Models of development, models of knowledge: philosophical implications of ‘living experiments’

STEM Education Seminar Series
Northern Arizona University
March 3, 2025

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Department of Philosophy
University of Utah

Plan of the talk:

1. Living experiments: organoids and embryo models
2. Philosophical theories of models & modeling
3. Insights for philosophy: a fabric of models
4. Image of scientific knowledge & implications

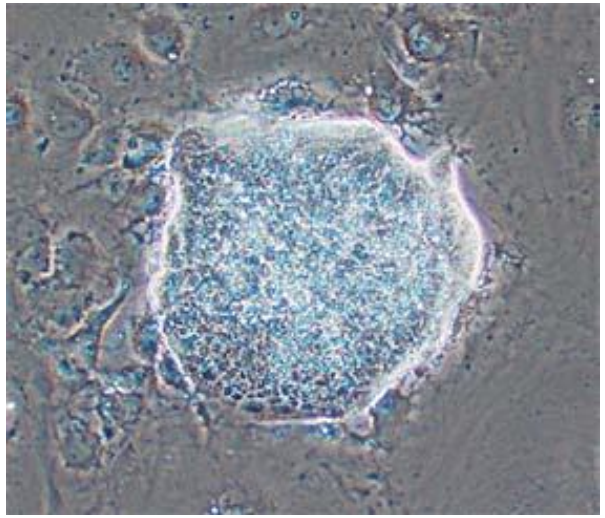
Organoids and embryo models are constructed "using stem cells to model human development and disease in novel ways" (Rossant 2025, 1).

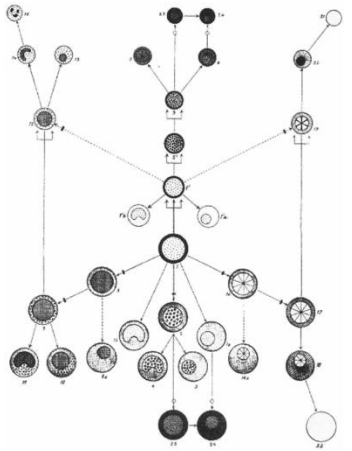
Stem cells: reproduction & development

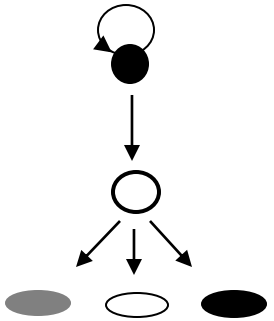
Stem cell: "functionally defined as having the capacity to self-renew and the ability to generate differentiated cells." (Melton 2013, *Essentials of Stem Biology*, 7)

Self-renewal: cell division producing one or more cells similar to the parent

Differentiation: loss of developmental potential and acquisition of specialized traits of a mature cell type







Varieties of stem cell (a partial list):

- adult
- amniotic/amniotic fluid
- bone marrow
- cancer
- cardiac
- cord blood hematopoietic
- dental pulp
- embryonic
- embryonic germ
- embryonic kidney
- embryonal carcinoma
- epiblast
- epidermal
- hair follicle
- germline
- hematopoietic
- induced pluripotent
- intestinal
- keratinocyte
- leukemic
- liver
- mesenchymal
- multipotent
- myogenic
- neural
- pancreatic
- pancreatic liver
- pluripotent
- pluripotent
- post-natal
- renal
- skeletal
- skeletal muscle
- solid tumor cancer
- somatic
- tongue
- trophoblast
- very small embryonic-like

From: *Essentials of Stem Cell Biology*, 3rd edition. Lanza and Atala, eds., Elsevier, 2013

Abstract stem cell model:

(1) origin: the multicellular organism from which the stem cell is derived ***S***

(2) interval of persistence: number and rate of self-renewing stem cell divisions ***n***

(3) component traits: characters of cells occupying the various positions in a lineage ***C***

(4) developmental process: positions in the lineage are ordered ***D***

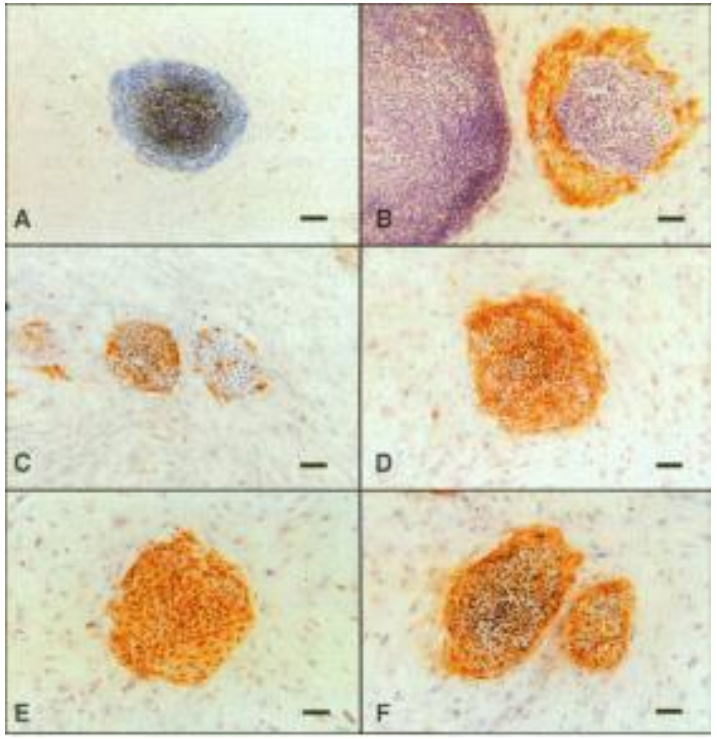
TABLE 1: Model-based classification of stem cells				
Type	**S (source)**	**C**	**n**	**D**
ESC	5d embryo ICM	cell size, cell shape, gene expression, karyotype, telomerase activity, alk-phos, cell surface molecules	≥50 divs	traits of cells from three germ layers
HSC	BM, cord, peripheral blood	cell size, density, light scatter, surface molecules, cell cycle status	>6 months	traits of main blood and immune cell lineages
NSC	basal lamina of ventricular zone	cell morphology, surface markers, gene expression, cytokine response	months to years	traits of neurons, astrocytes, and oligodendrocytes
iPSC	various (relatively mature cells)	colony shape, cell size, cell shape, nucleus/cytoplasm ratio, cell surface molecules, activity and expression of specific proteins, gene expression (specific and global), histone modifications at key locations	≥50 divs	traits of cells from three germ layers
GSC	5-9wk gonadal ridge	colony shape, alk-phos, surface expression (SSEA-1, SSEA-3, SSEA-4, TRA-1–60,TRA-1–81)	20-25 wks	traits of cells from three germ layers
EC	teratocarcinoma (129)	cell shape, morphology, production of embryoid bodies, surface molecules, enzymes	unlimited	traits of cells from three germ layers, teratocarcinoma

Stem cell lines: embryonic & more

Embryonic Stem Cell Lines Derived from Human Blastocysts

James A. Thomson,* Joseph Itskovitz-Eldor, Sander S. Shapiro, Michelle A. Waknitz, Jennifer J. Swiergiel, Vivienne S. Marshall, Jeffrey M. Jones

Human blastocyst-derived, pluripotent cell lines are described that have normal karyotypes, express high levels of telomerase activity, and express cell surface markers that characterize primate embryonic stem cells but do not characterize other early lineages. After undifferentiated proliferation in vitro for 4 to 5 months, these cells still maintained the developmental potential to form trophoblast and derivatives of all three embryonic germ layers, including gut epithelium (endoderm); cartilage, bone, smooth muscle, and striated muscle (mesoderm); and neural epithelium, embryonic ganglia, and stratified squamous epithelium (ectoderm). These cell lines should be useful in human developmental biology, drug discovery, and transplantation medicine.



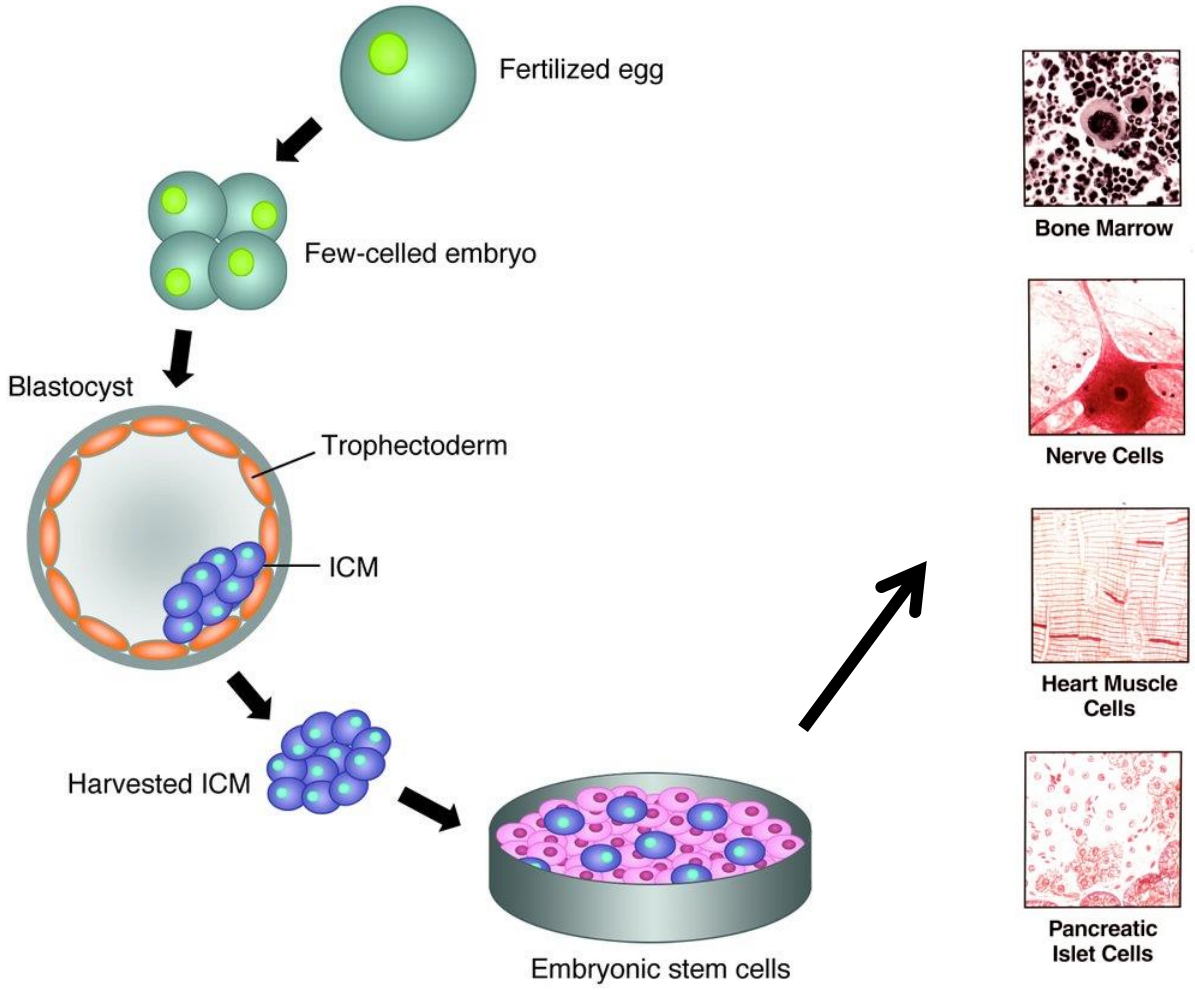
- concrete experimental systems in stem cell biology embody conceptual models of the process of development

