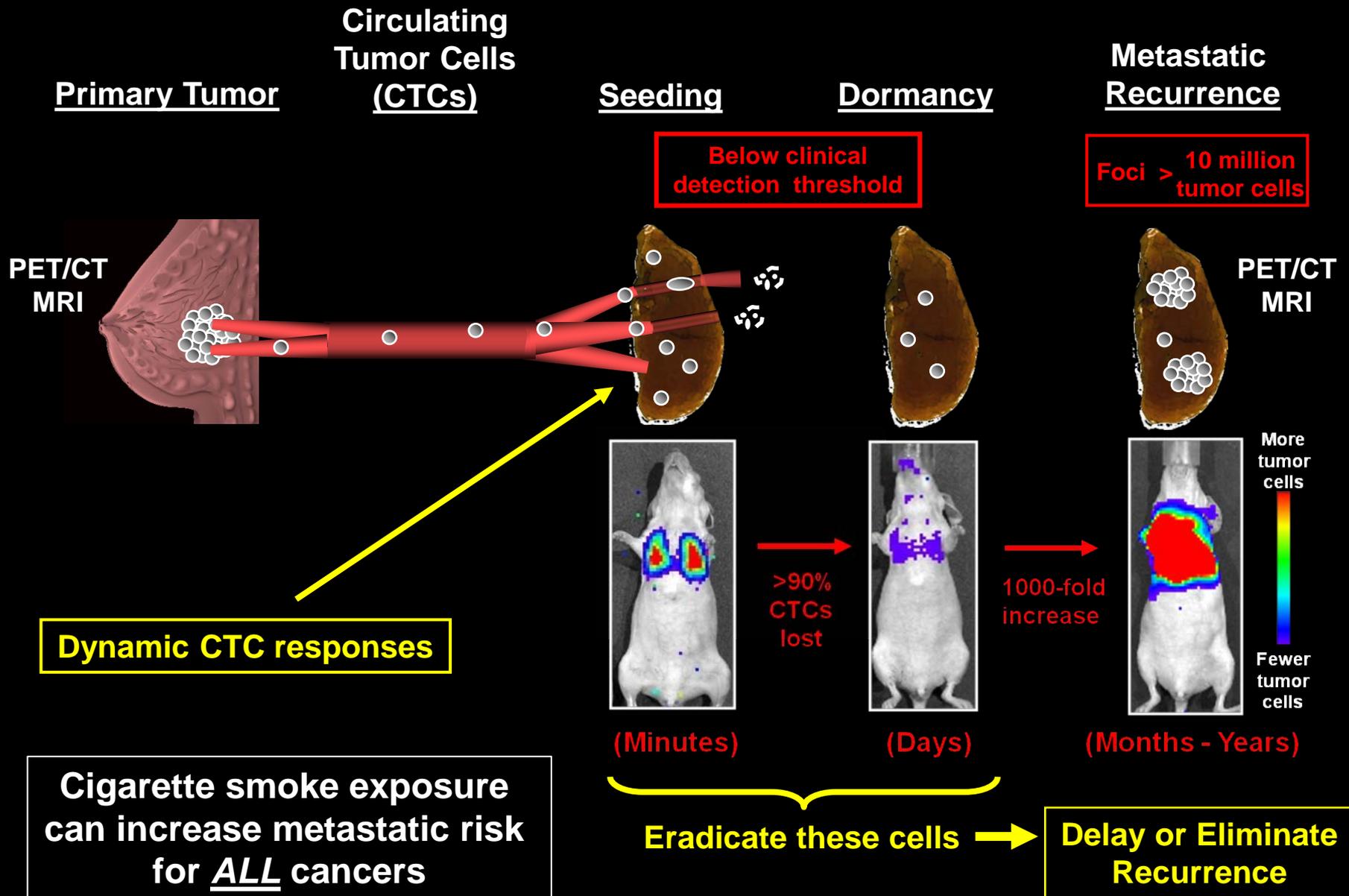# Targeting microtentacles on circulating breast tumor cells to reduce metastasis.

Stuart S. Martin, Ph.D.
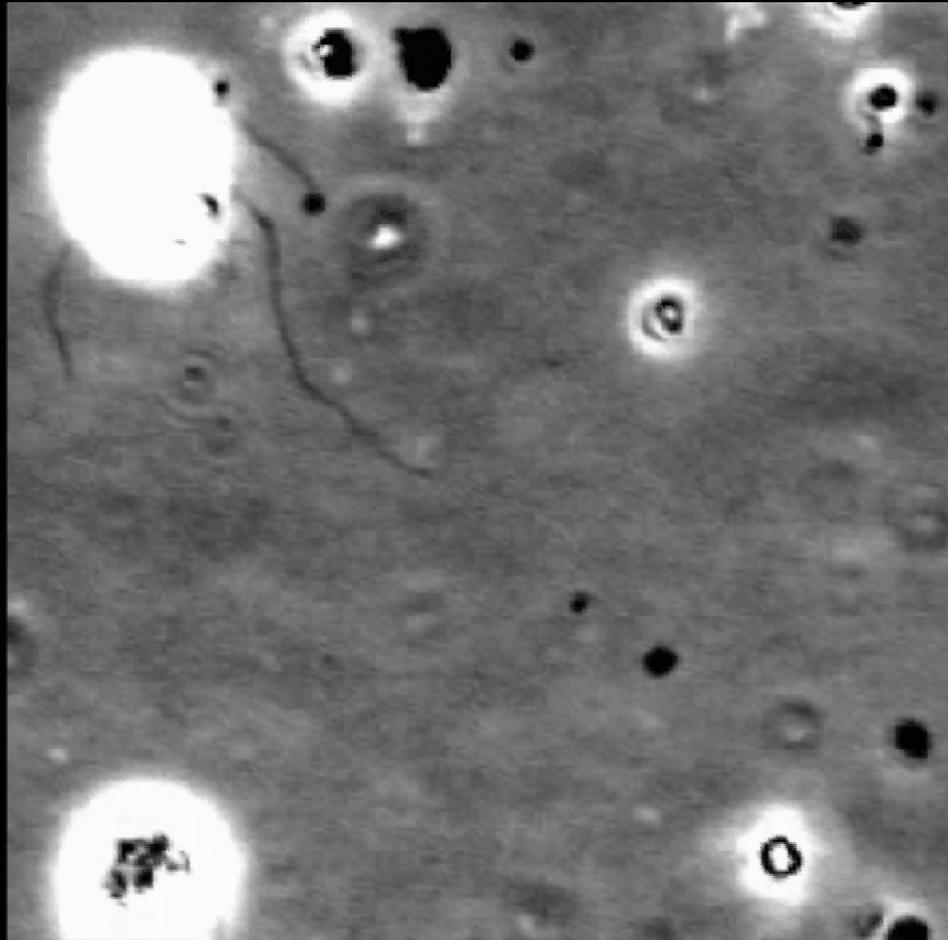*Associate Professor of Physiology*
University of Maryland School of Medicine

The limits of clinical imaging shape our understanding of cancer recurrence

Primary Tumor | **Circulating Tumor Cells (CTCs)** | **Seeding** | **Dormancy** | **Metastatic Recurrence**

Below clinical detection threshold

Foci > 10 million tumor cells

PET/CT MRI

PET/CT MRI

Dynamic CTC responses

>90% CTCs lost

1000-fold increase

More tumor cells

Fewer tumor cells

(Minutes)   (Days)   (Months - Years)

