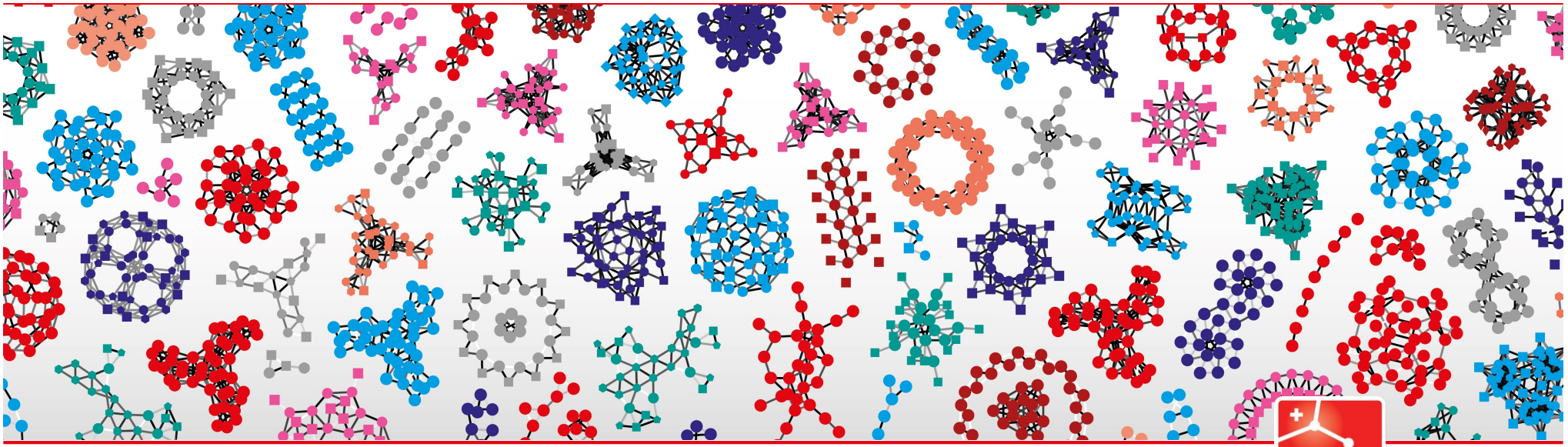

Creation and unification of development and life stage ontologies for animals

Anne Niknejad, Christopher J. Mungall, David Osumi-Sutherland, Marc Robinson-Rechavi, Frederic B. Bastian

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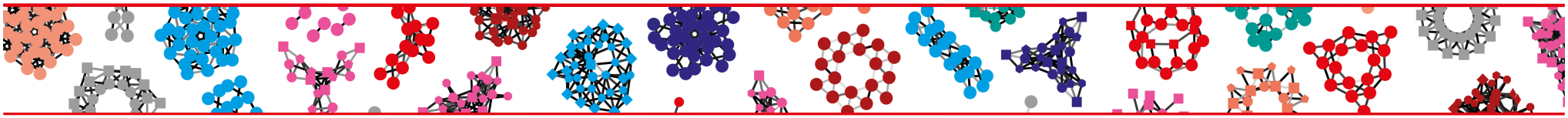
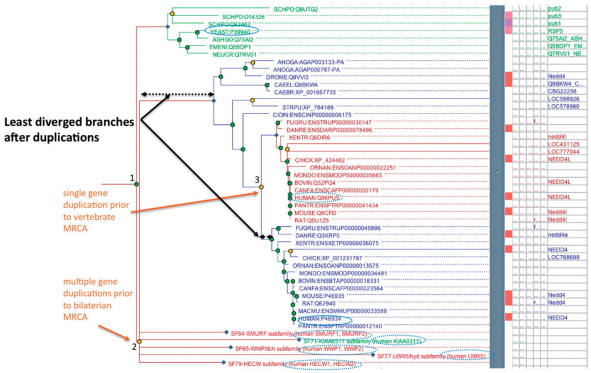


The necessity for multi-species comparative approaches

Multi-species data integration

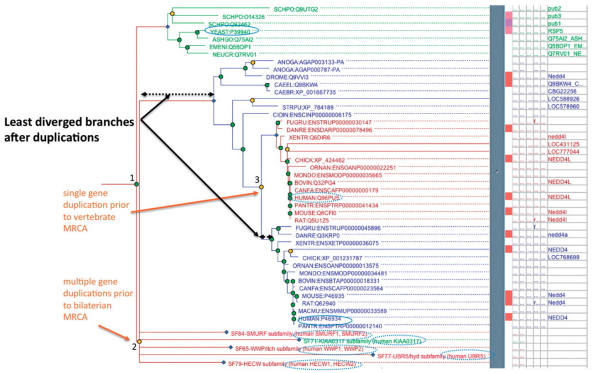
- PANTHER: GO annotations using phylogenetic trees



