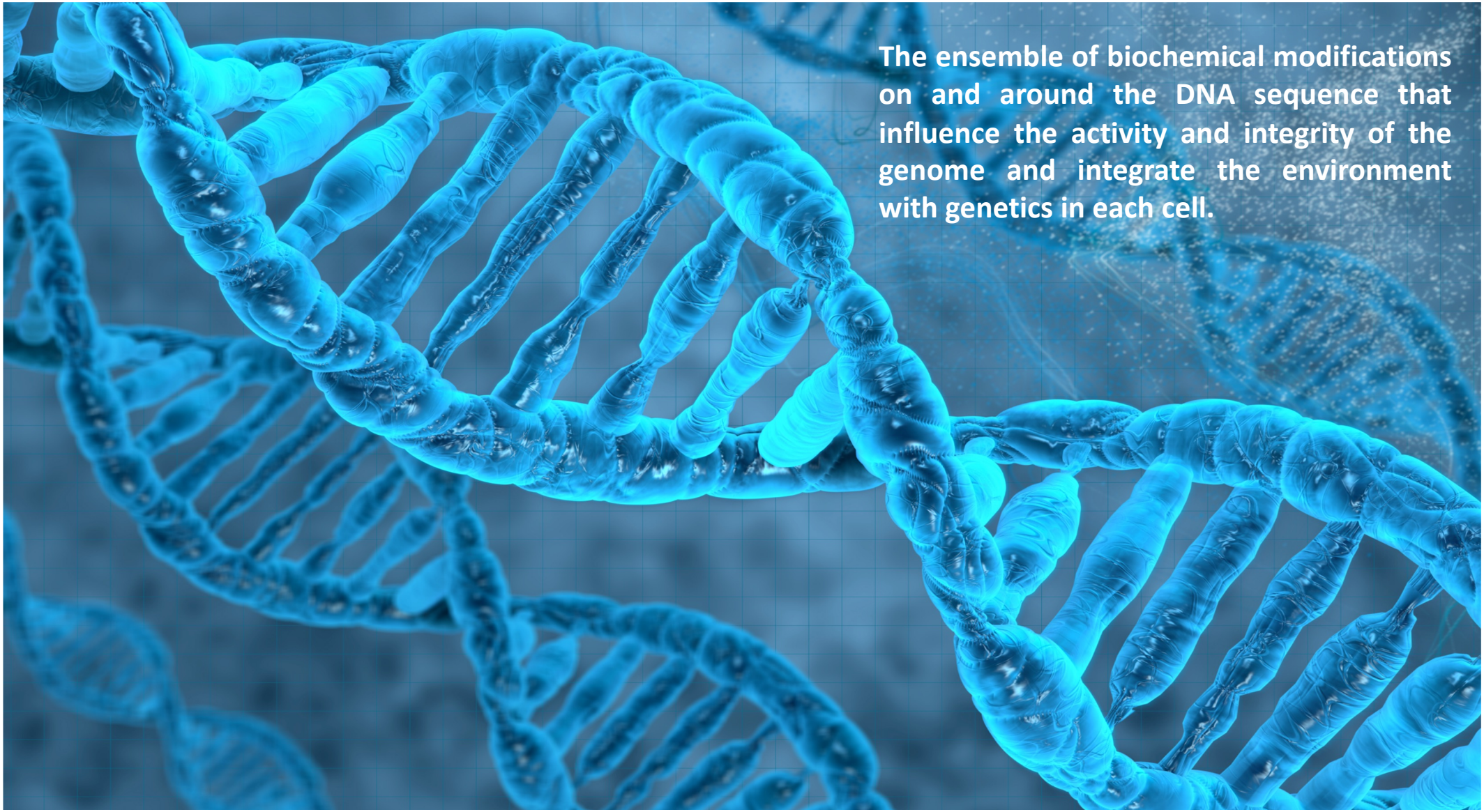
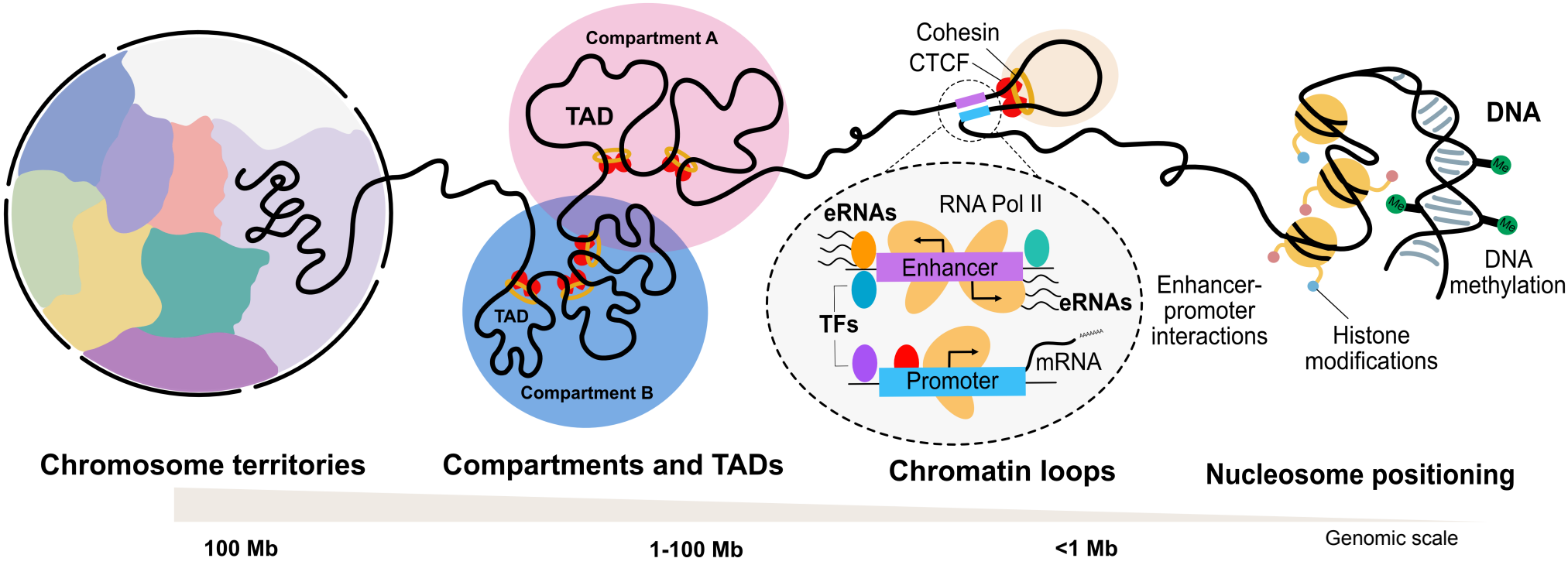
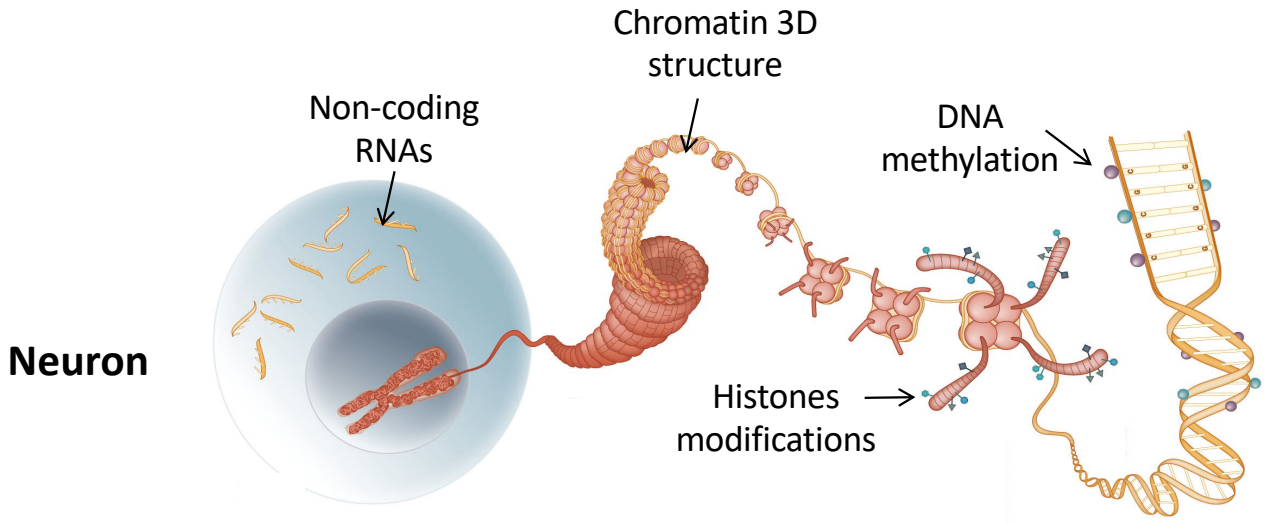
Epigenetics in health and disease



