Recent Developments in
The Transmission of Human Life

מכון ויצמן למדע
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How to extend embryo development *in vitro*: Future chances for ectogenesis?

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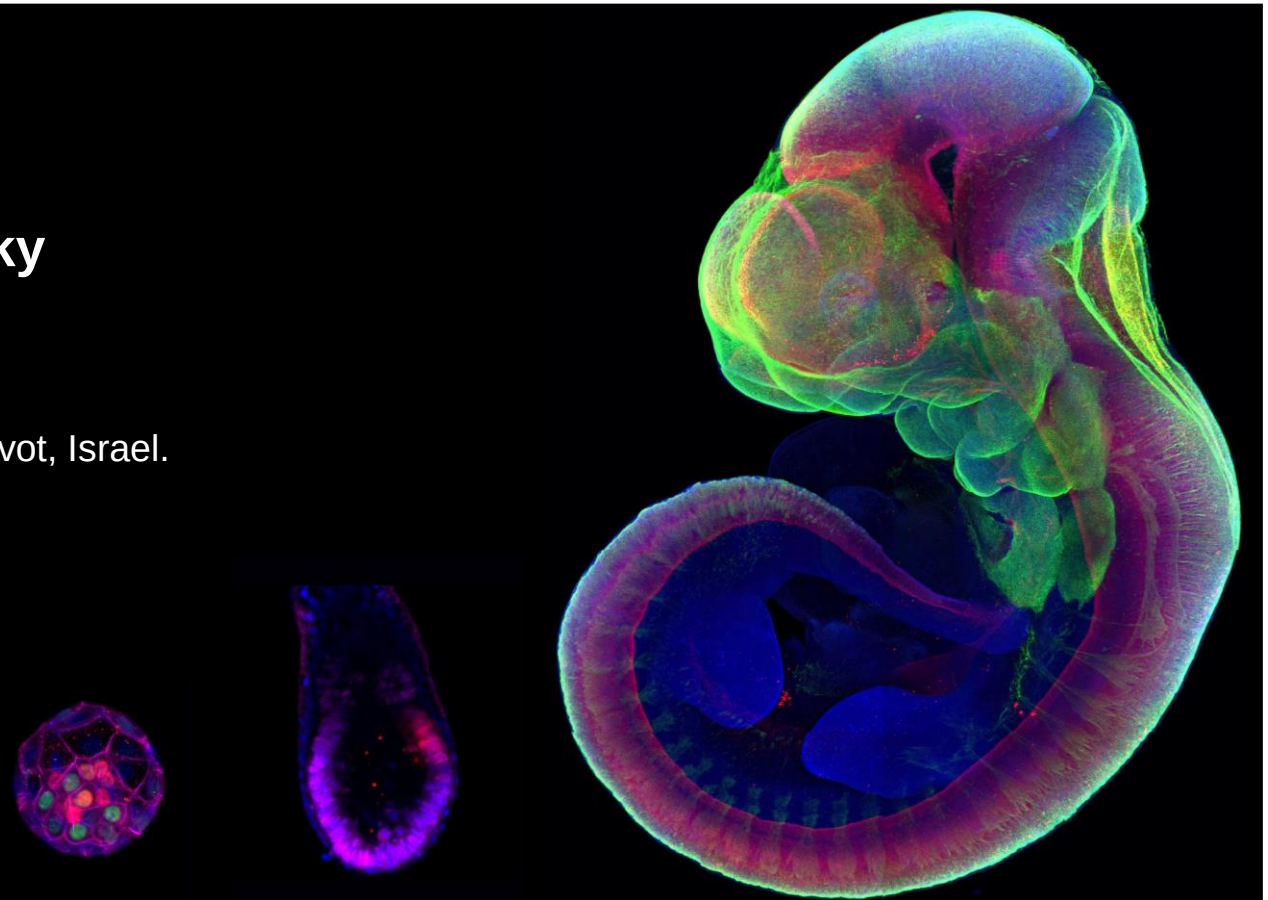


Ectogenesis

Ecto-

from Greek *ektos* outside

Genesis

an origin, creation, or beginning.

XIX Century Haldane

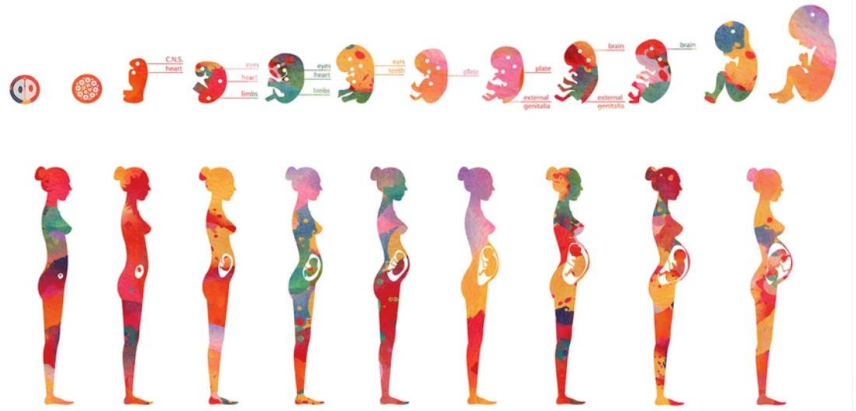
"we can take an ovary from a woman, and keep it growing in a suitable fluid for as long as twenty years, producing a fresh ovum each month, of which 90 percent can be fertilized, and the embryos grown successfully for nine months, and then brought out into the air."

