Novel Ways to Target and Develop Therapies for Cancer Metastases: Stop Spreading the New

Moderator: **Joel S. Sandler**, PhD, Associate Principal, Cello Health BioConsulting, previously Defined Health

Panelists:

- **Yibin Kang**, PhD, Warner-Lambert/Parke-Davis Professor of Molecular Biology, Princeton University
- **Llew Keltner**, MD, PhD, Chief Executive Officer, Epistat
- **Chand Khanna**, DVM, PhD, DACVP, Director, Vuja De Sciences Chief Science Officer, Ethos Veterinary Health, President, Ethos Discovery Vuja De
- **Jackson Streeter**, MD, Senior VP Corporate Development and Strategy, Quanterix
- **Maurice Zauderer**, PhD, President & Chief Executive Officer, Vaccinex, Inc.

The Challenge

UNMET NEED

- Vast majority (~90%) of cancer deaths attributable to mets
- Clin-reg path selects for tumor shrinkage, not anti-mets activity
- Dearth of clinical candidates and validated biomarkers for patient selection, real-time detection

BIOLOGICAL COMPLEXITY

- Genetically unstable cells adapted to survive selective forces
- Absence of any single dominant pathway for therapeutic targeting
- Ill-defined TME, distinct from that of 1° tumors
- Metastatic dormancy during lengthy DFIs

Stage of Diagnosis is Topmost Prognostic Indicator

Table 8. Five-year Relative Survival Rates* (%) by Stage at Diagnosis, US, 2006-2012

	All stages	Local	Regional	Distant		All stages	Local	Regional	Distant
Breast (female)	90	99	85	26	Ovary	46	92	73	29
Colon & rectum	65	90	71	14	Pancreas	8	29	11	3
Esophagus	18	41	23	5	Prostate	99	>99	>99	29
Kidney†	74	93	66	12	Stomach	30	67	31	5
Larynx	61	76	45	35	Testis	95	99	96	74
Liver‡	18	31	11	3	Thyroid	98	>99	98	55
Lung & bronchus	18	55	28	4	Urinary bladder§	78	70	35	5
Melanoma of the skin	92	98	62	18	Uterine cervix	68	91	57	17
Oral cavity & pharynx	64	83	63	38	Uterine corpus	82	95	69	17