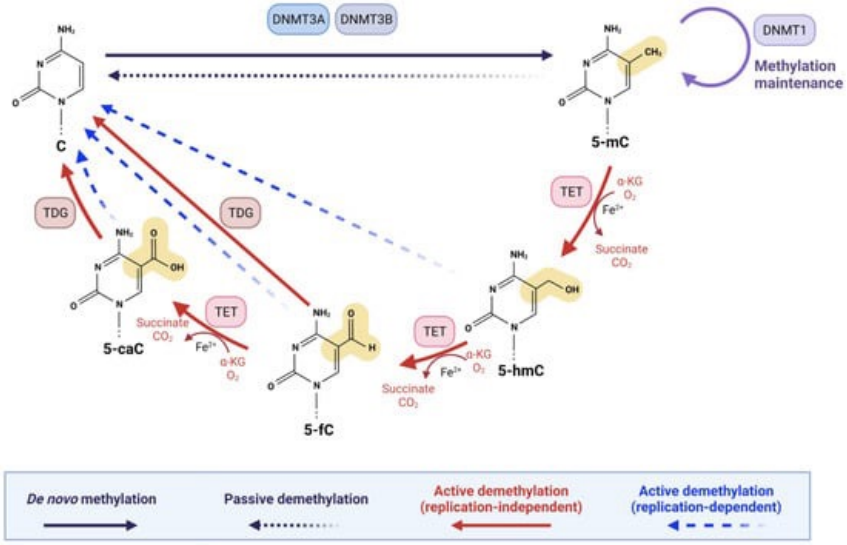
Epigenetic factors control genome activity and architecture