COLLINS ENGLISH DICTIONARY - COMPLETE & UNABRIDGED
2012 DIGITAL EDITION
CHIRSTINE ROSEN. JSTOR. 2003

Ectogenesis

Complete ectogenesis

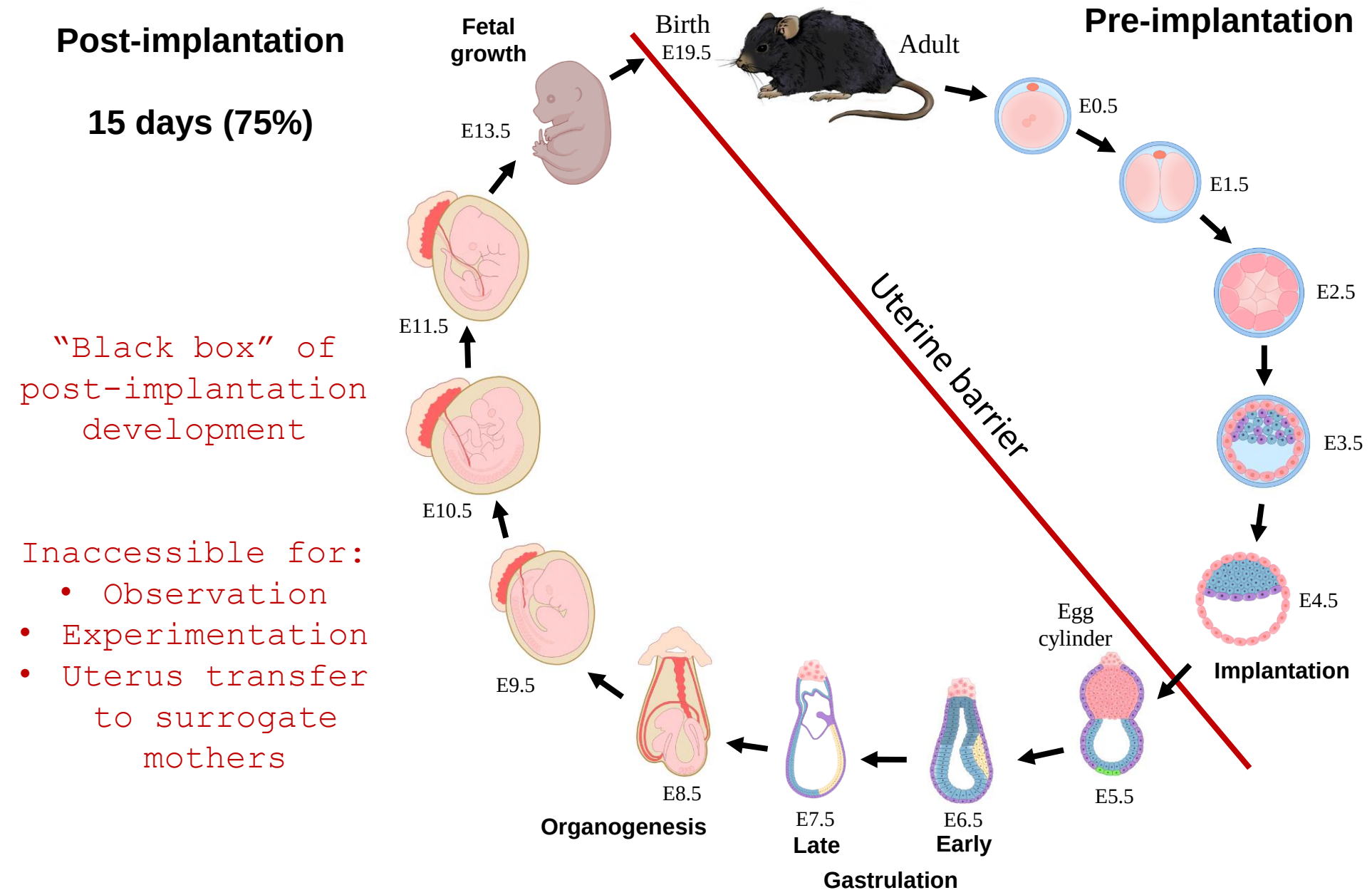
- Gestation outside a human body from conception to birth completely.



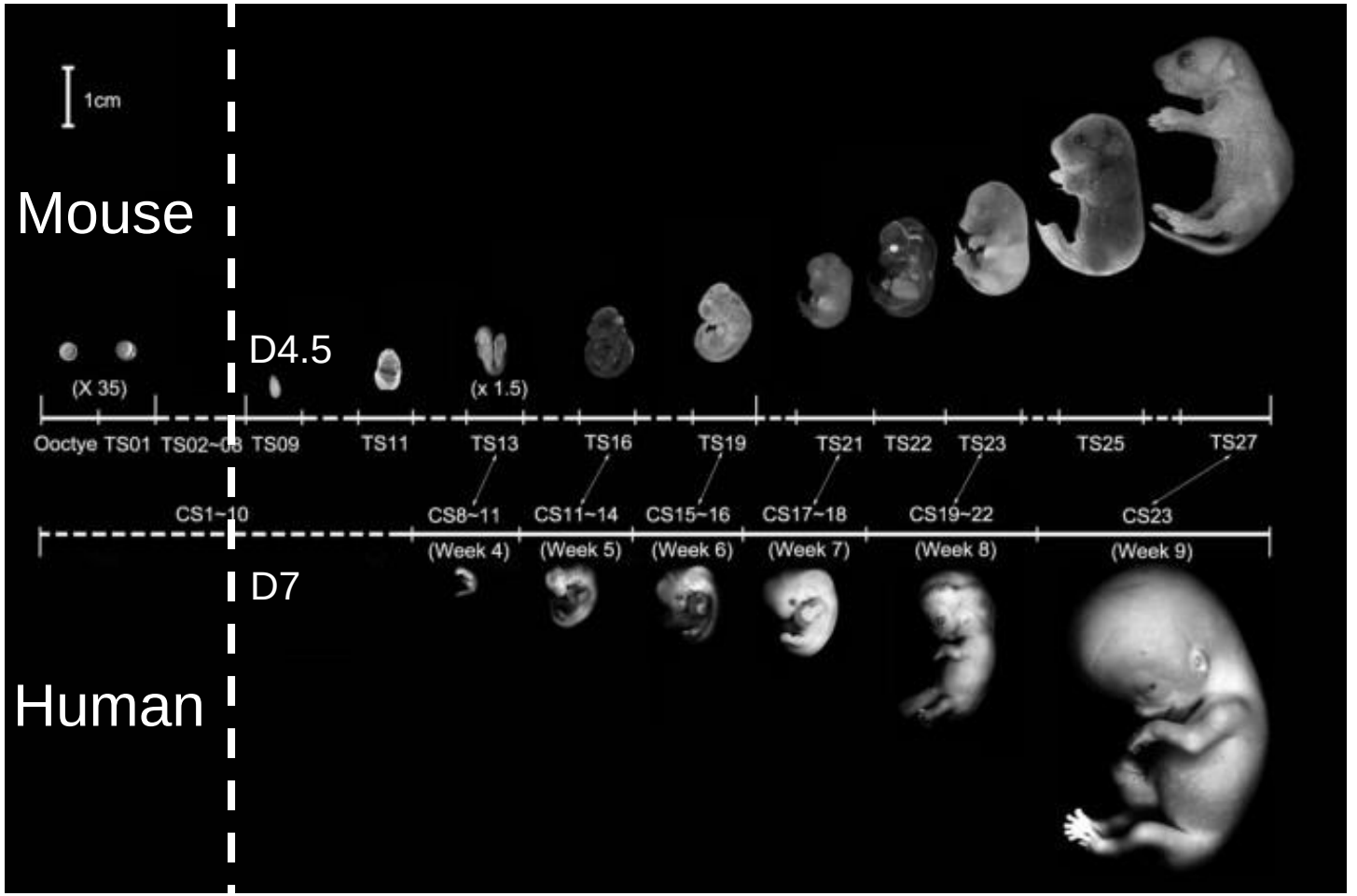
Partial ectogenesis

- Transfer of a partially developed embryo or fetus from the female body to an external womb for the remainder of the gestation period