Mi H., *et al.*, *Nucleic Acids Research*, 2010

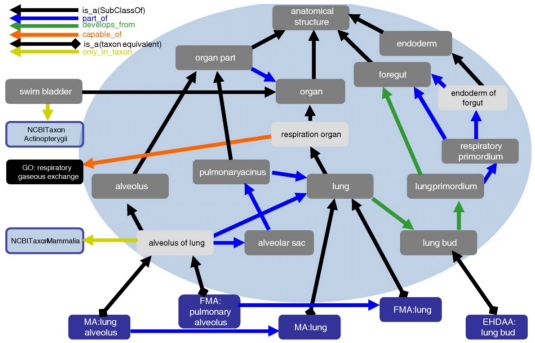
Multi-species data integration

- PANTHER: GO annotations using phylogenetic trees



Mi H., *et al.*, *Nucleic Acids Research*, 2010

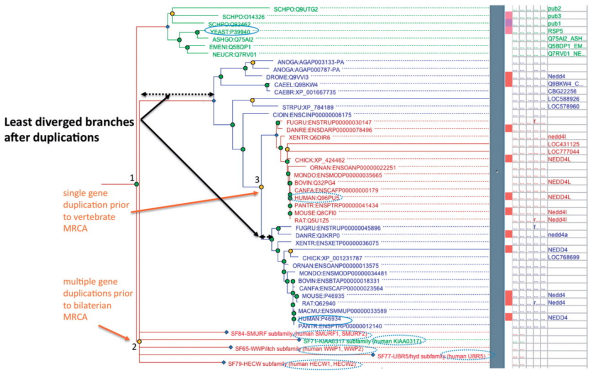
- UBERON: comparative anatomy



Mungall C.J., *et al.*, *Genome Biol*, 2012

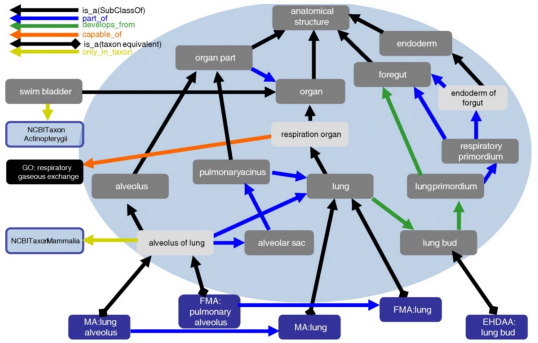
Multi-species data integration

- PANTHER: GO annotations using phylogenetic trees



Mi H., *et al.*, *Nucleic Acids Research*, 2010

- UBERON: comparative anatomy



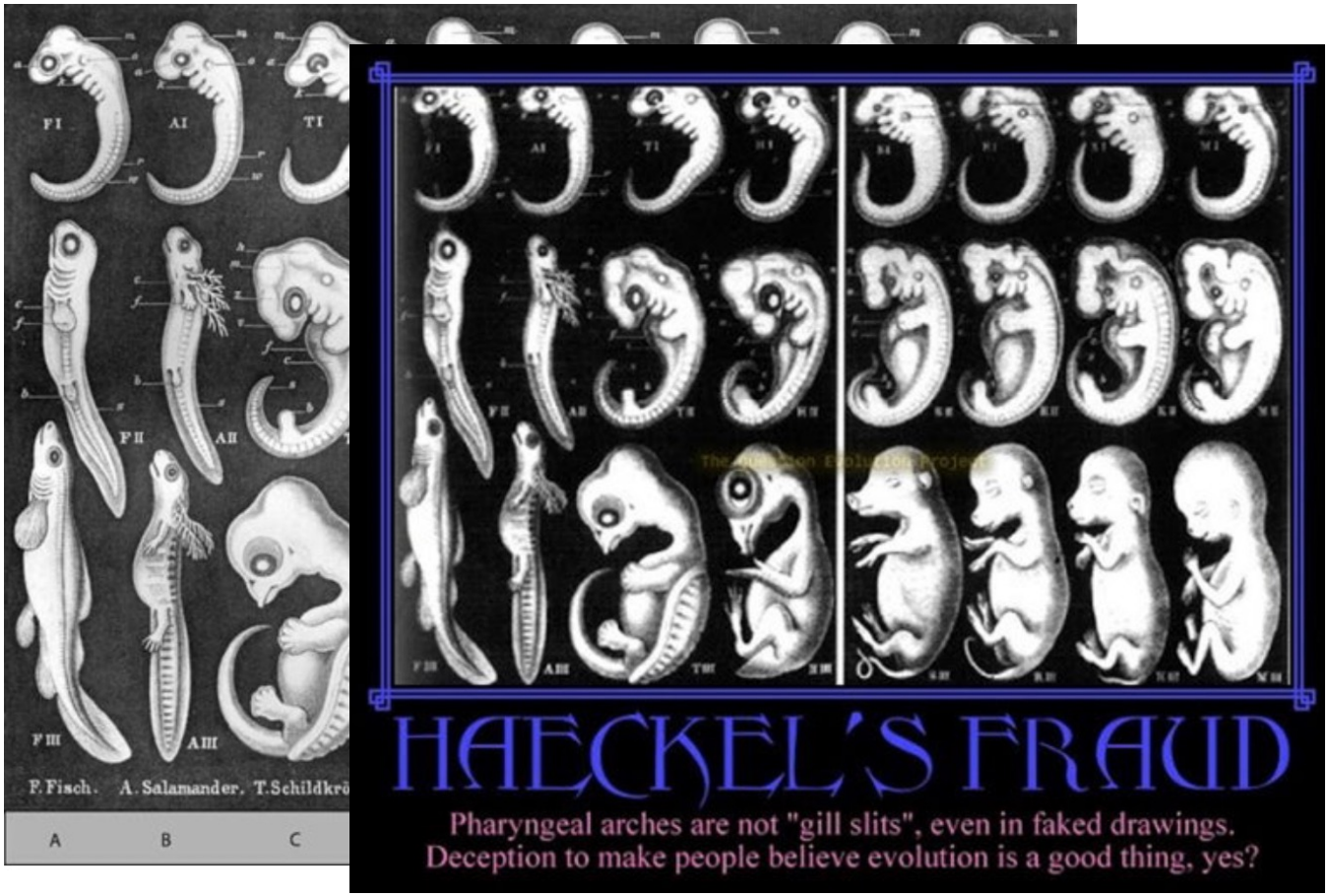
Mungall C.J., *et al.*, *Genome Biol*, 2012