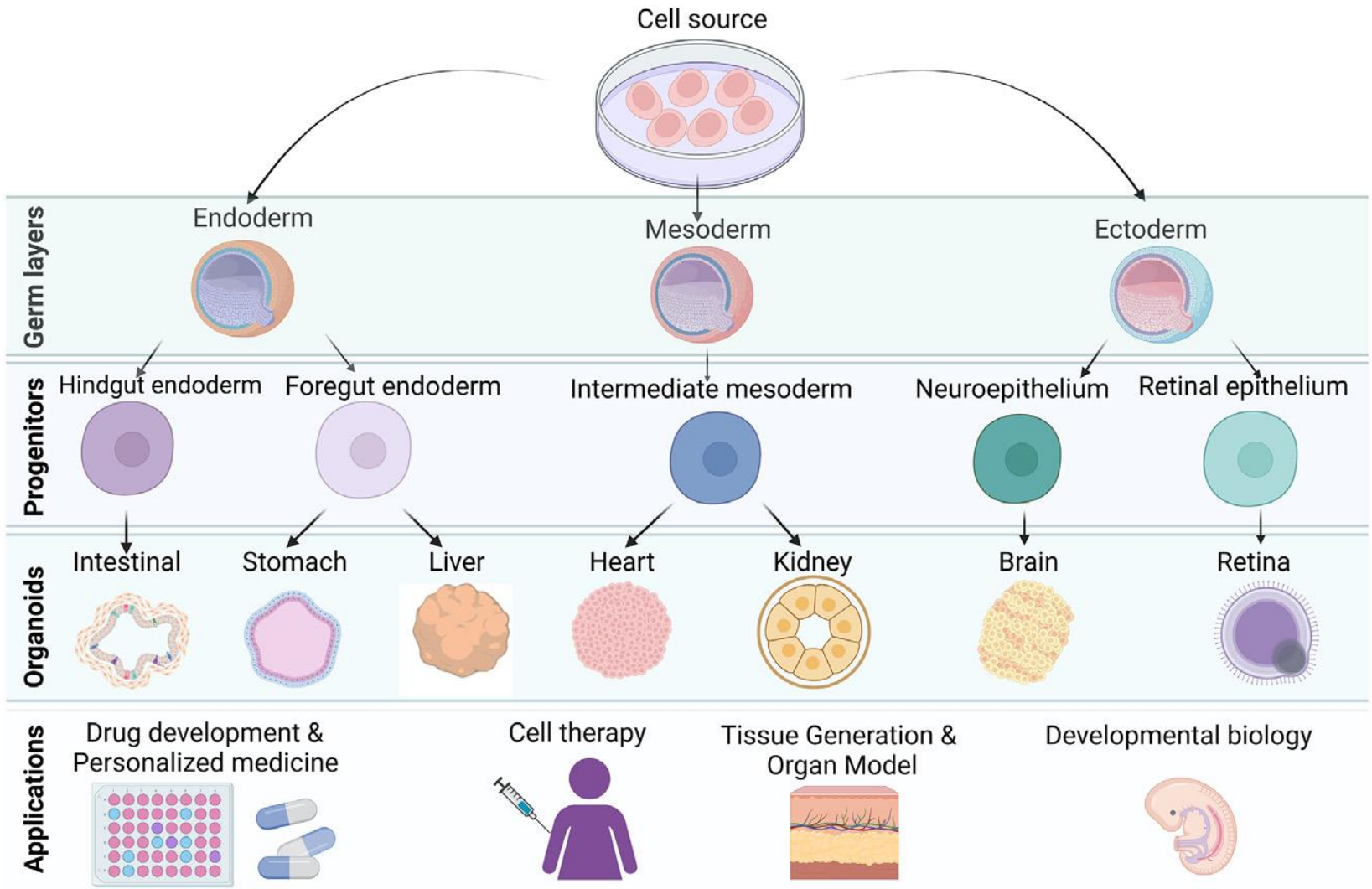
Human embryonic stem cells: method

Totipotency: the ability to produce an entire organism (in mammals, this includes extra-embryonic tissues)

Pluripotency: the ability to produce all cell types of an adult organism

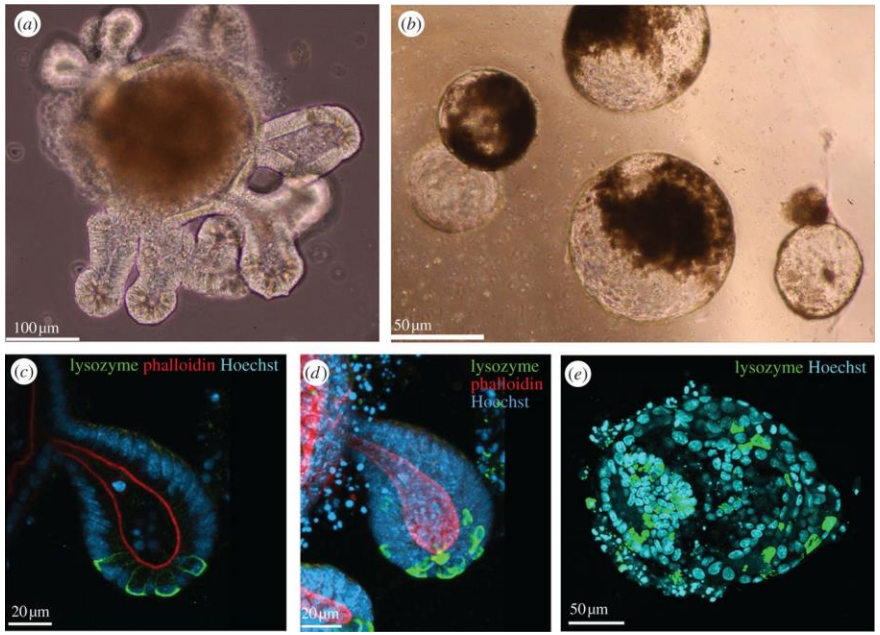
Multi-potency: the ability to produce some (but not all) cell types of an adult organism





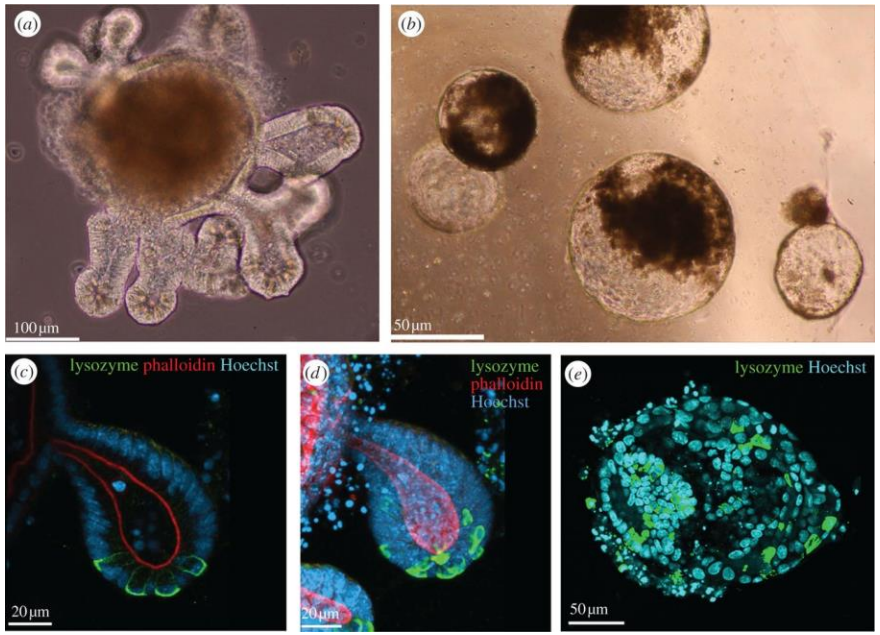
From: Moss, SP, Bakirci, E, Feinberg, AW (2025) Engineering the 3D structure of organoids. Stem Cell Reports 20: 1-14

Organoids: “approximating” organs



“a collection of organ-specific cell types that develops from stem cells or organ progenitors and self-organizes through cell sorting and spatially restricted lineage commitment in a manner similar to in vivo.” (Lancaster and Knoblich 2014, 283)

Organoids: “approximating” organs



1) produced from stem cells (that “self-organize” in experimental context)
2) includes multiple differentiated cell types characteristic of some specific organ
3) cell types spatially arranged so as that resemble that organ
4) exhibits some functionality associated with that organ

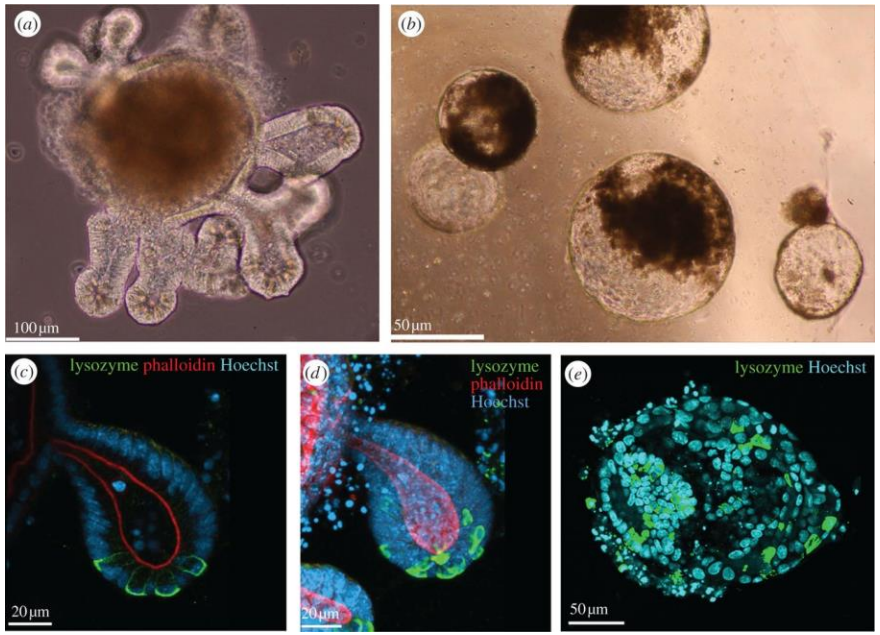
Organoids: potential applications

(1) access to human prenatal development and tissue maintenance
(2) source of tissue to study many previously-inaccessible phenomena of human development
(3) disease models for developmental studies, personalized medicine, anti-cancer strategies
(4) genome editing to probe genotype-phenotype relation
(5) comparative studies bearing on primate evolution
(6) experimental access to the unique human brain

And:

(7) screening for drug efficacy and toxicity
(8) pre-clinical research
(9) autologous organ replacement