Cigarette smoke exposure can increase metastatic risk for _ALL_ cancers

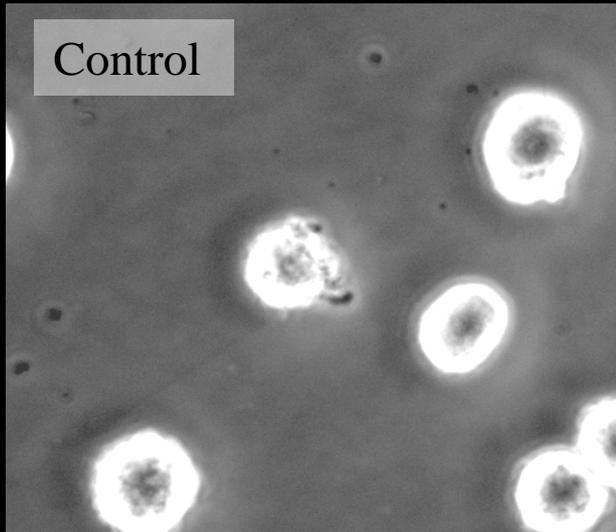**Eradicate these cells** → **Delay or Eliminate Recurrence**

"Dormant" cells produce dynamic membrane protrusions when detached
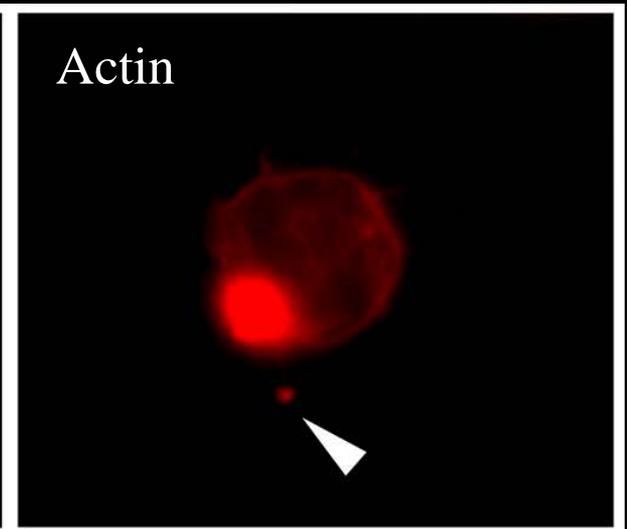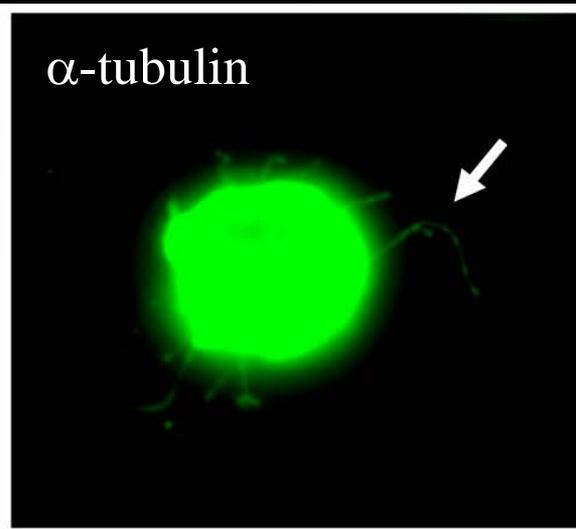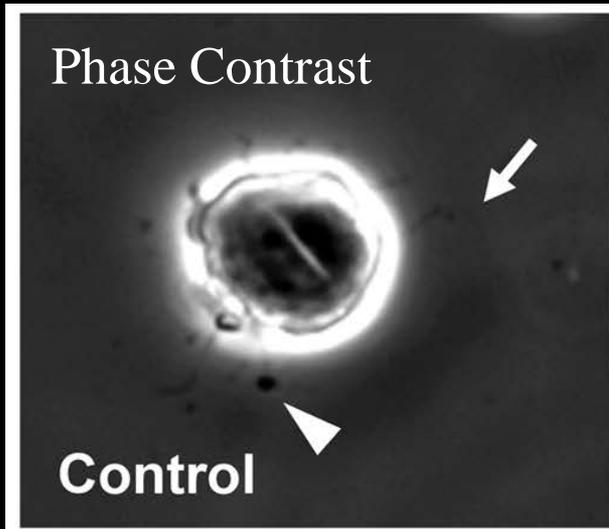

MCF10A mammary epithelial cells
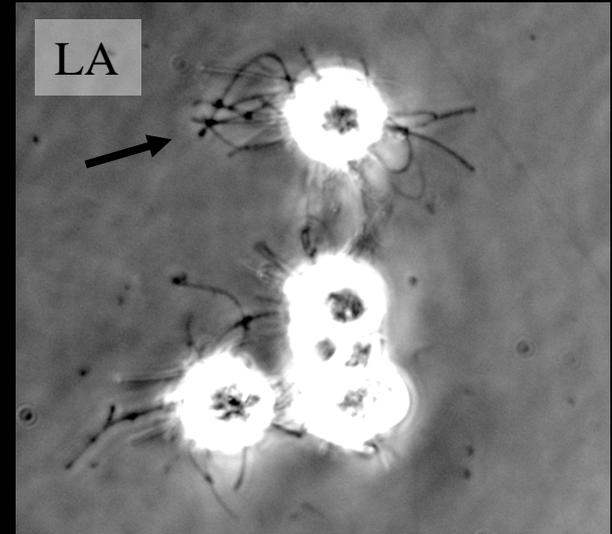
Frame / 1 sec.

Cytoskeletal support of membrane protrusions

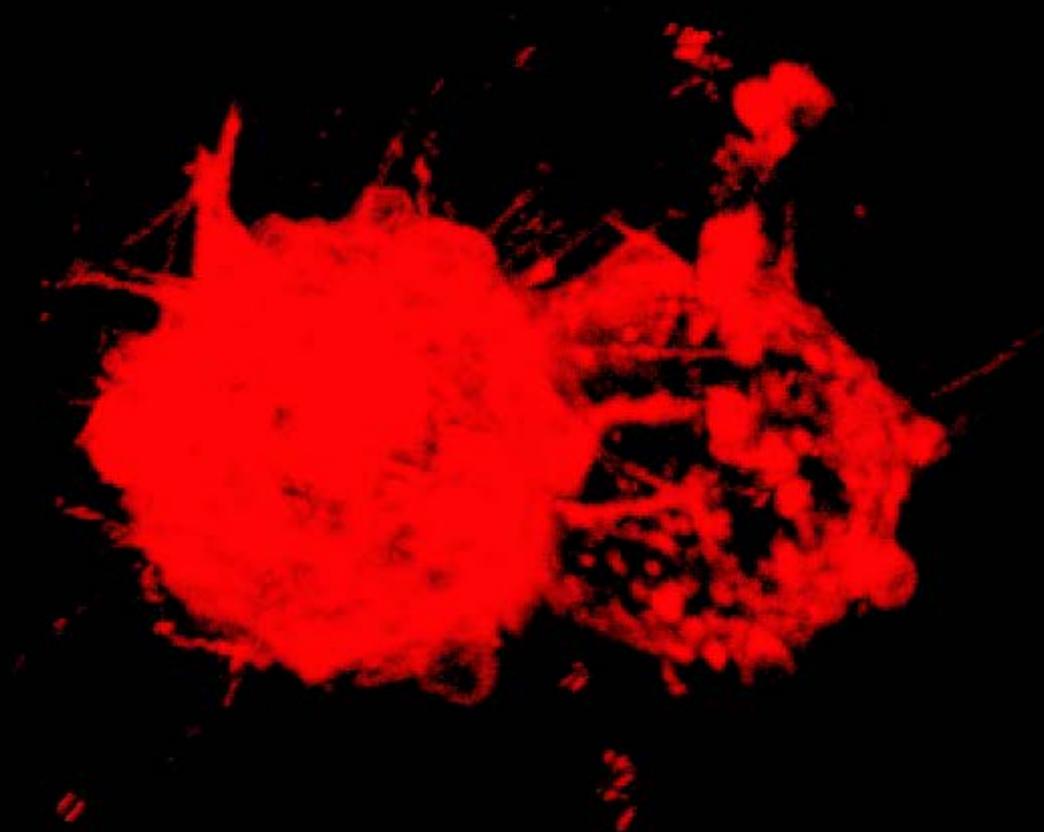**Rebecca Bettes et al., *Exp. Cell Res*. 313:1326-36 (2007).**