Mammalian embryo development is dependent on the maternal uterus

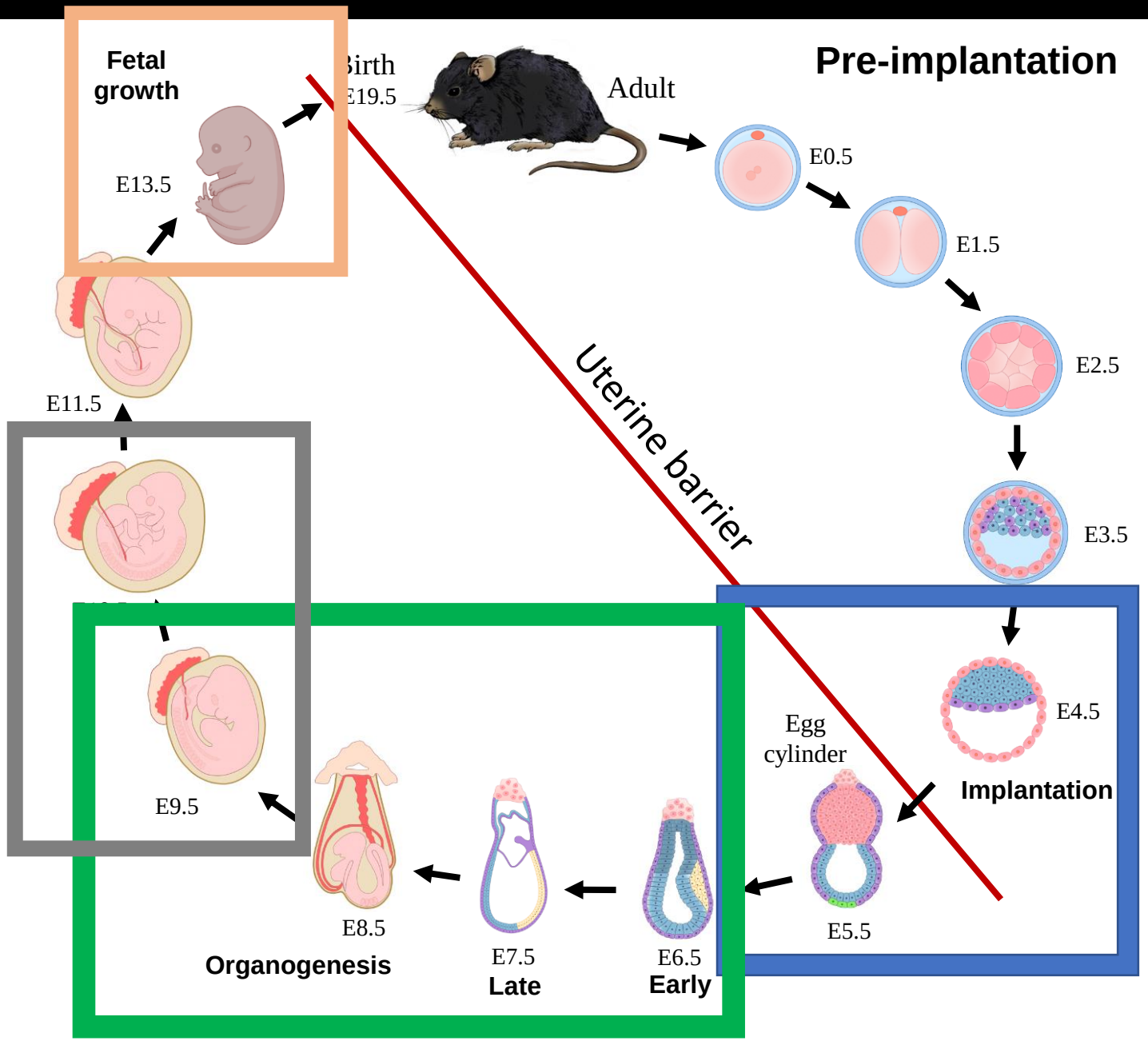


Mouse vs Human embryo development

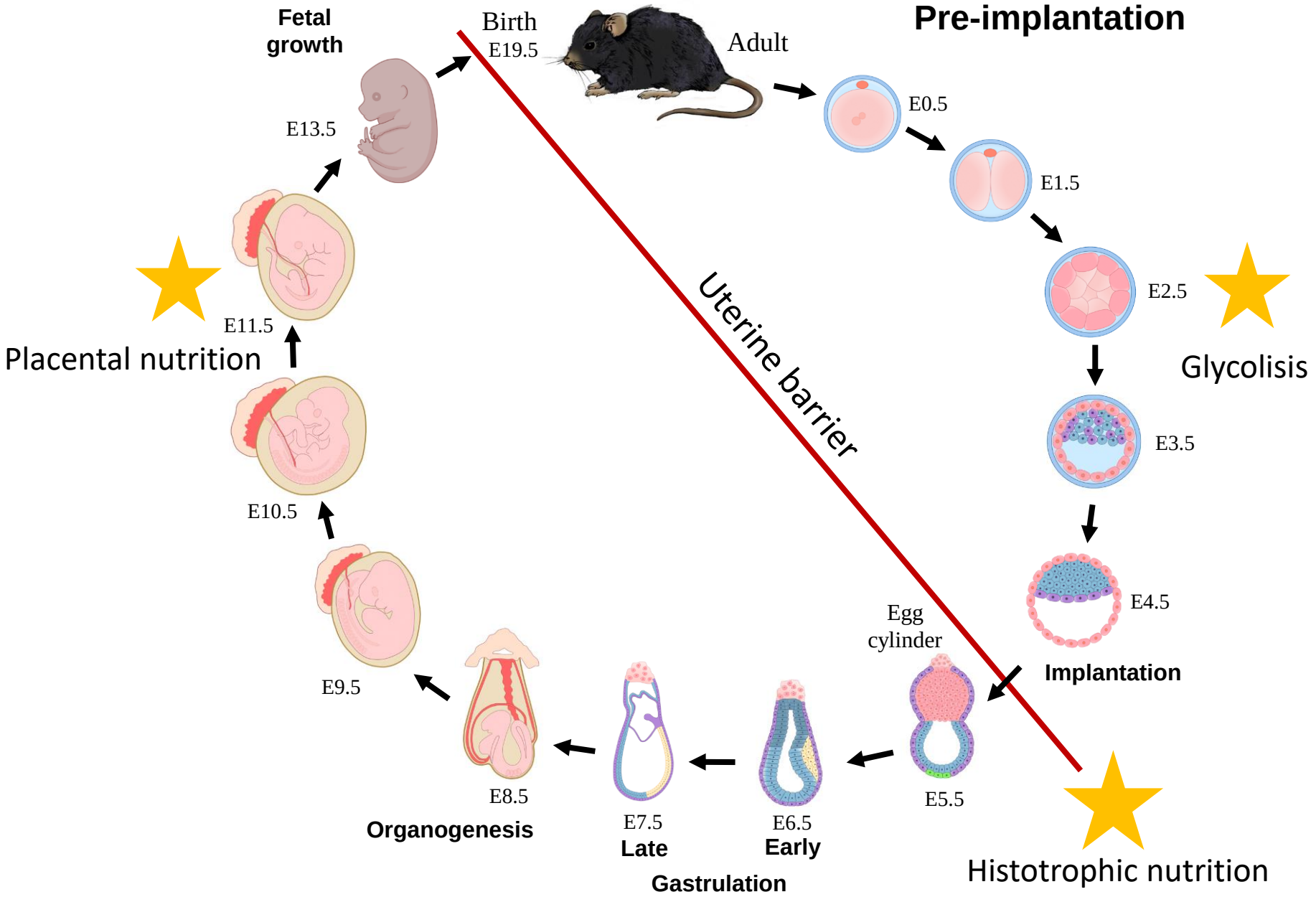


Xue et. al., *BMC Genomics*, 2013

Different Approaches

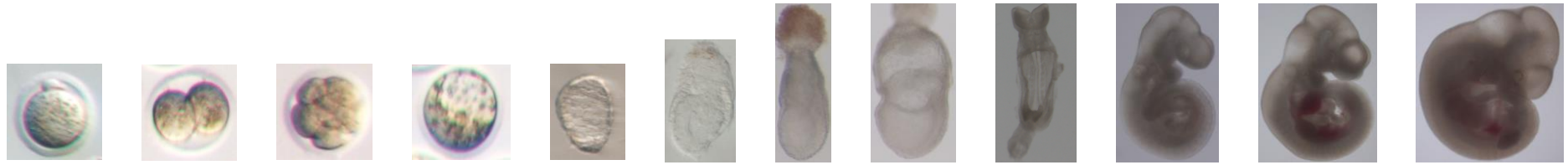


Mayor nutritional changes during development affecting *in vitro* culture



In vitro culture of mouse embryos

Pre-implantation	Post-implantation

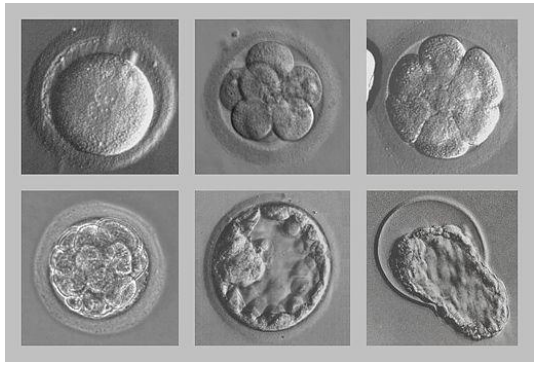


Zygote to blastocyst