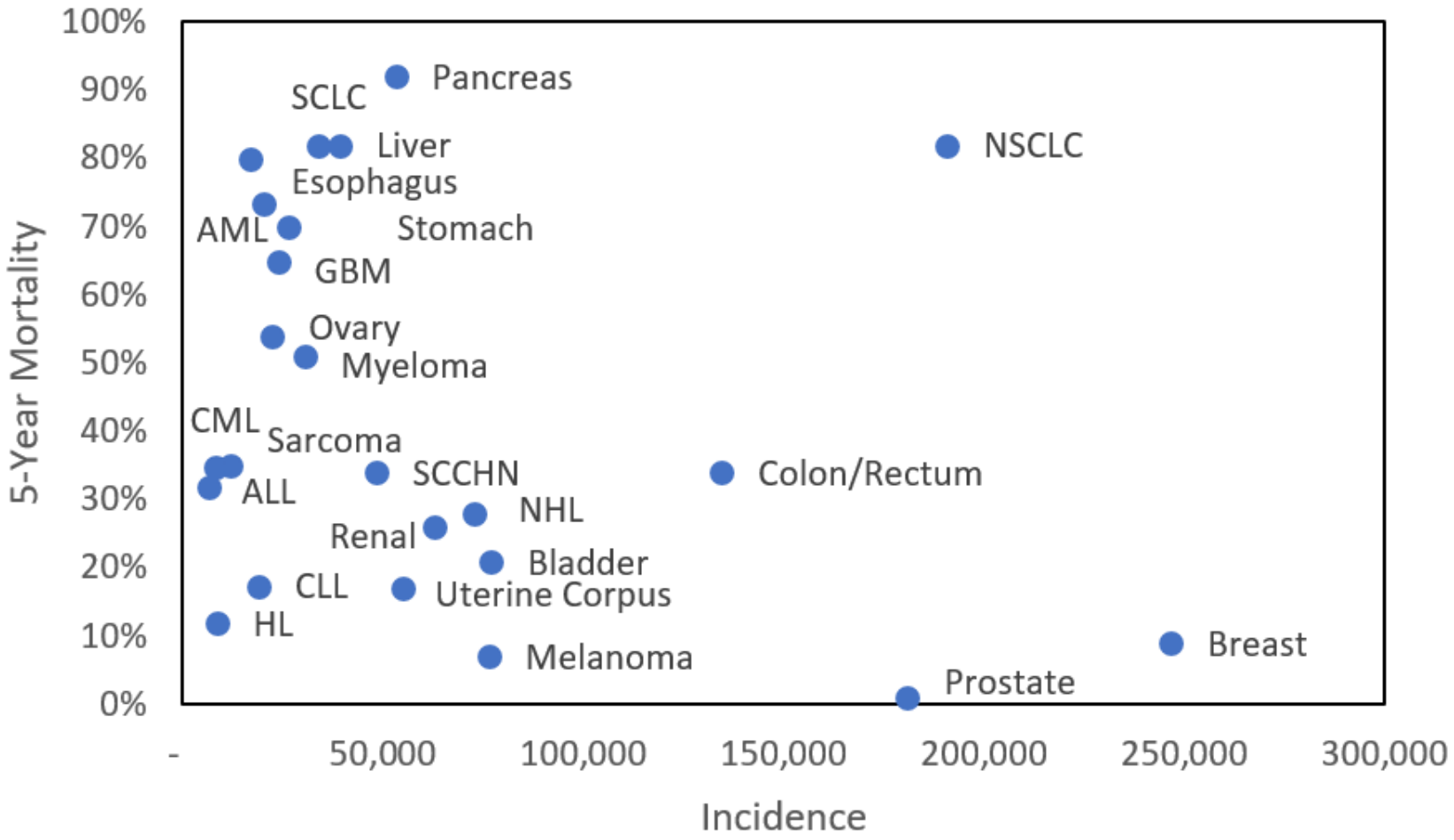
*Rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2006-2012, all followed through 2013. †Includes renal pelvis. ‡Includes intrahepatic bile duct. §Rate for in situ cases is 96%.

Local: an invasive malignant cancer confined entirely to the organ of origin. **Regional:** a malignant cancer that 1) has extended beyond the limits of the organ of origin directly into surrounding organs or tissues; 2) involves regional lymph nodes; or 3) has both regional extension and involvement of regional lymph nodes. **Distant:** a malignant cancer that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis to distant organs, tissues, or via the lymphatic system to distant lymph nodes.

