STEM CELLS IN EXPERIMENTAL GENE THERAPIES

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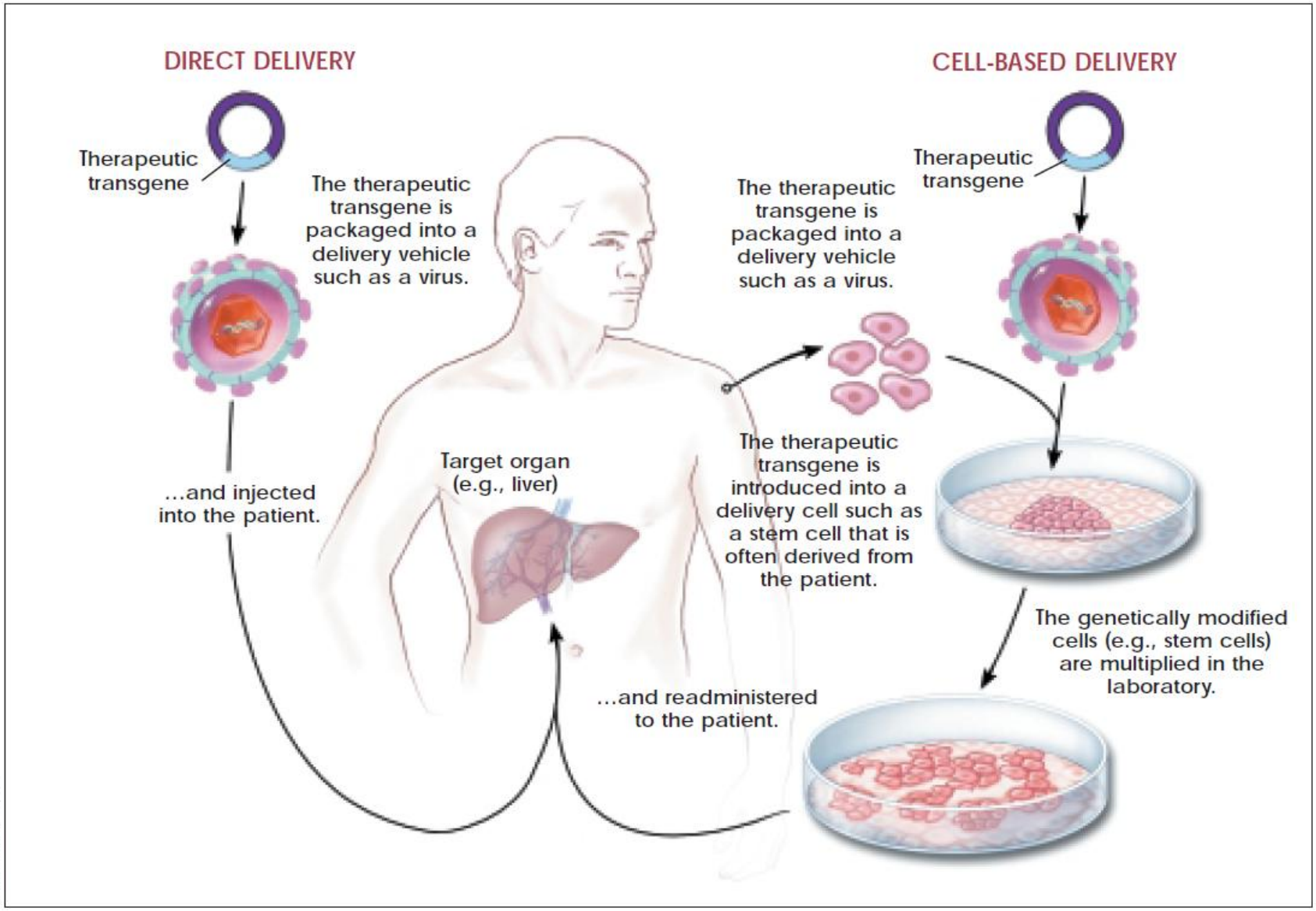

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Figure 11.1. Strategies for Delivering Therapeutic Transgenes into Patients.

WHY STEM CELLS ARE USED IN SOME CELL-BASED GENE THERAPIES?

First, although small in number, they are **readily removed from the body via the circulating blood or bone marrow** of adults or the **umbilical cord blood** of newborn infants.

In addition, they are **easily identified and manipulated** in the laboratory and can be returned to patients relatively easily by injection.

The ability of hematopoietic stem cells to give rise to many different types of blood cells means that once the engineered stem cells differentiate, **the therapeutic transgene will reside** in cells such as T and B lymphocytes, natural killer cells, monocytes, macrophages, granulocytes, eosinophils, basophils, and megakaryocytes.