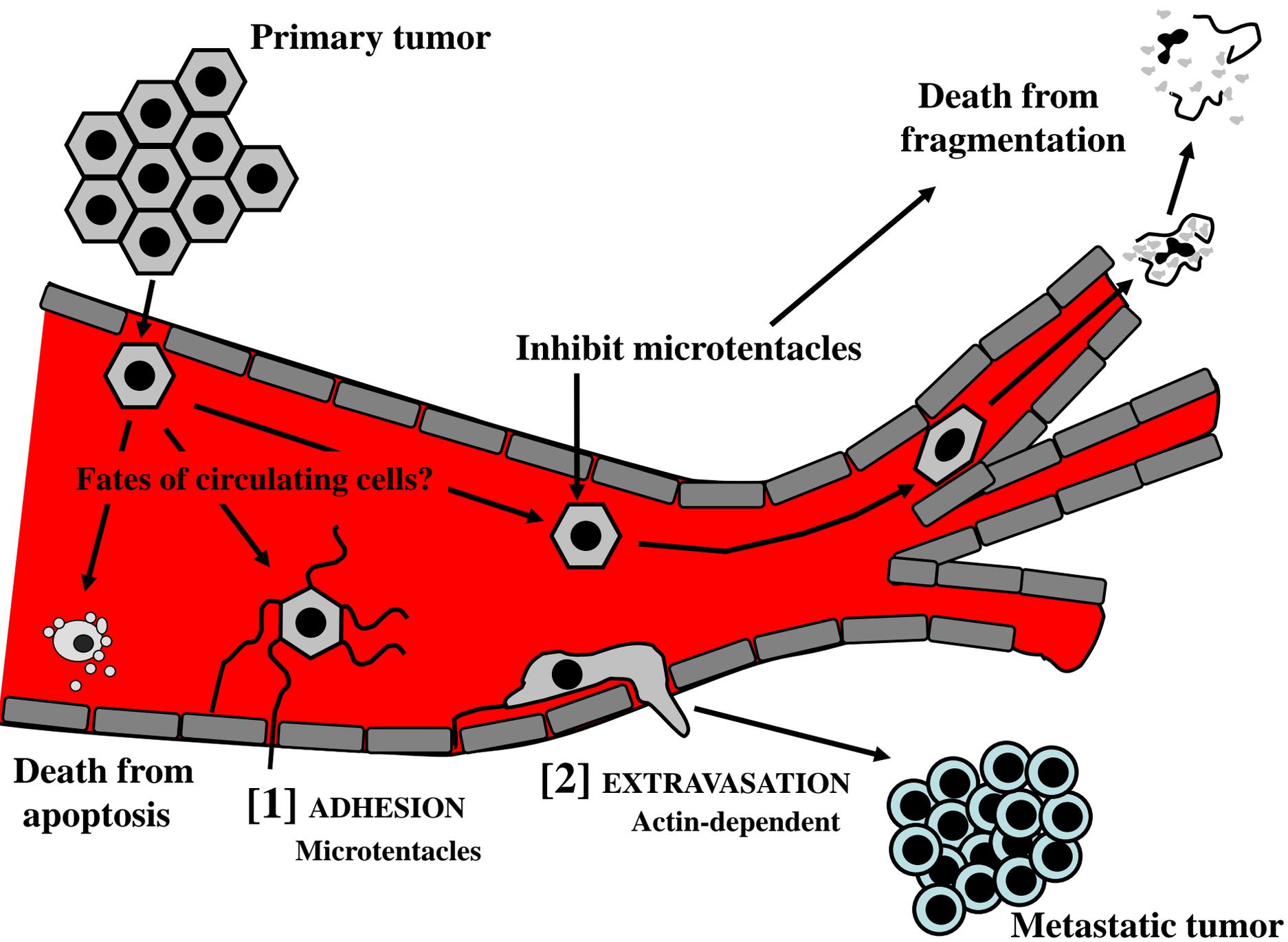# *Microtentacles* promote tumor cell aggregation (Live confocal imaging)