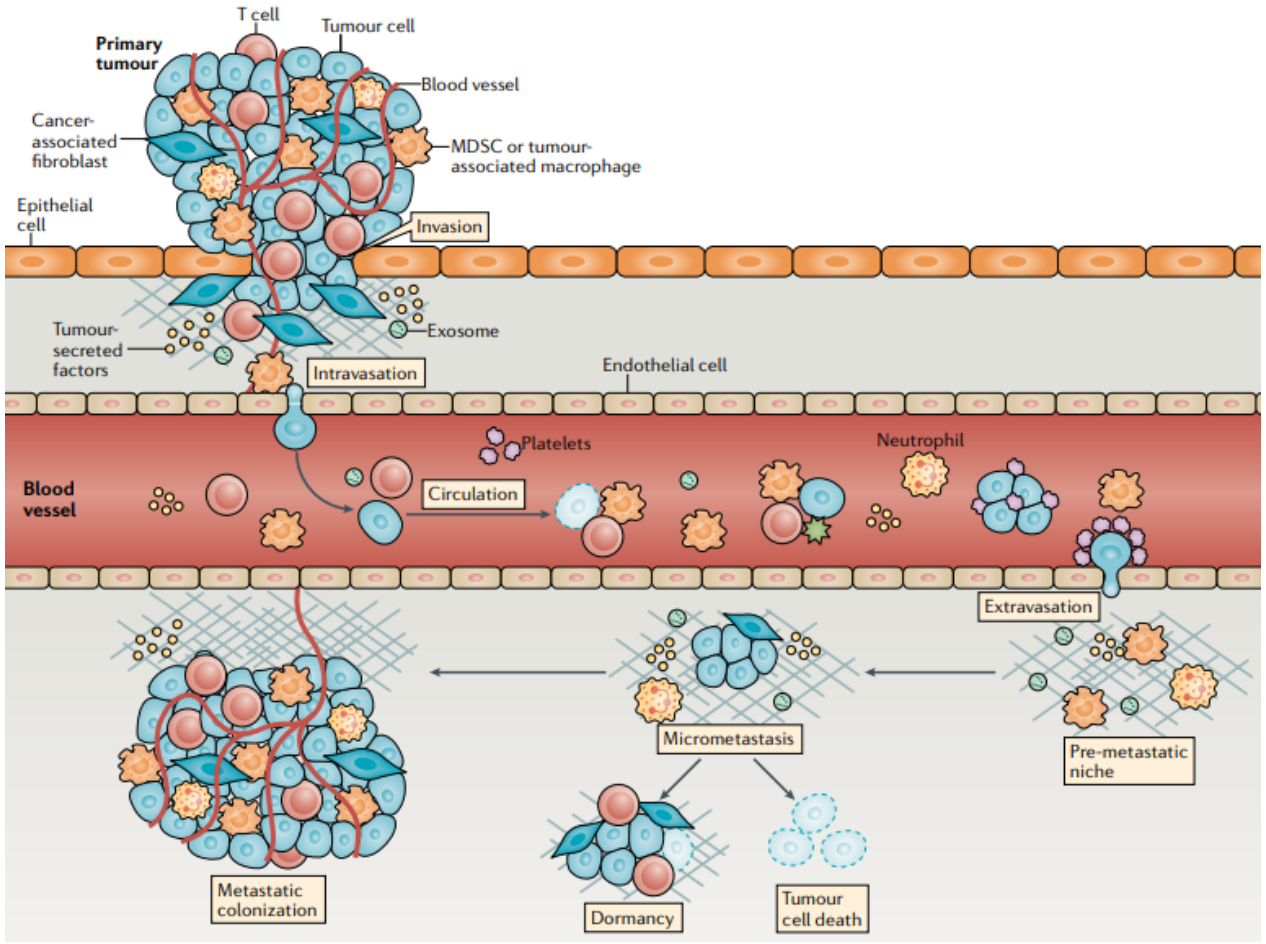
Source: Howlader N, Noone AM, Krapcho M, et al. (eds). *SEER Cancer Statistics Review, 1975-2013*, National Cancer Institute, Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER website April 2016.