- **Need for comparative developmental and life staging**

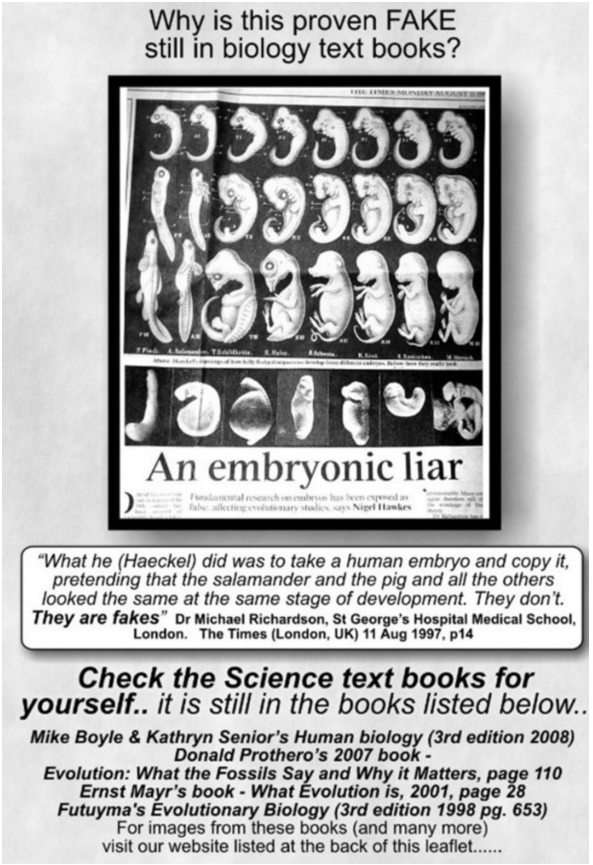
Comparing developmental stages

Haeckel, *Natürliche Schöpfungsgeschichte*, 1868

Comparing developmental stages

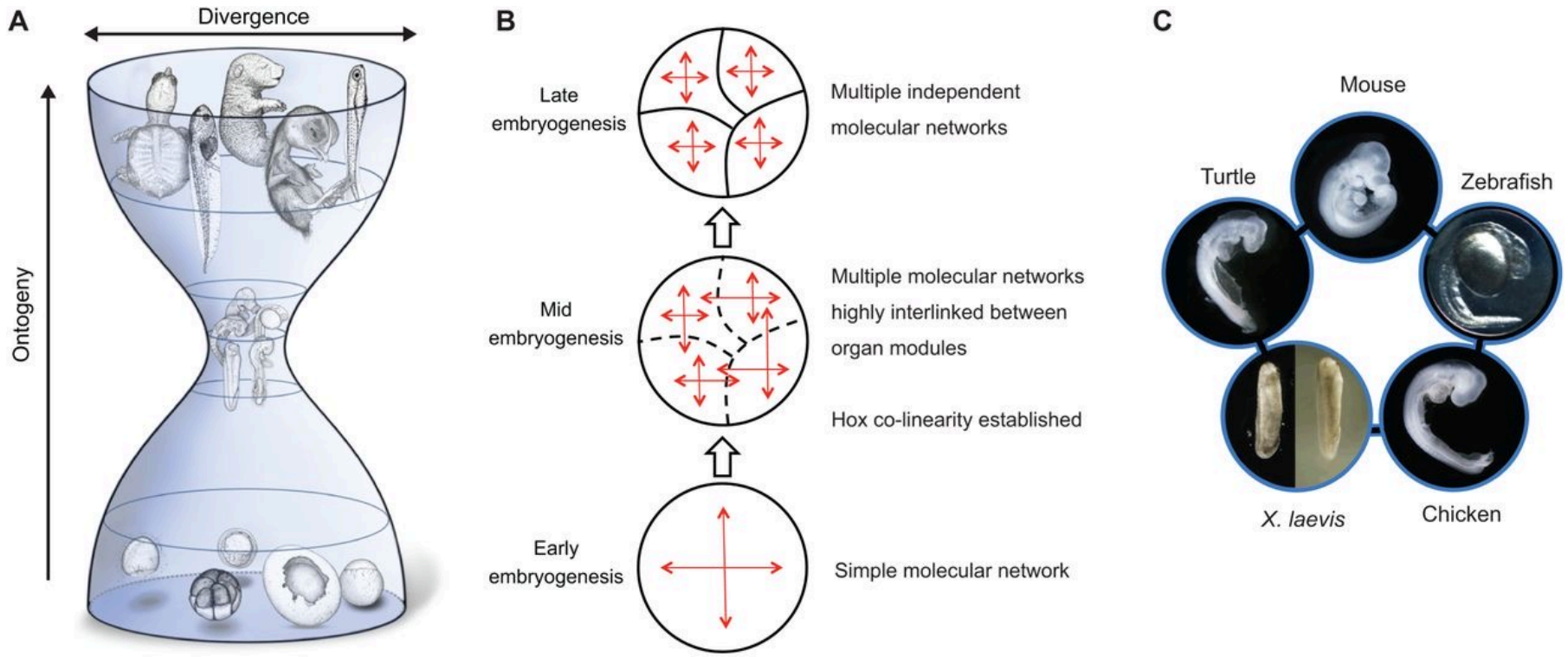


Haeckel, *Natürliche Schöpfungsgeschichte*, 1868



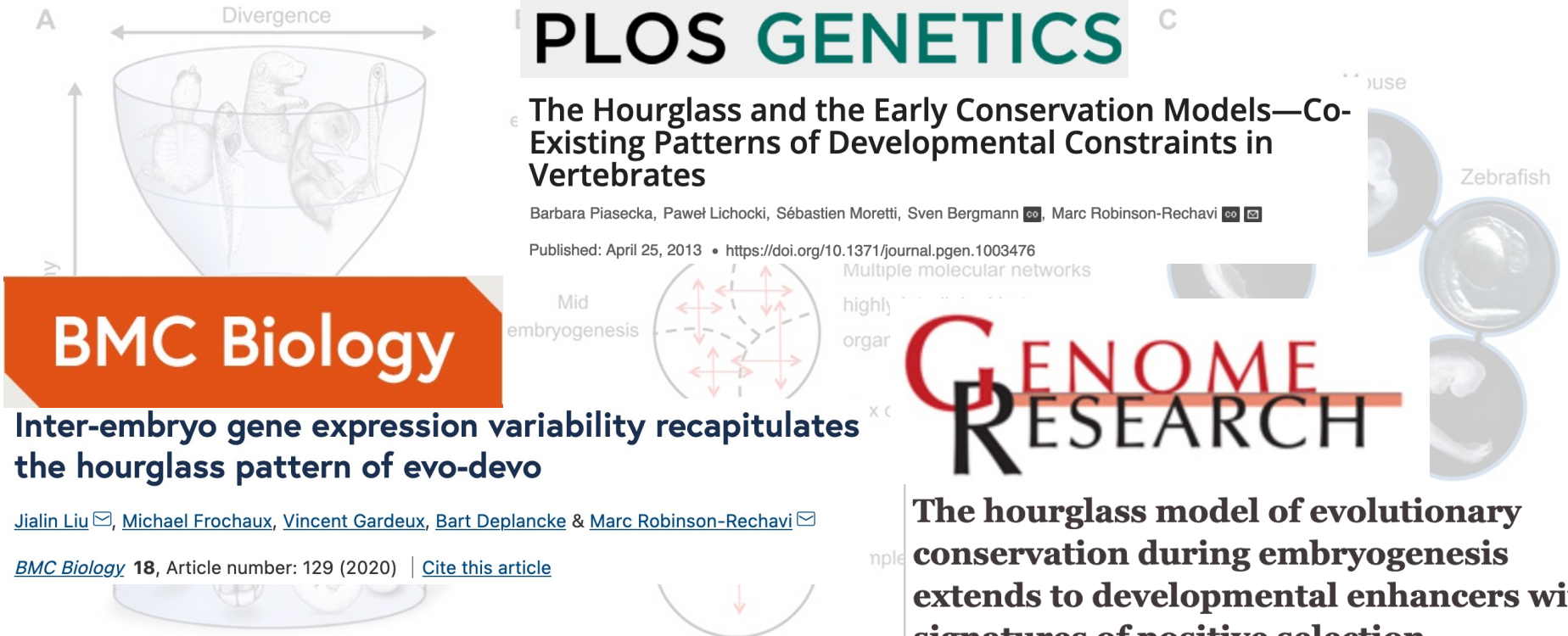
Watts et al., *Theory in Biosciences*, 2019

Comparing developmental stages



Irie N., *et al.*, *Development*, 2014, adapted from Wang *et al.* 2013

Comparing developmental stages



PLOS GENETICS

The Hourglass and the Early Conservation Models—Co-Existing Patterns of Developmental Constraints in Vertebrates