Microtentacles increase in invasive/metastatic breast tumor cell lines

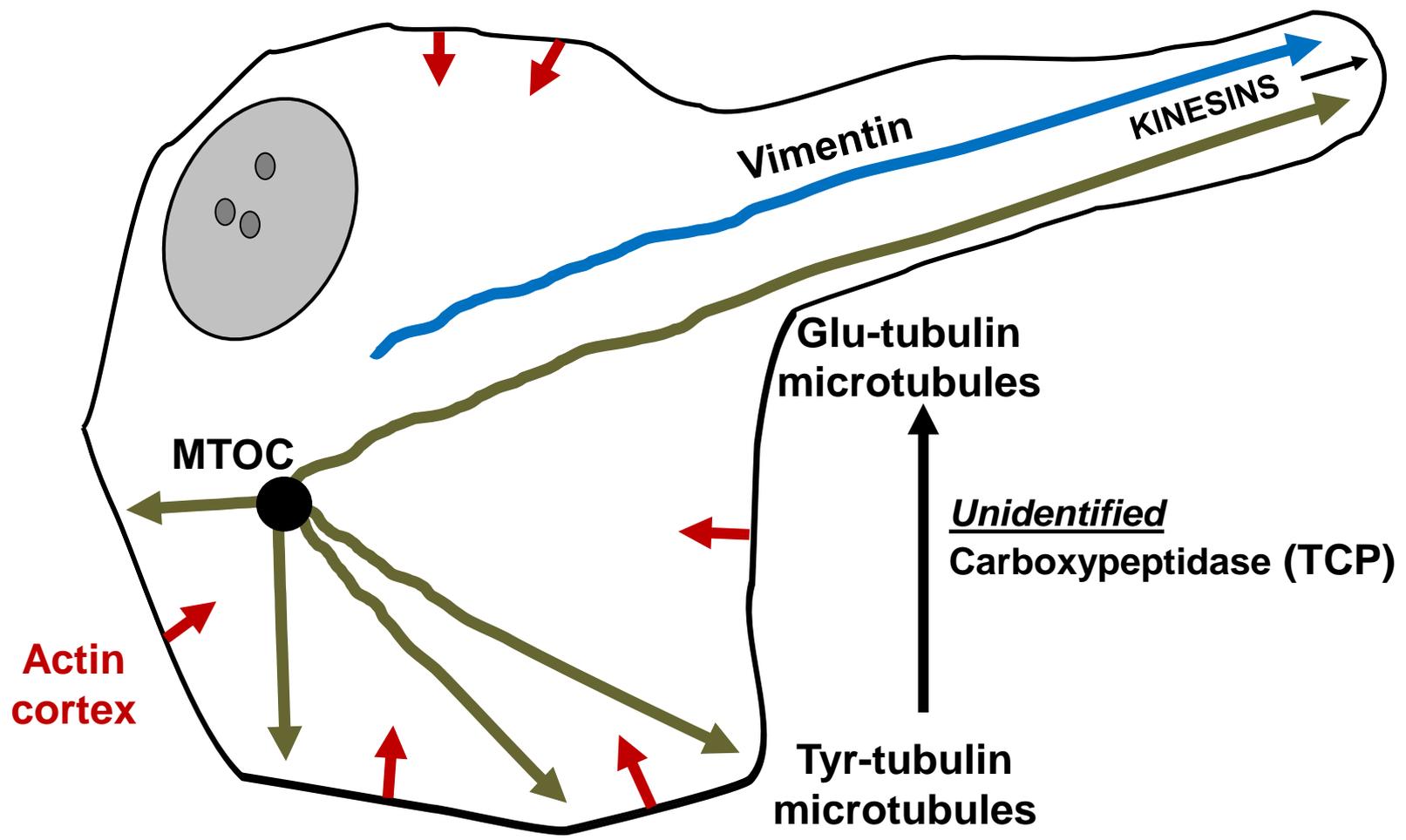Rebecca Whipple et al., *Cancer Research* 68:5678-5688 (2008).
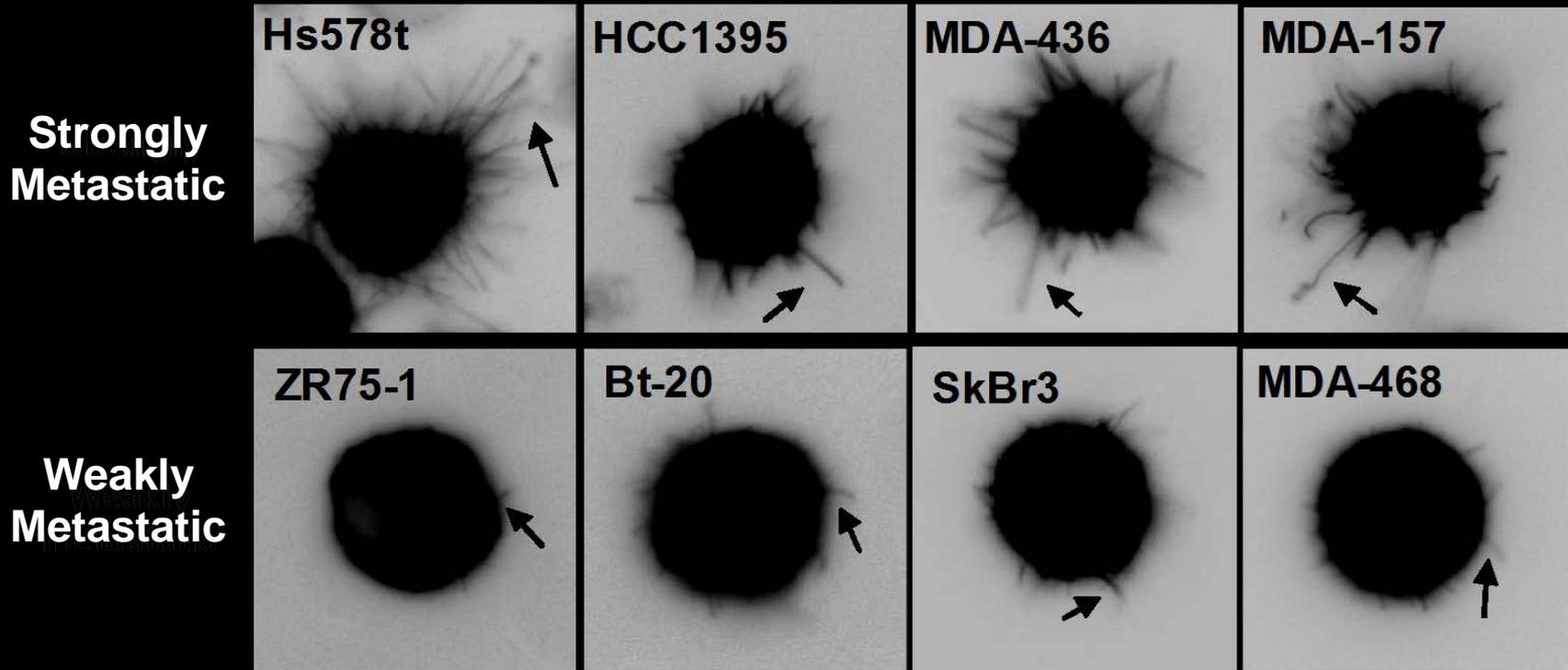
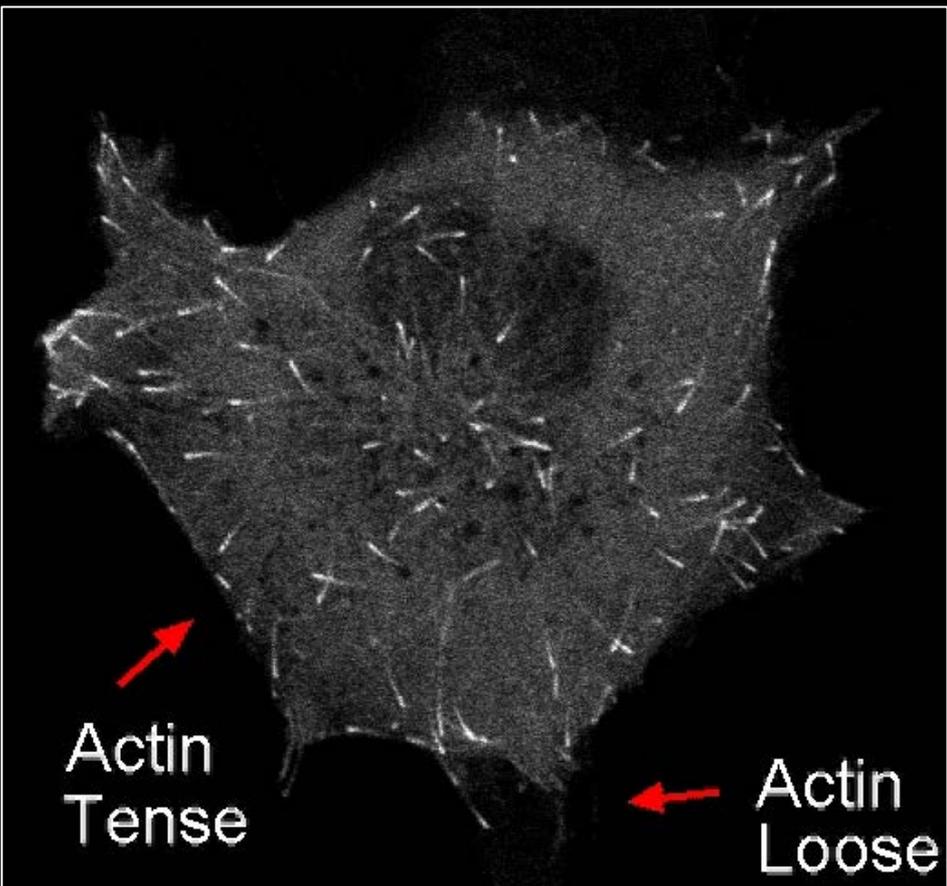# Confocal imaging of live tumor cell attachment to endothelial cells

Primary tumor

Death from fragmentation

Inhibit microtentacles

Fates of circulating cells?