cancer.org

Incidence and Unmet Need are Separate Entities



Biological Complexity and Therapeutic Strategies



Nat Rev Clin Oncol. 2019 Mar;16(3):185-204

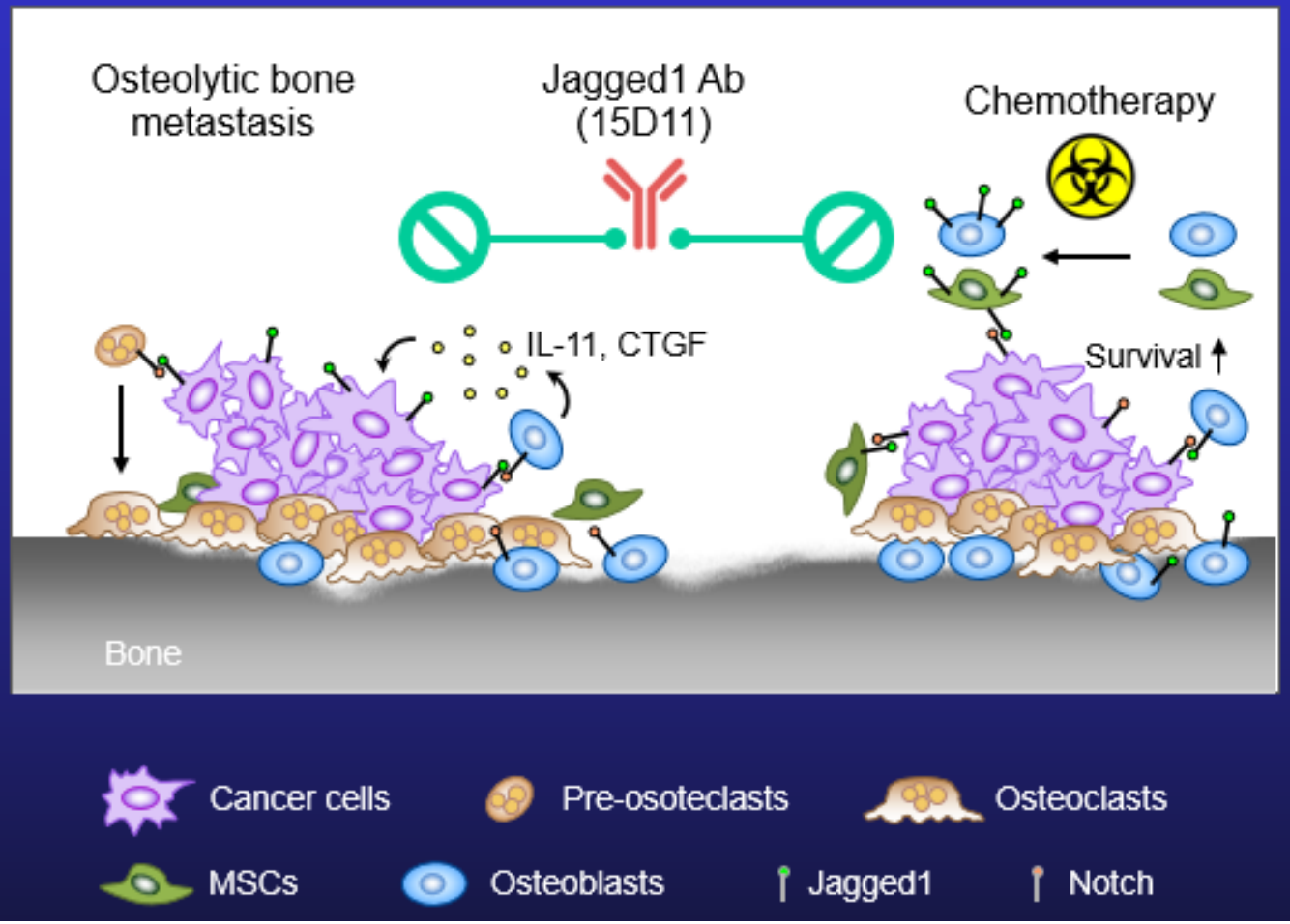
Process	Pathways/Targets
Tissue remodeling	Angiogenic factors, TGFβ, stromal elements
Intravasation	TAMs, fibroblasts, neutrophils, protease production, EMT signaling, migratory capacity
Vascular transport	Platelets, platelet-CTC binding, granulocyte recruitment
Metastatic colonization	MDSCs, neutrophils, exosomes, other EVs
Dormancy and re-animation	extracellular matrix components, cytokines, inflammation

Questions for the Panel Discussion

- What are the leading therapeutic approaches (targets, modalities, programs) to address cancer mets?
- What can we learn from prior failures (MMPs, SRC, BCR-ABL) and successes (RANKL, bisphosphonates)? Preclinical models, clinical development, regulatory pathways.
- What is the value proposition and current status of diagnostics as means to unlock value? Validation of surrogate endpoints?
- How must anti-metastatic approaches be viewed in the context of immunotherapy? Competing vs. complementary vs. distinct?

Yibin (Princeton)

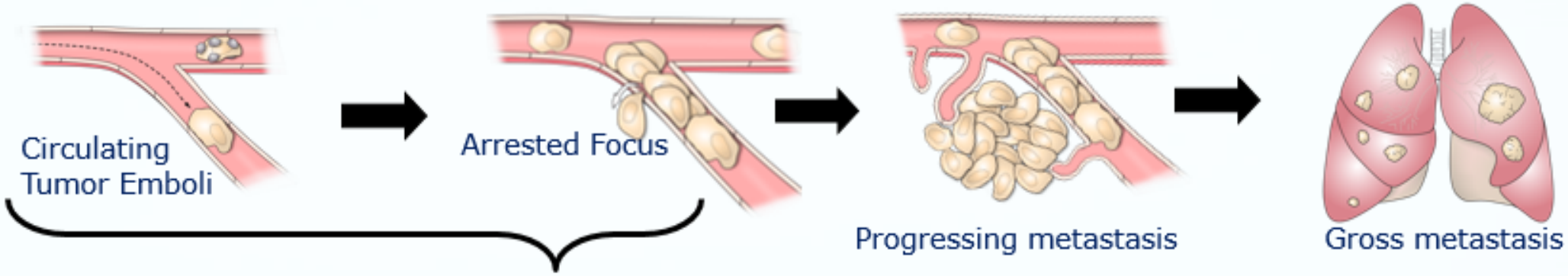
Therapeutic Benefits of Jagged1 Neutralizing Antibody



