–environment



Asgharzadeh et al., 2017



Buenrostro et al., 2013



H&E staining

Epigenetic changes that occur in rare cells may capture the early transition to aggressive prostate cancer.

Changes in the tumor μ–environment can predict patient outcome.

Delineate the tumor and its environment spatially and at single-cell resolution by integrating IHC and ATAC-seq

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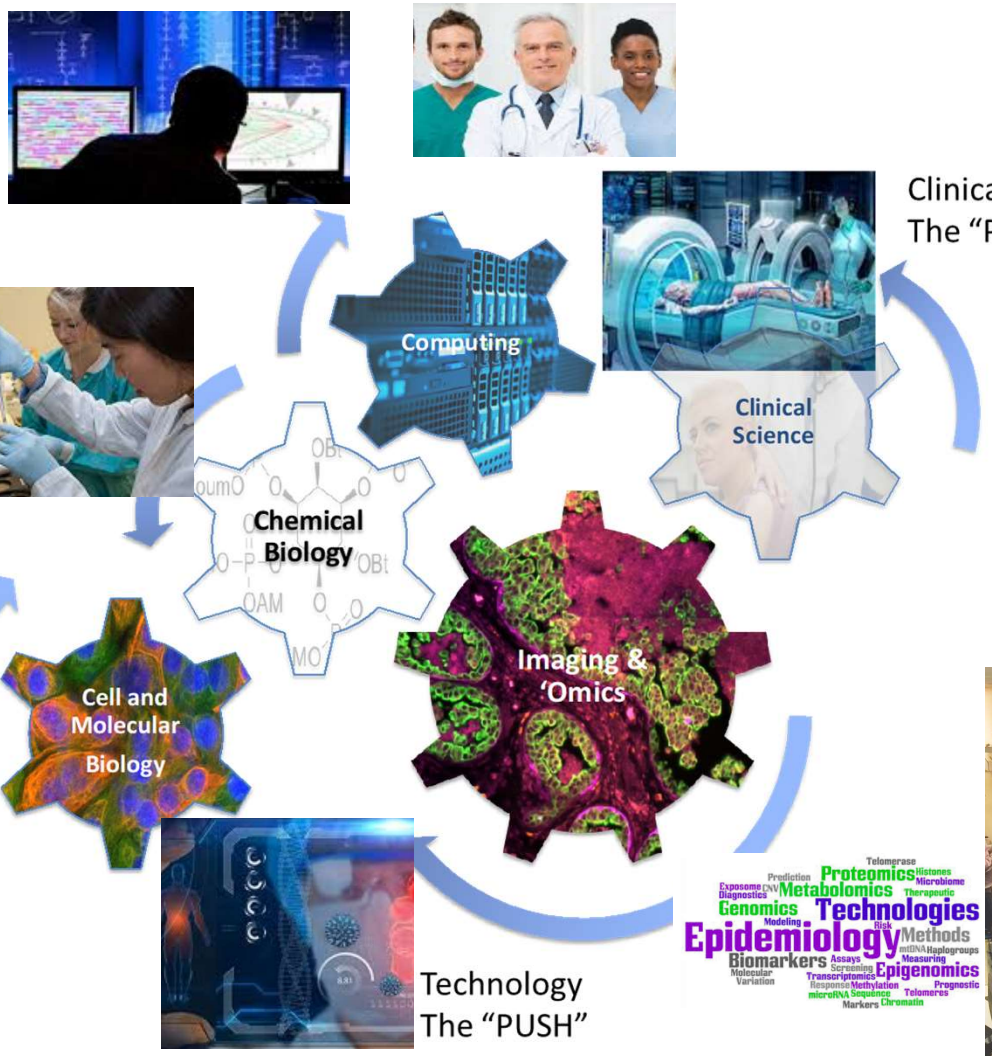
Our Expertise and Philosophy



Bringing together a social group whose members

- **have diverse backgrounds**
- **share government and**
- **have a common culture**
- **meet in a specific project neighborhoods**

Our guiding philosophy: teaming for the success of projects

A Flat Organizational Structure with a Diverse Talent Pool

3 Co-directors
Administrative Team

Mentors	Innovator
COLLABORATE (Integrators) Do Things That Last 15%	**CREATE *(Pioneers)*** Do New Things 10%
CONTROL (*Guardians*) Do Things Right 25%	**COMPETE (*Drivers*)** Do Things Now 50%
Specialists	**Students & Postdocs**

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Teaming to complement CEDAR capabilities