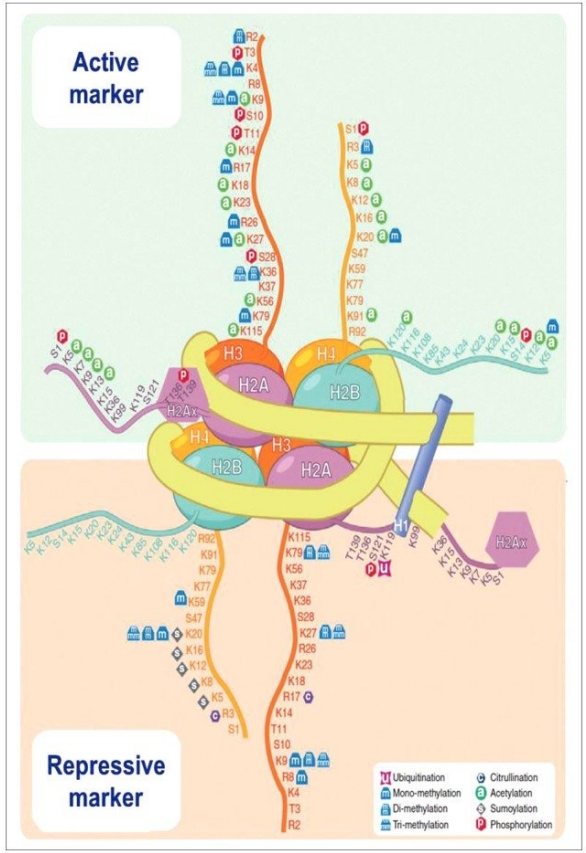


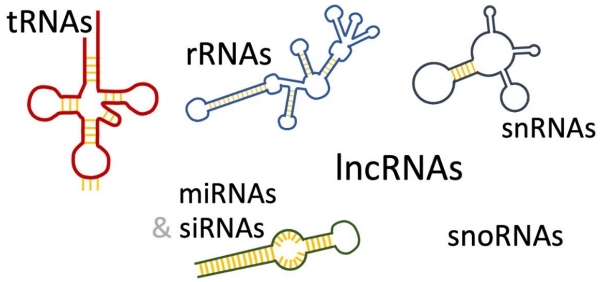
Multiple epigenetic factors and mechanisms act together