Death from apoptosis

[1] ADHESION
Microtentacles

[2] EXTRAVASATION
Actin-dependent

Metastatic tumor

Current working model of microtentacle (McTN) structure

Vimentin

KINESINS

Glu-tubulin
microtubules

MTOC

Unidentified
Carboxypeptidase (TCP)
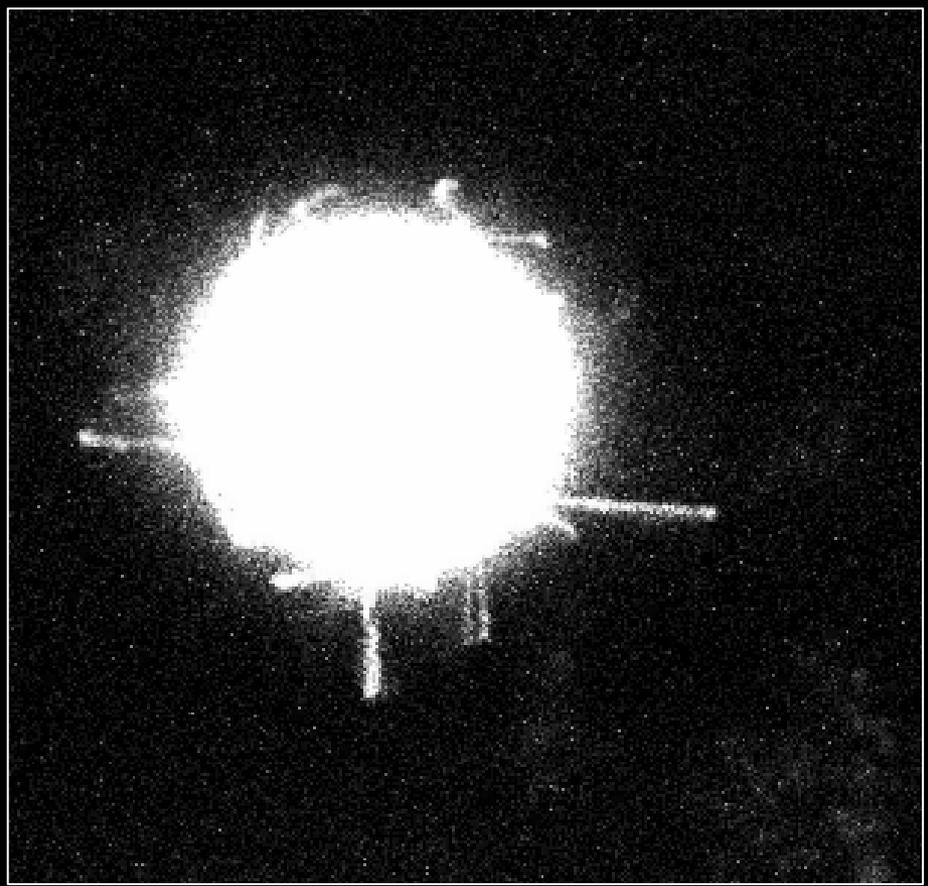
Actin
cortex

Tyr-tubulin
microtubules

Microtubule expansion is counteracted by actin cortical contraction
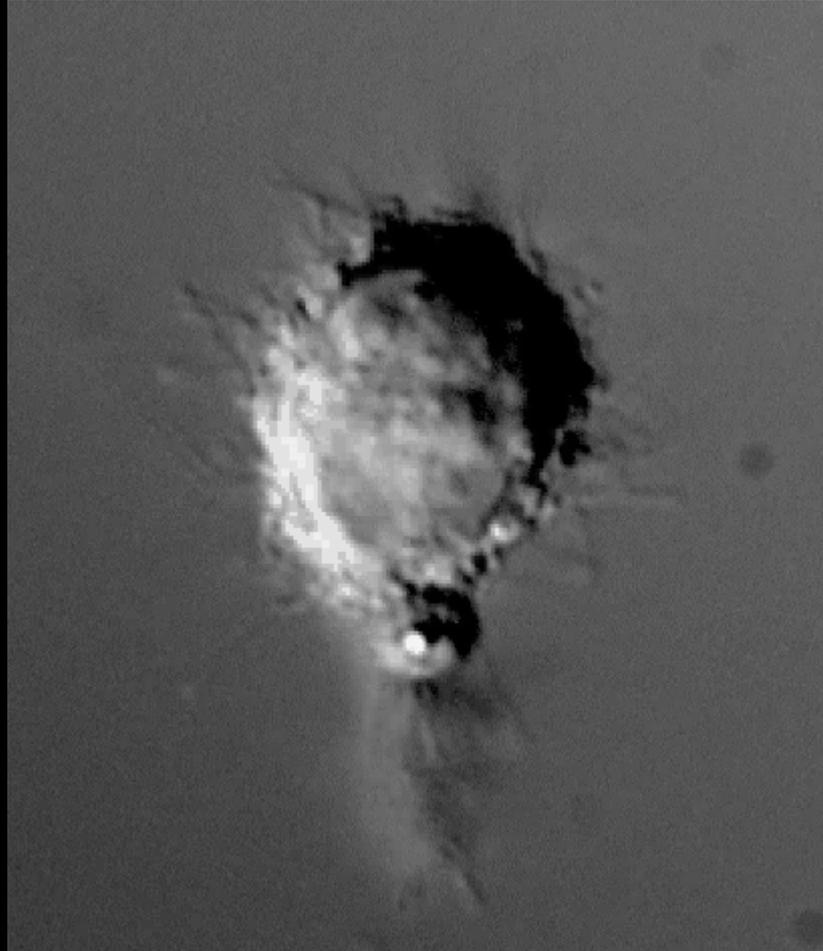## EB1-GFP imaging

ECM-attached cell

Detached cell
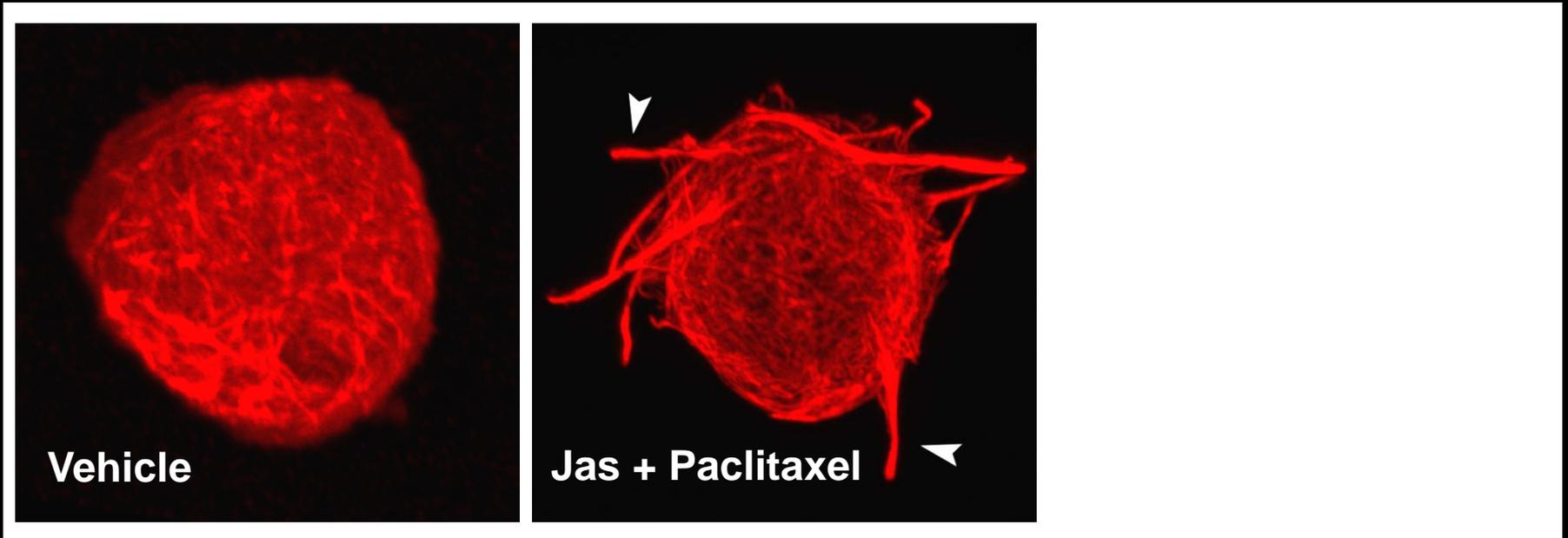
Kinesin inhibitors reduce microtentacles