- Teaming among CEDAR Researchers
- Teaming with Oregon Institutions
- Teaming across the Nation
  Academic + Health care + Insurance
- **Teaming with Industry**
  Pharma and Instrumentation
- **Teaming with International Partners**

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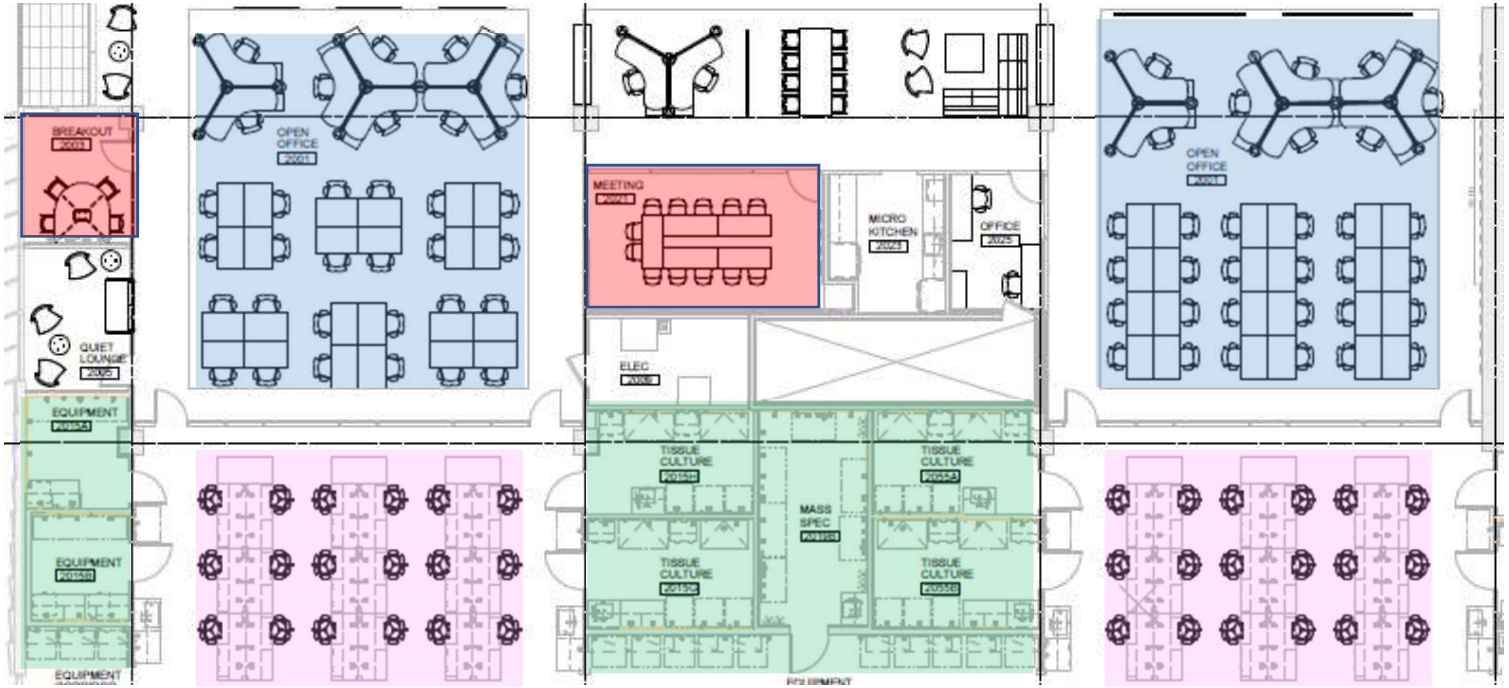
Shaping a Collaborative Environment



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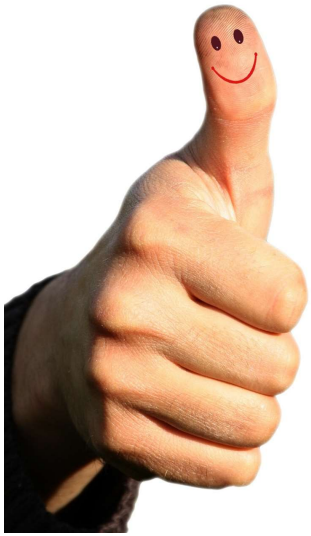
Defining Success

- Have we improved quality of life?
- Have we discovered something about cancer that wasn't known before?
- Have we created a global network of researchers focused on early cancer detection?
- Have we trained people for a diversity of careers?
- Have we made a positive impact to Oregon's economy?



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