DNA epicode, histone code and RNA world



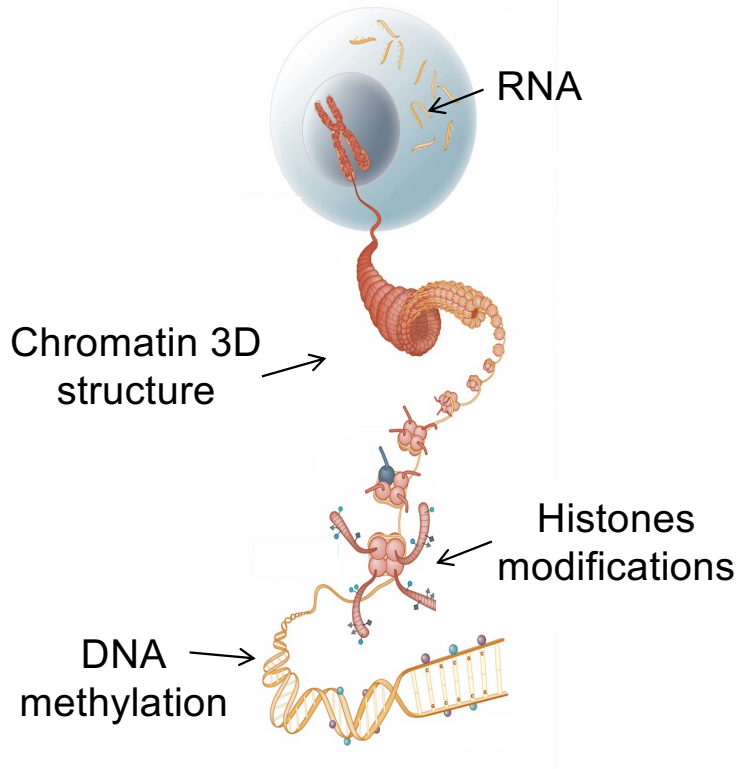




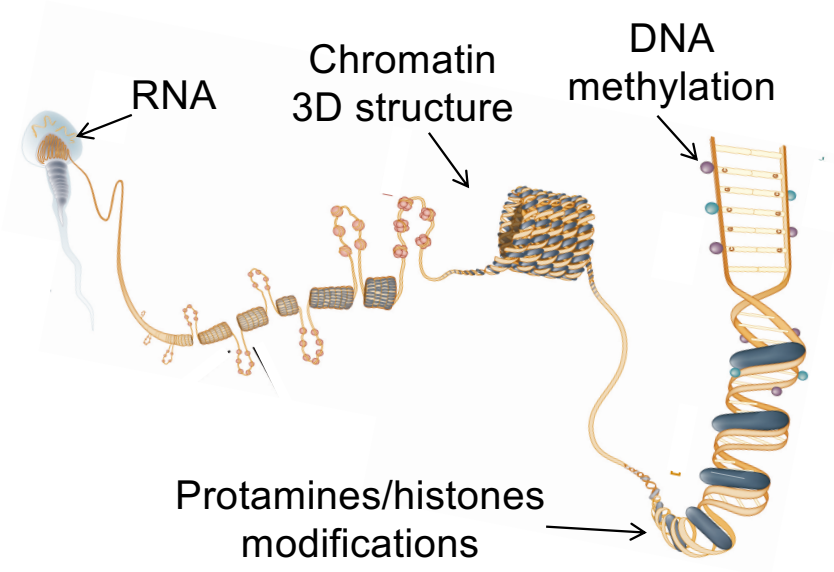
Properties of the epigenome relevant to brain functions

- Is extraordinarily rich and exquisitely refined to encode specific information
- Responds to neuronal activity and environmental factors such as stress, diet, endocrine disruptors
- Is plastic but can capture and embed signals stably
- Unique to each cell type but can be different in cells of the same type depending on experience
- Subjected to aging

Germ cells also have an epigenome



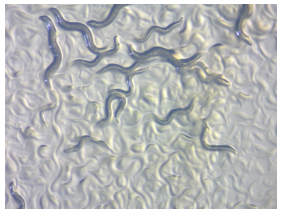
Oocyte



Sperm cell

Transgenerational transmission of acquired traits across species

C elegans



Rechavi et al, 2014: **Starvation**, developmental arrest, 3rd generation

Gamez-del-Estali et al, 2014: **Testosterone**, behavior, 4th generation

Schultz et al, 2016: **Silver exposure**, male fertility, 10th generation

Klosin et al, 2017: **Temperature**, genome derepression, 14th generation

Rodents

Franklin et al, 2010: **Postnatal trauma**, depressive-like symptoms, 3rd generation

Fullston et al, 2013: **Paternal obesity**, metabolic health, 3rd generation

Choi et al, 2016: **Valproic acid**, autism-like behaviors, 3rd generation

Anway et al, 2005: **Endocrine disruptors**, male fertility, 4th generation

Van Steenwyk et al, 2018: **Postnatal trauma**, risk taking, 4th generation (5th/6th in prep)

Humans

Perroud et al, 2014: **Rwanda genocide**, depression, PTSD, children

Yehuda et al, 2015: **Holocaust**, psychiatric disorders, children

Santavirta et al. 2017: **Parental separation,** PTSD, children

Bygren et al, 2014: **Childhood nutrition**, cardiovascular mortality, grandchildren

