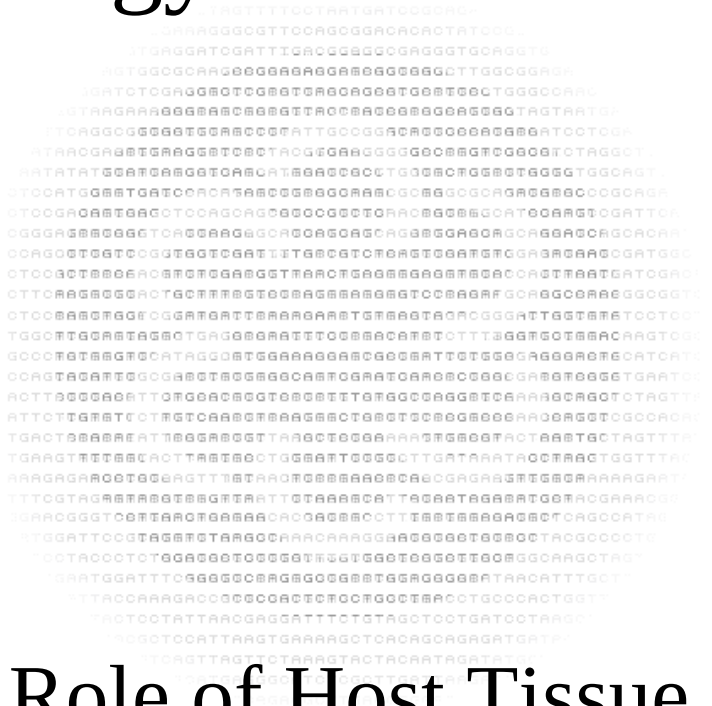
Team Recamier:
Host Biology in Cancer Therapy

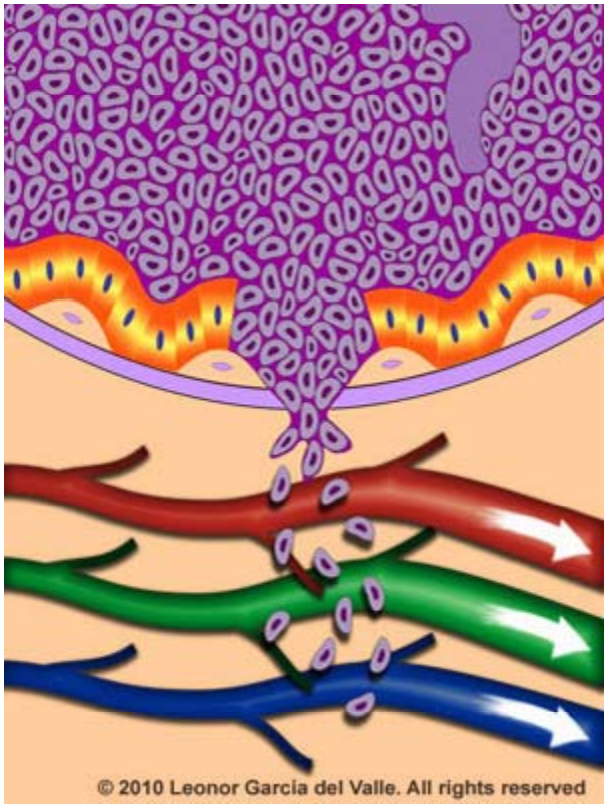


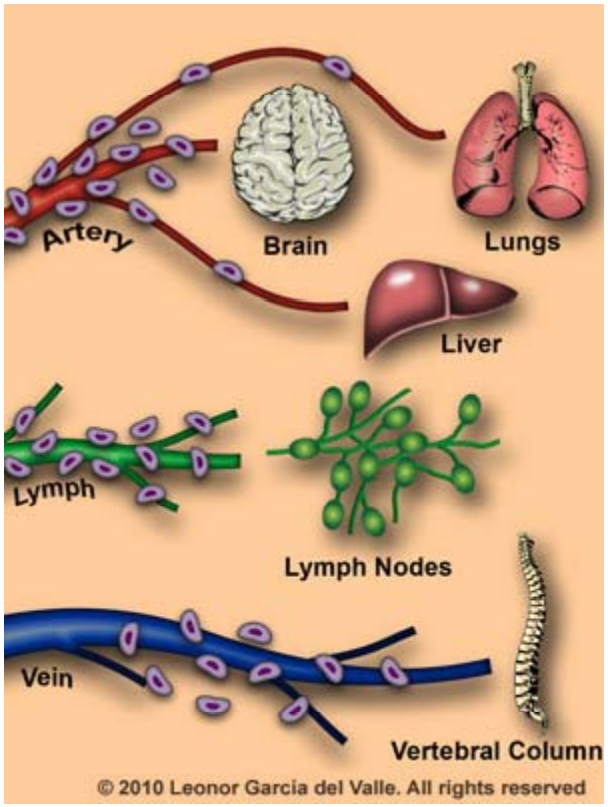
The Role of Host Tissue Gene Expression in Breast Cancer Metastasis to the Lungs and Bones

Joseph-Claude-Anthelme Recamier

- French scientist
- November 6, 1774- June 28, 1852
- In 1829, he recognized the ability of tumors to invade, colonize, and destroy distant organs
- He termed this phenomenon <u>metastasis</u>