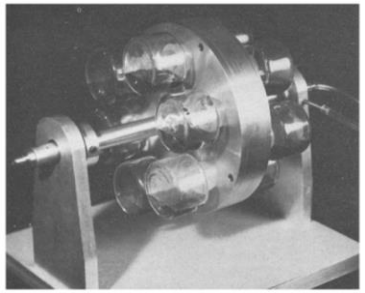
In vitro implantation

Post-implantation stages
Static or Rotating bottles cultures

Mouse, monkey & human embryos



Bedzhov et. al., 2014



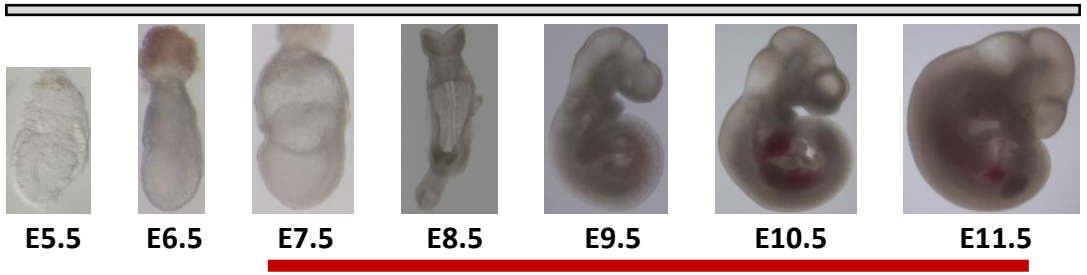
New, 1966-1978

Short term (24-36 hours)
Inefficient – abnormal embryos
Not from pre-gastrulation

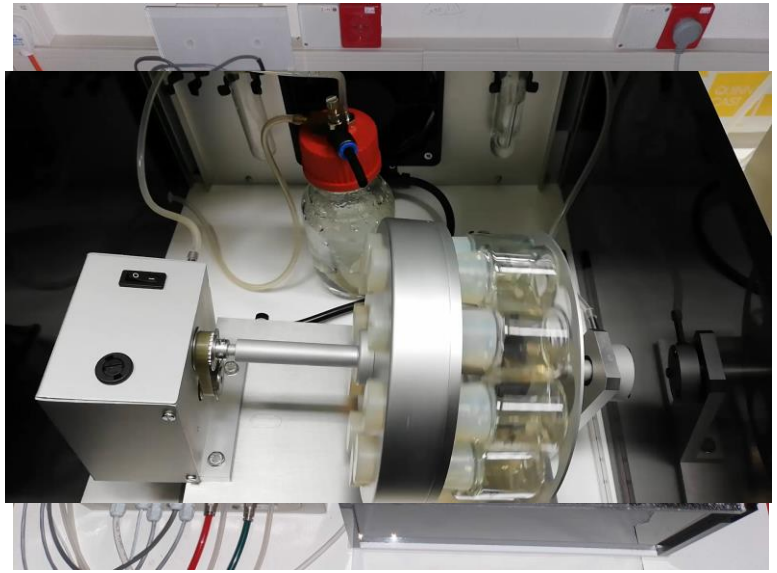
Letters to the Editor

BIRTH AFTER THE REIMPLANTATION OF A HUMAN EMBRYO

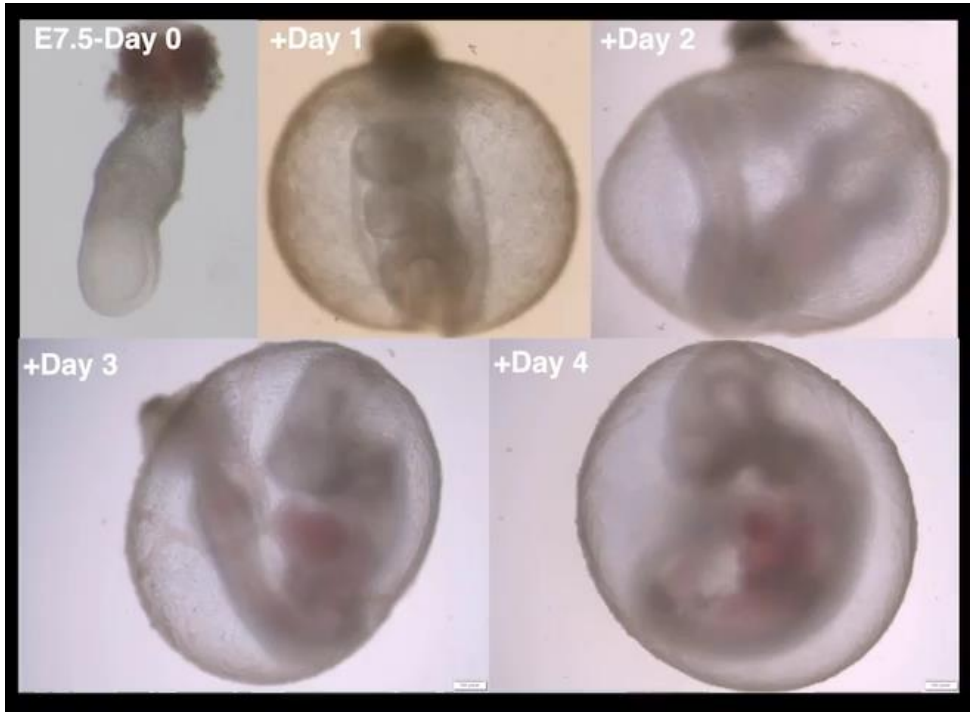
Enhanced *ex utero* roller culture platform