The clinical applications of hematopoietic stem cell-based gene therapies are thus also diverse, extending to organ transplantation, blood and bone marrow disorders, and immune system disorders.

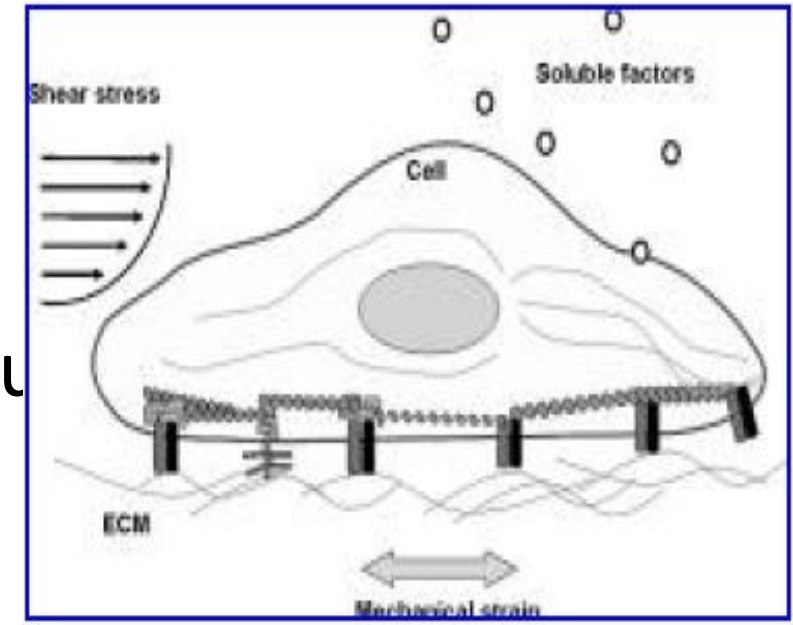
In addition, hematopoietic stem cells "home," or migrate, to a number of different spots in the body—primarily the bone marrow, but also the liver, spleen, and lymph nodes. These may be strategic locations for localized delivery of therapeutic agents for disorders unrelated to the blood system, such as liver diseases and metabolic disorders.

Myoblasts appear to be good candidates for use in gene therapy because of an unusual and advantageous biological property: when injected into muscle, they fuse with nearby muscle fibers and become an integral part of the muscle tissue.

In a series of experiments in rodents, a team of investigators has been testing **neural stem cells** as vehicles for cell-based gene therapy for brain tumors known as **gliomas**.

Another cell-based gene therapy system under investigation involves the use of **osteoblasts**, or bone forming stem cells.

Tissue Engineering



- Repair/replace damaged tissu
  - Enhance natural regeneration

Cell Source

Embryonic stem cells
Adult stem cells
Progenitor cells

Signals

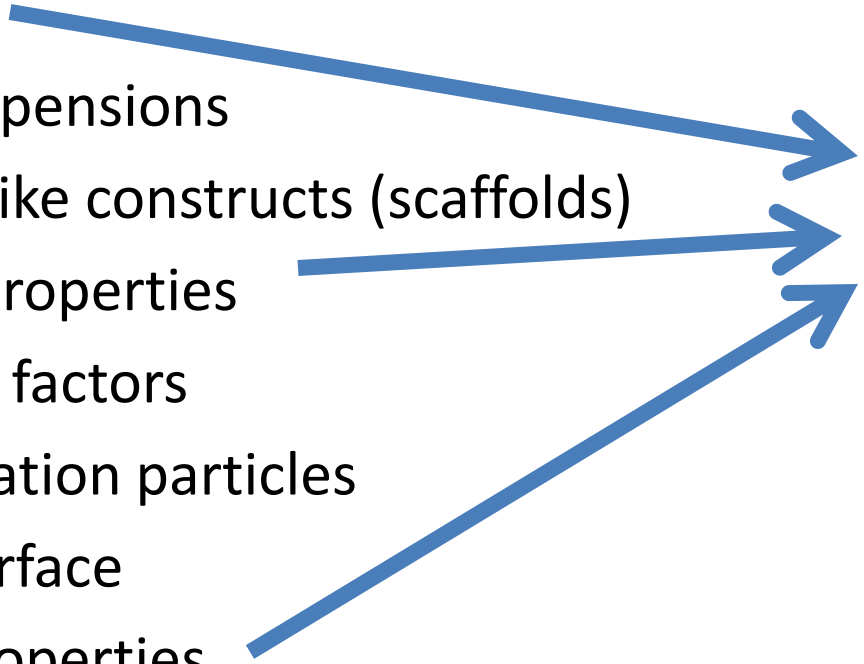
Growth factors
Drugs
Mechanical forces

ECM

Metals
Ceramics
Synthetic polymers
Natural polymers

Important Variables

- Delivery
  - Cell Suspensions
  - Tissue-like constructs (scaffolds)
- Chemical properties
  - Growth factors
  - Degradation particles
  - ECM surface
- Physical properties
  - Structure
  - Topography
  - Rigidity
  - Mechanical Loading