Organoids: “approximating” organs



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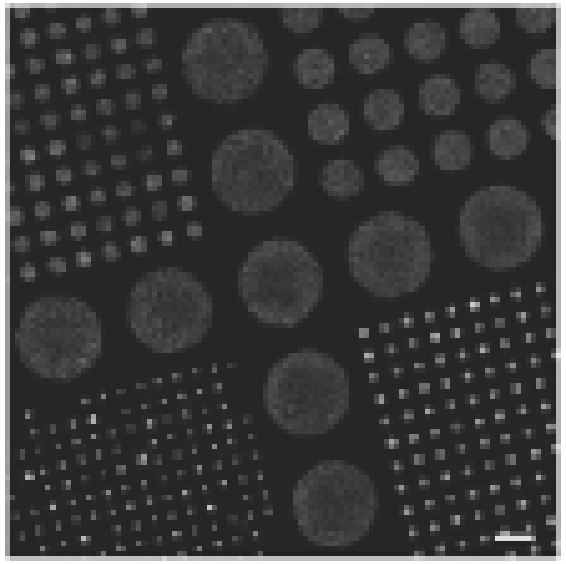
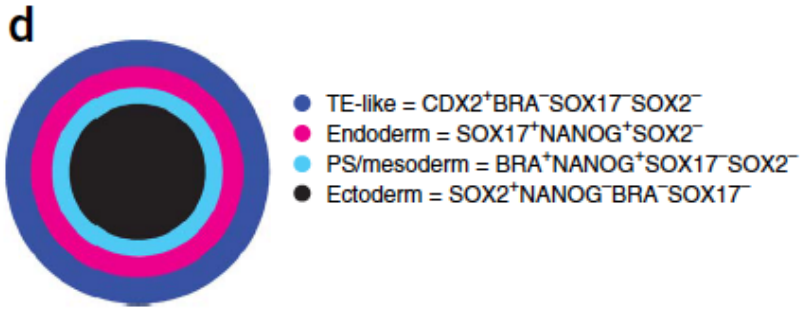
Embryo models: embryo-like structures



Human embryonic stem cells (hESC) growing in micro-patterned cell culture. (Warmflash et al. 2014, 848, Figure 1b)



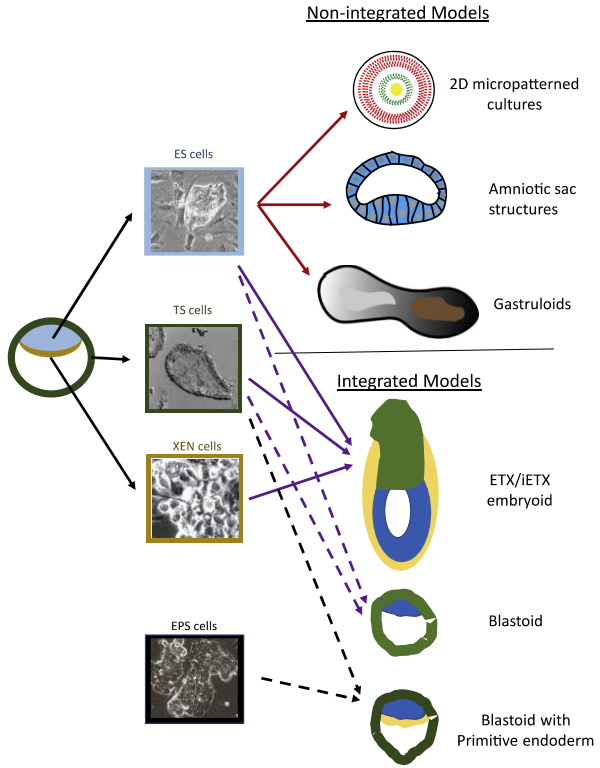
Warmflash et al (2014, 848) Schematic of the results of 42 h of BMP4 treatment in micro-patterned culture. TE, trophectoderm; PS, primitive streak.

Embryo models of early development:

"an accurate reconstruction of the in vivo events of mammalian embryogenesis, particularly at the early stages when the basic body plan is laid down and when the embryo in vivo is at its most inaccessible for experimentation."

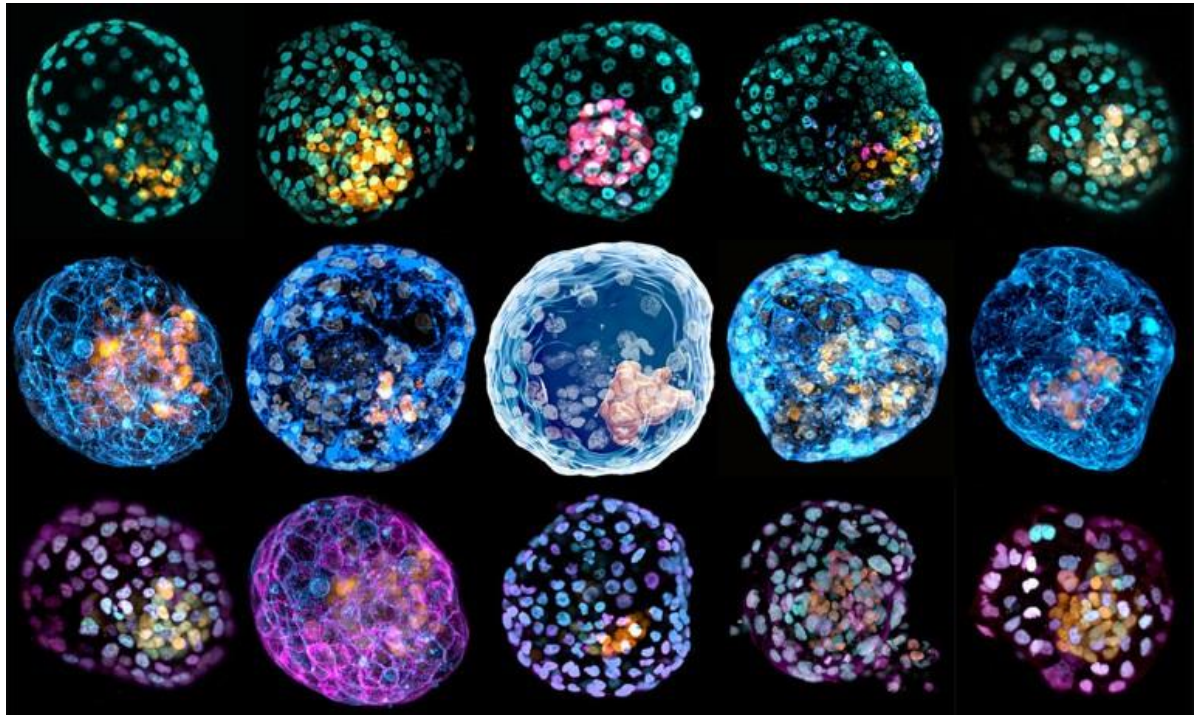
(Rossant and Tam 2021, 1031)

"embryogenesis, cell lineage differentiation, tissue morphogenesis, and organogenesis in mammalian development" (ibid)



Rossant and Tam (2021, Figure 1)

Embryo models of early development:



Nature News, Sept 11, 2024 (Image from Monash University)

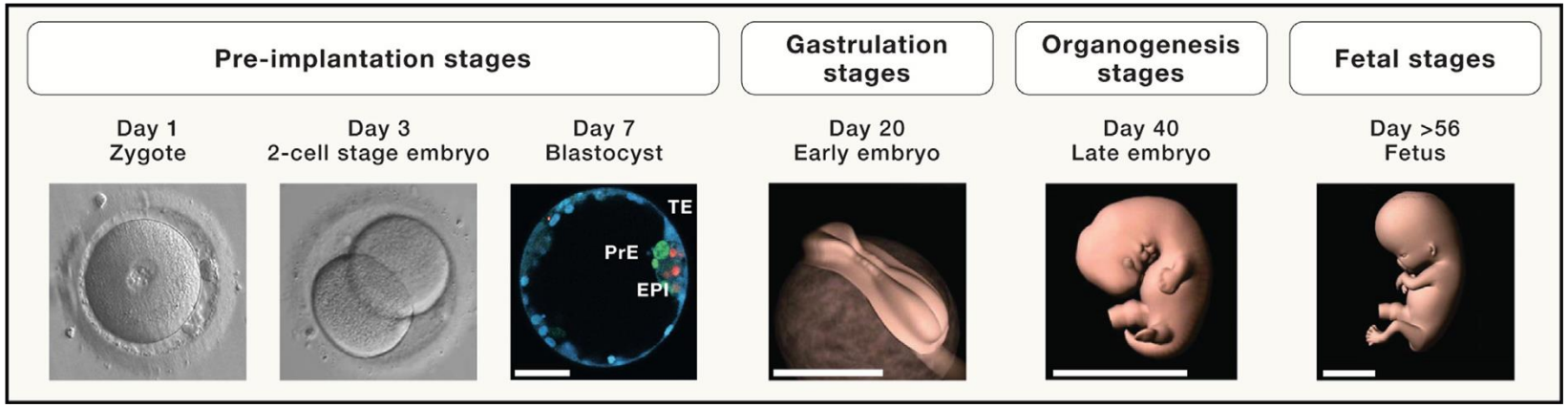
“models to recapitulate the underlying developmental events of embryonic-extraembryonic axis formation and the establishment of the basic body plan at gastrulation as well as the kinetics of embryonic patterning at early organogenesis stages…

we do not yet know how well these models are suited to mimic actual human embryo development. ”

(Rossant and Tam 2021, 1032)

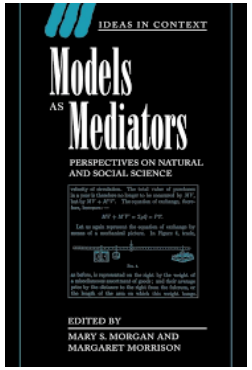
Scientific and philosophical issues:

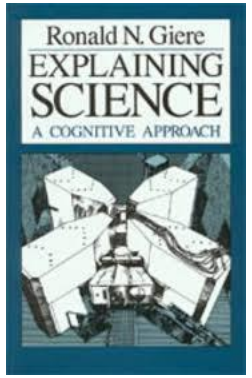
- re-visiting legal and scientific definitions of "the embryo"
- new ethical guidelines
- prospects for combining different organoids into a proto-organism
- concerns about consciousness or experience of 'realistic' brain organoids
- public communication, trust, transparency
- scientific metaphysics: "the way a human embryo is formed…is relatively unimportant …since what matters most is what these cells are and could become" (Rivron et al 2023, 3550).