Vågerö et al, 2018: **Poor nutrition**, life span and mortality, grandchildren

Golding et al, 2022: **Smoking**, fat mass, great-grandchildren

Many examples of transmission

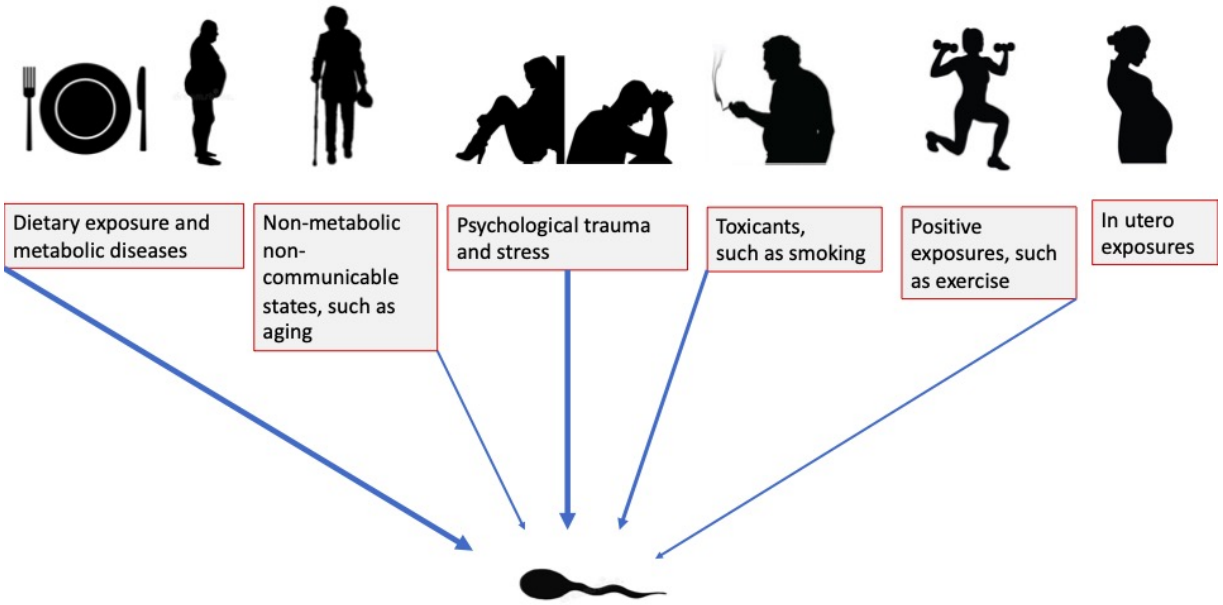
Trends in Genetics

CellPress

Review

Impact of Parental Exposure on Offspring Health in Humans

Ali Jawaid,[1,2,3,4,6] Katherina-Lynn Jehle,[5,6] and Isabelle M. Mansuy [1,2,*]