Modify Cell Behavior

Survival
Organization
Migration
Proliferation
Differentiation

Optimize Cellular Response

Models for Tissue Engineering

- *In vitro* differentiation
  - Construct tissues outside body before transplantation
  - Ultimate goal
    - Most economical
    - Least waiting time
- *In situ* methodology
  - Host remodeling of environment
- *Ex vivo* approach
  - Excision and remodeling in culture

Combine physical and chemical factors → Optimize stem cell differentiation and organization

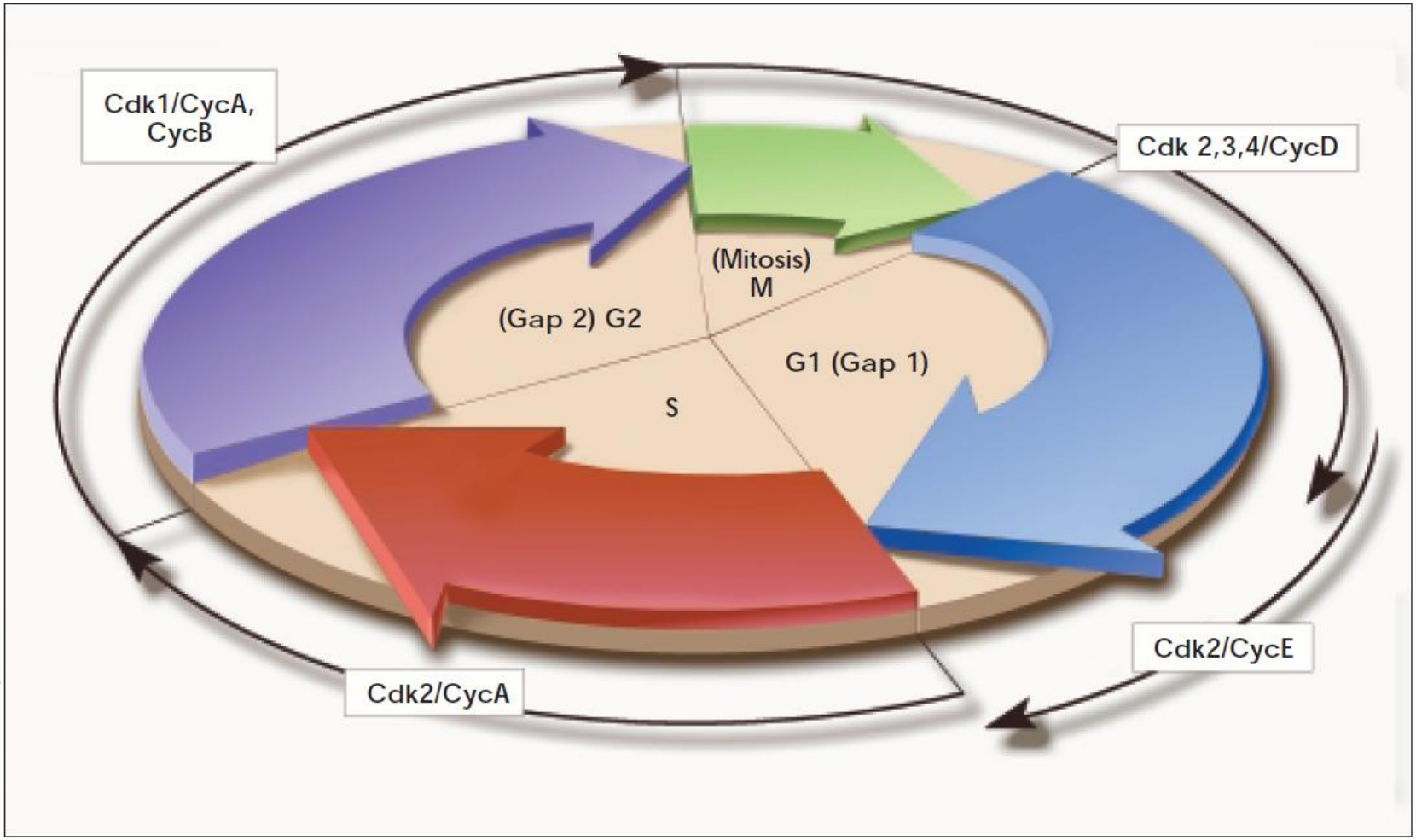


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Figure A.1. Cell Cycle.