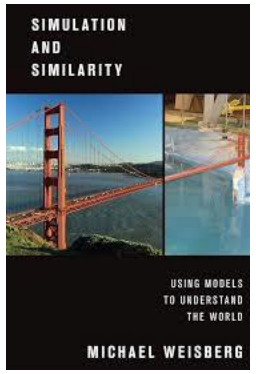


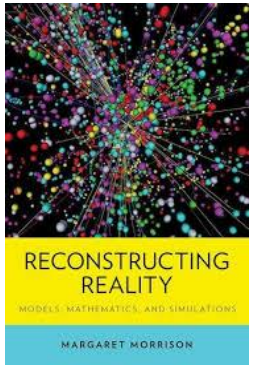
From: Rivron, NC, Martinez Arias, A, Pera, MF, Moris, N, and M'hamdi, HI (2023) An ethical framework for human embryology with embryo models. Cell 186: 3548-3557

Philosophy of science: models and modeling







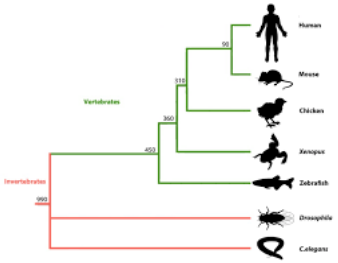


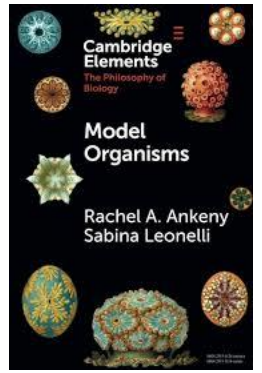
"Agents
(1) intend;
(2) to use model, M;
(3) to represent a part of the world W;
(4) for purposes, P.
So agents specify which similarities are intended and for what purpose."

(Giere 2010, 274)

Defining models: equations, abstract imaginary objects (e.g., infinite populations, perfect spheres), scale models, computer-generated visualizations, whole organisms

Analyzing models' scientific role: representational, generalized, hypothetical, targetless (Weisberg 2013)





Philosophy of science: model-target relation

Models Of and Models For: Theory and Practice in Contemporary Biology

Evelyn Fox Keller†‡
Massachusetts Institute of Technology

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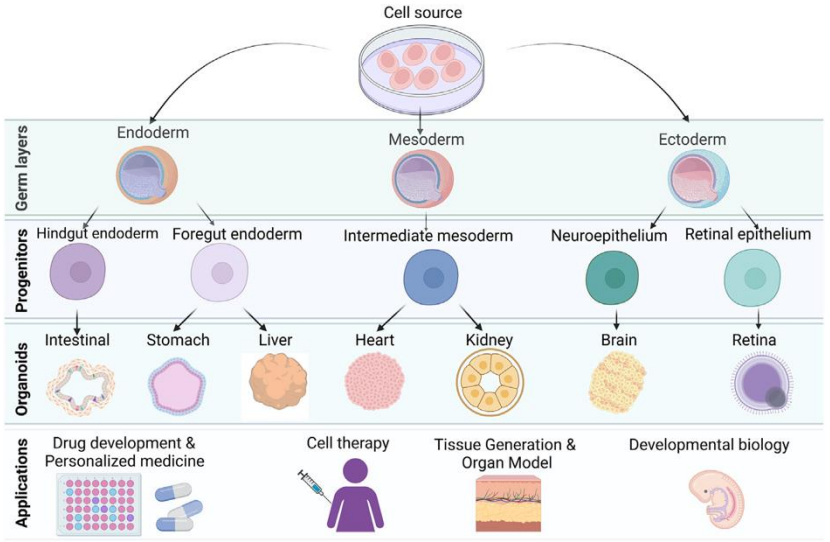
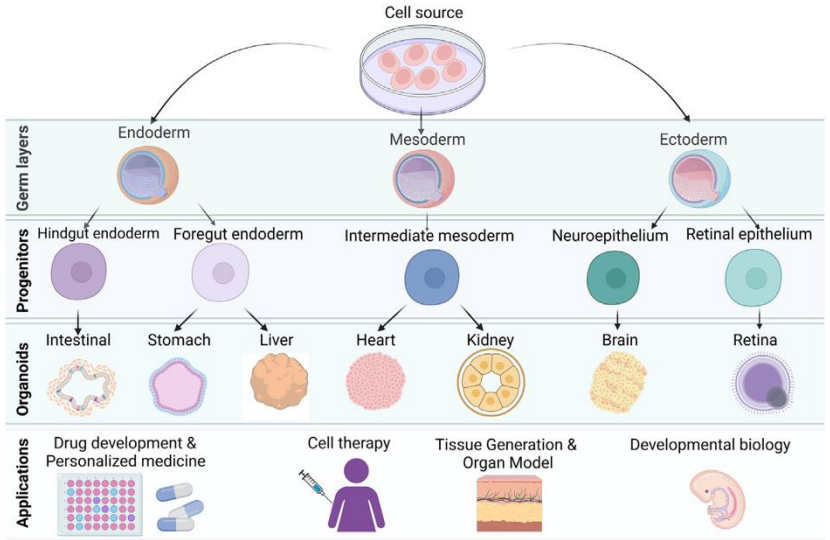
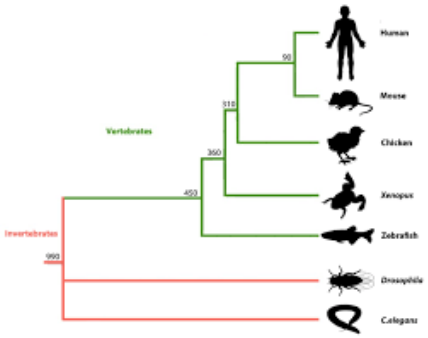


Organoids and embryo models: models of in vivo organs and whole embryos, respectively

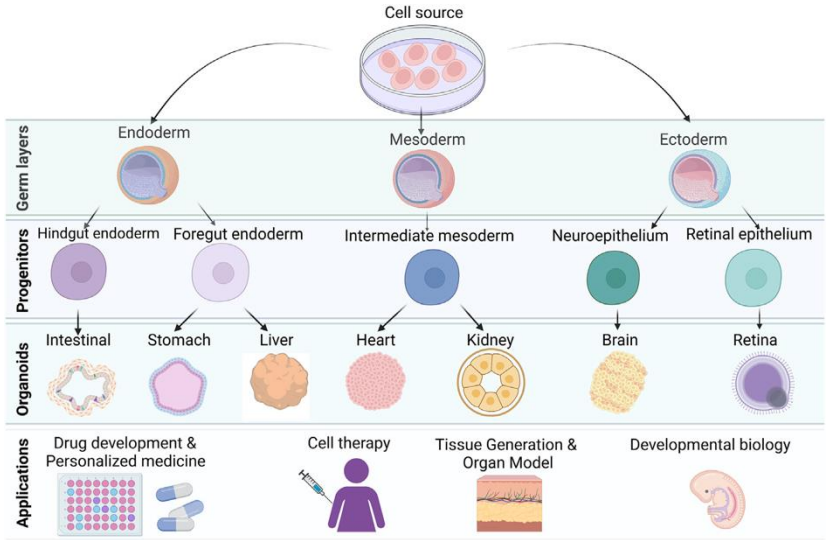
Model-target complexity: organoids





- phylogenetic scope
- "one organoid, one organ" not the whole story
  - (1) "multiplexing"
  - (2) stem cell derivation
  - (3) model-target 'looping'
  - (4) target very complex

Model-target complexity: organoids



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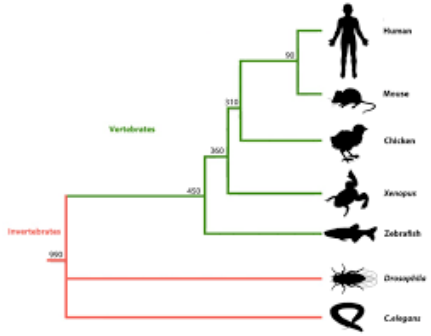
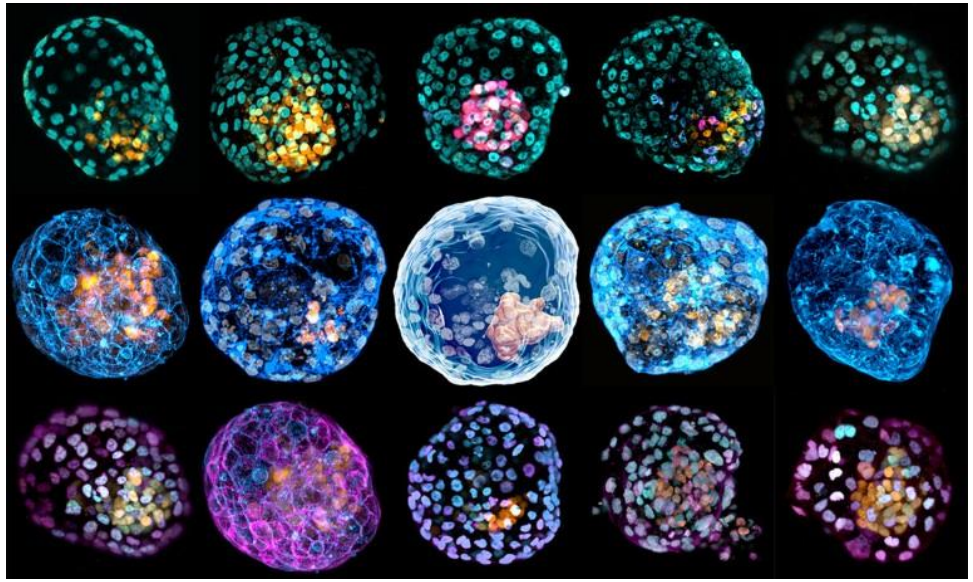


Multiplexing: engineer "more complex organoids with improved function and translational relevance… size and complexity of organoids reach a plateau due to limitations of the self-organization process in vitro, such as the lack of organism-scale mechanical forces and little to no development of vasculature to provide adequate nutrient and oxygen transport to the growing tissues."

(Moss et al 2025 1)

Model-target complexity: embryo models

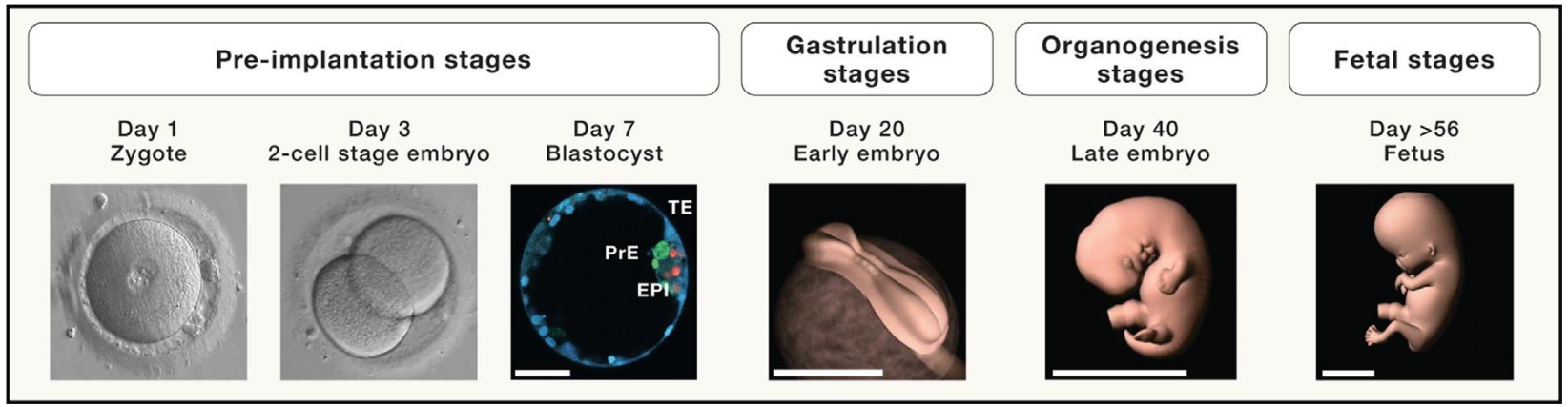


"…scientific advances are narrowing the biological and therefore ethical and legal gaps between embryo models and embryos."

