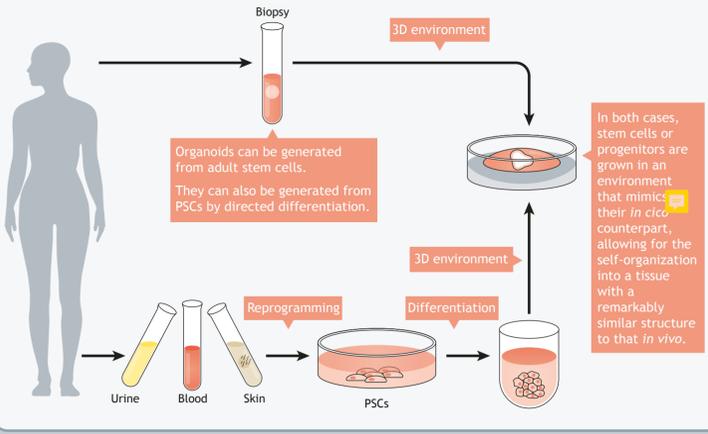


Introduction

Successful modelling of human disease has been the primary goal of biomedical research. While animal models have provided a strong foundation, many human diseases are species-specific. Organoids generated from humans have the potential to bridge this gap and to provide a new system in which to test novel therapeutic approaches.



Organoid definition

Organoid
An artificial, self-organizing tissue that resembles an organ.

PSC-derived: Recapitulate developmental program to result in proper identity

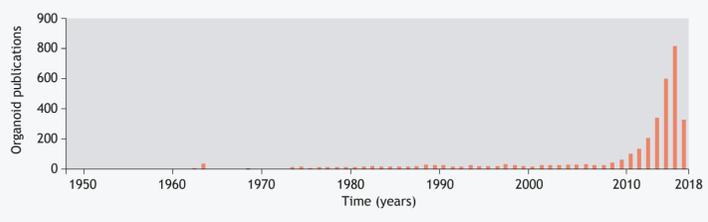
Adult-derived: Retain the identity of the organ from which cells are isolated

Multiple cell types: Contain more than one cell type, as in the organ

Function: Exhibit specialized function of the organ

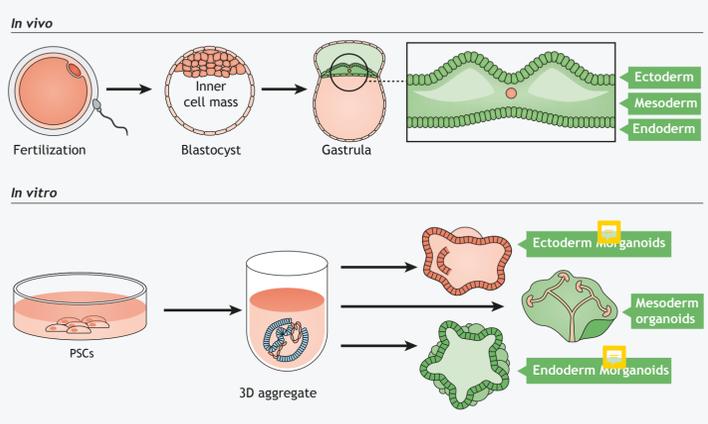
Self-organize: Develop and mature according to intrinsic organizing principles, as in the organ