Jawaid et al. 2020 Trends in Genetics 37:373

Transgenerational impact of early life experiences on mental and physical health

Exposure

Mother — 1st generation — Father

Foetus — 2nd generation

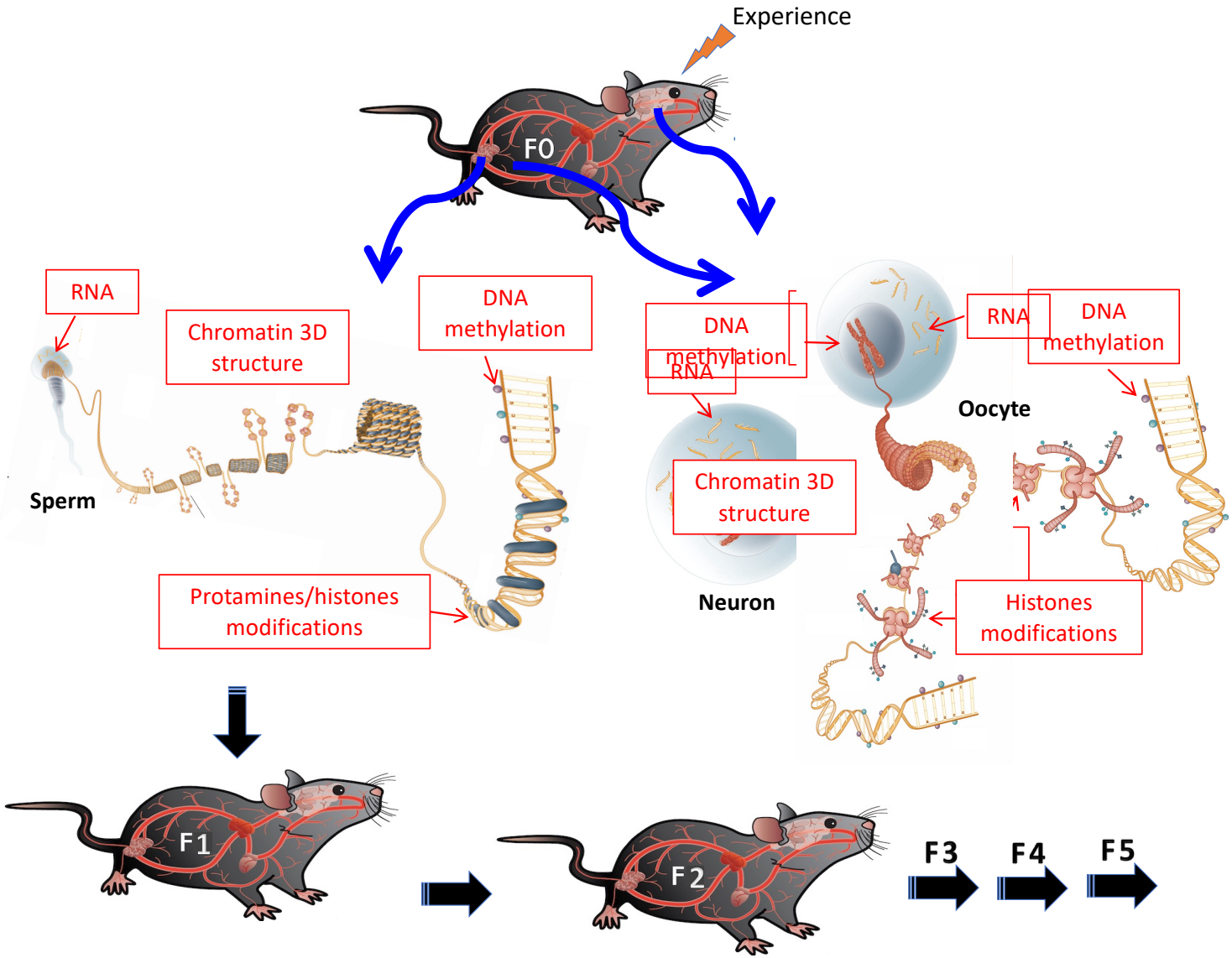
Future gametes — 3rd generation

Germ cells

Germ cells

4^{th}, 5^{th}… generation ?

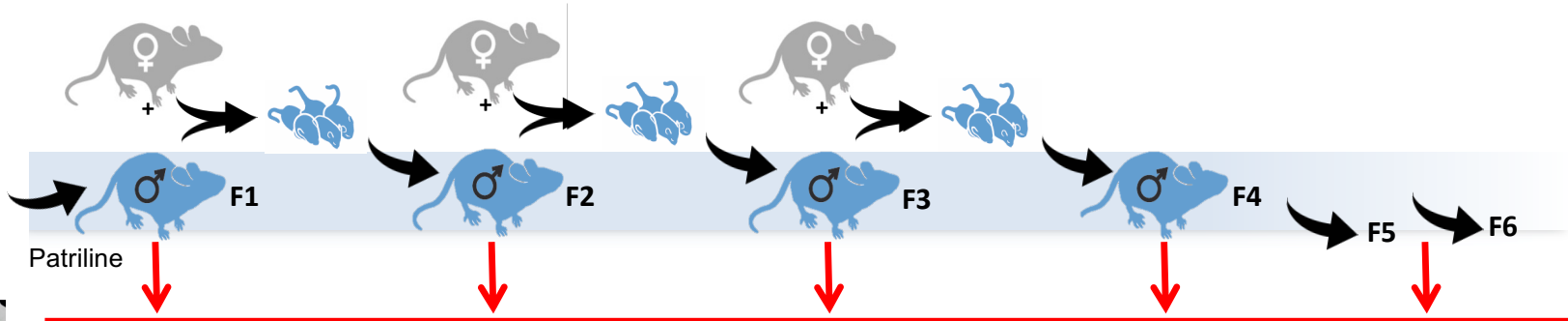
Concept of non-DNA sequence-based mechanisms of traits acquisition and inheritance



Behavioral, physiological and cardiometabolic symptoms of postnatal trauma across generations

Controls

MSUS



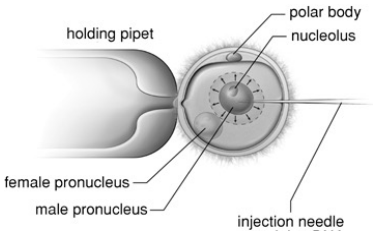
F1	F2	F3	F4	F5
Risk-taking	Risk-taking	Risk-taking	Risk-taking	Risk-taking
Altered glucose/insulin	Altered glucose/insulin	Altered glucose/insulin	Altered glucose/insulin	Altered gluc/insulin
Lower weight	Lower weight	Normal weight	Increased weight	Increased weight
Depressive symptoms	Depressive symptoms	Depressive symptoms	Other parameters non-significant or not examined	Other parameters non-significant or not examined
Cardiac dysfunction	Cardiac dysfunction	Cardiac dysfunction		
Social deficits	Social deficits	Lung congestion		
Cognitive impairment	Cognitive impairment	Other parameters non-significant or not examined		
Impaired brain plasticity and metabolism	Impaired brain plasticity and metabolism			
Lung congestion	Lung congestion			
Less white blood cells	More erythroipoiesis			

Patriline: Franklin et al 2010 Biol Psych, Gapp et al 2014 Nat Neurosci, Gapp et al 2014 Nat Commun, Bohacek et al. 2015 Mol Psy, van Steenwyk et al 2018 Env Epig, Boschardin et al 2022 Env Epig, Kourouma et al In prep, Paneni et al In prep.