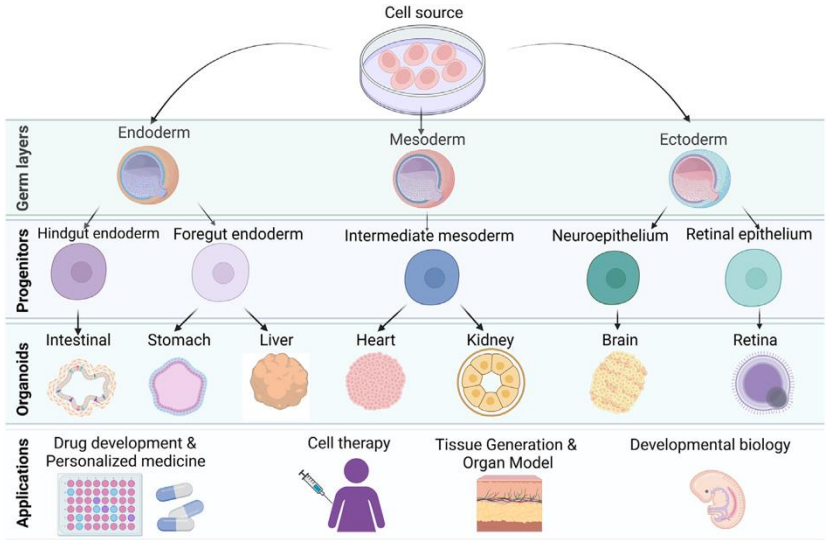
(Rivron et al 2023, 3550)

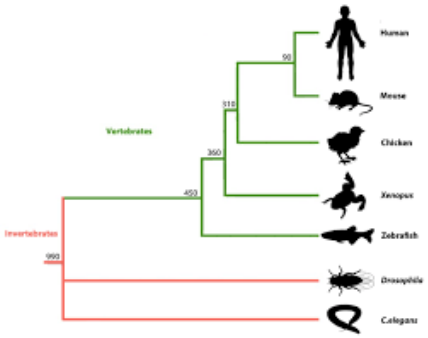
In theory, "**a model could become an embryo**."

(ibid, 3552)



Model-target complexity: organoids





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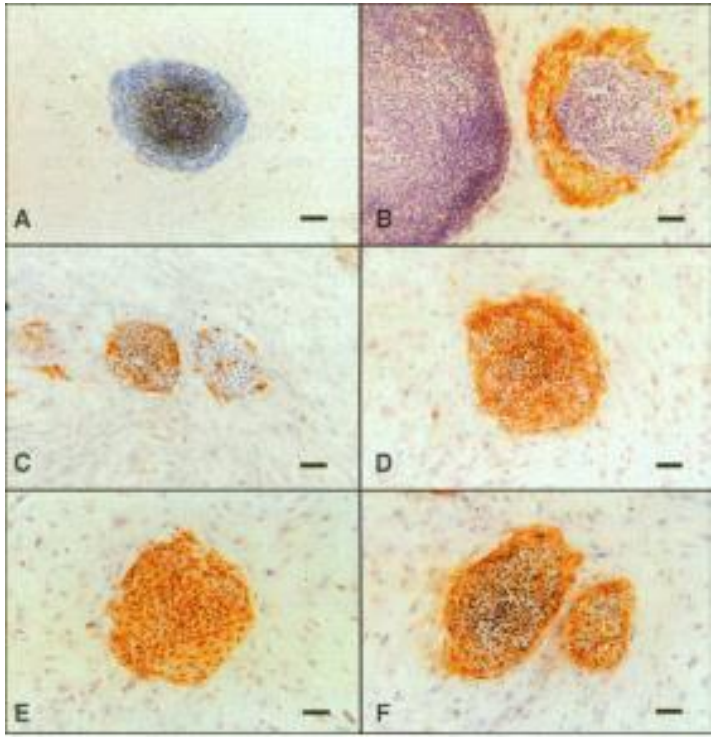

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Propagation of models: cultured SC

Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 13726–13731, November 1998
Developmental Biology

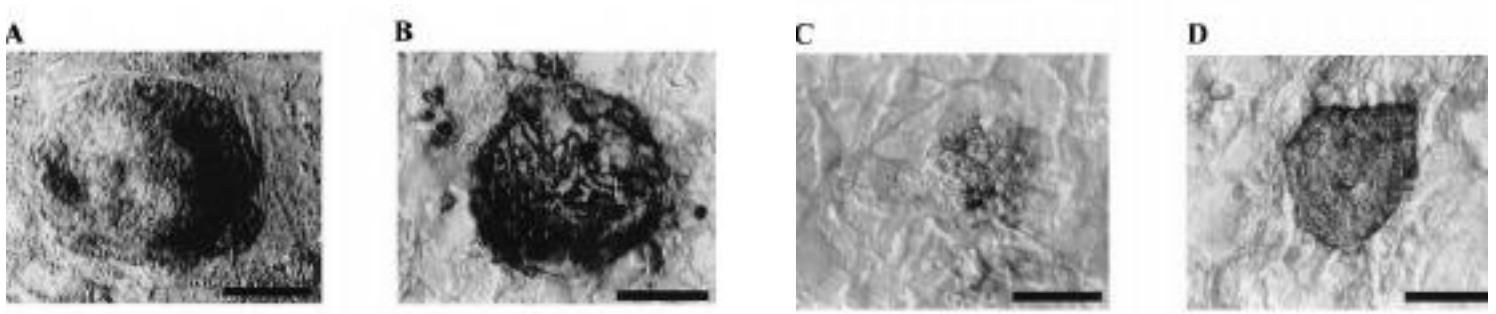
Derivation of pluripotent stem cells from cultured human primordial germ cells

(alkaline phosphatase/embryoid body/embryonic stem cell/embryonic germ cell)

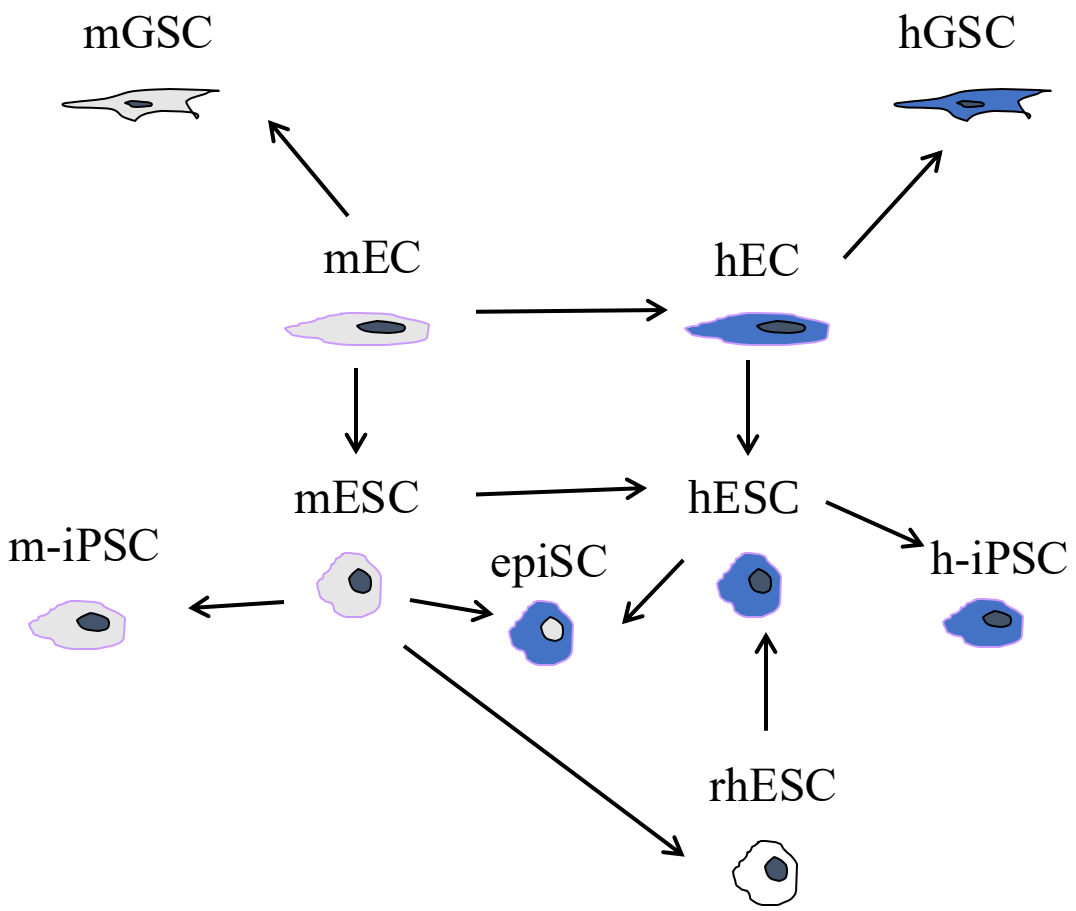
MICHAEL J. SHAMBLOTT*, JOYCE AXELMAN*, SHUNPING WANG*, ELIZABETH M. BUGG*, JOHN W. LITTLEFIELD†, PETER J. DONOVAN‡, PAUL D. BLUMENTHAL§, GEORGE R. HUGGINS§, AND JOHN D. GEARHART*†¶

Departments of *Gynecology and Obstetrics and †Physiology, Johns Hopkins University School of Medicine, Baltimore, MD 21287; ‡Kimmel Cancer Institute, Jefferson Medical College, Philadelphia, PA 19107; and §Department of Gynecology and Obstetrics, Johns Hopkins Bayview Hospital, Baltimore, MD 21224

Contributed by John W. Littlefield, September 29, 1998



Stem cell lines: a family of models

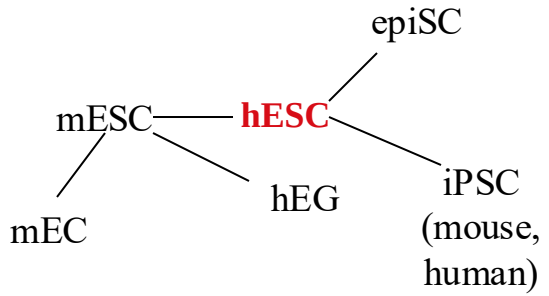


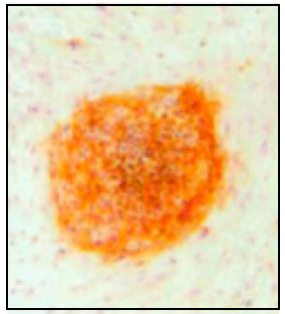
Timeline: pluripotent stem cell models

1954	teratocarcinoma-129
1964	embryoid bodies
1970	mouse EC (many lines, 1970-74)
1975-77	human EC
1981	mouse ESC
1987	knockout mice (ESC method)
1992	mouse GSC
1995	monkey ESC
1998	human ESC, human GSC
2006	mouse iPSC
2007	human iPSC, mouse epiSC

A family of living experimental models:

- organized by similarity relations
- mouse, human, cancer
- broad similarities and subtle differences

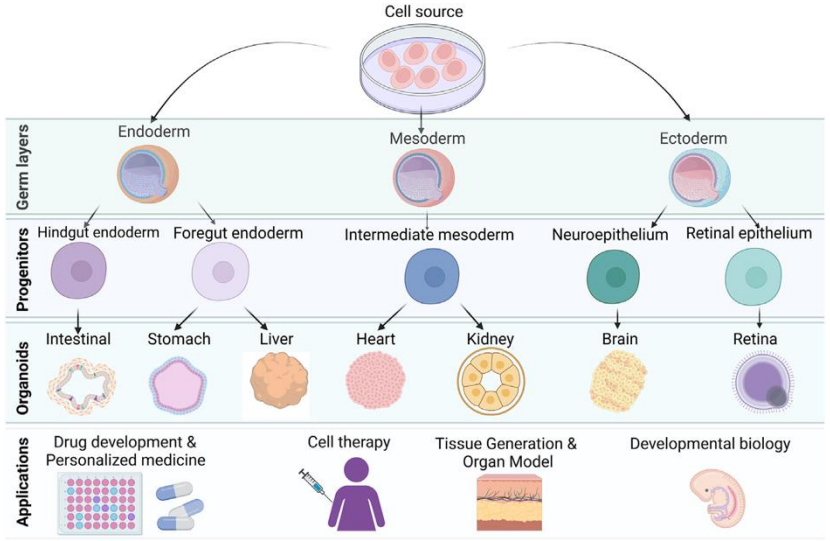




Knowledge emerges from comparisons among different model systems.

