The Metastasis Research Network (MetNet)

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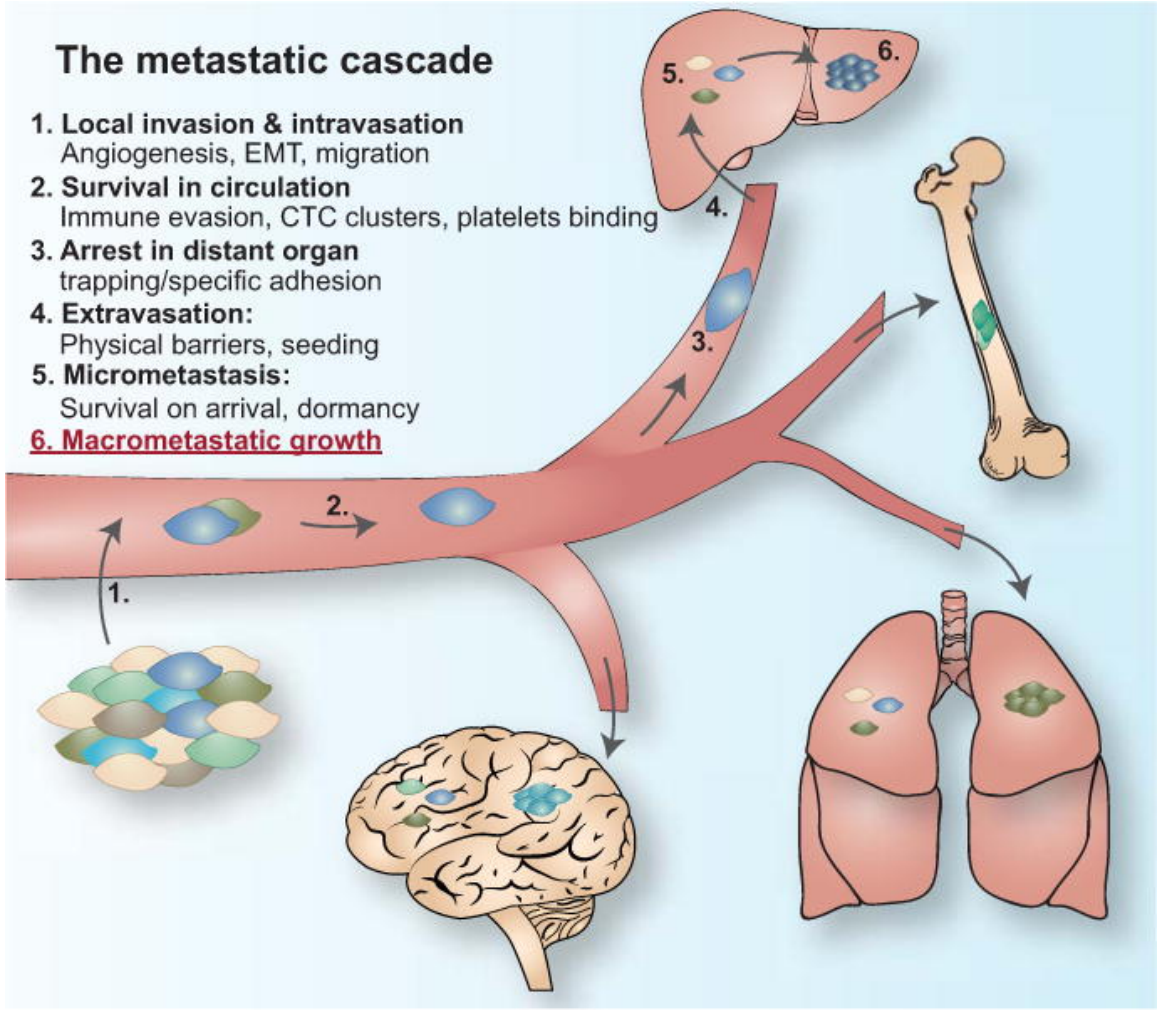
Metastasis and the “Metastatic Cascade”

- Metastasis accounts for the vast majority of deaths in patients with solid tumors, yet therapeutic strategies to manage metastatic disease are lacking