Jennifer Yoon et al., *Breast Cancer Research and Treatment* **(2011)**

Tetracaine (125μM)

Drugs targeting cell division can enhance microtentacles

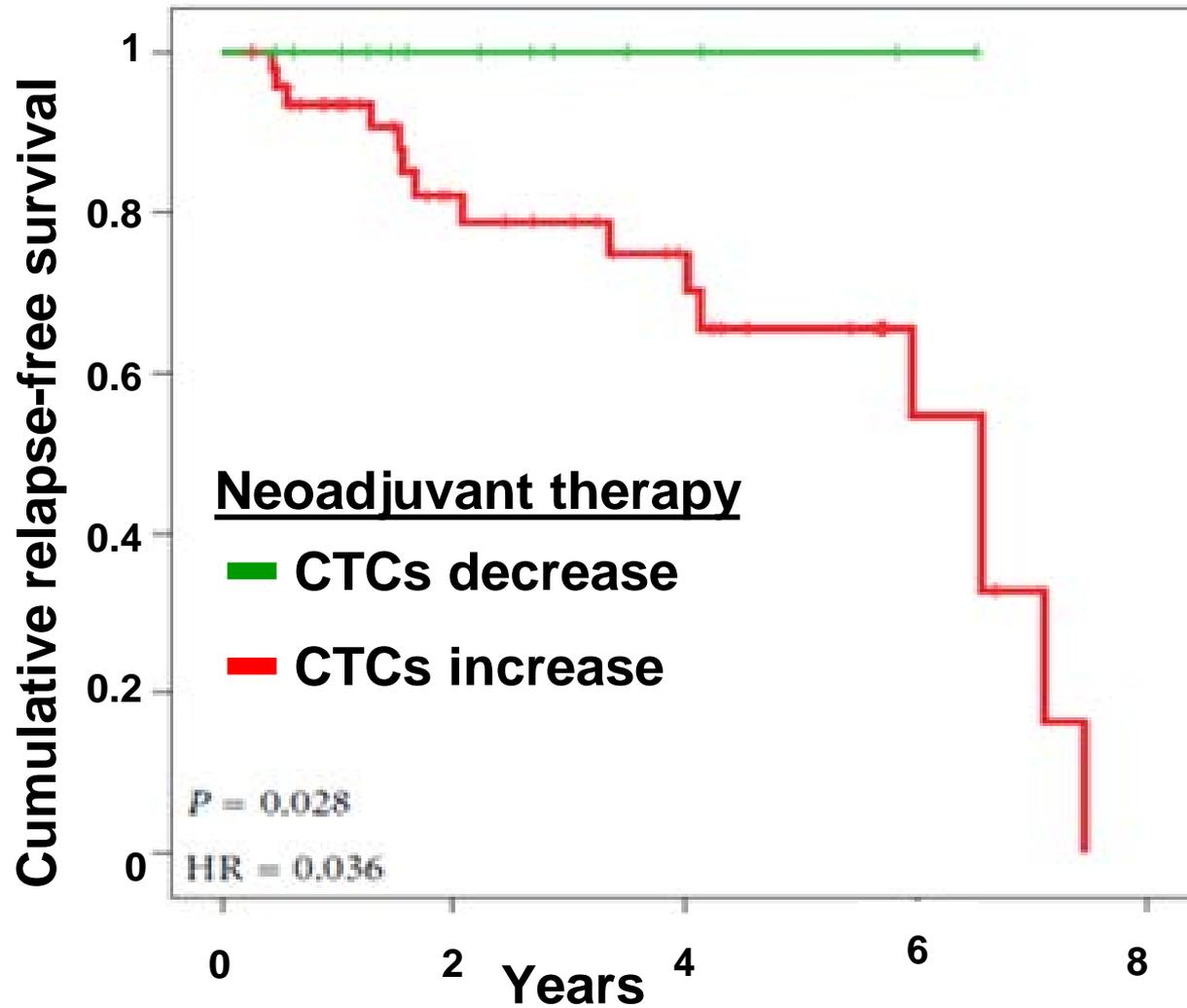Eric Balzer et al., *Breast Cancer Research and Treatment* (2010)

Vehicle

Jas + Paclitaxel

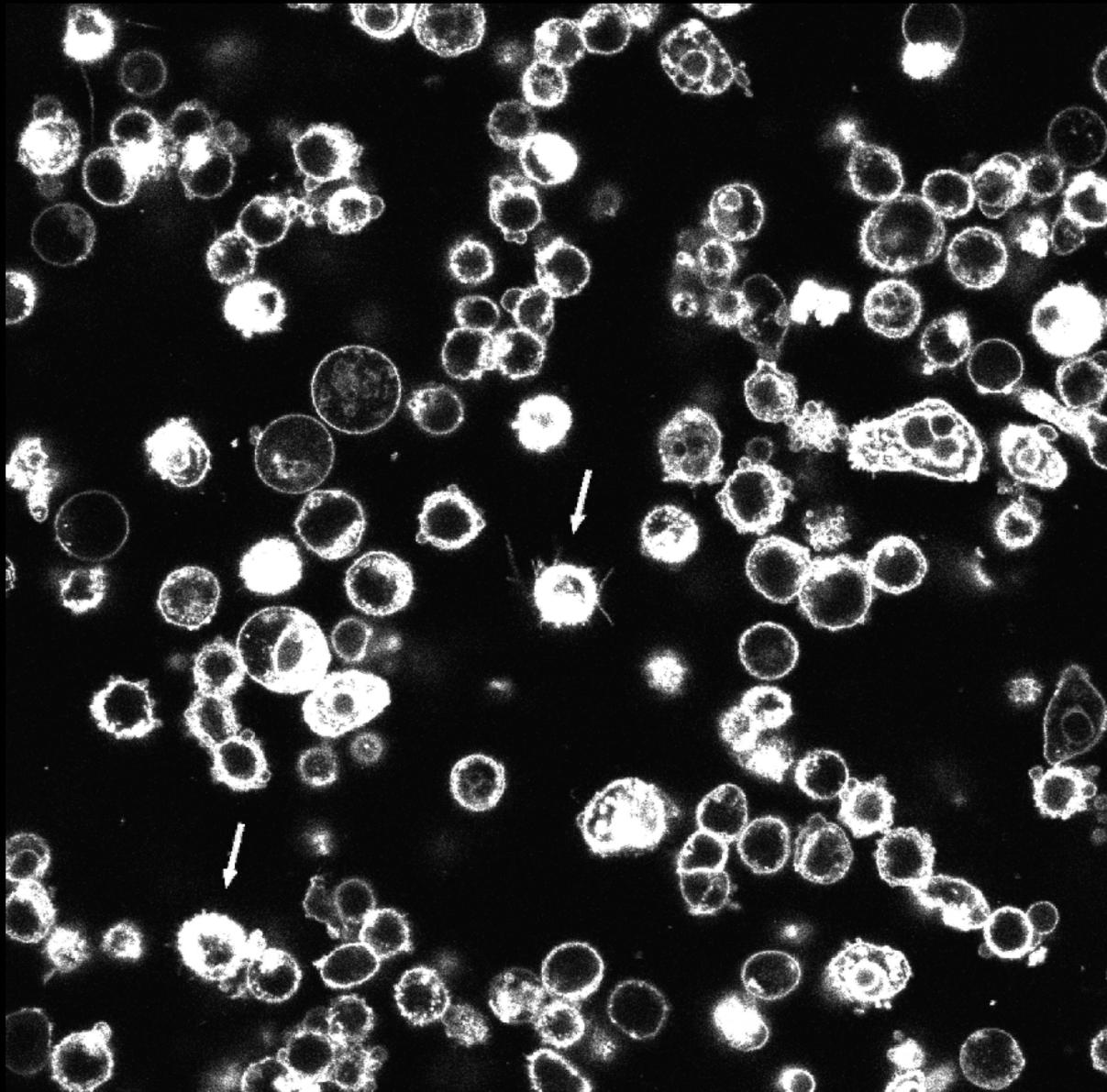↓ Tumor Growth · · · · · · · · · · → ↑ CTC Metastasis?