Modeling role for understanding organismal development.

Model-target complexity: organoids



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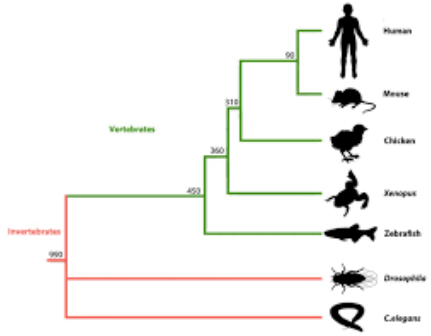
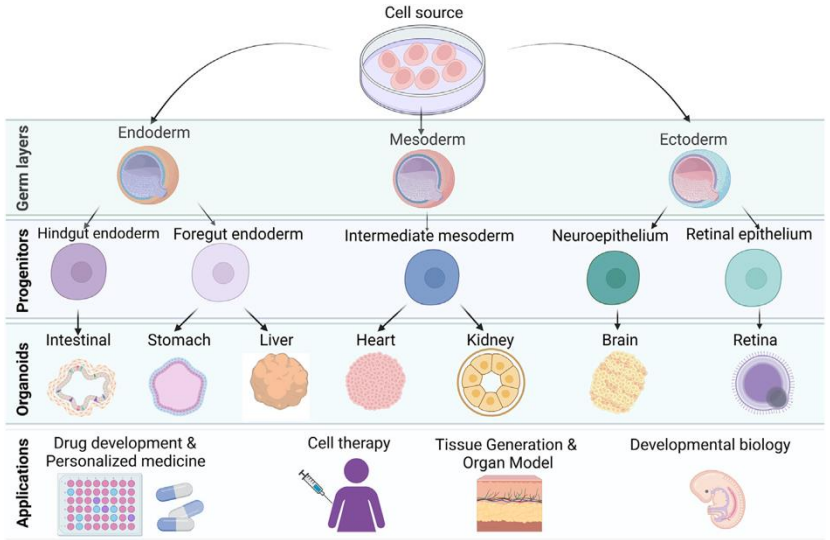
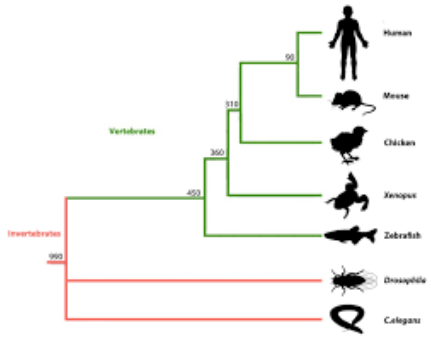


Generative models: cultured stem cell lines are models that generate other models, via (1) stem cells' defining abilities (reproduction & development) and (2) scientists' interests and purposes.

Model-target complexity: organoids

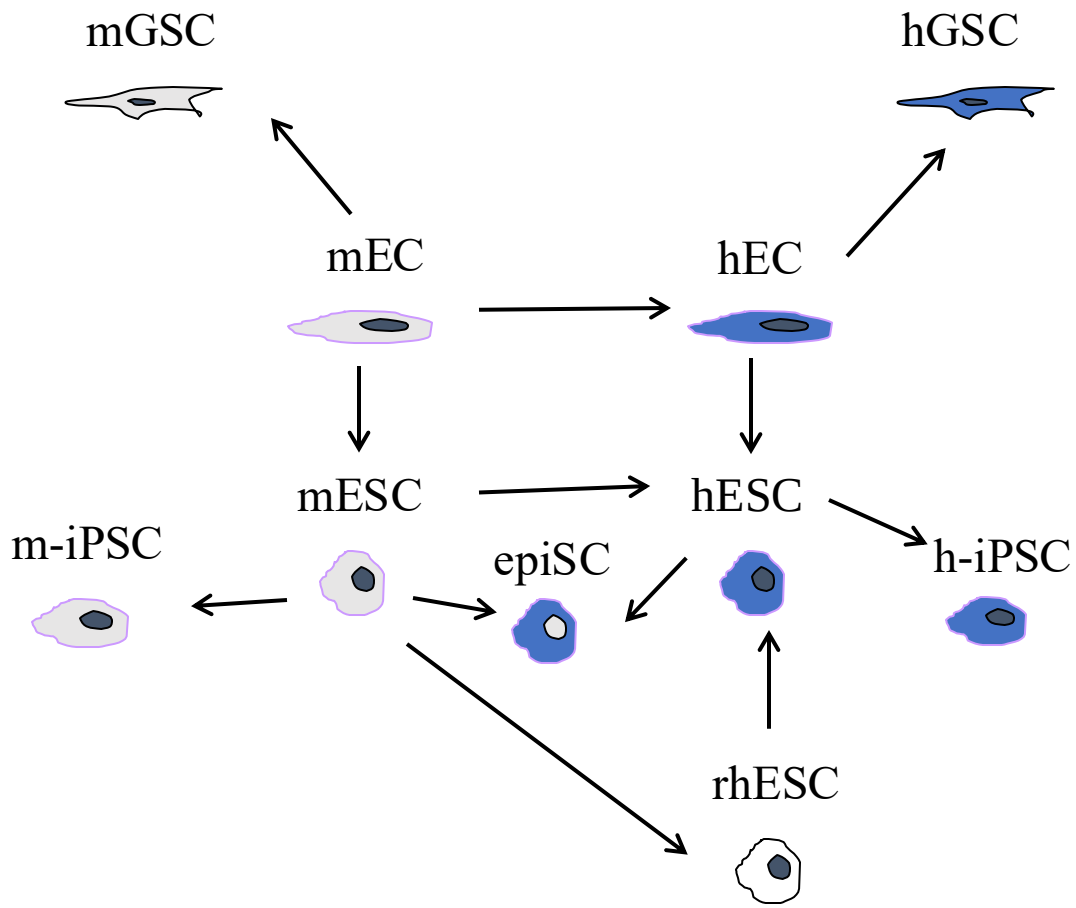


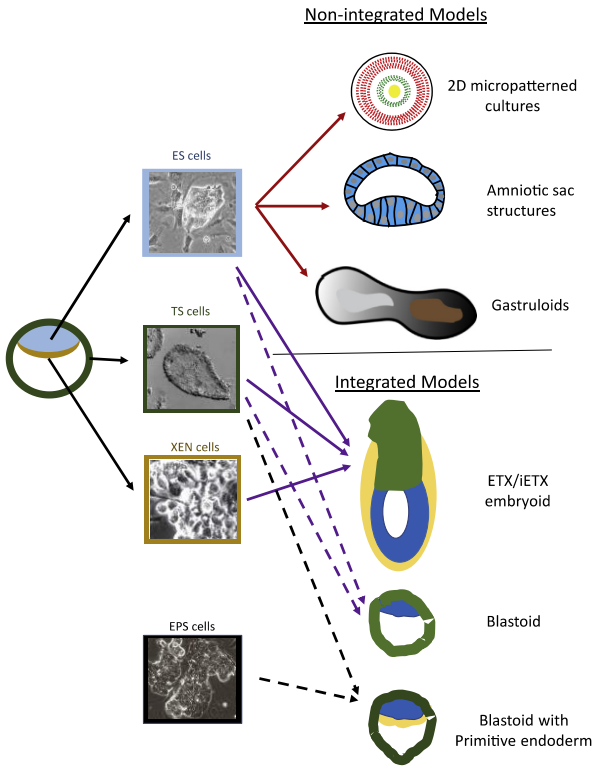
- phylogenetic scope
- "one organoid, one organ" not the whole story
  (1) "multiplexing"
  (2) stem cell derivation
  (3) model-target 'looping'
  (4) target very complex



Embryo model aspirations: "an interdisciplinary approach that encompasses systems biology, cell and developmental biology, biophysics, mechanobiology, bioengineering, machine learning, data science, and computational modeling will enable the redirection of stem cells into new functional forms. The integrated knowledge will be used to design an embryo model in silico (Levin et al., 2020; Libby et al., 2019), followed by the experimental generation of this digital twin in reality" (Rossant and Tam 2021, 1036).