Matriline: Weiss et al 2011 Frontiers Behav. Neurosci, Efimova et al In prep

Sperm RNA as causal vector of heredity

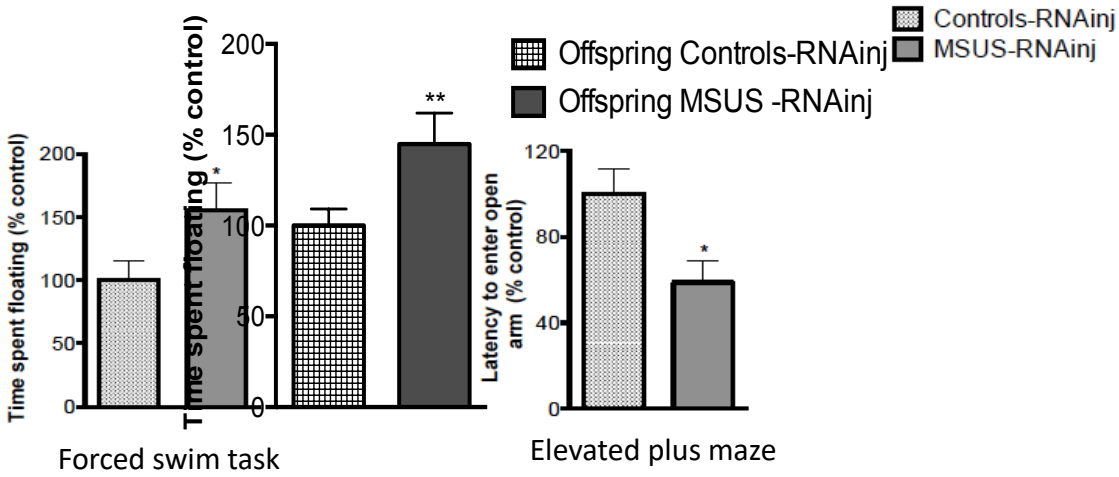
Injection of sperm RNA in fertilized control eggs