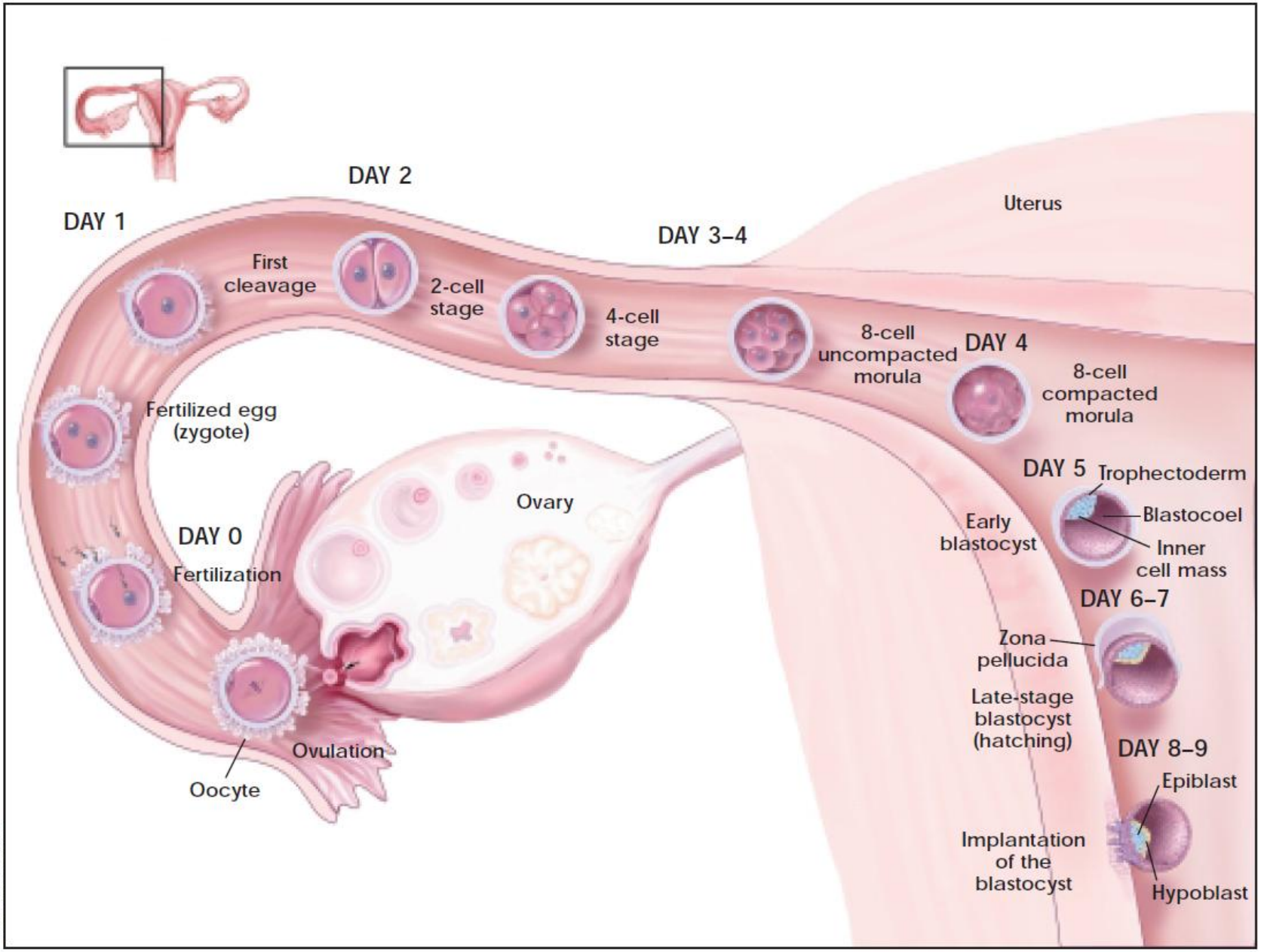

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Figure A.2. Development of the Preimplantation Blastocyst in Humans.