Stem cell lines, organoids, embryo models:

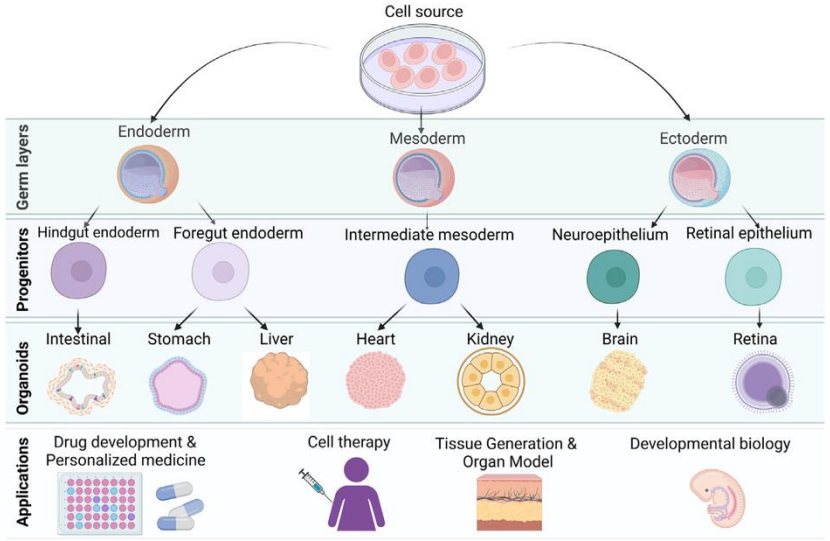




Stem cells: developmental versatility

Experiment	Mode of development	Aspect of organization
n/a	normal	all, complex, robust
embryoid body	simplified	generic cell types, simple 3D structure
teratoma	pathological	specialized cell types, 3D structure, non-robust
organoid	organ-like	specialized cell types, complex 3D structure, non-robust
embryo-like structure	embryo-like	generic cell types, simple 2D structure, polarity
directed differentiation	cellular	specialized cell types

Model-target complexity: generative models



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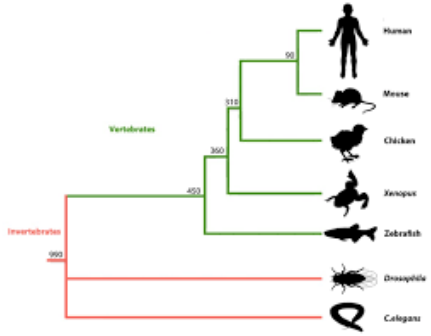

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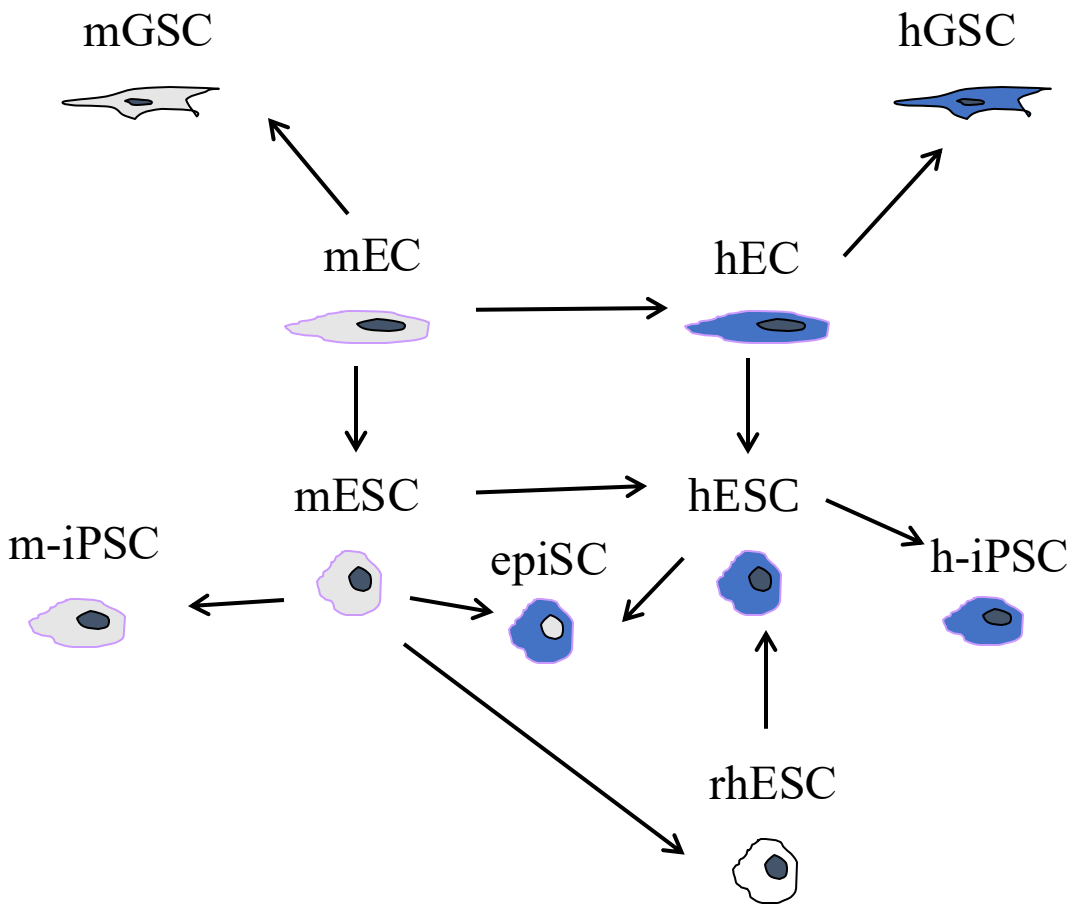
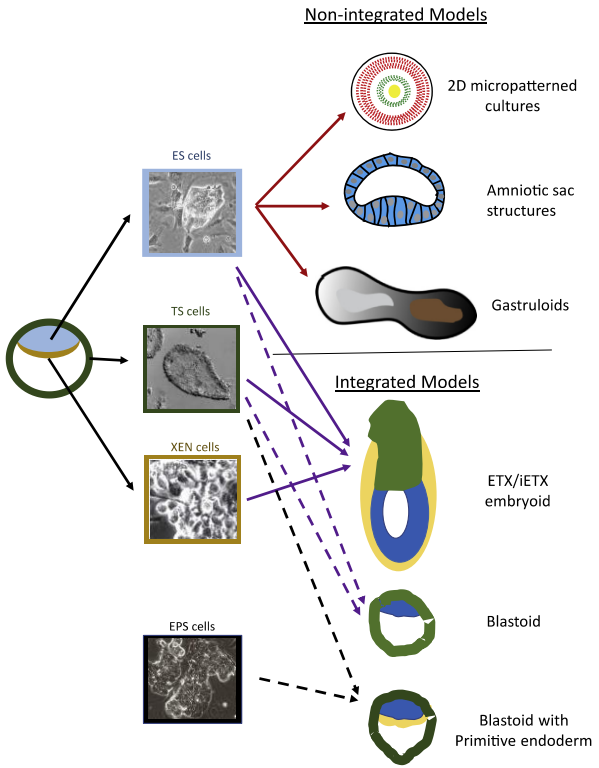
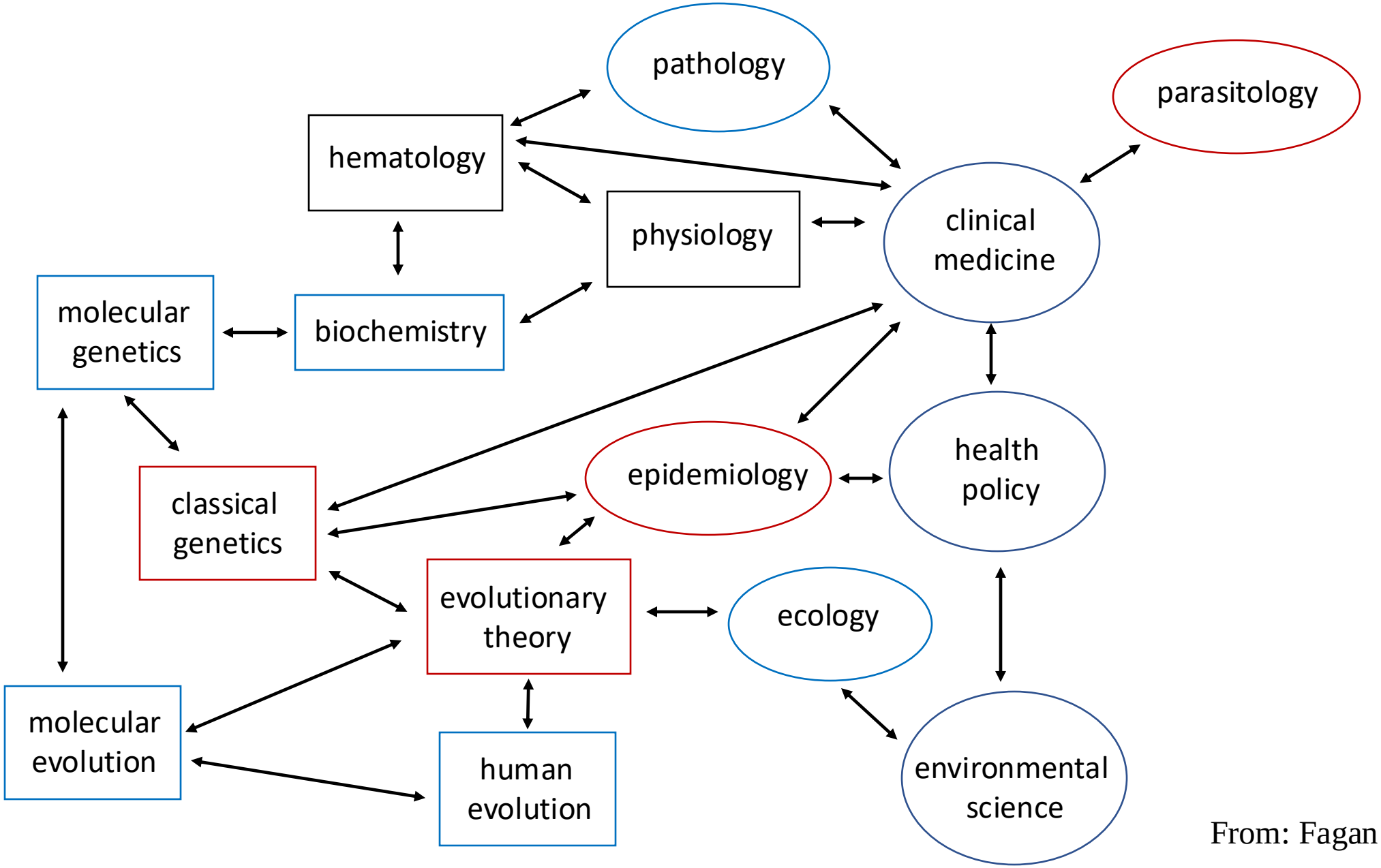
A fabric of models: form of knowledge?