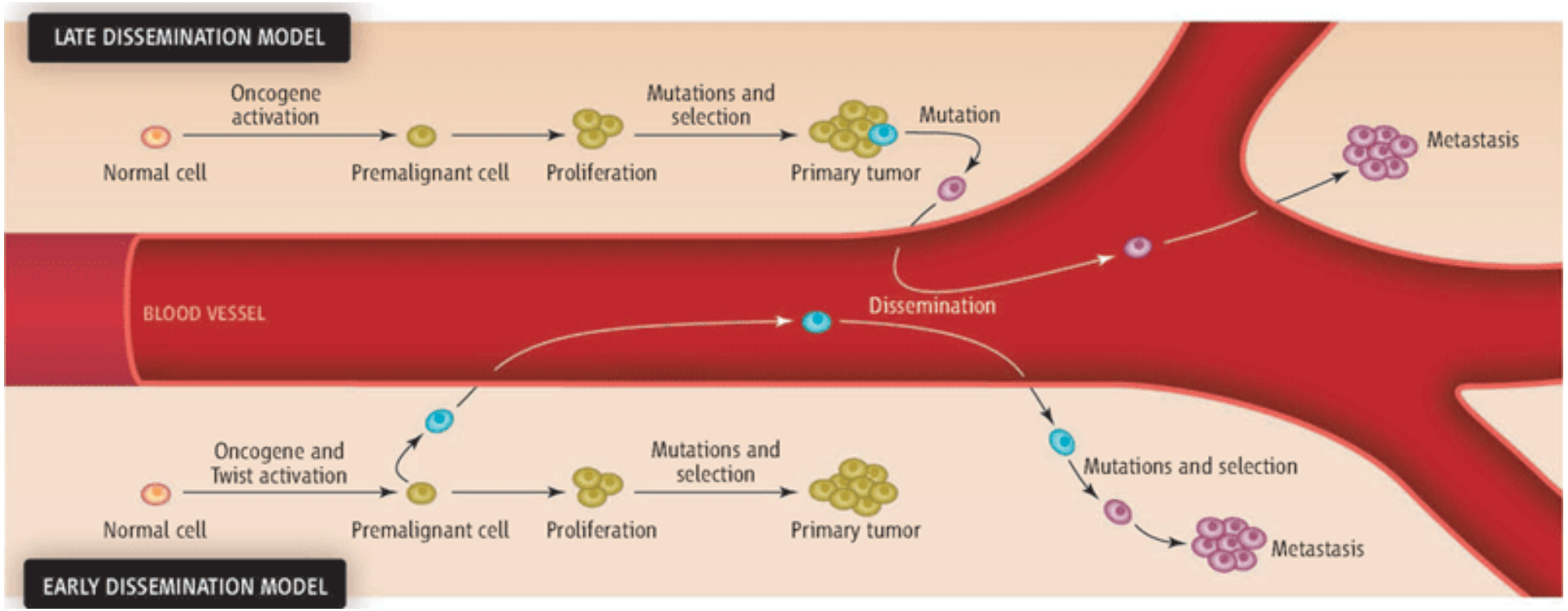
- Metastasis was considered the late end product of a linear process, the “metastatic cascade”