E7.5 to E11



Late gastrulation to hindlimb stage

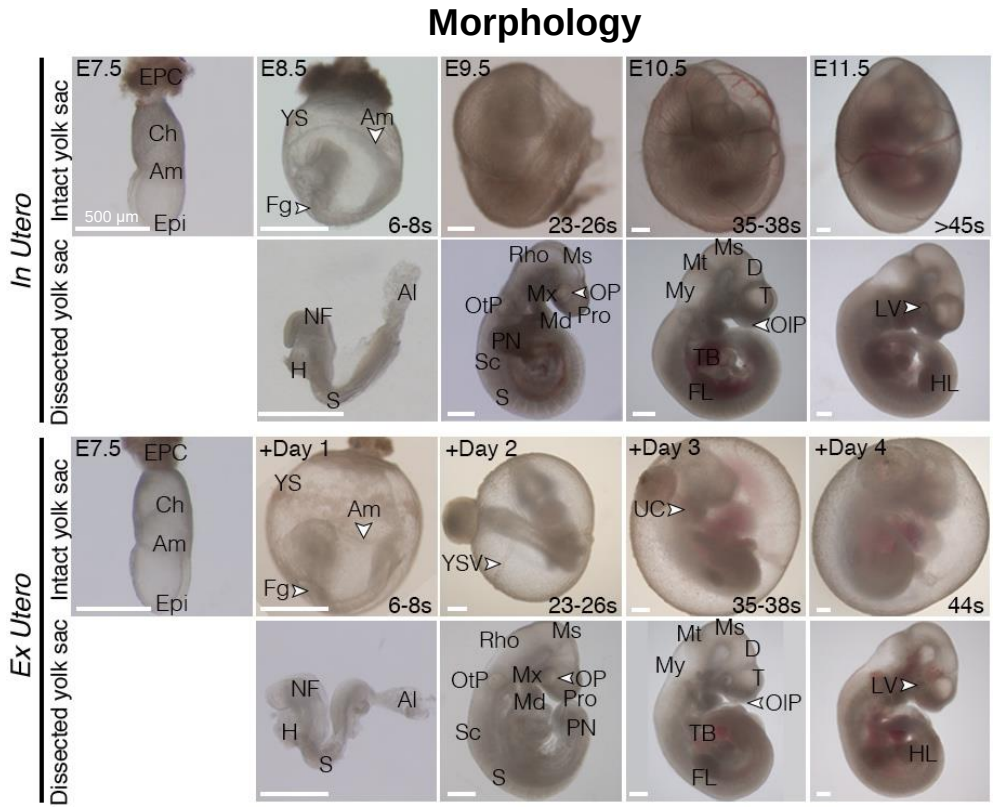


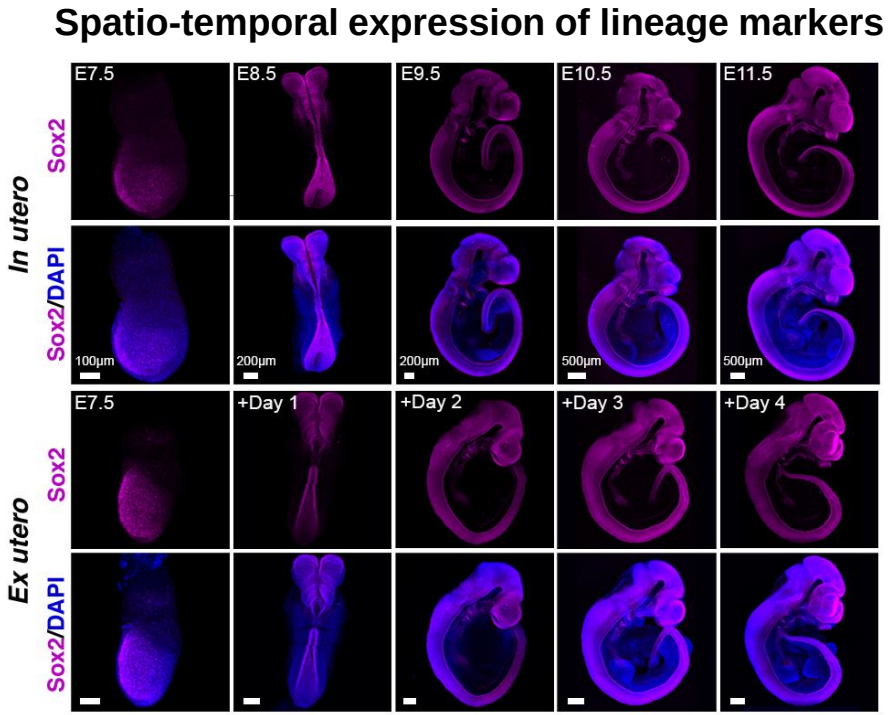
~75% efficiency (at day 4)
Consistent across several mouse lines

- **Continuous and stable gas pressure**
- **Regulation of O_2 and CO_2**
- **Adequate gas humidification, medium pH buffering**
- ***Ex Utero* Culture Media:**
  Rat Serum
  Human Serum
  High Glucose

Aguilera-Castrejon*, Bernardo Oldak* et. al., *Nature* 2021

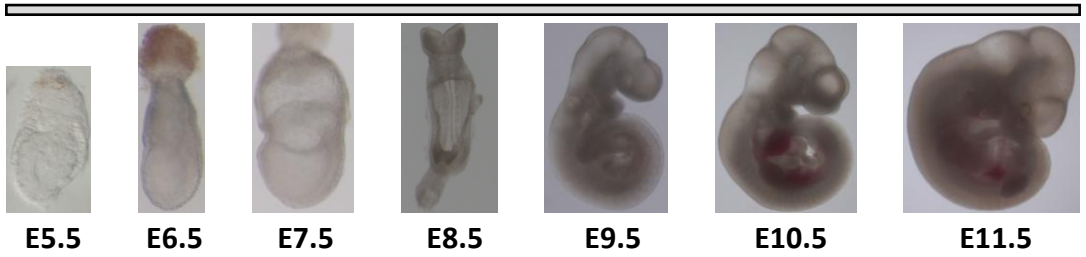
Ex utero embryos faithfully recapitulate development from E7.5 - E11





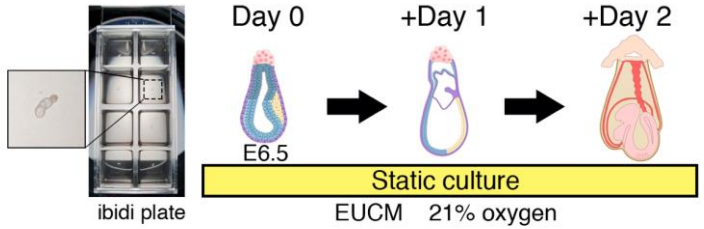
Aguilera-Castrejon*, Bernardo Oldak* et. al., *Nature* 2021