Barbara Piasecka, Paweł Lichocki, Sébastien Moretti, Sven Bergmann, Marc Robinson-Rechavi

Published: April 25, 2013 • https://doi.org/10.1371/journal.pgen.1003476

BMC Biology

Inter-embryo gene expression variability recapitulates the hourglass pattern of evo-devo

Jialin Liu, Michael Frochaux, Vincent Gardeux, Bart Deplancke & Marc Robinson-Rechavi

BMC Biology **18**, Article number: 129 (2020) | Cite this article

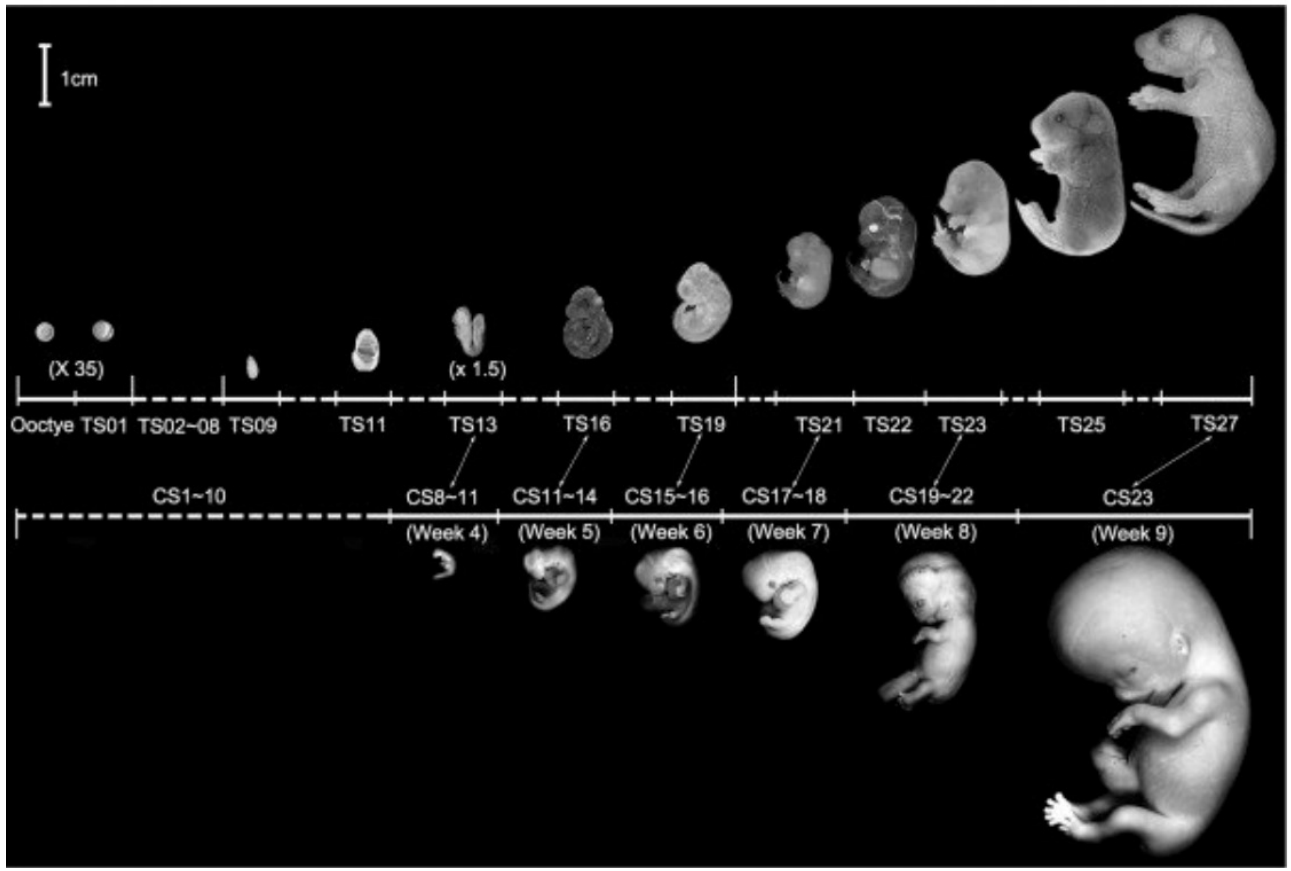
GENOME RESEARCH

The hourglass model of evolutionary conservation during embryogenesis extends to developmental enhancers with signatures of positive selection