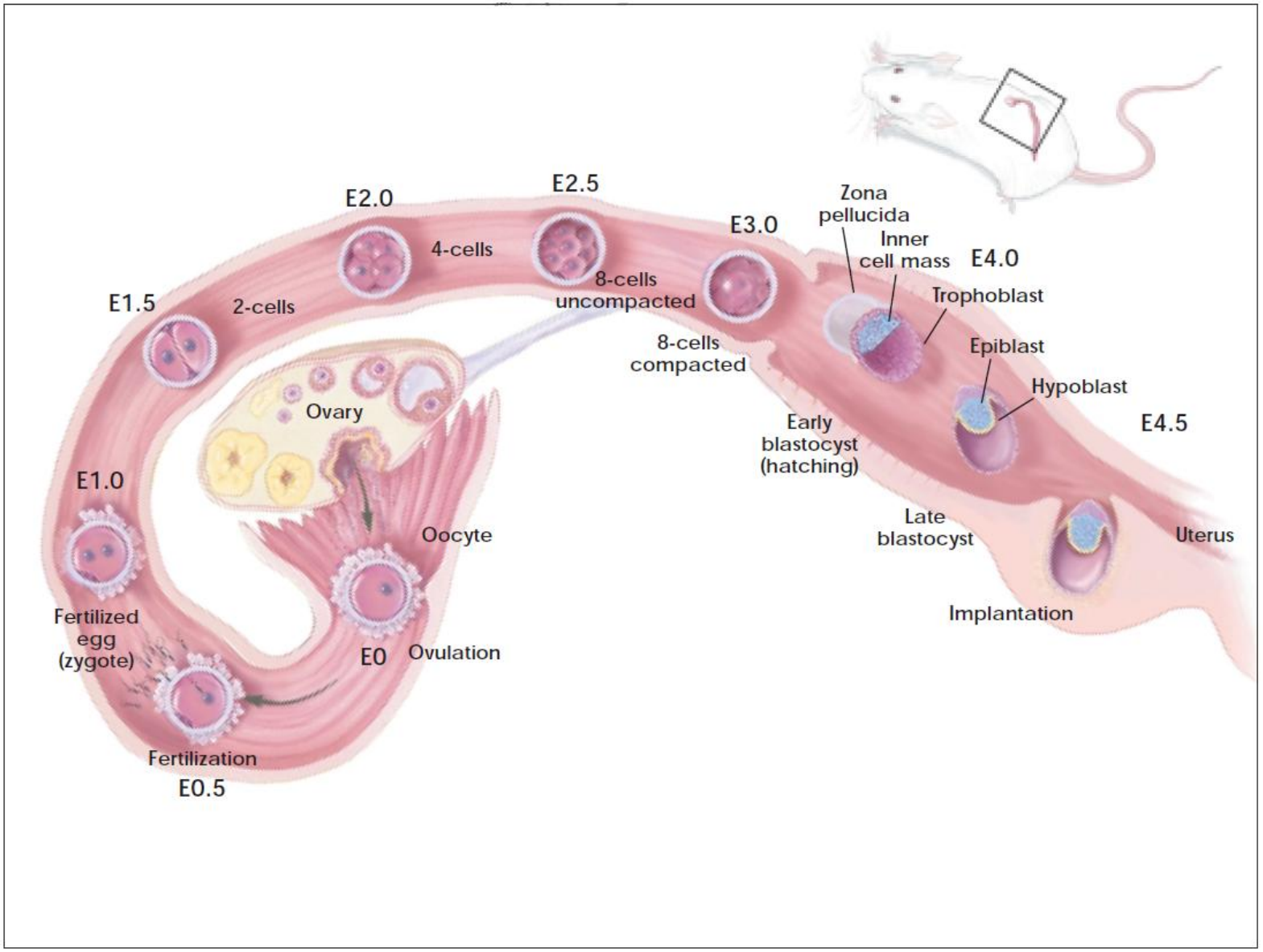

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Figure A.3. Development of the Preimplantation Blastocyst in Mice from Embryonic Day 0 (E0) Through Day 5 (E5.0).