Capturing full gastrulation *ex utero*

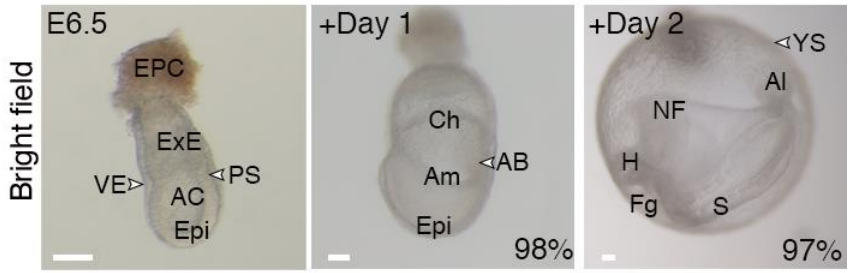


E7.5 to E11

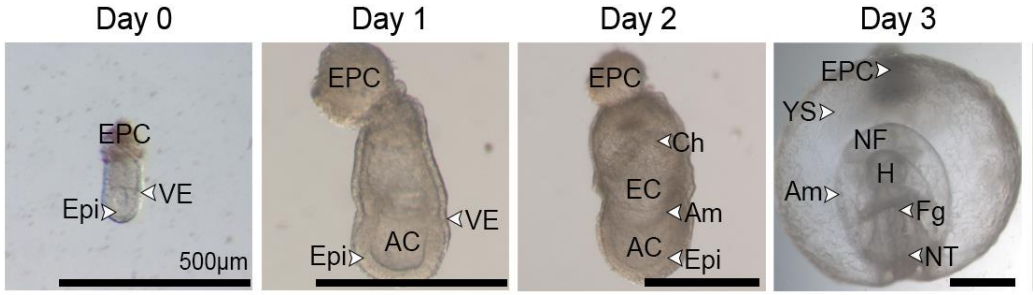
E5.5 to E11



Optimized static culture conditions from pre-gastrulation to organogenesis

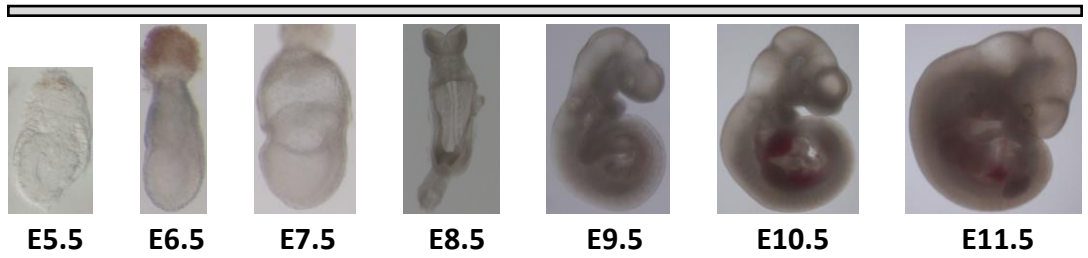


E6.5 to E8.5



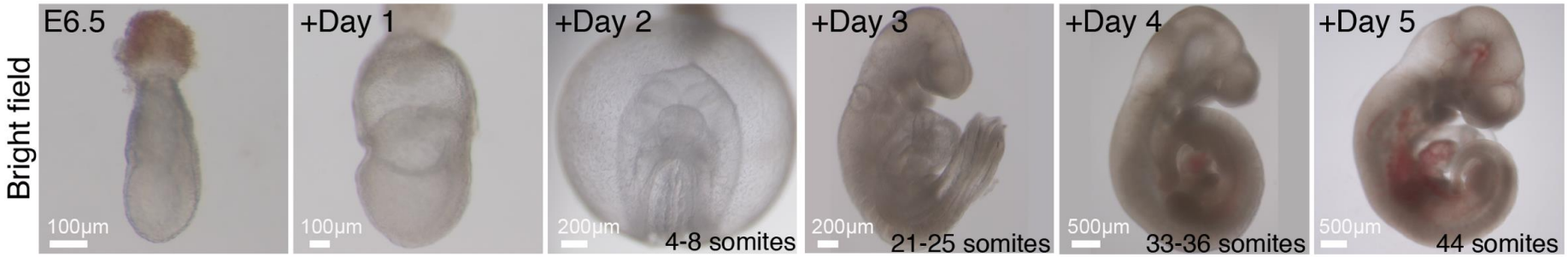
E5.5 to E8.5

Extended *ex utero* embryo culture to advanced organogenesis



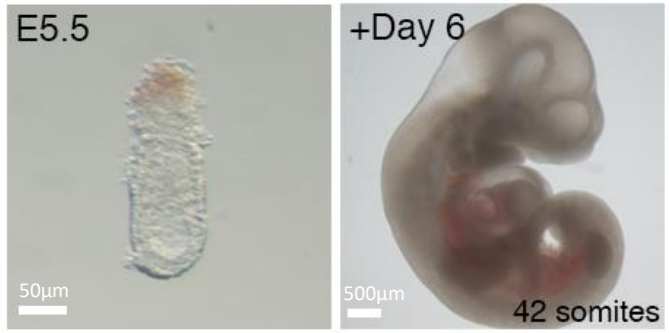
Early gastrulation

Morphology



55% efficiency

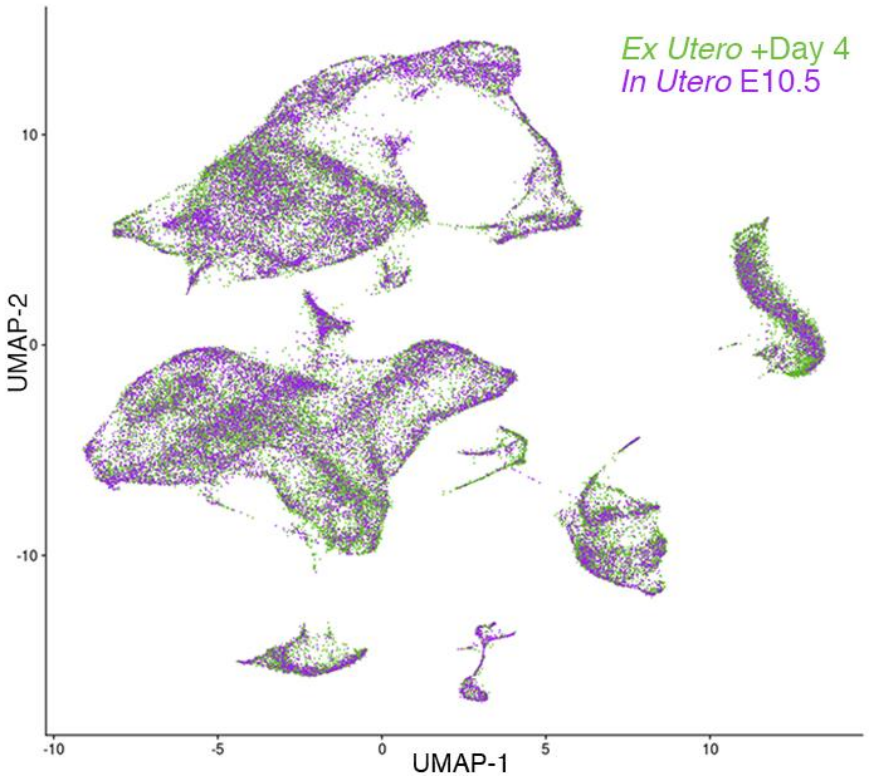
Pre-gastrulation



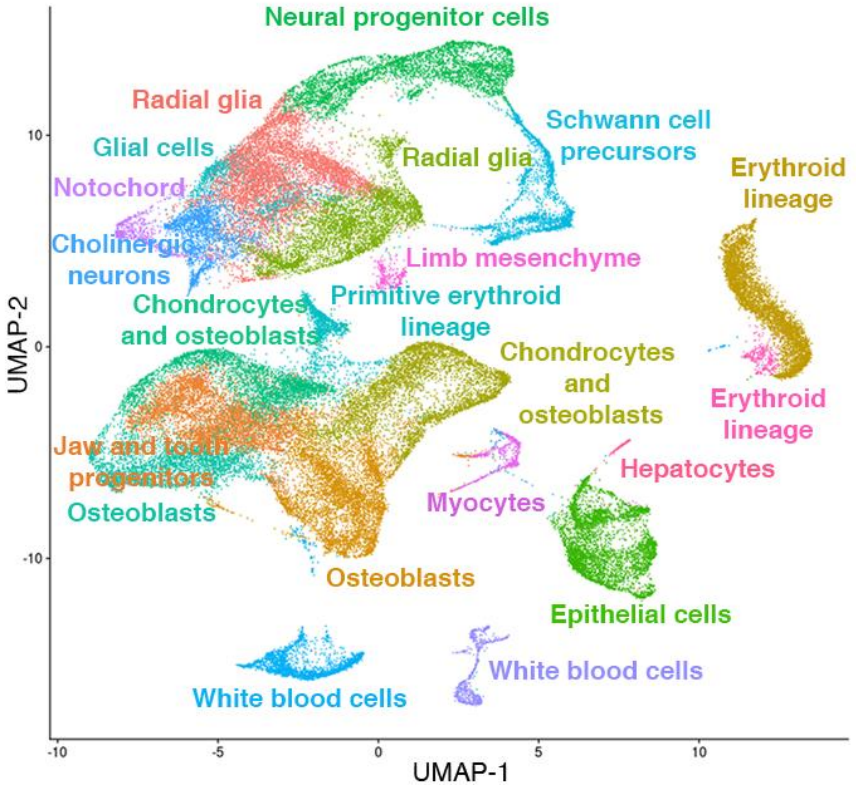
~20% efficiency

Do *ex utero* embryos present all cell lineages found in control *in utero* embryos?