Jialin Liu[1,2,4], Rebecca R. Viales[3], Pierre Khoueiry[3,5], James P. Reddington[3], Charles Girardot[3], Eileen E.M. Furlong[3] and Marc Robinson-Rechavi[1,2]

Irie N., *et al.*, *Development*, 2014, adapted from Wang *et al.* 2013

Comparing developmental stages



- Mouse Theiler stages based on somite number and characteristics
- Carnegie stages standardized 23 stages based on development of structures

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

Comparing life stages

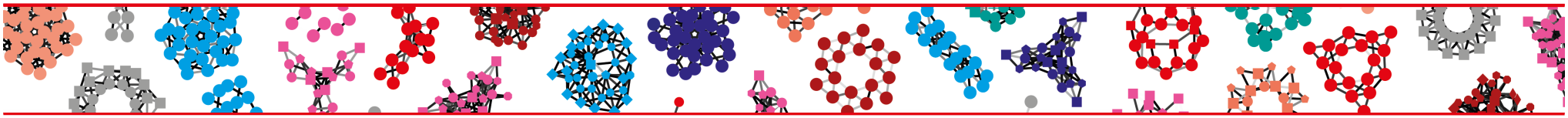
Aging

Human photo sources: wikipedia users WiLPrZ and Trocaire

Developmental stages capture phenotypic features

Ages during post-embryo are not based on phenotypic features

Development is heterochronous



Multi-species core development and life stage ontology

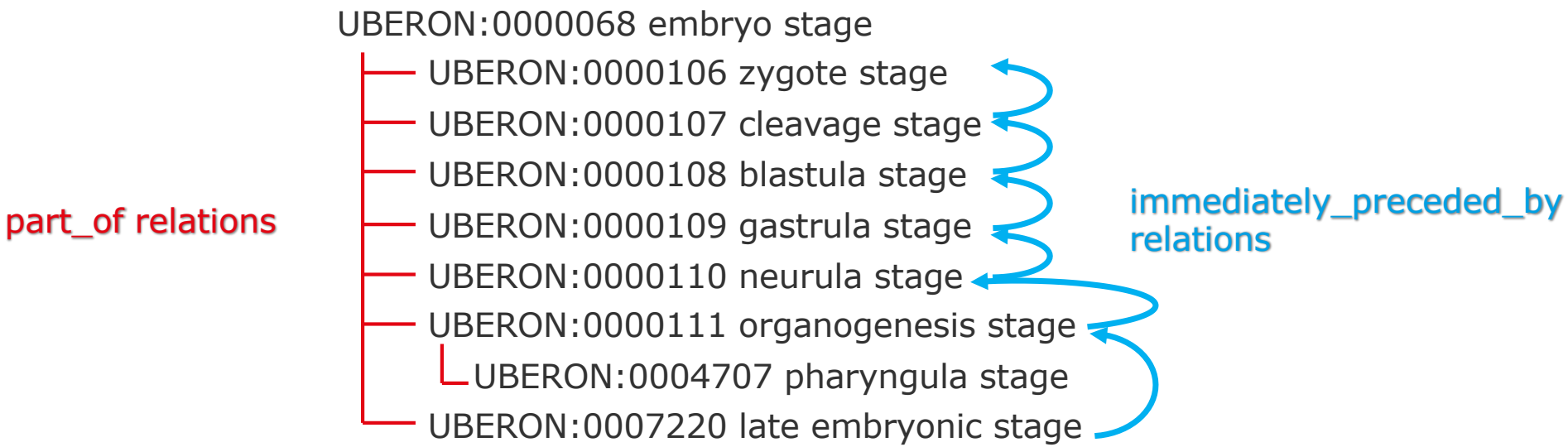
Uberon core ontology

UBERON:0000104 life cycle
- UBERON:0000068 embryo stage
- UBERON:0000092 post-embryonic stage

UBERON:0000068 embryo stage
- UBERON:0000106 zygote stage
- UBERON:0000107 cleavage stage
- UBERON:0000108 blastula stage
- UBERON:0000109 gastrula stage
- UBERON:0000110 neurula stage
- UBERON:0000111 organogenesis stage
  - UBERON:0004707 pharyngula stage
- UBERON:0007220 late embryonic stage

UBERON:0000092 post-embryonic stage
- UBERON:0000069 larval stage
  - ...
- UBERON:0000070 pupal stage
- UBERON:0000066 fully formed stage
  - UBERON:0000112 sexually immature stage
    - UBERON:0018685 nursing stage
      - UBERON:0007221 neonate stage
        - UBERON:0035946 start of neonate stage
      - UBERON:0034920 infant stage
    - UBERON:0034919 juvenile stage
  - UBERON:0000113 post-juvenile
    - UBERON:0018241 prime adult stage
    - UBERON:0007222 late adult stage