Organoid publications in PubMed

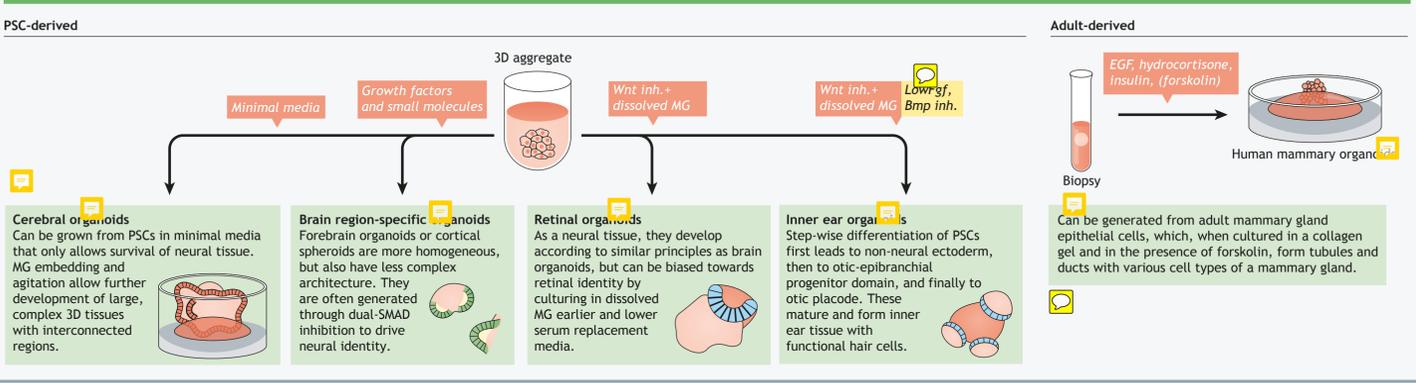


Mimicking development to derive organoids from PSCs

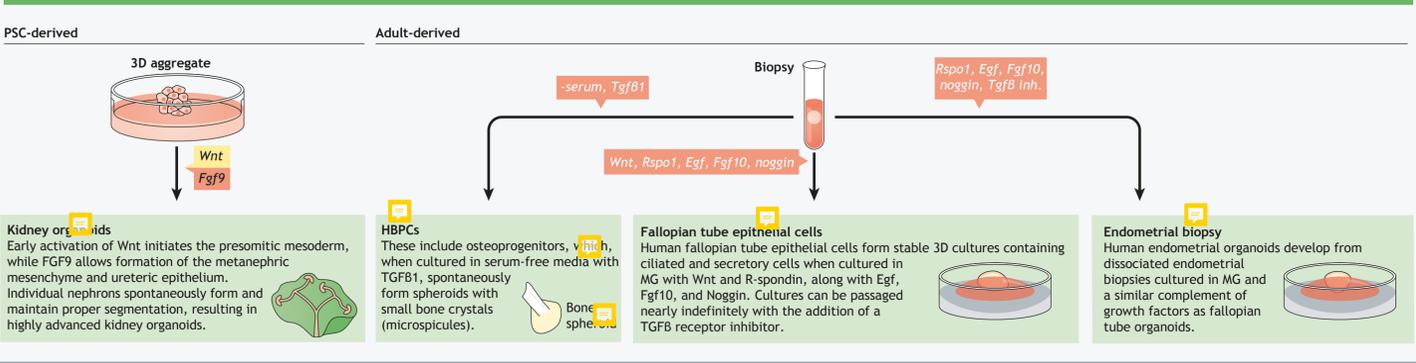
By mimicking early human embryonic development, stem cells can be guided toward a specific organ fate in a stepwise fashion, from PSC to germ-layer identity to organ precursor and eventually more mature organ-like structures.