Obenauf AC, Massague J. Trends in Cancer, 2015

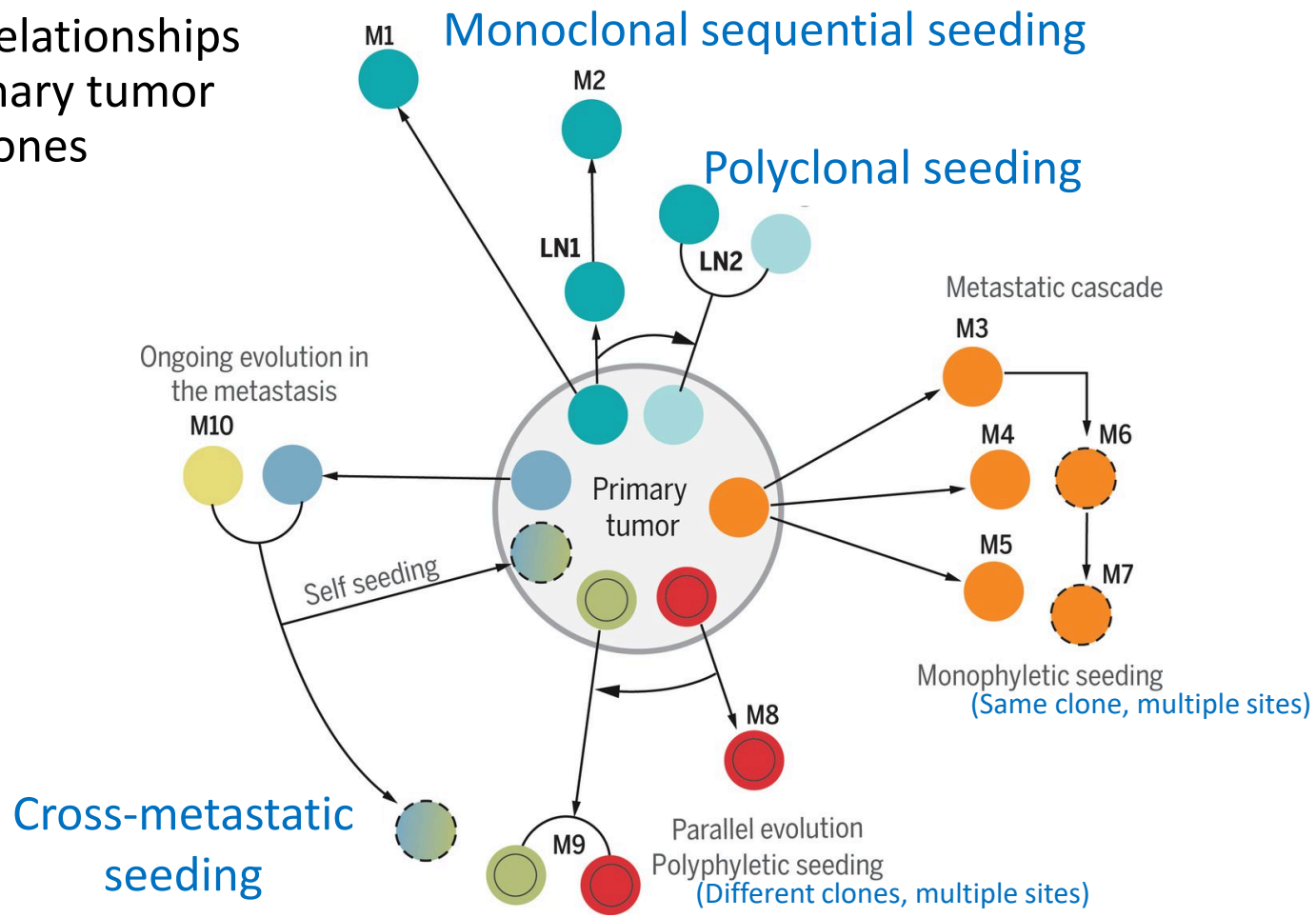
Metastasis can occur early and often

- Detect disseminated cells in circulation and in secondary sites even before diagnosis
  - The likelihood, timing, frequency, and mechanisms of early dissemination for many cancers are unknown