Metastasis



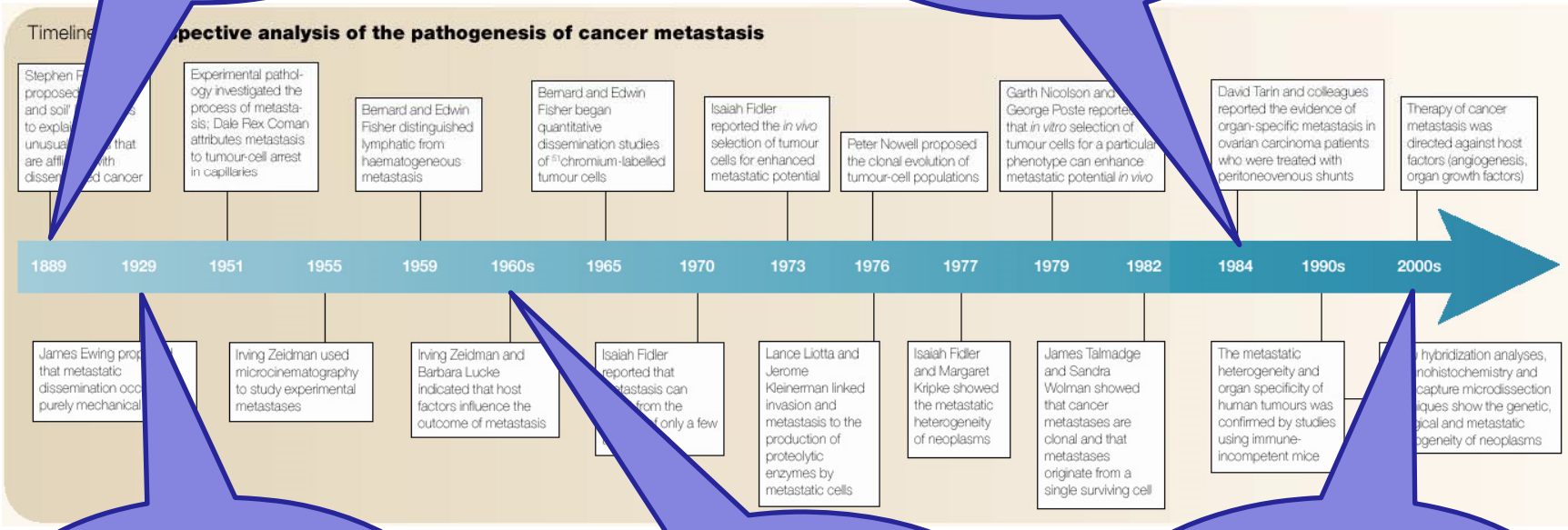


Definition: the sequential cascade of events that results in the spread of cells from the primary tumor site to distant organs

Retrospective Analysis of Metastasis

1889: Seed and soil hypothesis first proposed

1984: Evidence for organ specific metastasis in ovarian cancer



1929: Mechanical forces responsible for metastasis

1960s: Host factors influence the outcome of metastasis

2000s: Targeting host factors (eg. angiogenesis) as therapy for metastatic disease

Current definition of the 'seed and soil' hypothesis consists of 3 principles:

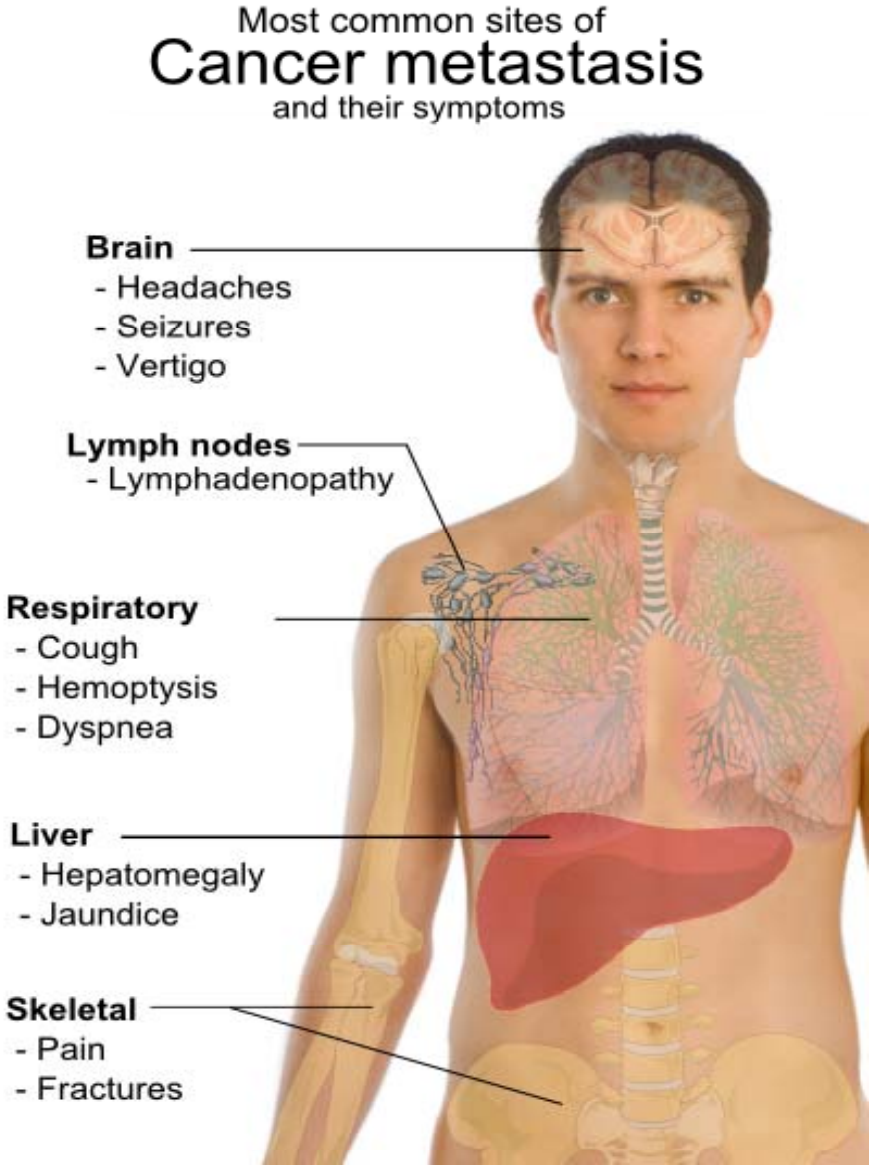
(1) Primary neoplasms (and metastases) consist of both tumour and host cells