Chemotherapy before surgery and CTC levels
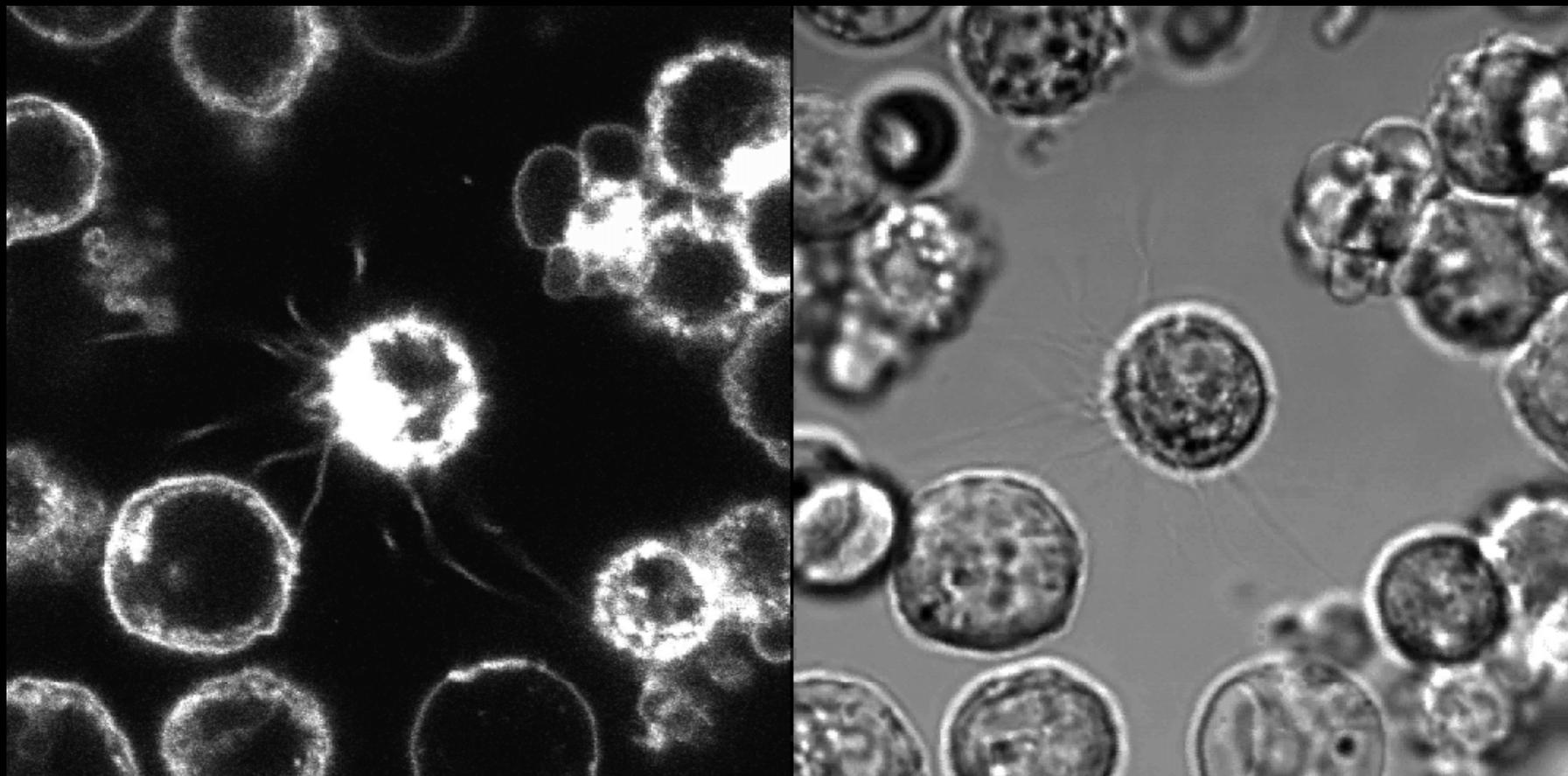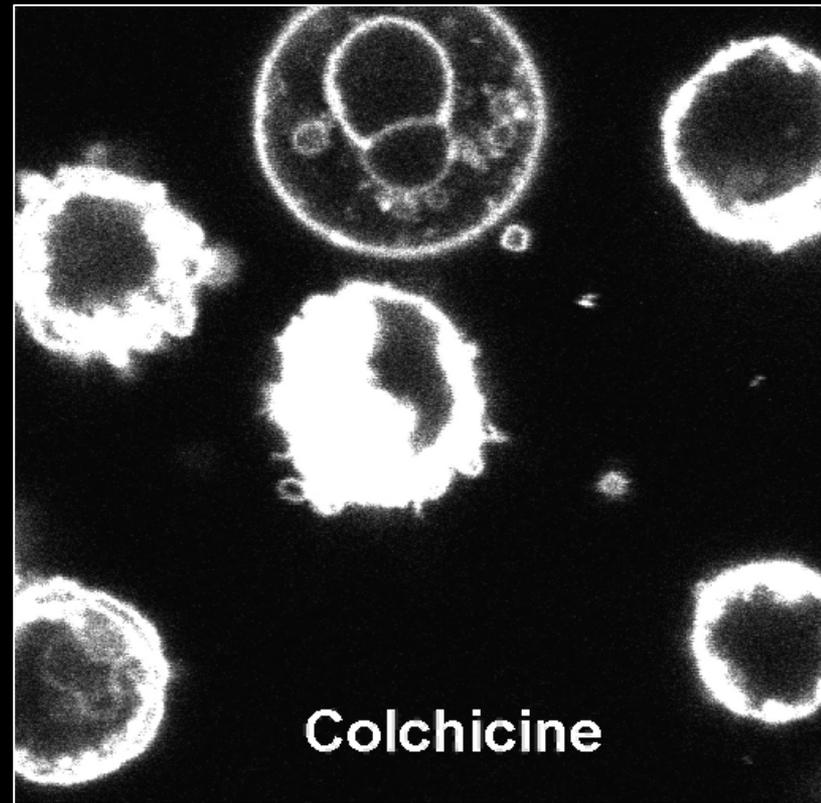
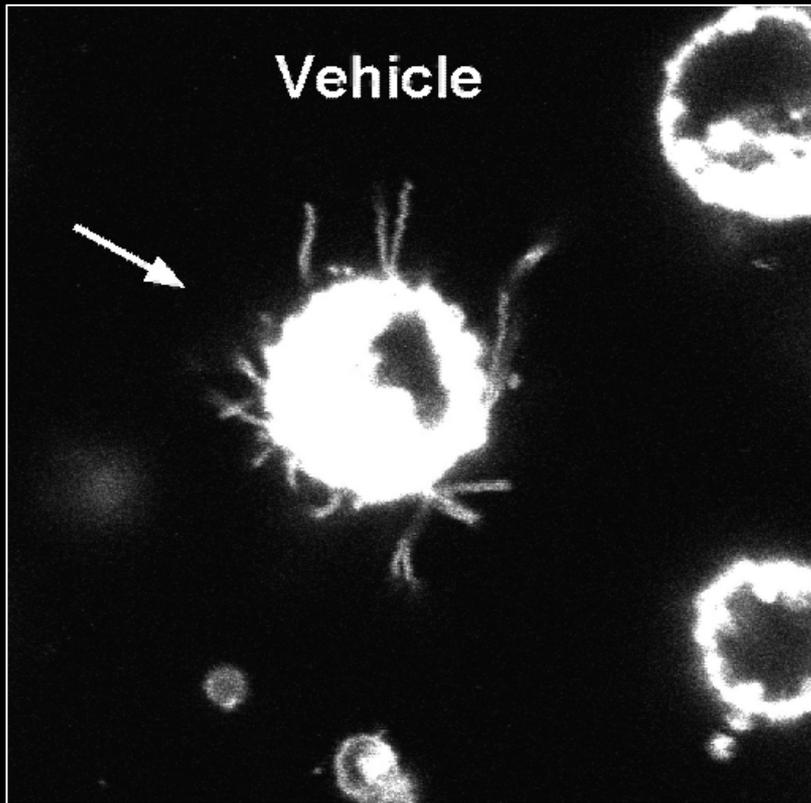(from Hekimian et al., 2012)