Animals arising from RNA-injected eggs

Breeding to wt females

Progeny of animals arising from RNA-injected eggs

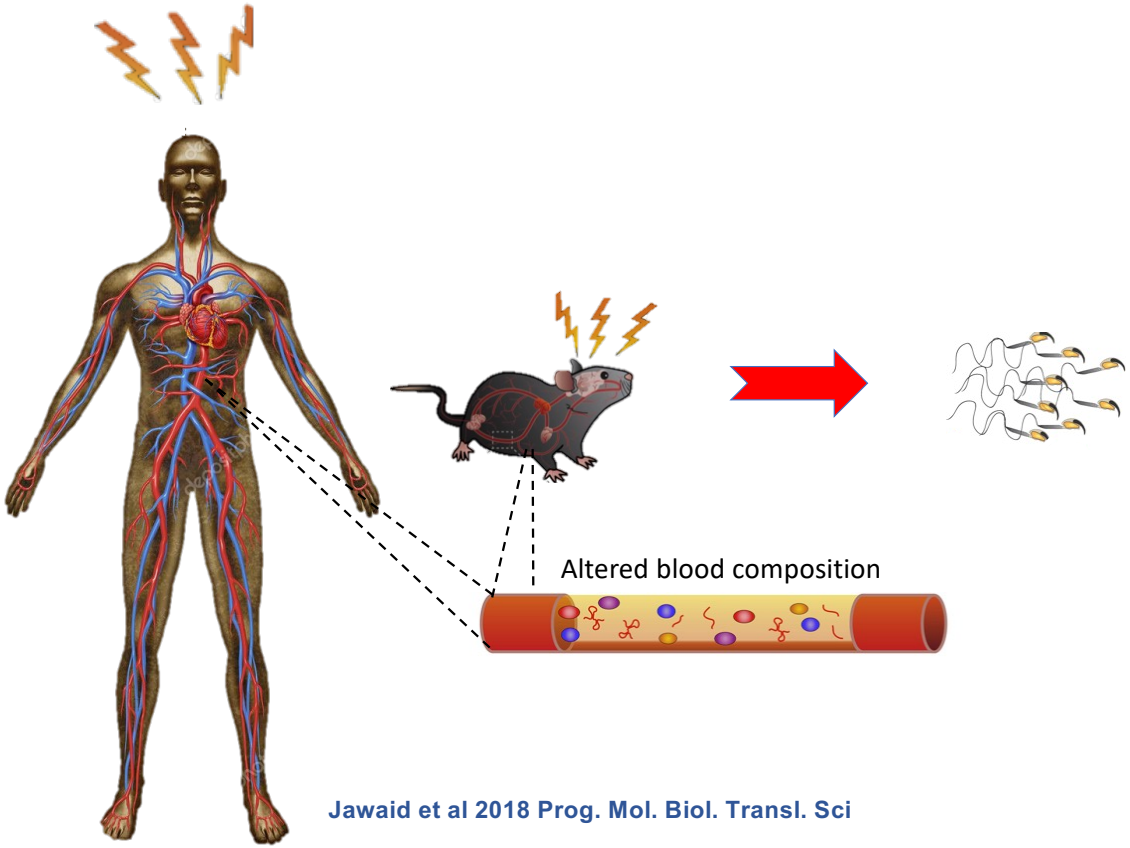


Forced swim task

Elevated plus maze

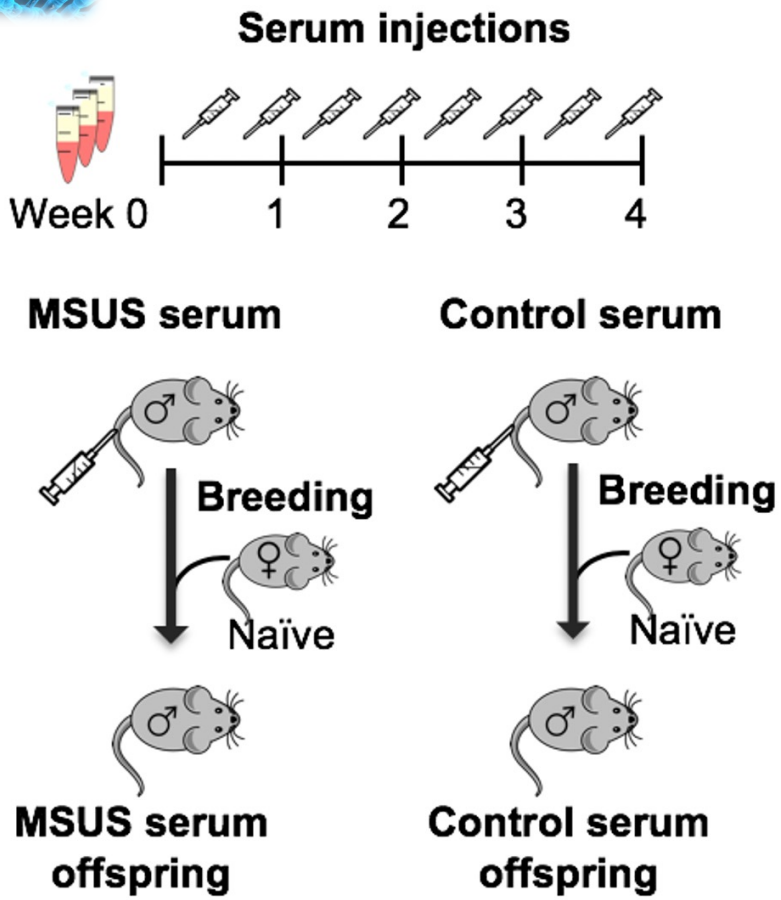
Gapp et al. 2014 Nature Neurosci, Gapp et al 2020 Mol Psy.

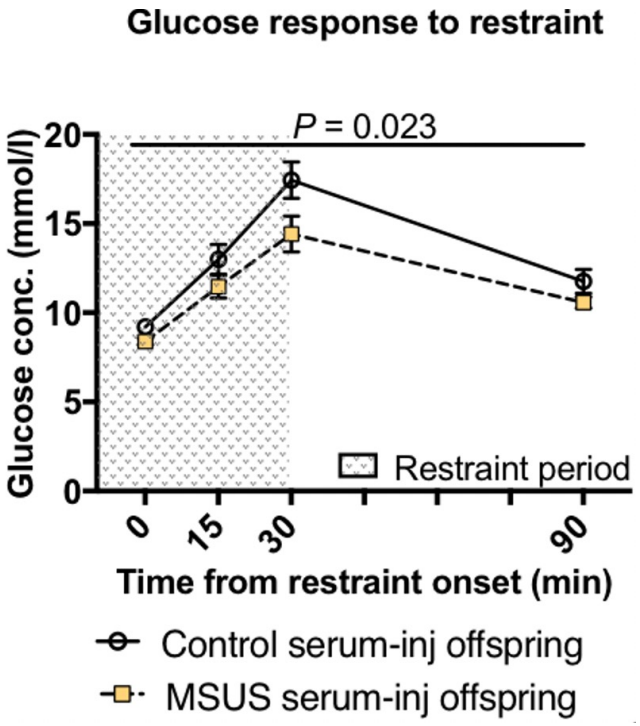
Circulating factors as vectors of communication with germ cells



Jawaid et al 2018 Prog. Mol. Biol. Transl. Sci

Circulating factors as vectors of communication with germ cells





Van Steenwyk et al 2020 EMBO J.

Perspectives

- **5 years:** Profiling of epigenome in individual brain cells in health and disease (AI)

- **10 years:** Functional and causal link between epigenome and brain functions

- **25 years**: Epigenome editing in brain, germline

A piece of art on transgenerational memory