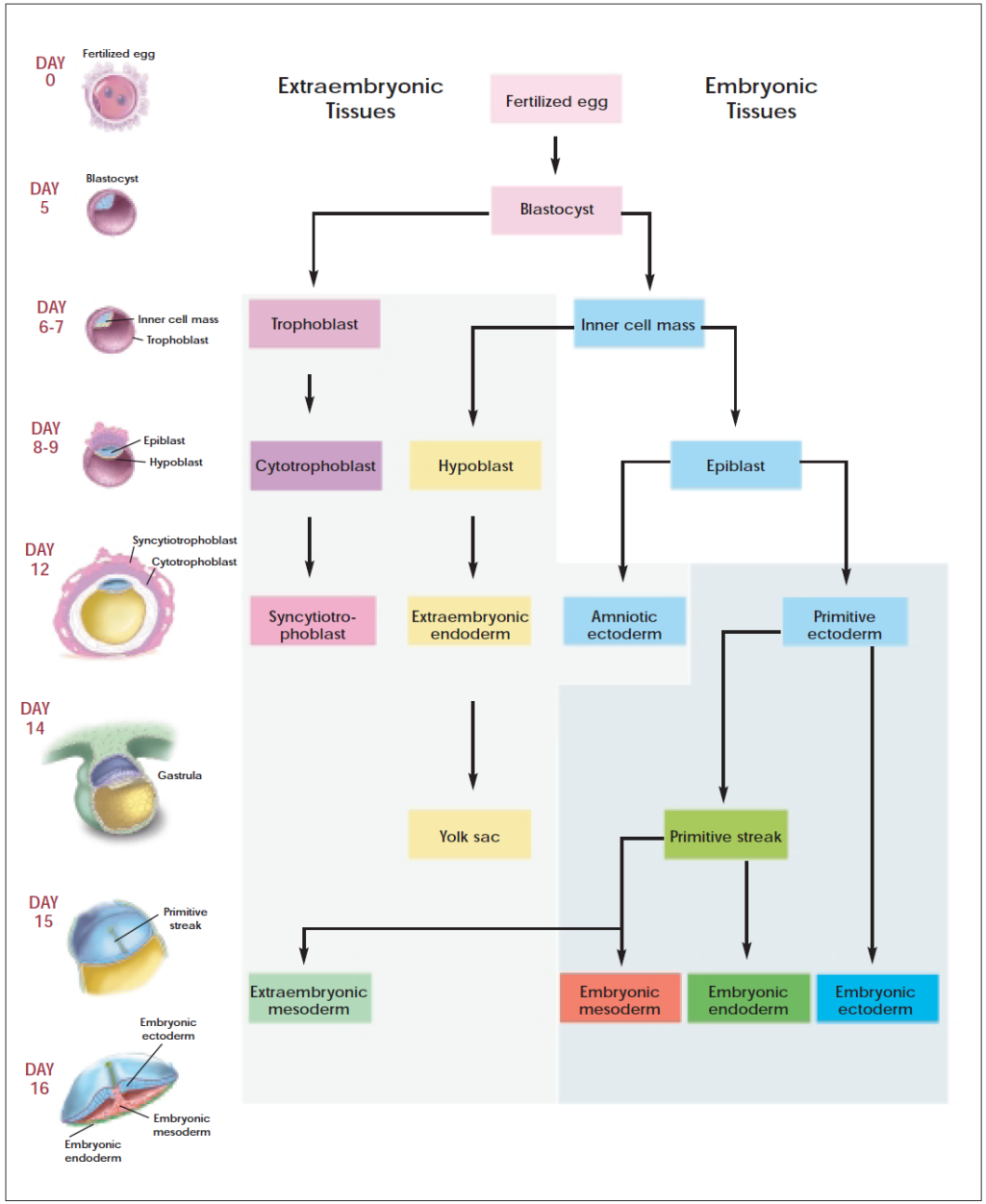

Figure A.4. Development of Human Embryonic Tissues.