Chand (Vuja De)

Vuja De Sciences

Early Metastatic Survival is a Defining Phenotype of Highly Metastatic Cells



Highly metastatic phenotype is defined early after the arrival of cells in the lung.

- Ezrin - Cytoskeleton Linker Protein: Osteosarcoma Nature Medicine 2004
- FAS expression leads to early cell death: Osteosarcoma Molecular Can Res 2007
- NM23-EDG2 - Metastasis Suppressor: Breast cancer Cancer Res 2007
- Gemin 5 - Alternative mRNA splicing: Breast cancer Cancer Res 2008
- FGFR4 - Fibroblast growth factor 4: Rhabdomyosarcoma Journal Clinical Investigation 2009
- PTEN - Phosphatase: Melanoma
- GP-78 - E3 ubiquitin ligase linked to ER Stress: STS Nature Medicine 2007

Successful metastatic cells must manage and endure a diversity of stresses during metastatic progression.

These stresses are most notable early after the arrival of cells at a secondary site.

We have developed assays to screen for agents that disrupt this necessary adaptation pathways and develop effective anti-metastatic agents.

Metabolic Stress/Flexibility

Cancer Research 2012

ER and UPR Stress

Nature Medicine 2007

NO/Redox Stress

Stress – Protein Translation Initiation

Neoplasia 2012

Jackson (Qunaterix)

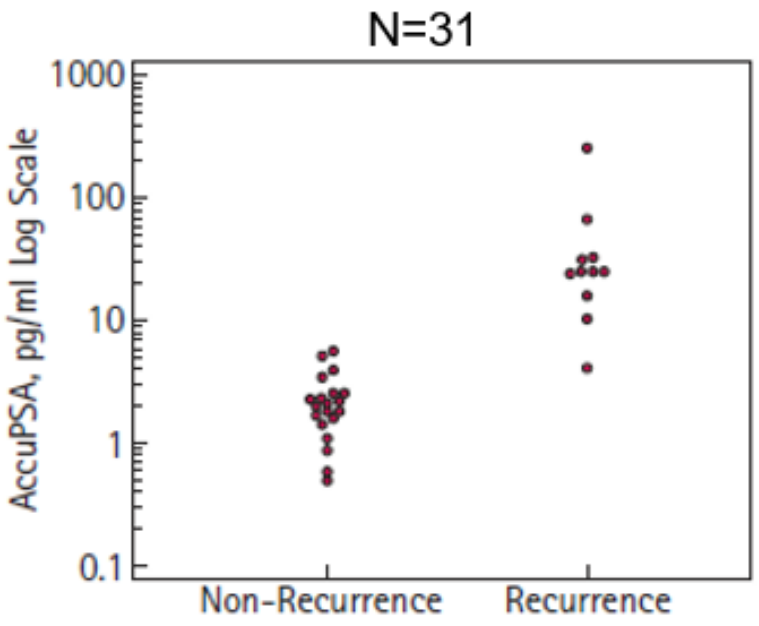
Simoa is the only test capable of precise measurement of PSA following prostatectomy

Quanterix
The Science of Precision Health

Achieved **1667-fold** greater sensitivity than commercial benchmark test

Demonstrated that a single AccuPSA result 3–6 months after surgery highly predictive of cancer recurrence over 5 year period after radial prostatectomy (RP)

Clinical value: Ability to target secondary radiation treatment for higher risk group, identification of ultra–low risk group for whom such treatment is unnecessary