Uberon core ontology

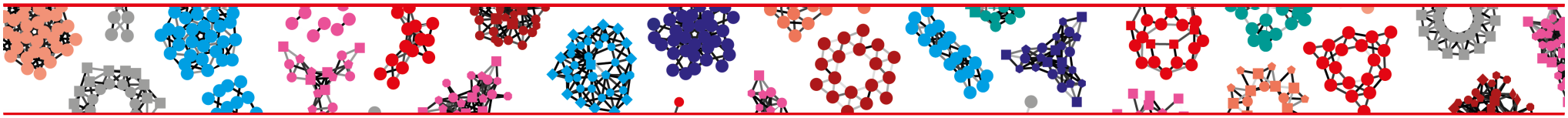


Uberon core ontology

UBERON:0000092 post-embryonic stage
- UBERON:0000069 larval stage
  - ...
  - UBERON:0000070 pupal stage → only_in_taxon Holometabola
  - UBERON:0000066 fully formed stage
    - UBERON:0000112 sexually immature stage
      - UBERON:0018685 nursing stage → only_in_taxon Mammalia
        - UBERON:0007221 neonate stage
          - UBERON:0035946 start of neonate stage
        - UBERON:0034920 infant stage → only_in_taxon Mammalia
      - UBERON:0034919 juvenile stage
    - UBERON:0000113 post-juvenile
      - UBERON:0018241 prime adult stage
      - UBERON:0007222 late adult stage

Uberon core ontology

UBERON:0000092 post-embryonic stage
- UBERON:0000069 larval stage
  - ...
- UBERON:0000070 pupal stage
- UBERON:0000066 fully formed stage
  - UBERON:0000112 sexually immature stage
    - UBERON:0018685 nursing stage → A mammalian developmental stage that covers the period from birth until weaning.
      - UBERON:0007221 neonate stage
        - UBERON:0035946 start of neonate stage
      - UBERON:0034920 infant stage → ends at weaning
    - UBERON:0034919 juvenile stage → The stage of being no more dependent of the nest and/or from caregivers for subsistence while having not reach sexual maturity.
  - UBERON:0000113 post-juvenile
    - UBERON:0018241 prime adult stage
    - UBERON:0007222 late adult stage



Species-specific ontologies

Human ontology: source ontology

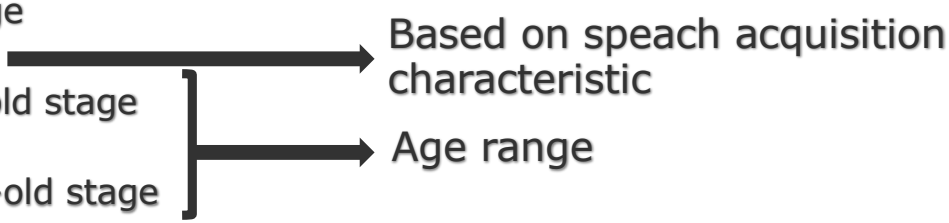
HsapDv:0000264 sexually immature stage
- HsapDv:0000260 nursing stage
  - HsapDv:0000262 newborn stage
  - HsapDv:0000261 infant stage
    - HsapDv:0000273 1-month-old stage
    - …
    - HsapDv:0000184 11-month-old stage
- HsapDv:0000265 child stage
  - HsapDv:0000246 1-year-old stage
    - HsapDv:0000185 12-month-old stage
    - …
    - HsapDv:0000196 23-month-old stage
  - HsapDv:0000270 2-4 year-old child stage
    - HsapDv:0000096 2-year-old stage
    - HsapDv:0000097 3-year-old stage
    - HsapDv:0000098 4-year-old stage
- HsapDv:0000271 juvenile stage
  - HsapDv:0000099 5-year-old stage
  - …
  - HsapDv:0000108 14-year-old stage

Human ontology: source ontology

[Term]
id: HsapDv:0000261
name: infant stage
namespace: human_developmental_stage
def: "Immature stage that refers to an infant who is over 28 days and is under 12 months old." [Bgee:curator "Bgee"]
comment: We consider that this pediatric stage refers to an infant who is over 28 days and under 12 months old, to follow HPO (Human Phenotype Ontology) which considers infant as between 28 days to one year of life, based on the ethymology of the word (infant), meaning not speaking, see HP:0003593 (Infantile onset) and see Peter Robinson's comment [[HPO:probinson] at https://github.com/obophenotype/human-phenotype-ontology/issues/5119#issuecomment-578882539.
synonym: "infantile stage" EXACT []
synonym: "under-1-year-old stage" EXACT []
xref: HP:0003593
xref: UBERON:0034920
is_a: HsapDv:0000000 ! life cycle stage
relationship: part_of HsapDv:0000260 ! nursing stage
relationship: immediately_preceded_by HsapDv:0000262 ! newborn stage
property_value: start_ypb "0.077" xsd:float
property_value: end_ypb "1.0" xsd:float
property_value: start_mpb "0.92" xsd:float
property_value: end_mpb "12.0" xsd:float

Human ontology: source ontology

HsapDv:0000264 sexually immature stage
- HsapDv:0000260 nursing stage
  - HsapDv:0000262 newborn stage
  - HsapDv:0000261 infant stage
    - HsapDv:0000273 1-month-old stage
    - …
    - HsapDv:0000184 11-month-old stage
- HsapDv:0000265 child stage
  - HsapDv:0000246 1-year-old stage
    - HsapDv:0000185 12-month-old stage
    - …
    - HsapDv:0000196 23-month-old stage
  - HsapDv:0000270 2-4 year-old child stage
    - HsapDv:0000096 2-year-old stage
    - HsapDv:0000097 3-year-old stage
    - HsapDv:0000098 4-year-old stage
- HsapDv:0000271 juvenile stage
  - HsapDv:0000099 5-year-old stage
  - …
  - HsapDv:0000108 14-year-old stage



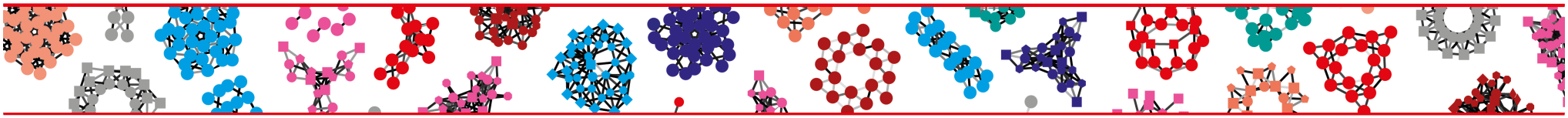
Human ontology: source ontology

[Term]
id: HsapDv:0000260
name: nursing stage
…
comment: The definition of an age for human weaning is difficult to define due to individual and cultural variations. The natural age of weaning in humans could be 2.5 years, with maximum 7.0 years (see https://www.health-e-learning.com/articles/A_Natural_Age_of_Weaning.pdf), but we decide to stop this period at 1 year-old, before usually language acquisition.