(2) Metastasis is selective for cells that succeed in invasion, mobilization, survival in the circulation, arrest in distant capillaries, and extravasation into and multiplication within the organ parenchyma

(3) Metastasis can only develop in certain organs

The outcome of metastasis depends on multiple interactions of metastasizing cells with homeostatic mechanisms, which the tumour cells can usurp

Fidler et al, Nature 2002



Tumor type	Principle sites of metastasis
Breast	Bone, lungs, liver and brain
Lung adenocarcinoma	Brain, bones, adrenal gland and liver
Skin melanoma	Lungs, brain, skin and liver
Colorectal	Liver and lungs
Pancreatic	Liver and lungs
Prostate	Bones
Sarcoma	Lungs
Uveal melanoma	Liver

Nguyen et al, 2009
www.reference.findtarget.com/search/metastasis/

Not all cancer patients develop metastases

Not all metastases have a known primary tumor site

It is important to understand the interactions between metastatic tumors and the site of metastasis in order to be able to treat metastatic malignancies

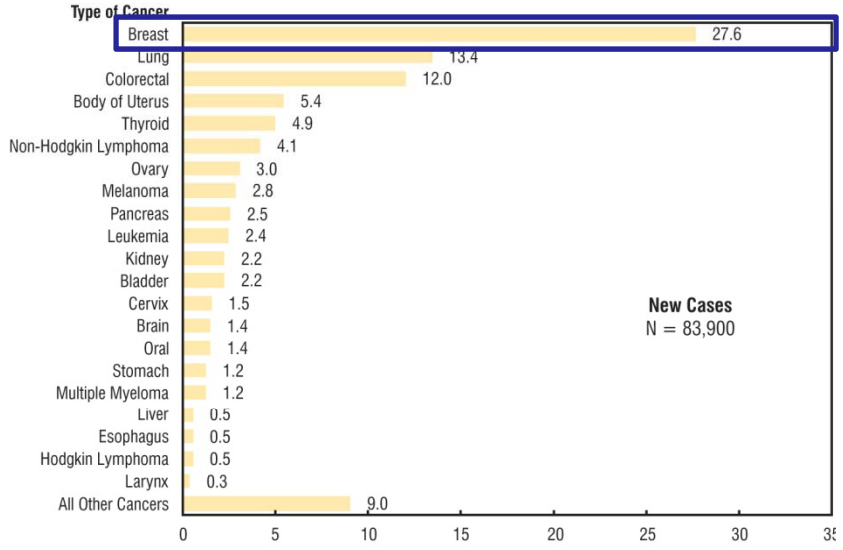
Hypothesis

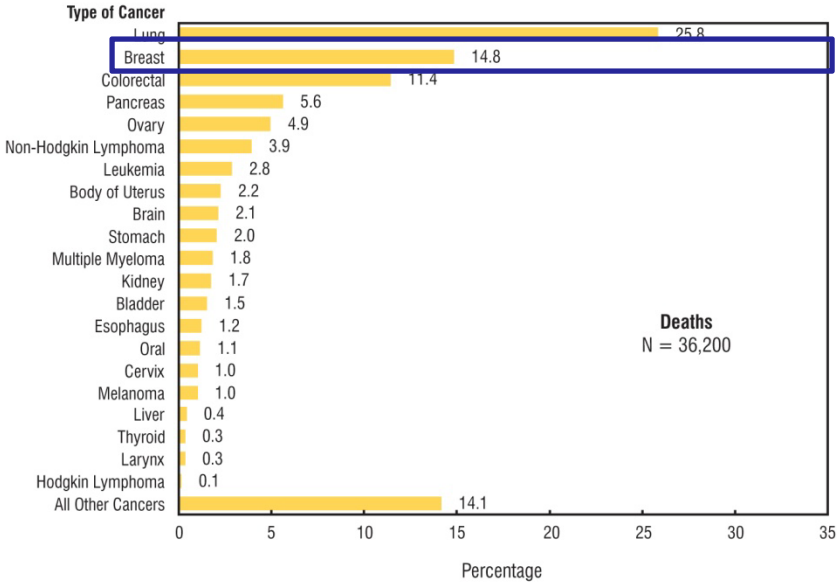
We hypothesize that there are somatic alterations and/or expression changes unique to a subset of breast tumor cells, the ‘seeds’, that interact with and target specific host tissues, the ‘soil’, to form secondary tumors. The unique tissue microenvironments or ‘soils’ encountered in each individual, may in part explain the differences we observe in metastatic events in patient groups