Metastasis can result from concurrent overlapping routes

- Cartoon depicts relationships between the primary tumor and metastatic clones

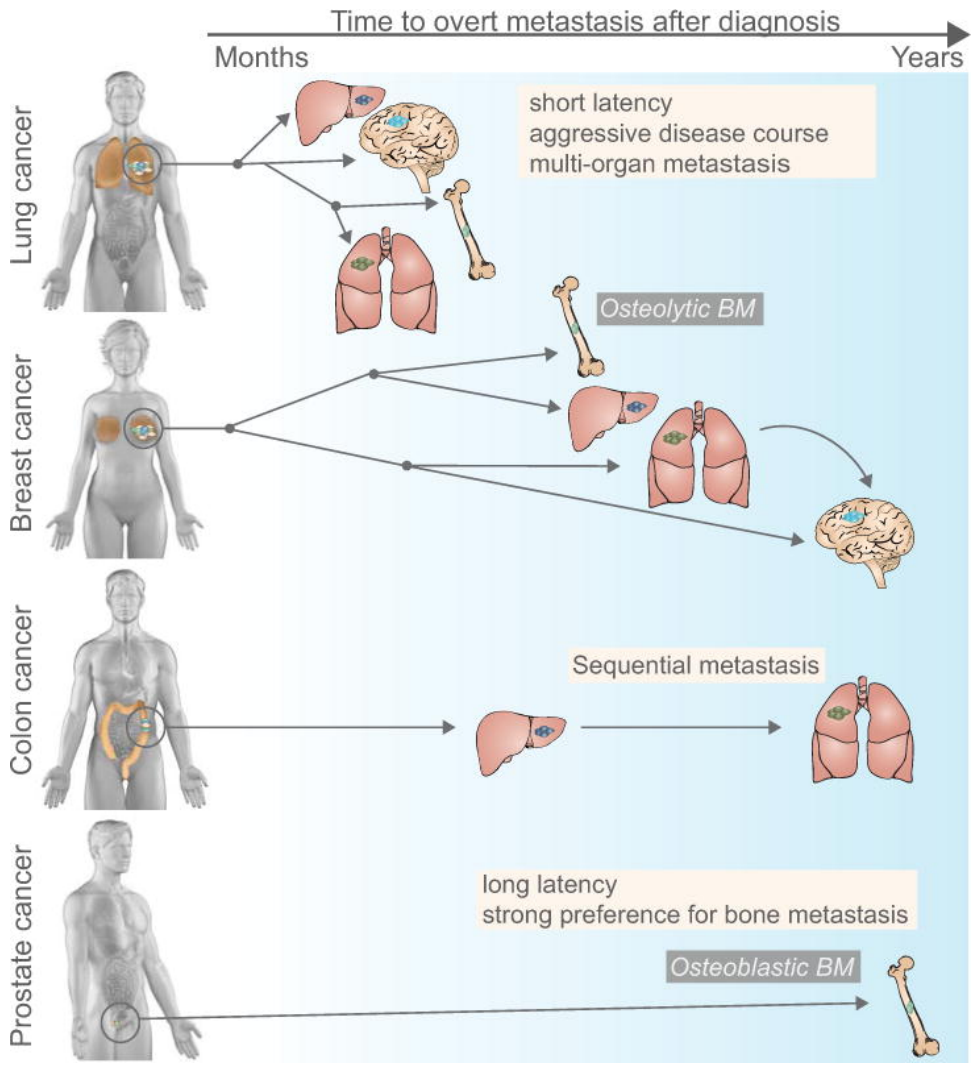


LN = lymph node
M = metastatic clone

Turajlic S, Swanton C. Science, 2016

Current Challenges in metastasis research

- Tumors preferentially metastasize to specific organs and tissues
  - In general, mechanisms that regulate tropism are not well understood
- Metastatic cells can remain dormant for weeks, months, or years before clinical manifestations
  - In general, mechanisms that regulate dormancy are poorly understood, and likely include strong microenvironmental and systemic components
- Phenotypic plasticity of metastatic cells can underlie therapeutic resistance
  - The role of dynamic molecular, cellular, and microenvironmental interactions are not well characterized and experimental systems are lacking
- Current model systems are not representative
  - Physiologically relevant in vitro and in vivo models that capture the entire metastatic process to mimic that seen in humans are lacking



Obenauf AC, Massague J. Trends in Cancer, 2015

A comprehensive picture of metastasis does not currently exist

Rapid autopsy studies have provided a catalog of sites of metastasis, however:

- Knowledge of metastasis is fragmented because of siloed studies that concentrate on one stage of the “metastatic cascade”
  - Studying each stage in isolation misses the others
- Approaches and technologies that provide a physiological description of overlapping, non-linear processes are limited (i.e., approaches that span scales from cell →tissue → organ → body).

Need: A new view of metastasis that accounts for the dynamic, non-linear, multi-scale physiological interactions required for tumor cell dissemination, colonization, growth, and drug resistance.

Opportunities to advance metastasis research

- New viewpoints on “old” ideas are percolating within the community
  - Metastasis occurs early, is dynamic, and non-linear
  - Cell plasticity is not limited to EMT or MET
  - Cooperativity between multiple cell types contributes to metastasis

- New approaches and tools will facilitate a comprehensive view
  - Surgical approaches that improve human relevance
  - *In vivo* bar coding and lineage tracing tools
  - Advanced imaging techniques for *in vivo* and multi-modal measurements
  - Single cell data collection and integrative analyses

Proposal: The Metastasis Research Network

- Develop a network of 4 – 5 Metastasis Research Centers (U54 mechanism)
- Each center will focus on the intersection of **two or more emerging themes** that span the metastatic process:
  - The likelihood, timing, and frequency of **early dissemination**
  - The **interactions** and crosstalk between metastatic cells, including circulating tumor cells, and other host non-cancer cells or systems (e.g., immune or nervous)
  - The acquisition of, maintenance of, or emergence from metastatic **dormancy**
  - The response of metastatic cells, including those that are dormant, to **therapies**
- Teams will be expected to propose **multidisciplinary approaches** that incorporate appropriate technology and analysis capabilities that lead to a comprehensive and mechanistic understanding of metastasis

What would a Center look like?