Human ontology: source ontology

HsapDv:0000226 prime adult stage
- HsapDv:0000266 young adult stage
  - HsapDv:0000268 15-19 year-old
    - HsapDv:0000109 15-year-old stage
    - ...
    - HsapDv:0000113 19-year-old stage
  - HsapDv:0000237 third decade stage
    - HsapDv:0000114 20-year-old stage
    - ...
    - HsapDv:0000123 29-year-old stage
  - HsapDv:0000238 fourth decade stage
    - HsapDv:0000124 30-year-old stage
    - ...
    - HsapDv:0000133 39-year-old stage

HsapDv:0000267 middle aged stage
- HsapDv:0000239 fifth decade stage
  - HsapDv:0000134 40-year-old tage
  - ...
  - HsapDv:0000143 49-year-old stage
- HsapDv:0000240 sixth decade stage
  - HsapDv:0000144 50-year-old stage
  - ...
  - HsapDv:0000153 59-year-old stage



Alignment with Uberon

Human ontology: bridge file

[Term]
id: HsapDv:0000045
property_value: IAO:0000589 "prenatal stage (human)" xsd:string
intersection_of: UBERON:0000068
intersection_of: part_of NCBITaxon:9606

[Term]
id: HsapDv:0000262
property_value: IAO:0000589 "newborn stage (human)" xsd:string
intersection_of: UBERON:0007221
intersection_of: part_of NCBITaxon:9606

[Term]
id: HsapDv:0000192
property_value: IAO:0000589 "19-month-old stage (human)" xsd:string
relationship: only_in_taxon NCBITaxon:9606 ! human

…

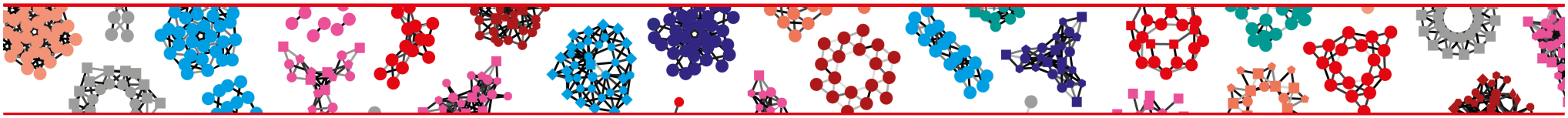
Human ontology: merge with Uberon

UBERON:0000104 life cycle
- **UBERON:0000068 embryo stage**
  - **UBERON:0000106 zygote stage**
  - **UBERON:0000107 cleavage stage**
    - HsapDv:0000205 morula stage (human)
  - **UBERON:0000108 blastula stage**
    - HsapDv:0000007 Carnegie stage 03 (human)
    - HsapDv:0000008 Carnegie stage 04 (human)
    - HsapDv:0000009 Carnegie stage 05 (human)
      - HsapDv:0000031 Carnegie stage 05a (human)
      - HsapDv:0000032 Carnegie stage 05b (human)
      - HsapDv:0000033 Carnegie stage 05c (human)
  - **UBERON:0000109 gastrula stage**
    - HsapDv:0000011 Carnegie stage 06 (human)
      - HsapDv:0000034 Carnegie stage 06a (human)
      - HsapDv:0000035 Carnegie stage 06b (human)
  - **UBERON:0000110 neurula stage**
    - HsapDv:0000013 Carnegie stage 07 (human)
    - HsapDv:0000014 Carnegie stage 08 (human)

UBERON:0000111 organogenesis stage
- HsapDv:0000016 Carnegie stage 09 (human)
- HsapDv:0000017 Carnegie stage 10 (human)
- HsapDv:0000018 Carnegie stage 11 (human)
- HsapDv:0000019 Carnegie stage 12 (human)
- HsapDv:0000020 Carnegie stage 13 (human)
- HsapDv:0000021 Carnegie stage 14 (human)
- HsapDv:0000022 Carnegie stage 15 (human)
- HsapDv:0000023 Carnegie stage 16 (human)
- HsapDv:0000024 Carnegie stage 17 (human)
- HsapDv:0000025 Carnegie stage 18 (human)
- HsapDv:0000026 Carnegie stage 19 (human)
- HsapDv:0000027 Carnegie stage 20 (human)
- HsapDv:0000028 Carnegie stage 21 (human)
- HsapDv:0000029 Carnegie stage 22 (human)
- HsapDv:0000030 Carnegie stage 23 (human)