Breast cancer is the most common cancer among Canadian women

Figure 1.2

Percentage Distribution of Estimated New Cases and Deaths for Selected Cancers, Females, Canada, 2010





Metastasis is the main cause of mortality in breast cancer patients

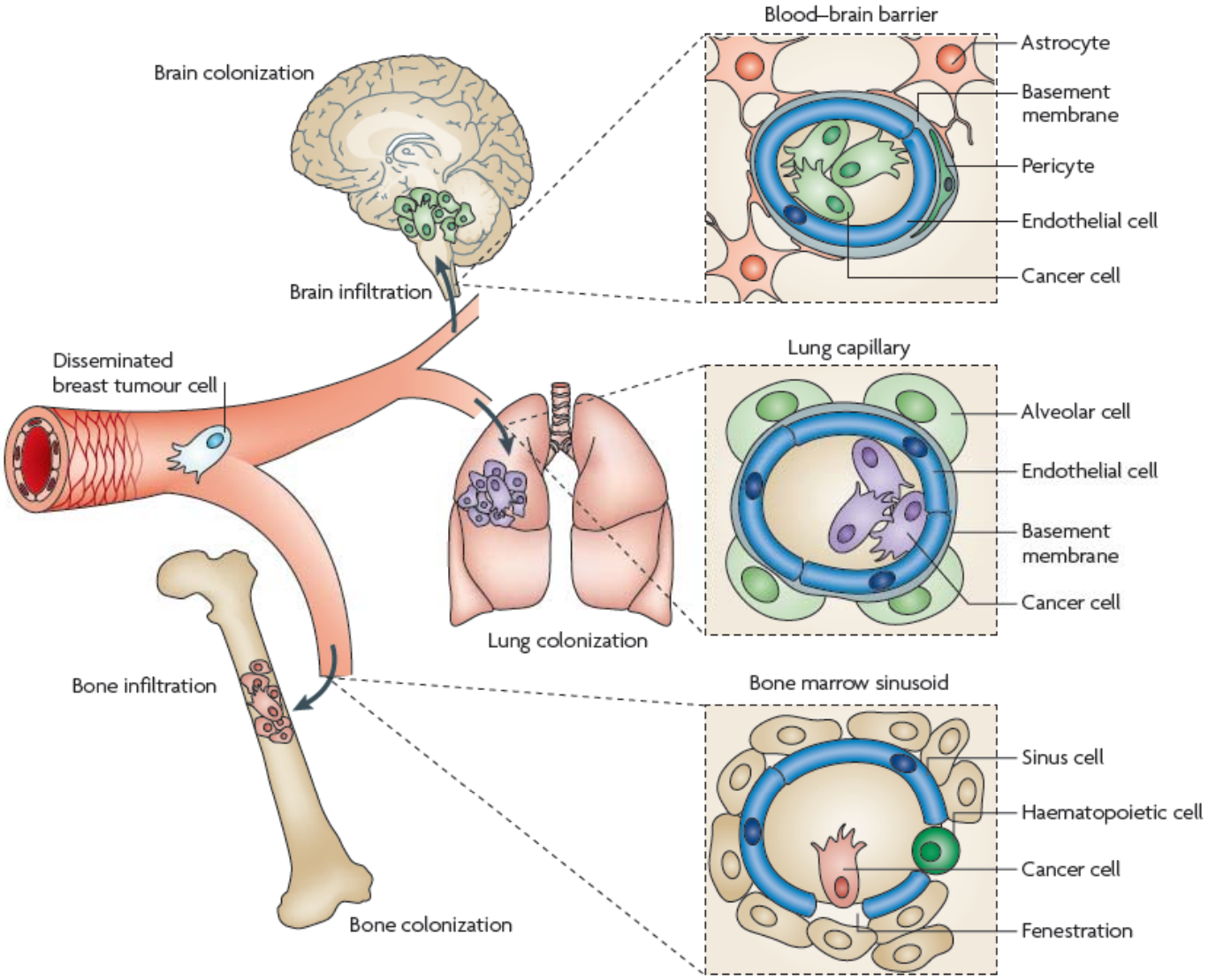
Note: New cases exclude an estimated 34,300 of non-melanoma skin cancer (basal and squamous). Deaths for "All Other Cancers" include about 110 deaths with underlying cause "other malignant neoplasms" of skin.

Analysis by: Chronic Disease Surveillance Division, CCDPC, Public Health Agency of Canada

Data sources: Canadian Cancer Registry and Canadian Vital Statistics Death databases at Statistics Canada