JOHNS HOPKINS MEDICINE

NYU

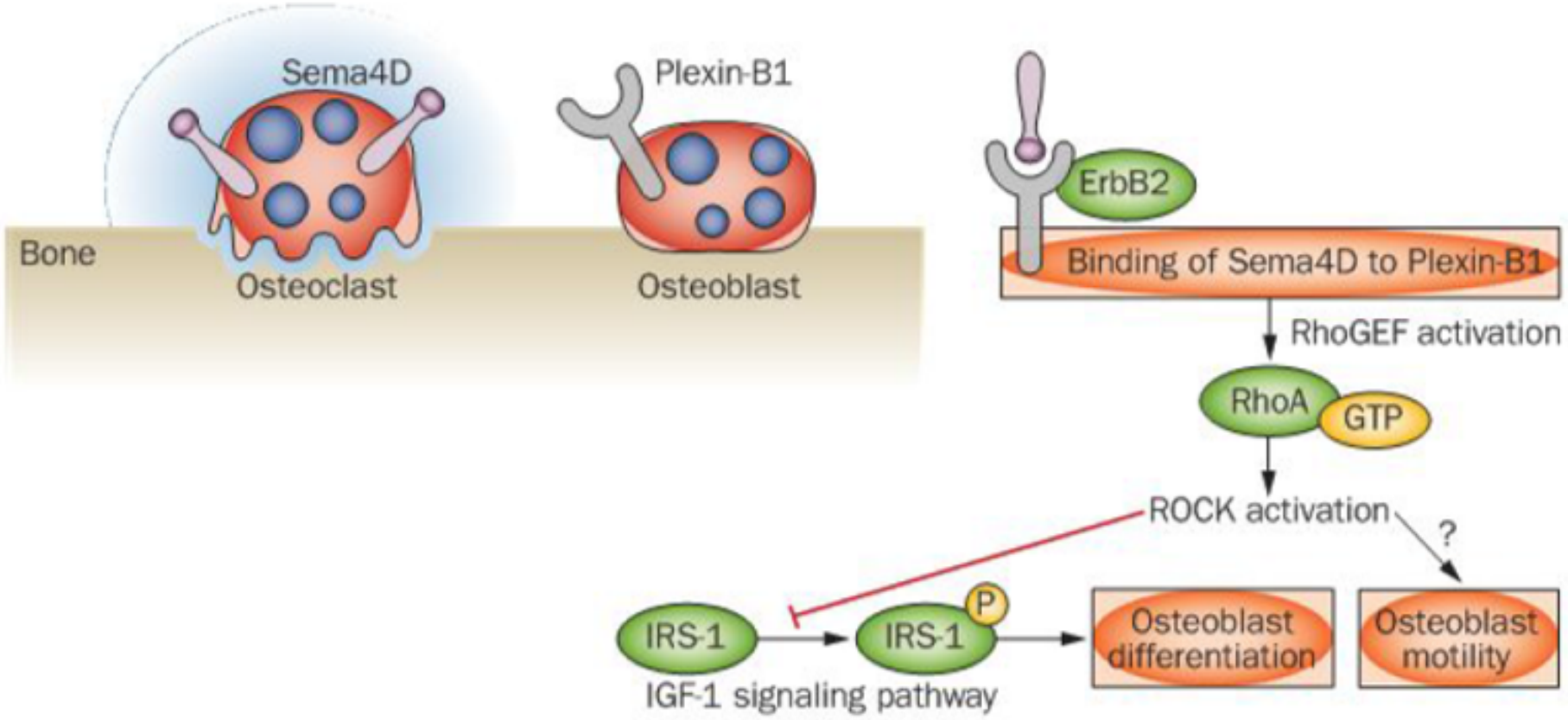
	BCR in <5 years	No BCR in ≥5 years	PPV/NPV
AccuPSA™ ≥3 pg/mL	11	5	69% PPV
AccuPSA™ <3 pg/mL	0	15	100% NPV
Sensitivity	100%	–	
specificity	–	75%	

Lepor et al., Br. J. Urol. Int., 2012

Wilson et al., Clin. Chem., 2011

Maurice (Vaccinex)

SEMA4D Secreted by Osteoclasts Inhibits Bone Formation by Osteoblasts and Induces Osteolytic Niche for Metastases



Osteoblast activity in the vicinity of osteoclasts is suppressed by SEMA4D-Plexin B1 interaction. This stimulates ErbB2-mediated Rho kinase (ROCK) activation and insulin receptor substrate 1 (IRS1) phosphorylation which suppresses insulin like growth factor (IGF1)-dependent signaling required for osteoblast differentiation.