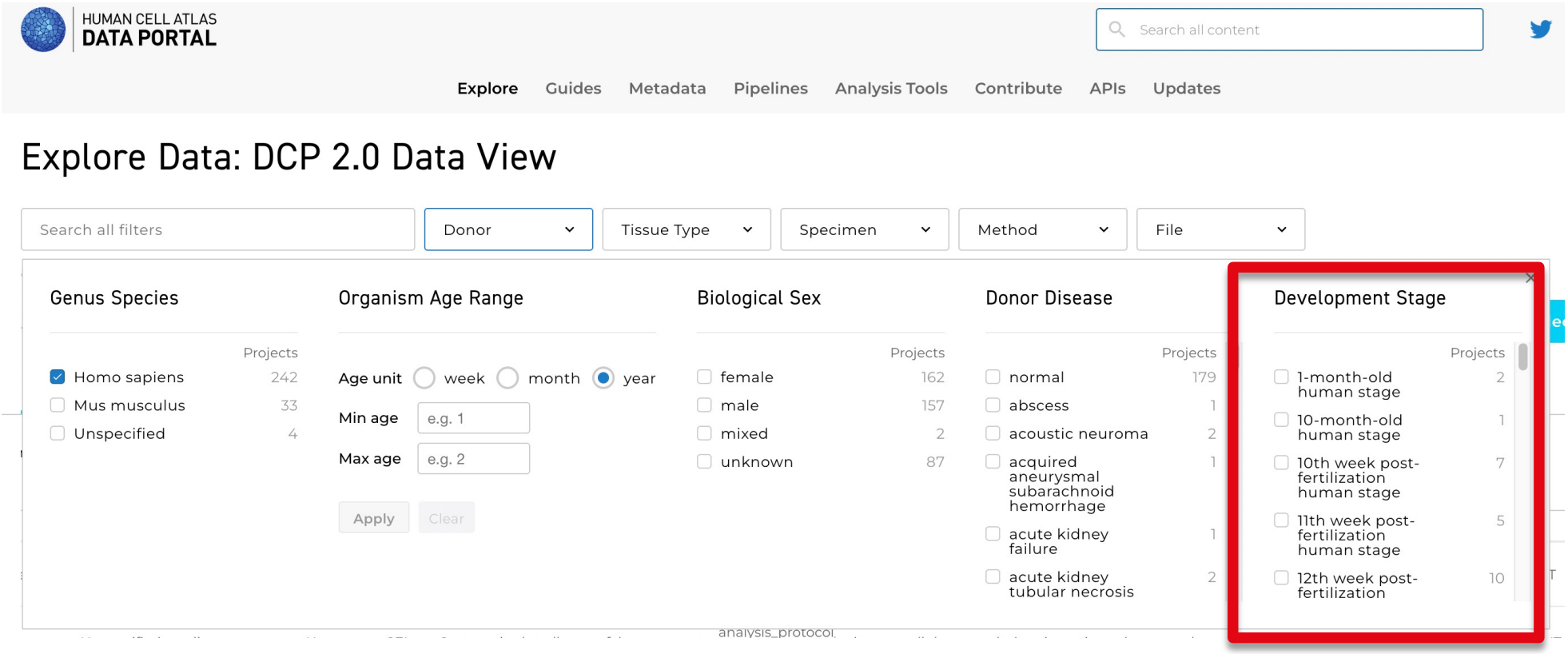
Integration of 21 species

Ontology name	Species	Number of classes	Number of classes linked to Uberon
AcarDv	Anolis carolinensis	20	20
BtauDv	Bos taurus	78	8
CfamDv	Canis lupus familiaris	24	24
CporDv	Cavia porcellus	24	24
DpseDv	Drosophila pseudoobscura	21	18
DsimDv	Drosophila simulans	21	18
EcabDv	Equus caballus	24	24
FcatDv	Felis catus	24	24
GgalDv	Gallus gallus	90	16
GgorDv	Gorilla gorilla	47	24
HsapDv	Homo sapiens	238	20
MdomDv	Monodelphis domestica	59	24
MmulDv	Macaca mulatta	66	24
MmusDv	Mus musculus	134	20
OanaDv	Ornithorhynchus anatinus	24	24
OariDv	Ovis aries	33	20
OcunDv	Oryctolagus cuniculus	24	24
PpanDv	Pan paniscus	56	24
PtroDv	Pan troglodytes	67	24
RnorDv	Rattus norvegicus	60	20
SscrDv	Sus scrofa	94	22



Application examples

Annotation in Human Cell Atlas



Expression data in Bgee: PAX6 example

Gene : PAX6 - ENSG00000007372 - *Homo sapiens* (human)

Function[i]

Transcription factor with important functions in the development of the eye, nose, central nervous system and pancreas. Required for the differentiation of pancreatic islet alpha cells (By similarity).

Anatomical entity	Dev. stage	Expression score	FDR	Sources
UBERON:0001812 palpebral conjunctiva	HsapDv:0000246 1-year-old stage (human)	99.55	0.002	A E I R FL
UBERON:0001812 palpebral conjunctiva	HsapDv:0000270 2-4 year-old child stage (human)	99.55	0.002	A E I R FL
UBERON:0001812 palpebral conjunctiva	UBERON:0034919 juvenile stage	99.53	0.002	A E I R FL
UBERON:0003053 ventricular zone	HsapDv:0000198 fourth LMP month stage (human)	99.33	<= 1.00e-14	A E I R FL
CL:0000169 type B pancreatic cell	UBERON:0000113 post-juvenile	99.28	0.002	A E I R FL

Expression data in Bgee: PAX6 expression in Euteleostomi

Anatomical entities	Conservation score ▼1	Max expression score ▼3	Genes with presence of expression	Genes with absence of expression ▲2	Genes with no data
cornea	1.00	99.72	3 genes	0 gene	48 genes
retinal neural layer	1.00	99.47	3 genes	0 gene	48 genes
ventricular zone	1.00	99.28	2 genes	0 gene	49 genes
germ cell	1.00	98.61	4 genes	0 gene	47 genes
metencephalon	1.00	98.54	24 genes	0 gene	27 genes
hindbrain	1.00	98.54	26 genes	0 gene	25 genes
cerebellum	1.00	98.54	24 genes	0 gene	27 genes
lens of camera-type eye	1.00	98.11	5 genes	0 gene	46 genes
optic cup	1.00	97.95	3 genes	0 gene	48 genes
optic fissure	1.00	97.95	1 gene	0 gene	50 genes

Anne Niknejad

David Osumi-Sutherland

Chris Mungall

Bgee

https://bgee.org/

SIB Swiss Institute of Bioinformatics

https://github.com/obophenotype/developmental-stage-ontologies

.ü

http://purl.obolibrary.org/obo/uberon/composite-metazoan.owl

elixir SWITZERLAND

www.sib.swiss