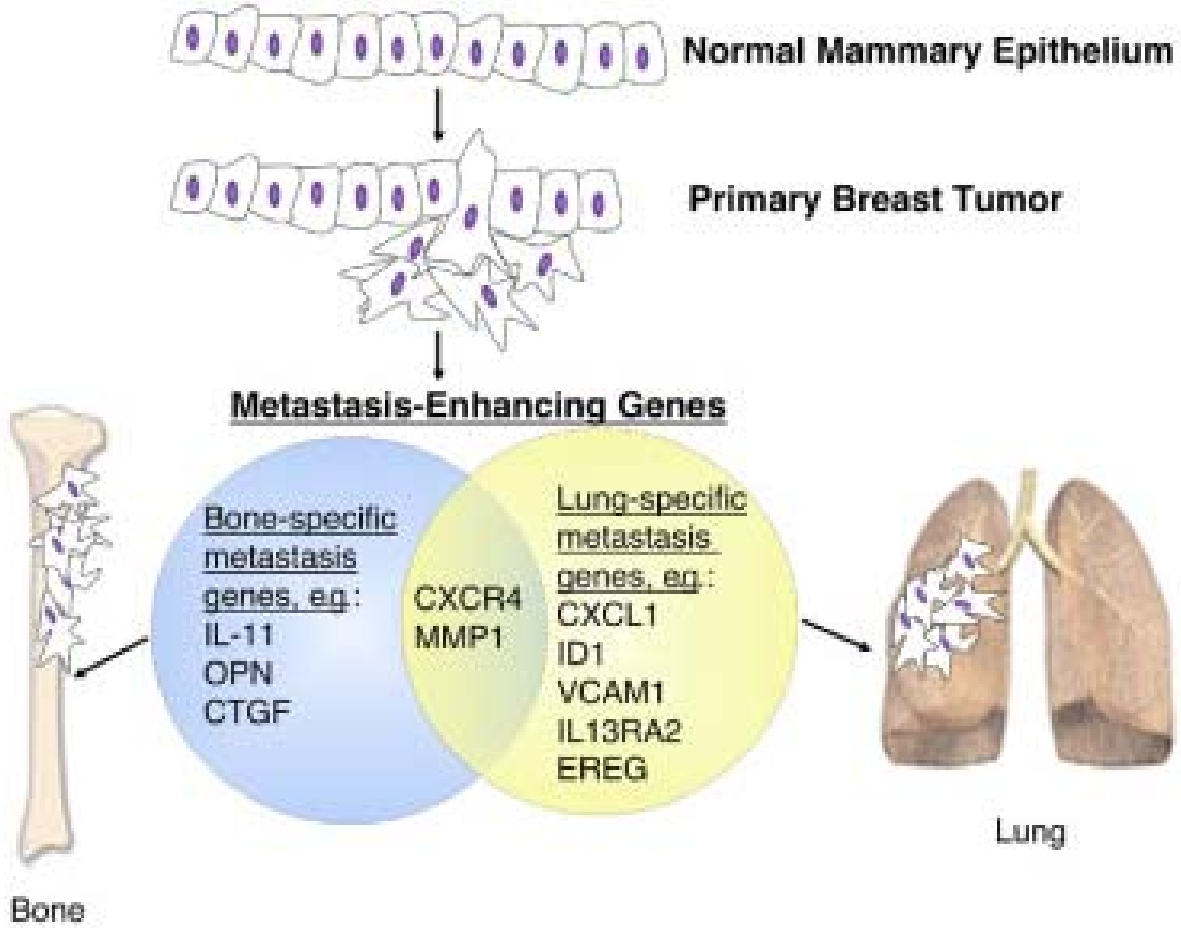
Canadian Cancer Statistics 2010

Breast cancer metastasis



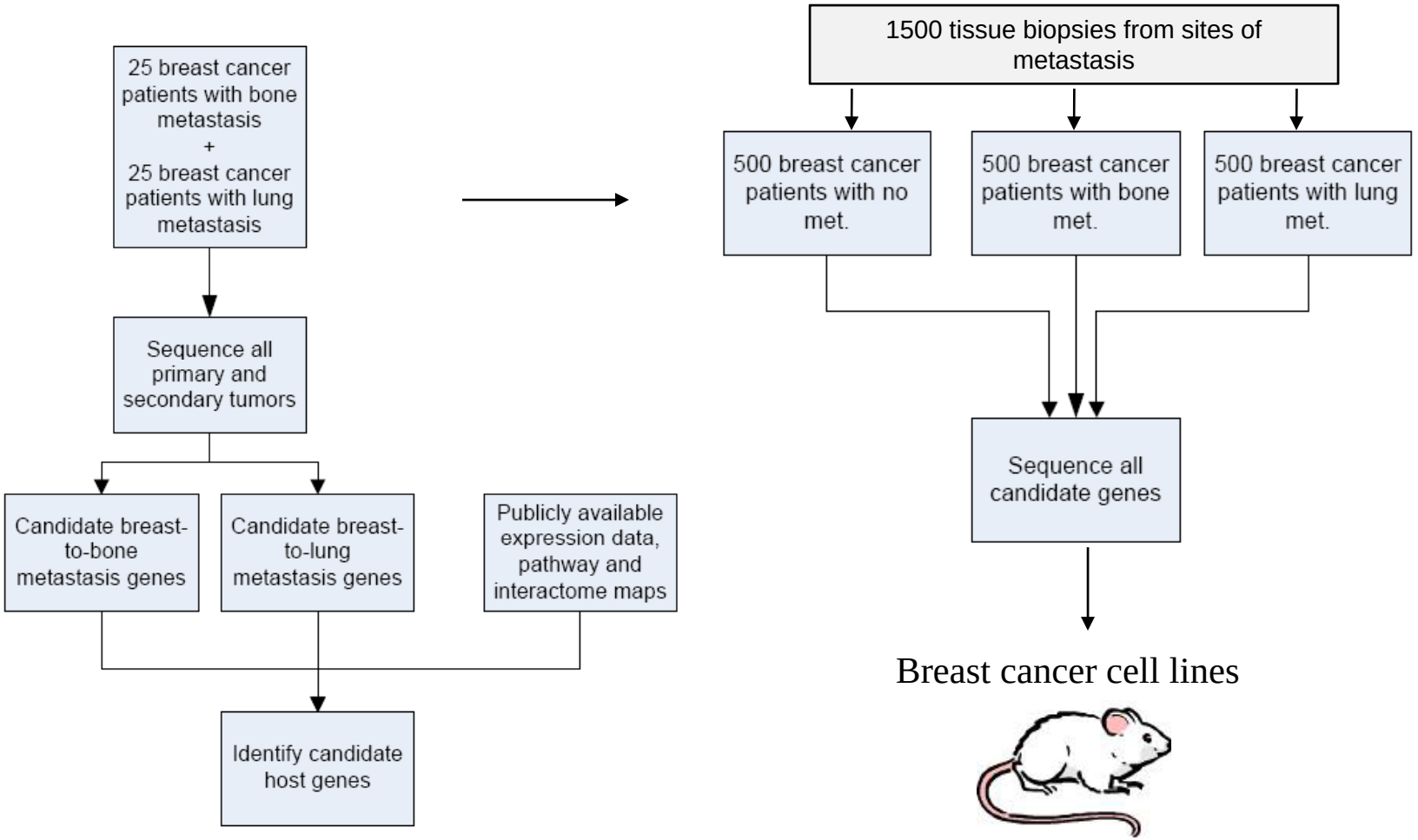
Nguyen et al, 2009

Breast cancer metastasis to the lungs and bones

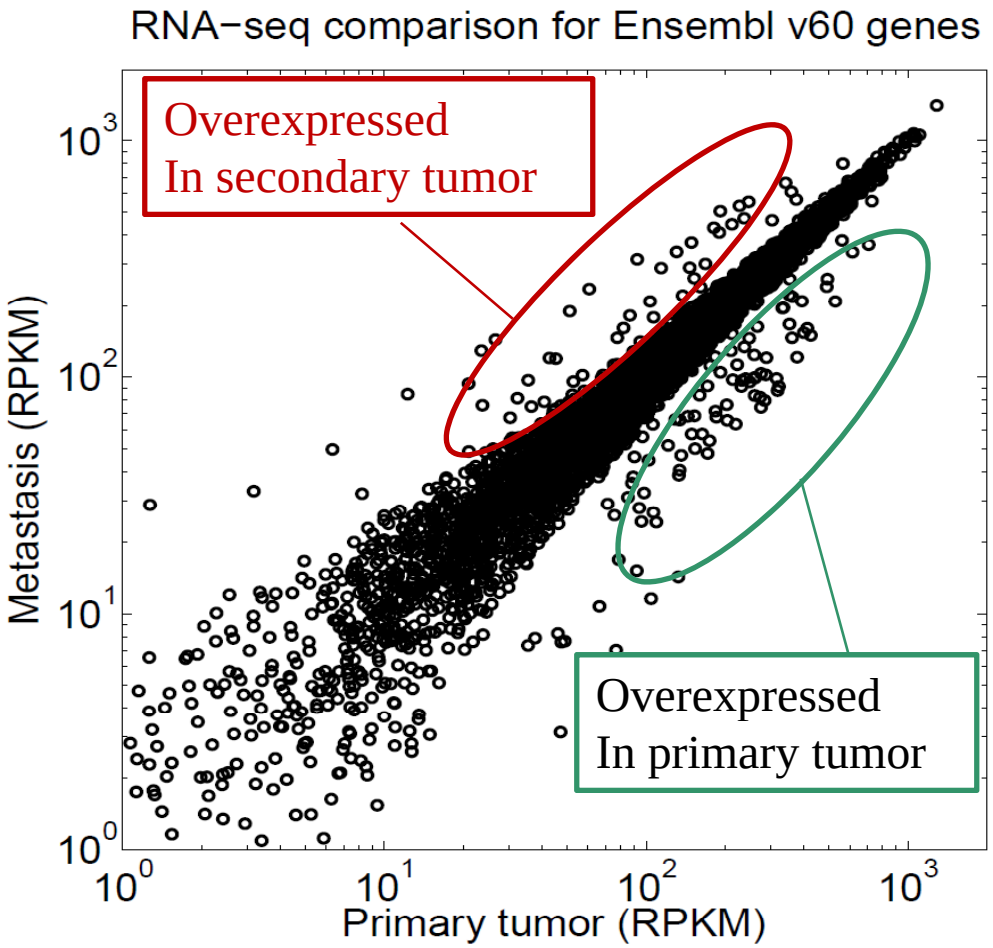