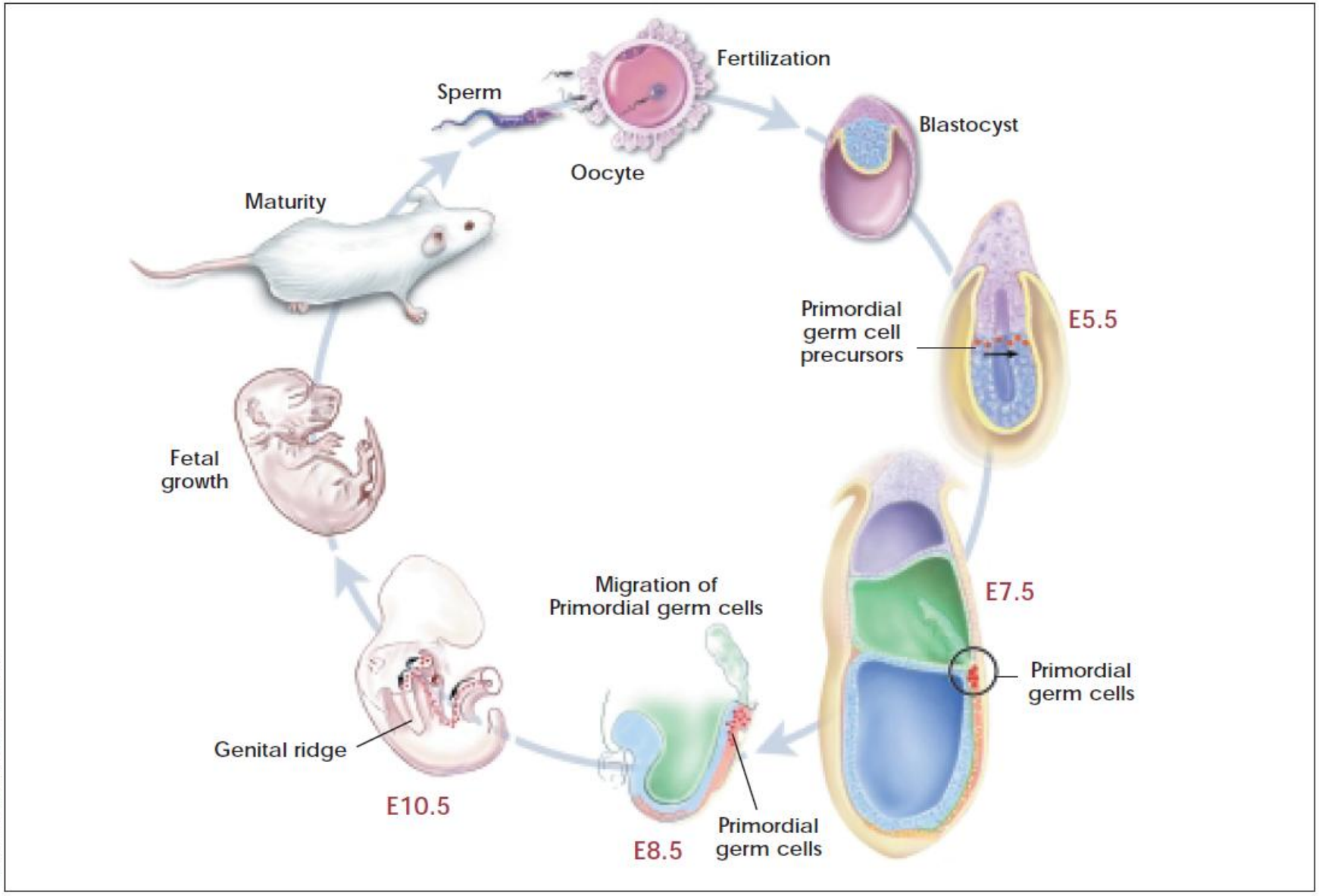

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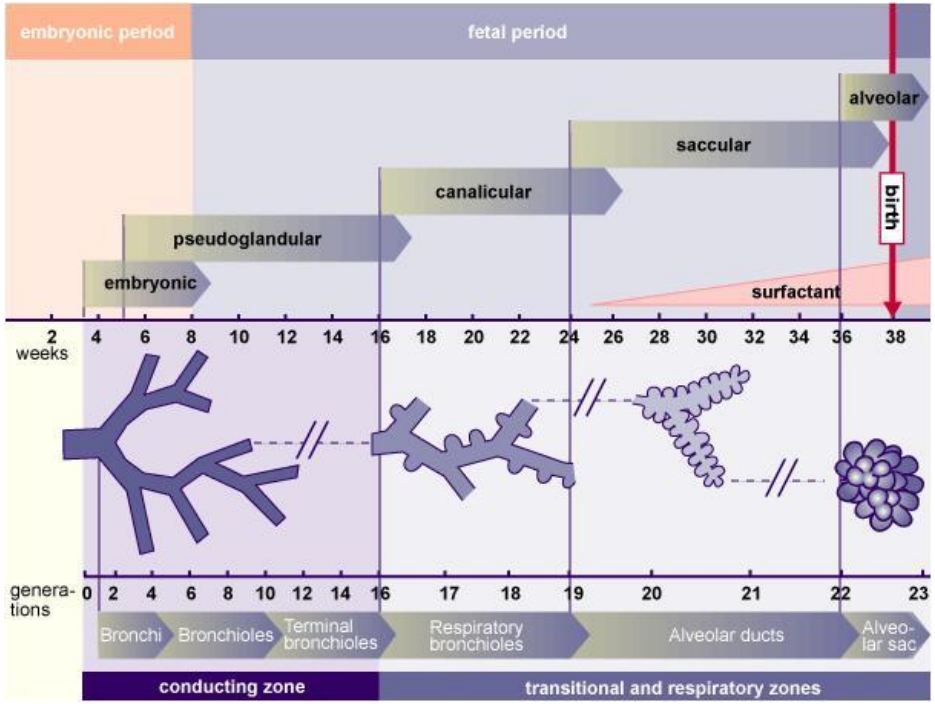
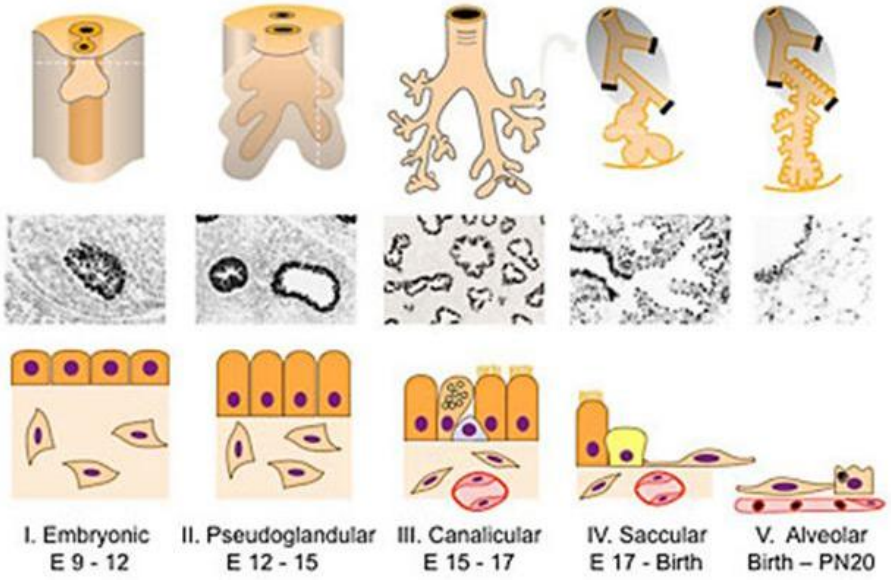
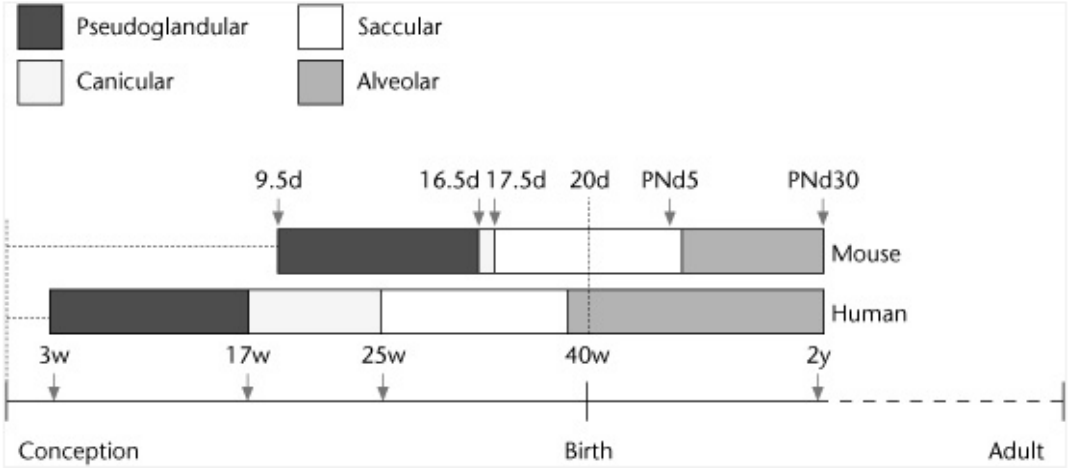
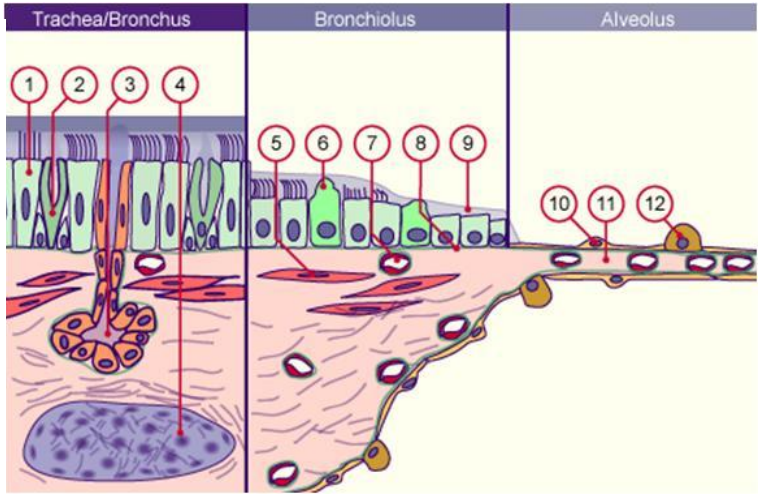
Figure A.5. Development of Mouse Embryonic Primordial Germ Cells.


embryonic period
fetal period
alveolar
saccular
canalicular
pseudoglandular
embryonic
birth
surfactant
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38
weeks
genera-tions
0 2 4 6 8 10 12 14 16 17 18 19 20 21 22 23
Bronchi
Bronchioles
Terminal bronchioles
Respiratory bronchioles
Alveolar ducts
Alveo-lar sac
conducting zone
transitional and respiratory zones


I. Embryonic
E 9 - 12
II. Pseudoglandular
E 12 - 15
III. Canalicular
E 15 - 17
IV. Saccular
E 17 - Birth
V. Alveolar
Birth – PN20


Pseudoglandular
Saccular
Canicular
Alveolar
9.5d
16.5d
17.5d
20d
PNd5
PNd30
Mouse
Human
3w
17w
25w
40w
2y
Conception
Birth
Adult


Trachea/Bronchus
Bronchiolus
Alveolus
1
2
3
4
5
6
7
8
9
10
11
12