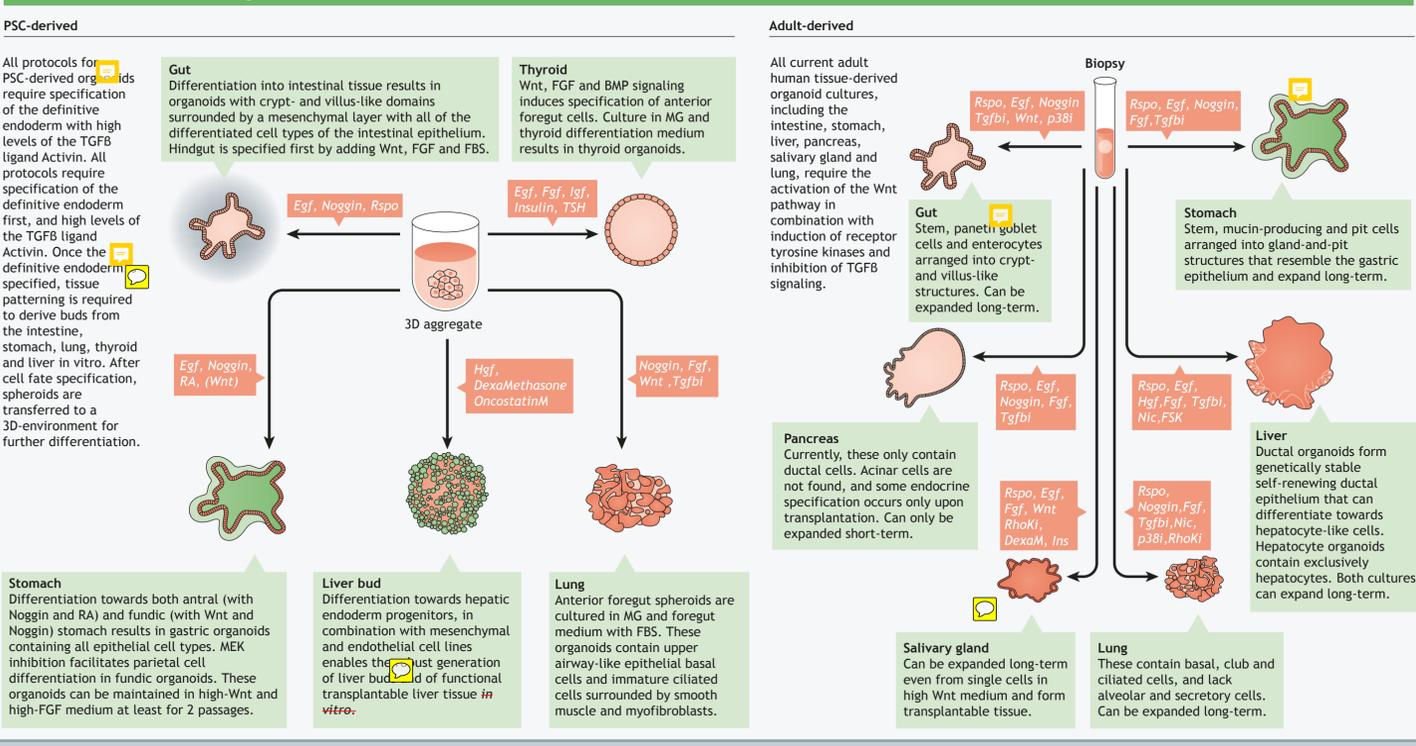
Ectoderm-derived organoids



Mesoderm-derived organoids



Endoderm-derived organoids



Disease modelling in organoids

Congenital

- Cystic fibrosis:** Organoids from CF patients' tissues (gut, lung, cholangiocytes) exhibit a defect in swelling upon cAMP treatment. This phenotype can be exploited to test personalized treatment approaches.
- Alpha-1-Antitrypsin deficiency:** Liver organoids from A1AT deficiency patients exhibit A1AT precipitates within the hepatocyte-like cells, a phenotype reminiscent of the patient's disease.
- Cystic kidney disorder:** Kidney tubule organoids with loss-of-function mutations in polycystic kidney disease genes show large fluid-filled cysts reminiscent of the in vivo phenotype.

Acquired

- Microcephaly:** Cerebral organoids from a patient with a genetic form of microcephaly are smaller and show premature neural differentiation, leading to neural stem cell depletion and, later, fewer neurons.
- Autism:** Forebrain organoids from patients with idiopathic autism with macrocephaly show increased numbers of inhibitory interneurons compared with organoids from unaffected family members.
- Lieber congenital amaurosis:** Optic cup organoids from patients with LCA display fewer and shorter cilia, which affects the extent of photoreceptor formation with stunted outer segments.
- Cancer:** Cancer patient-derived organoids have been established for colon, pancreas, prostate, liver, stomach ovary and endometrium. These recapitulate many aspects of the patient's tumour and are amenable for drug testing.
- Helicobacter pylori infection:** Gastric organoids infected with *Helicobacter* exhibit a strong inflammatory response reminiscent of the tissue reaction to infection.
- Zika virus infection:** Zika virus-infected cerebral organoids are much smaller, reflecting the prenatal infection-associated microcephaly. Neural stem cells are particularly susceptible to the virus and undergo massive cell death.

Current and future therapeutic applications of organoids