Horak and Steeg, 2005

Overview of experimental plan



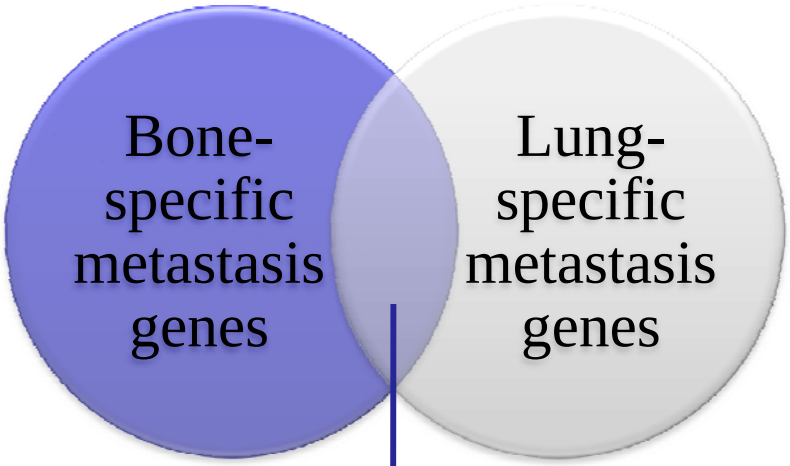
Aim 1: Identification of candidate genes involved in the etiology of site-specific breast cancer by sequencing of primary and secondary breast tumors