# Surgical samples from breast cancer patients (membrane dynamics)

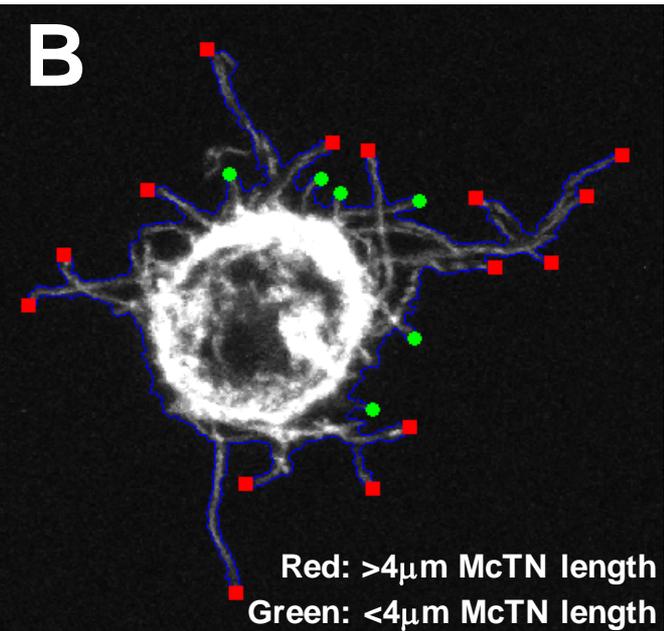**Surgical samples from breast cancer patients (membrane dynamics – 600x)**

Drug responses can be measured quickly in patient-derived tumor cells
(30 minute Colchicine response)

Automated measurement of McTN characteristics

Confocal imaging of patient tumorgraft cells (HCI-001)

Automated McTN Analysis (MATLAB)
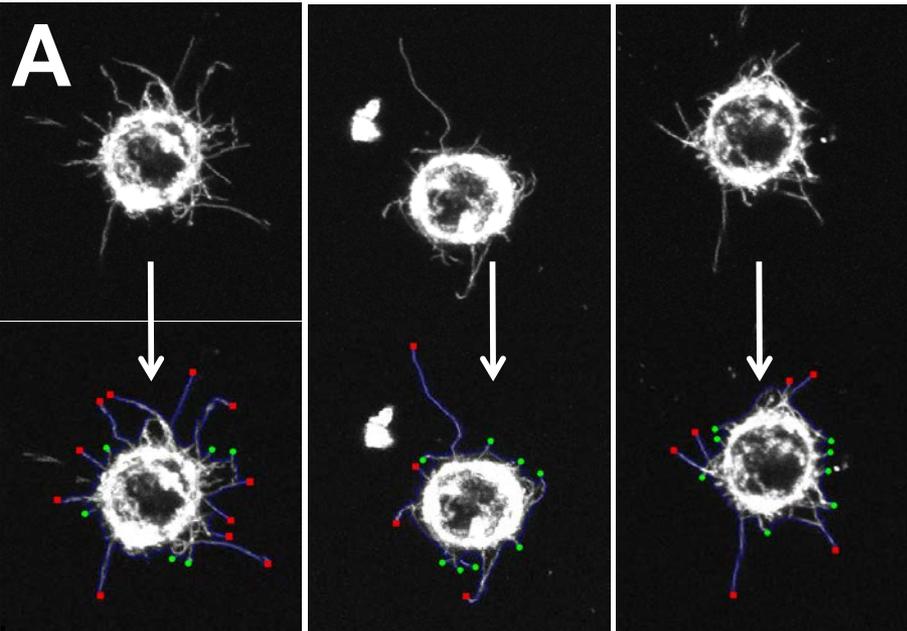
	A		
#McTNs/cell	11	4	6
Avg. McTN length (μm)	8.8	10.2	8.7

B

Red: >4μm McTN length
Green: <4μm McTN length

HCI-001 cell population
McTN frequency = 34%
Avg.# McTNs/cell = 9.0
Avg. McTN length = 9.1μm

Department of Physiology

University of Maryland
Marlene and Stewart
Greenebaum Cancer Center

NCI·CC
A Cancer Center Designated by the National Cancer Institute

Rebecca Whipple-Bettes

Eric Balzer

Agnes Cheung

Jennifer Yoon

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Mike Matrone

Michele Vitolo

Keyata Thompson

Monica Charpentier

Amanda Boggs
Lindsay Hessler

Susette Mueller (Georgetown)
Jing Yang (UCSD)
Josef Kas (Leipzig)
John Olson (Surgery)

UM-College Park
Wolfgang Losert
Chris Jewell
Ben Shapiro

Recruited from Harvard with CRF startup funds
Yielded 16 new grants to date
DoD Era of Hope Scholar – only 3 awards nationwide

$601,019 CRF funds → $11,138,912 new grant funding

<u>1,853</u>% return on CRF investment

Many new research and administrative jobs supported
(now and for years to come – through 2020 at least)

New collaborations and grant applications with:
College Park Engineering
Johns Hopkins
Local Maryland companies (SBIR)