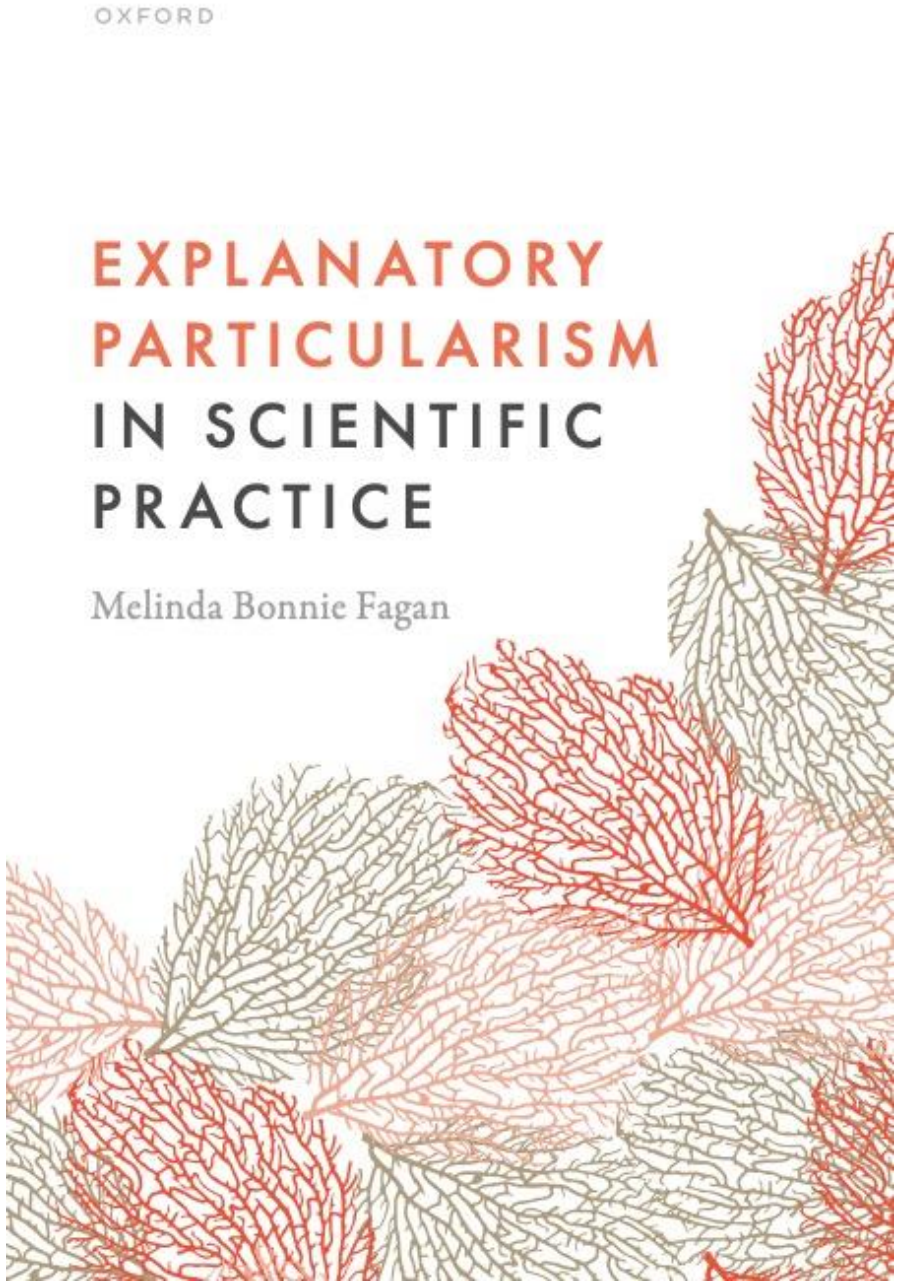




From: Fagan (forthcoming)

<https://global.oup.com/academic/product/explanatory-particularism-in-scientific-practice-9780198897453?>

- relational understanding
- insights for interdisciplinarity
- “patchwork” unity of science
- anti-hierarchical
- pro-social, collaborative explanation
- implications for science-society



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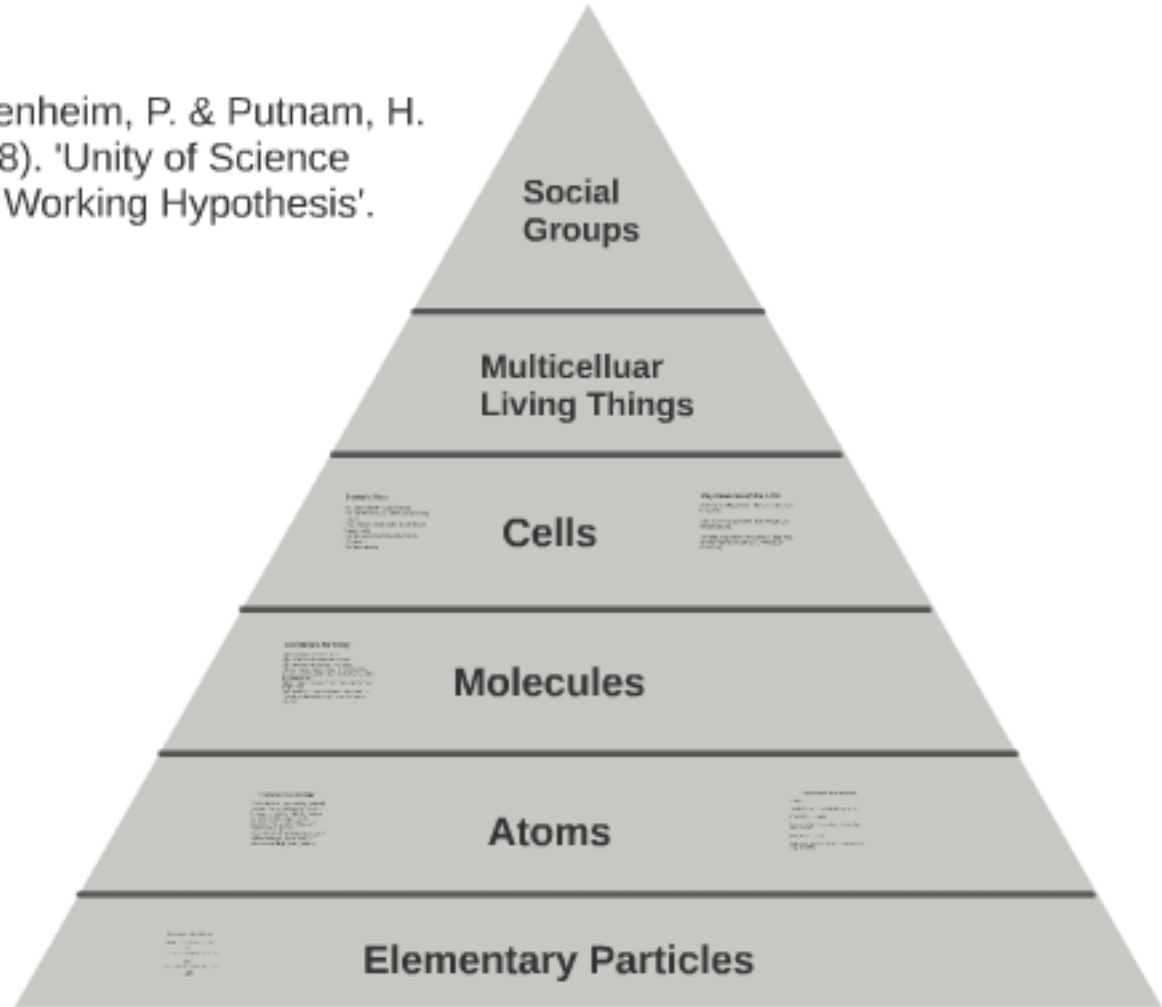
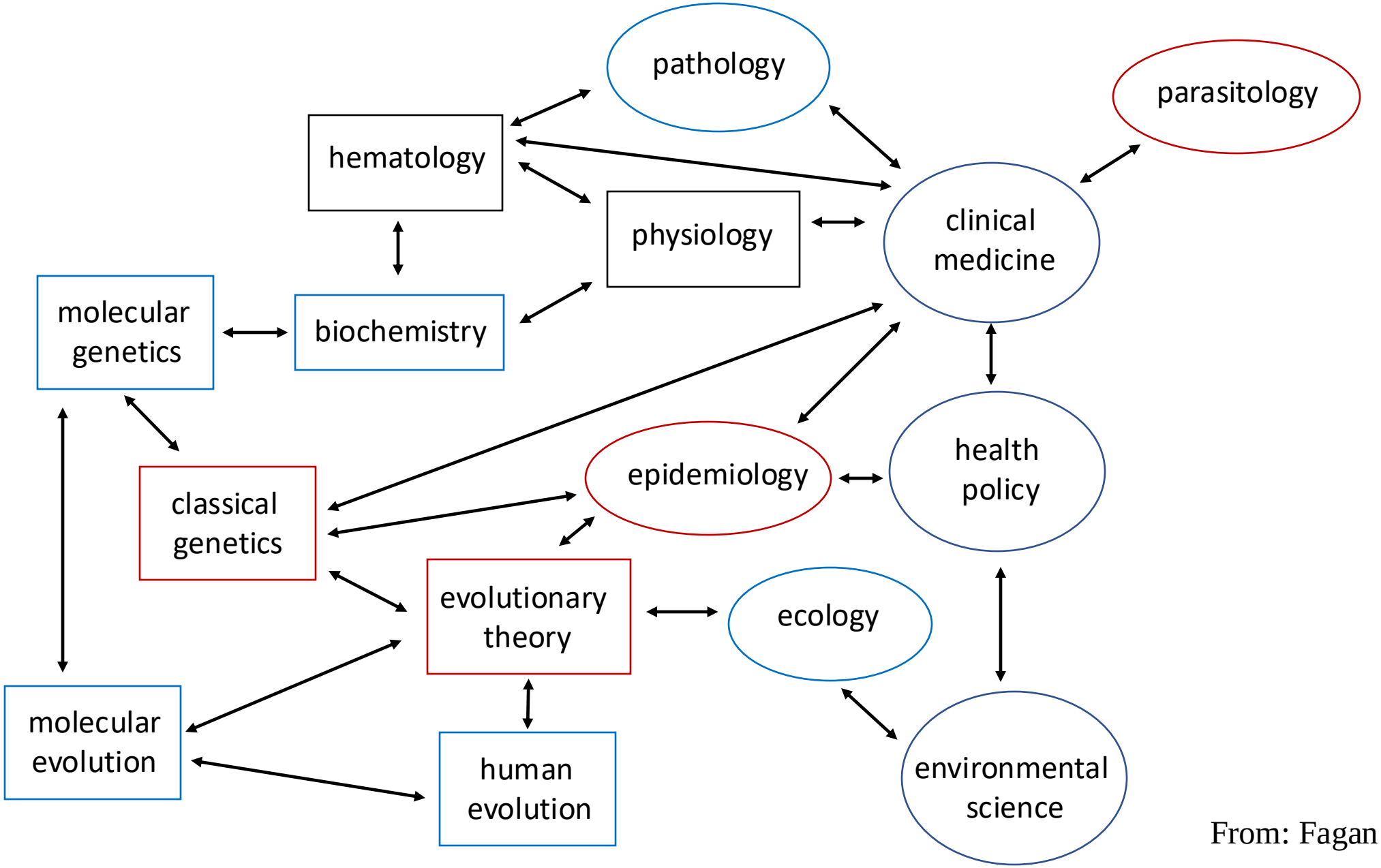
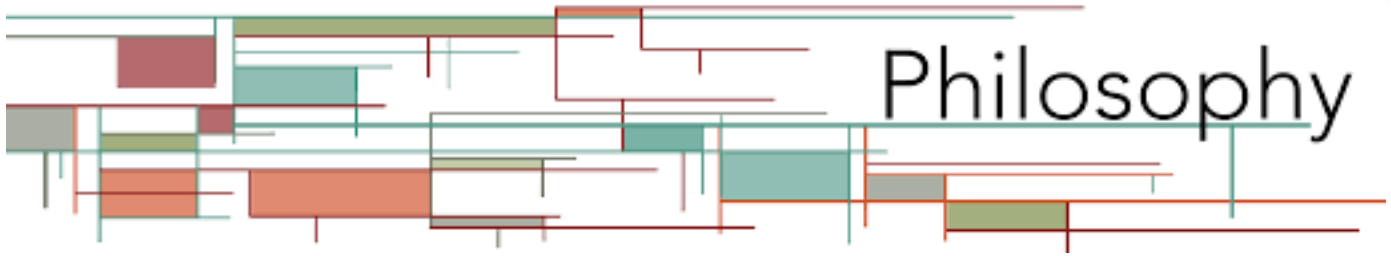




From: Fagan (forthcoming)

Thanks!

The
Sterling M. McMurrin
Foundation



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