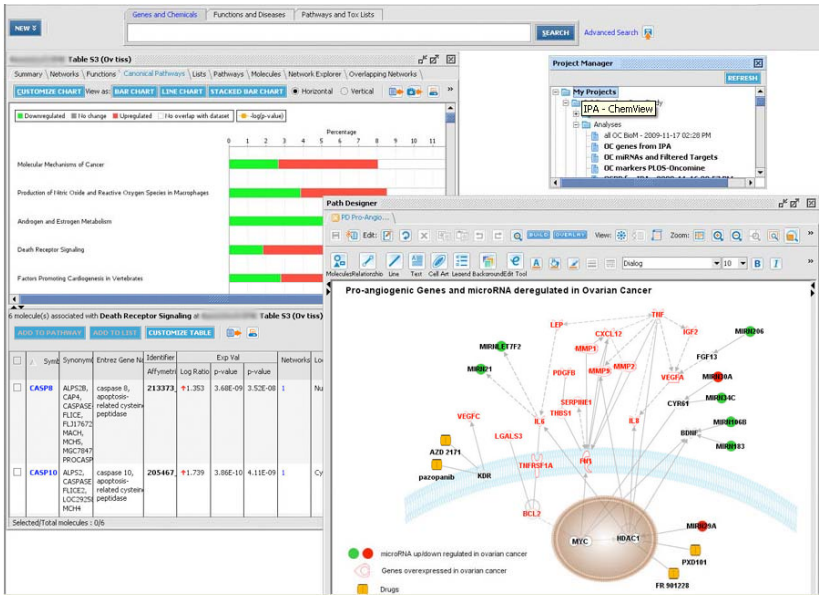
Aim 1: Identification of candidate genes involved in the etiology of site-specific breast cancer by sequencing of primary and secondary breast tumors