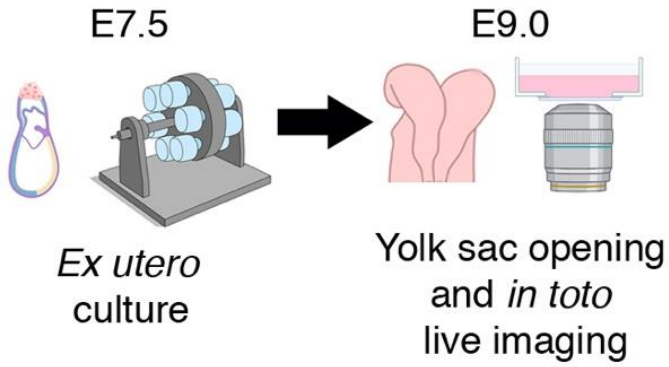
Single cell RNA-sequencing



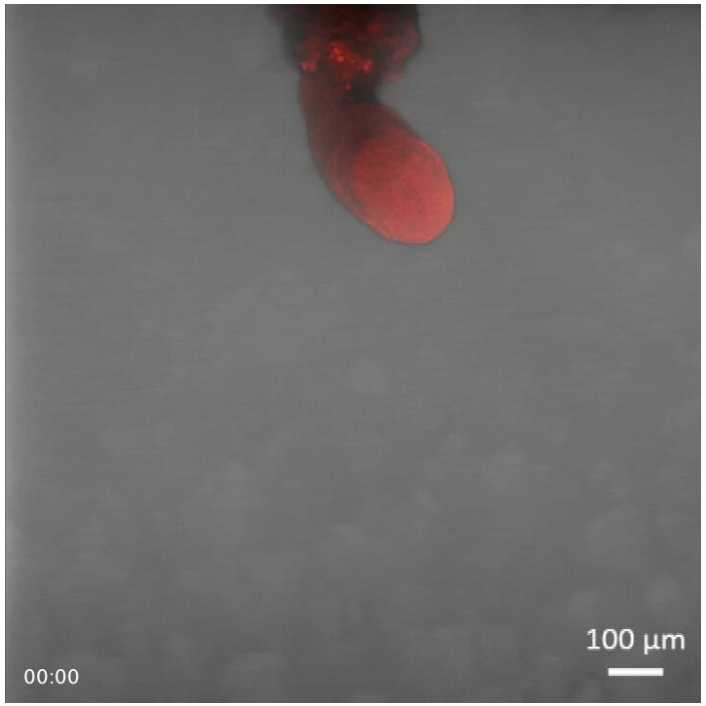
Cell types profile

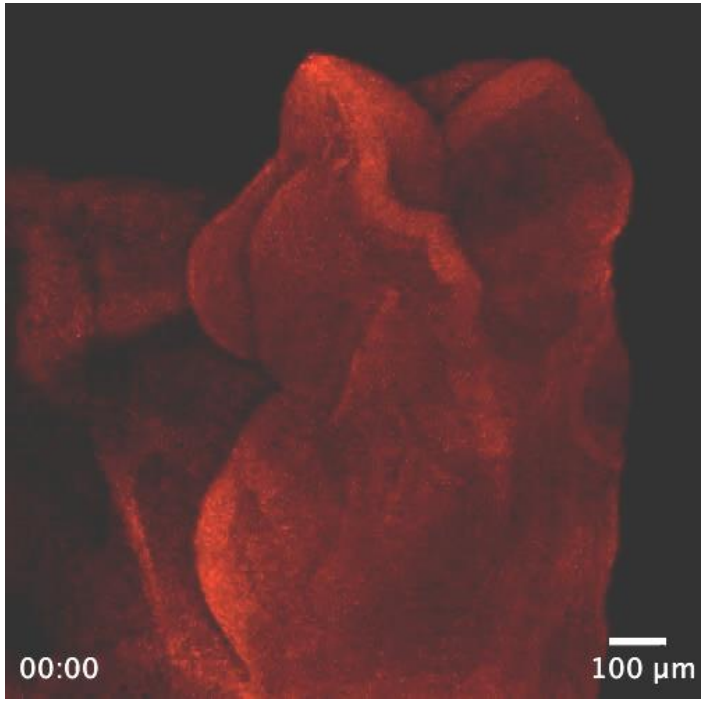


In toto live imaging of gastrulation and neural tube closure



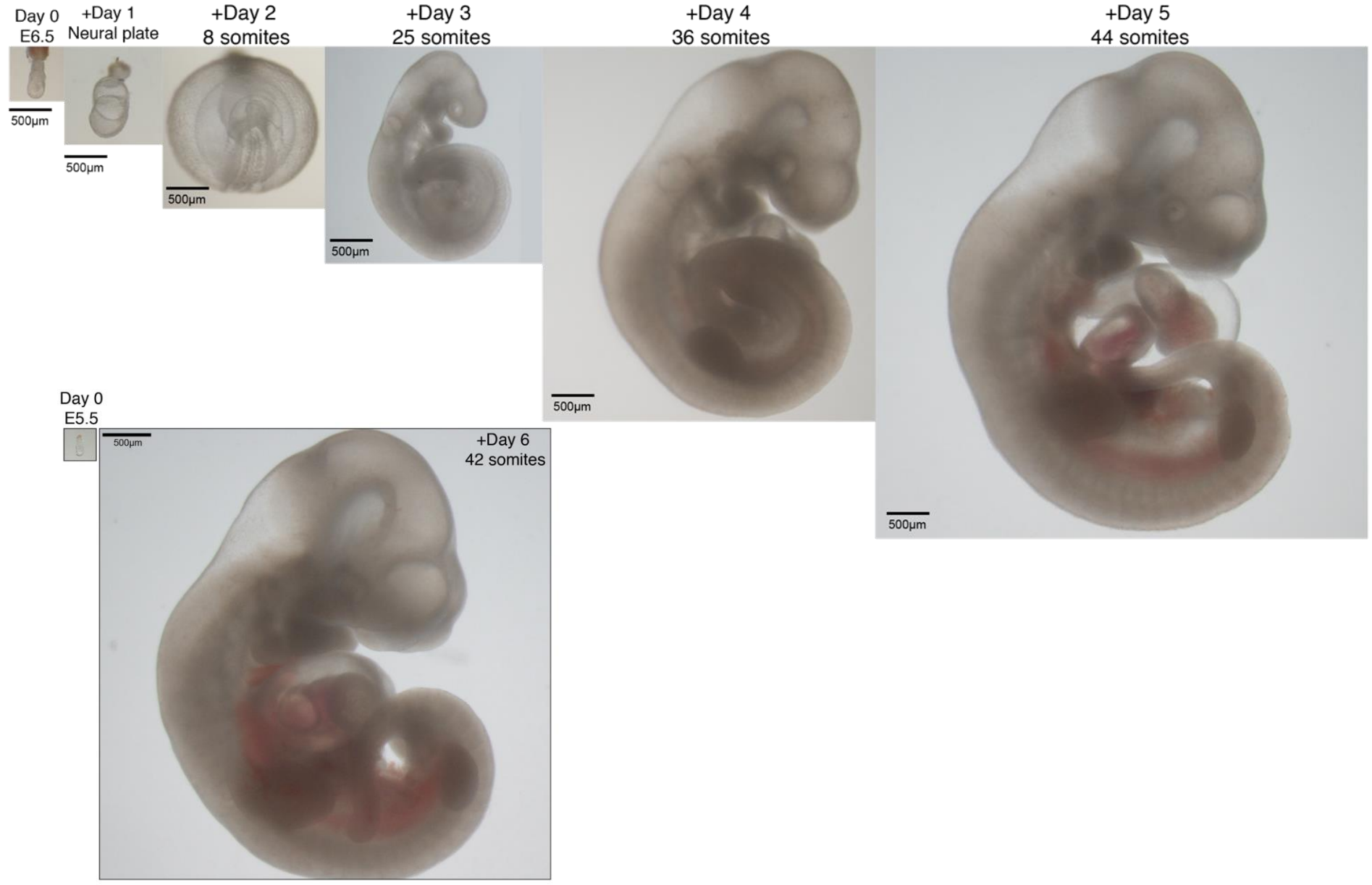
E6.5 to E8.5





Aguilera-Castrejon et. al., *Nature,* 2021

Embryo development without maternal interaction (self-organization)