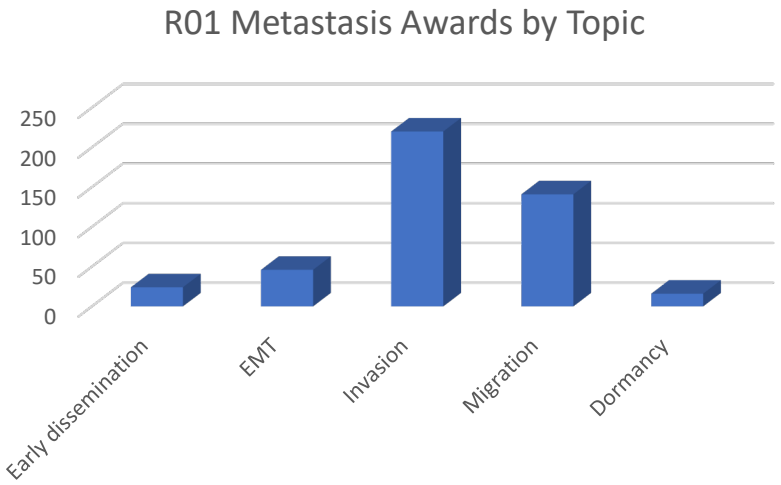
- A multi- and inter-disciplinary effort involving:
  - cancer biology, physiology and pathology, bioengineering, biophysics, systems biology, computational analyses

- Encompassing multiple themes simultaneously, for example:
  - From different primary sites to same secondary site
    - Focus: determinants of organotropism
    - Themes: **early dissemination** and **interactions**

  - How treatments influence the metastatic process
    - Focus: treatment-associated cell phenotypic and metabolic plasticity
    - Themes: **early dissemination**, **dormancy**, and **treatment**

Portfolio Analysis

- Despite advanced techniques and knowledge, the metastasis-related portfolio across NCI has remained static over the past 5-10 years.
- Portfolio consists of a spectrum of awards, with the majority being investigator-initiated R01 awards that focus on single elements of the metastatic cascade
  - Early events and late events poorly represented
  - Invasion/Migration more readily adaptable to in vitro study
- Portfolio also contains several projects within on-going programs that complement the MetNet, including:
  - DCB: CSBC, PS-ON
  - Trans-NCI: HTAN



Budget and Review considerations

- 4-5 Centers (U54 mechanism)
  - 2-3 projects
  - Shared resources cores (up to 2)
  - Administrative core
    - **Dedicated data manager and coordinator**
- $1.5M/ U54 total cost per year
- 5 years of support

- $37.5M total costs over 5 years

- Review:
  - Two receipt dates, one per year (2020, 2021).
  - Require review by a Special Emphasis Panel

Justification for use of the RFA and Cooperative Agreement U54 mechanism

- RFA:
  - Dedicated set-aside provides indication of NCI commitment
  - Energize the metastasis research community, and encourage new researchers to the field
  - Multidisciplinary effort using system-level approaches
    - Portal for bringing new researchers to the field
- Cooperative Agreement:
  - Foster interaction and collaboration across the network and with other programs
  - Facilitate interactions and opportunities for junior investigators
  - Facilitate interactions between the network and larger research community
    - Admin supplements for collaborations
    - Borrow from the RAS Initiative playbook for hosting a biannual meeting and/or blog discussion forum
  - Substantial NCI programmatic involvement to help maximize resources for PIs and the NCI

Evaluation of the Network

- Two-tier evaluation process:
  - Annual evaluation of individual centers and projects
    - Consider network participation, progress, accomplishments, publications
  - Evaluation of the network overall
    - Establishment of productive cross-network collaborations (publications/research grant applications),
    - Retention of junior investigators within the metastasis research field,
    - Development/sharing of new technologies and models,
    - Deposition of data in appropriate data bases,
    - Interaction with additional NCI-sponsored programs.

Measurements for the Overall Success of the MetNet

- A more comprehensive understanding of metastasis and how that knowledge can be translated into intervention strategies
- Sustained influx of new R01 applications into the biology of metastasis using systems-level approaches
- Generated resources accessible and useful to the larger research community
- Promotion and sustainability of the metastasis workforce

The MetNet

Pursuing a comprehensive and mechanistic understanding that accounts for the dynamic, non-linear, multi-scale physiological interactions required for metastasis.