Tumor specific candidate genes

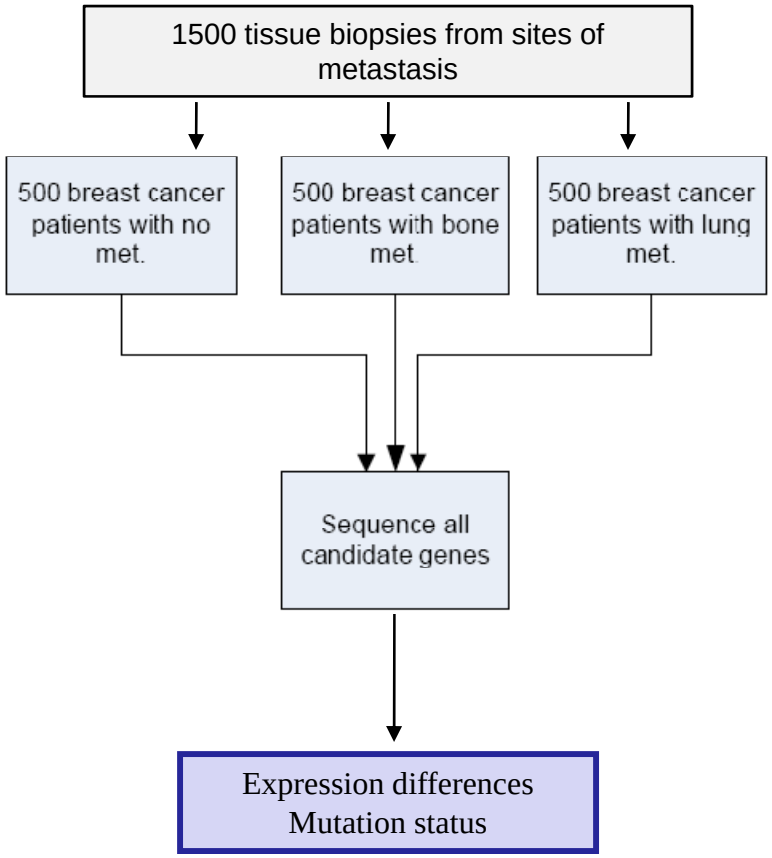
Host tissue specific candidate genes



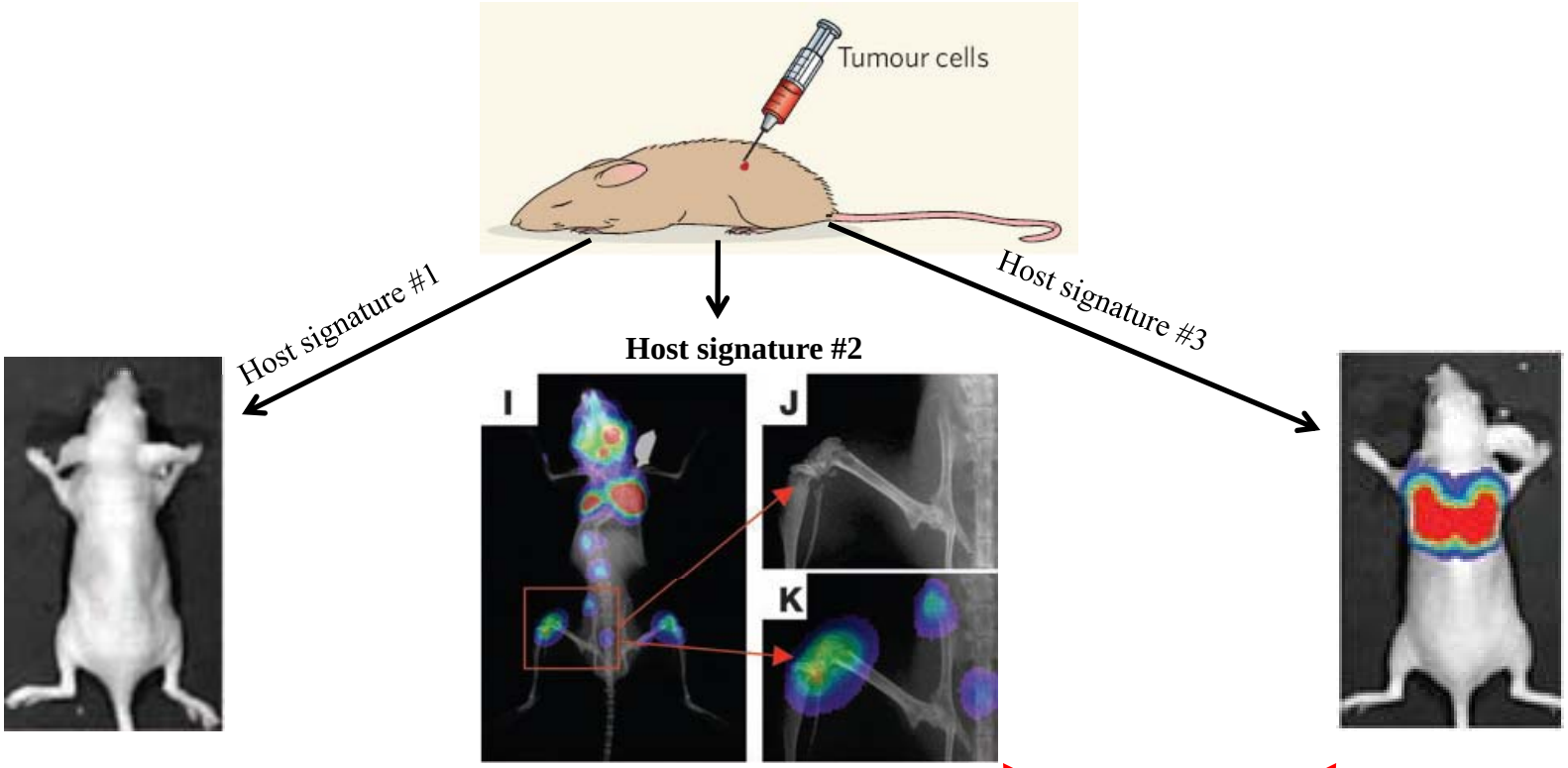
General metastasis genes



Aim 2: Identification of candidate host genes in patients with and without bone and lung metastasis



Aim 3: Validation of candidate genes as a prognostic factor and for the generation of novel cancer therapies targeting metastatic cancers *in vivo*



Cancer therapy approaches targeting the candidate tumor (seed) and corresponding candidate host (soil) genes

Future Directions

- Extension of analysis to other cancer types
- Candidate genes as prognostic indicators
- Combined therapy
  - Target both primary tumour and metastatic niche
- Prophylactic therapy

"The best work in the pathology of cancer is now done by those who…are studying the nature of the ***seed***. They are like scientific botanists, and he who turns over the records of cases of cancer is only the ploughman, but his observations of the properties of the ***soil*** might be useful."

Stephen Paget (1889)

References

Fidler, IJ. (2003). The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. *Nat. Rev. Cancer.* 3, 453-8.

Nguyen DX *et al*. (2009). Metastasis: from dissemination to organ-specific colonization. *Nat. Rev. Cancer.* 9(4):274-284.

Chambers AF *et al.* (2002). Dissemination and growth of cancer cells in metastatic sites. *Nat Rev Cancer*. 8:563-72.

Minn AJ *et al*. (2005). Genes that mediate breast cancer metastasis to lung. *Nature.* 436:518-24.

Weigelt, B, Peterse JL & Van ‘t Veer LJ. (2005). Breast cancer metastasis: markers and models. *Nature Rev. Cancer* 5, 591–602.

Morin RD *et al.* (2010). Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. Nat. Gen. 42(2):181-5.

Wiegand KC *et al.* (2010). *ARID1A Gene mutations in endometriosis-associated ovarian carcinomas.* NEJM.363(16):1532-1543.

Shah *et al.* (2009). Mutational evolution in a lobular breast tumour profiled at single nucleotide resolution. Nature. 8;461(7265):809-13.

Acknowledgements

Principle Investigators

Dr. Marco Marra
Dr. Aly Karsan

Team Recamier

Richard Moore
Diane Trinh
Chaoyang Jin
Katayoon Kasaian
Tao Wong
Misha Bilenky
Madalene Earp
Jae-Kyung Myung
Rawa Ibrahim