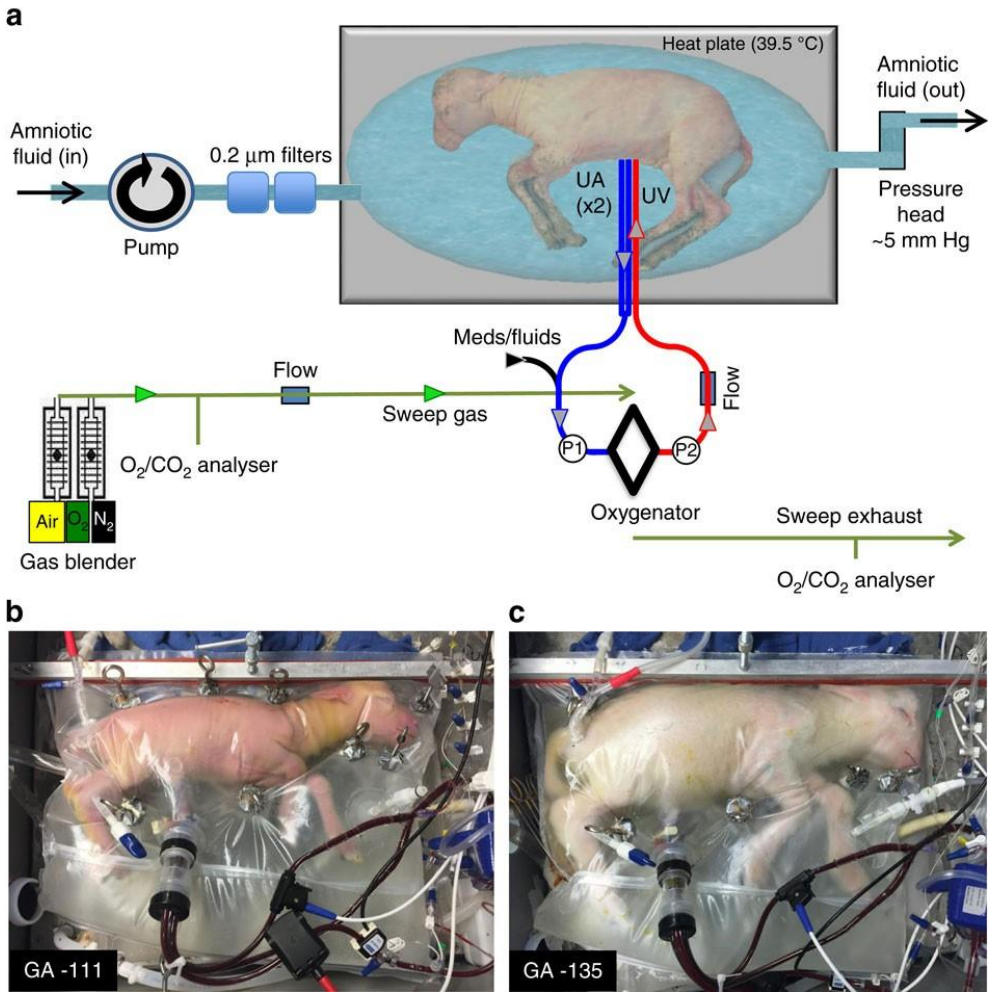
Efforts to Sustain Fetal Growth in-Vitro

Bigger animal models are required to reduce technical difficulties.

Adaptation of NICU technologies for feto-placental circulation

Support of premature fetal lambs in an extra-uterine device for up to 4 weeks.

Requiring continuous hemodynamic monitoring



Partridge et. al., *Nature Communications,* 2017

In vitro culture of human embryos beyond implantation

LETTER

doi:10.1038/nature17948

Self-organization of the *in vitro* attached human embryo

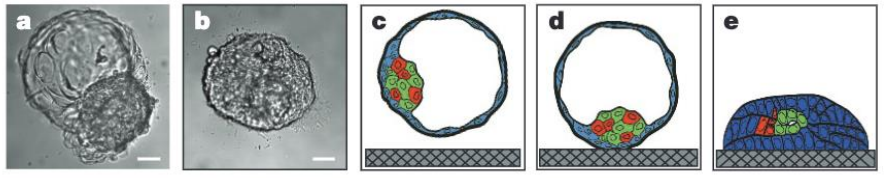
Alessia Deglincerti[1]*, Gist F. Croft[1]*, Lauren N. Pietila[1], Magdalena Zernicka-Goetz[2], Eric D. Siggia[3] & Ali H. Brivanlou[1]

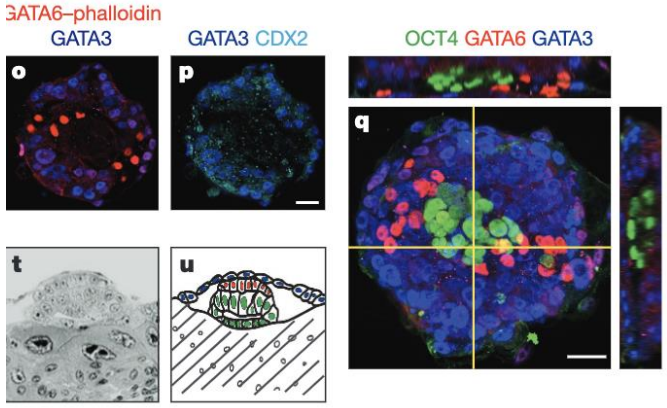
TECHNICAL REPORT

nature cell biology

Culture of human embryo from 6-14 days

Self-organization of the human embryo in the absence of maternal tissues





Low efficiency, short time in culture

Shahbazi et al. Nature Cell Biology, 2016
Deglincerti et al. Nature, 2016

How close are we to building an artificial uterus?

- Technologies have been generated to maintain up to half of mouse pregnancy outside the uterus.
- Early post-implantation embryo can be maintained up to advanced organogenesis
- Decreased embryo viability compared to intrauterine development
- Ectogenesis should be seen as a therapeutic option.
- Ex utero development of human embryos is limited due to ethical reasons, embryo size and pregnancy time
- Optimization of existing technologies and better understanding of embryonic nutrition are needed to take ectogenesis further.

Thank you!

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Alejandro Aguilera Castrejon
Rada Massarwa
Tom Shani
Itay Maza
Shadi Tarazi
Jonathan Bayerl
Daoud Sheban
Sergey Viukov
Shahd Ashouokhi
Noa Novershtern
Mirie Zerbib
Muneef Ayyash
Nir Livnat
Emilie Wildschutz
Francesco Roncato
Carine Joubran

Funding sources

European Research Council

NYSCF
The New York Stem Cell Foundation
NYSCF-Robertson Investigator

THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST

Ilana and Pascal Mantoux

Israel Science Foundation

ICRF Israel Cancer Research Fund

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