EPIGENETIC INHERITANCE SYMPOSIUM 2025

Impact for Biology and Society

27-29 August 2025
ETH Zurich, Switzerland

Universität Zürich[UZH] | ETH zürich

Important information

WIFI: public / public-5

Emergency: 144
Police: 117
Zurich Public Transport: www.zvv.ch
Zurich Public Bikes: www.publibike.ch
Taxi: +41 44 777 77 77

Venue

Paul Scherrer Auditorium (ETA F 5)
ETH Zurich ETA Building
Gloriastrasse 39
8092 Zurich
www.ethz.ch

Table of content

Summary of previous editions

Epigenetic Inheritance: Impact for Biology and Society

23-25 August 2023, Zurich, Switzerland
Leo Steg, Ellen Jaspers, Anar Alshanbayeva, Rodrigo G Arzate-Meija, Maria A Dimitriu, Katharina Gapp, Lola M Kourouma, Kerem Uzel, Isabelle M Mansuy

Environmental Epigenetics
Volume 10, Issue 1, Feb 2024
DOI: 10.1093/eep/dvae002

25-27 August 2021, Zurich, Switzerland
Rodrigo G Arzate-Mejía, Isabelle M Mansuy

Environmental Epigenetics
Volume 8, Issue 1, Nov 2022
DOI: 10.1093/eep/dvac021

26-28 August 2019, Zurich, Switzerland
Irina Lazar-Contes, Martin Roszkowski, Deepak K Tanwar, Isabelle M Mansuy

Environmental Epigenetics
Volume 6, Issue 1, May 2020
DOI: 10.1093/eep/dvaa004

Transgenerational epigenetic inheritance: from biology to society

28-30 August 2017, Zurich, Switzerland
Johannes Bohacek, Olivia Engmann, Pierre-Luc Germain, Silvia Schelbert, Isabelle M Mansuy

Environmental Epigenetics
Volume 4, Issue 2, April 2018
DOI: 10.1093/eep/dvy012

WELCOME

Dear colleague, student and friend,

It is a great pleasure to welcome you to the 5th edition of the Epigenetic Inheritance symposium in Zurich.

The symposium features important aspects of epigenetic inheritance across different disciplines, from epidemiology to behavior, metabolism, mechanisms and methodologies in humans and animal models. Discussion topics include new findings and discoveries, challenges of the discipline and perspectives for biology, medical research and the society.

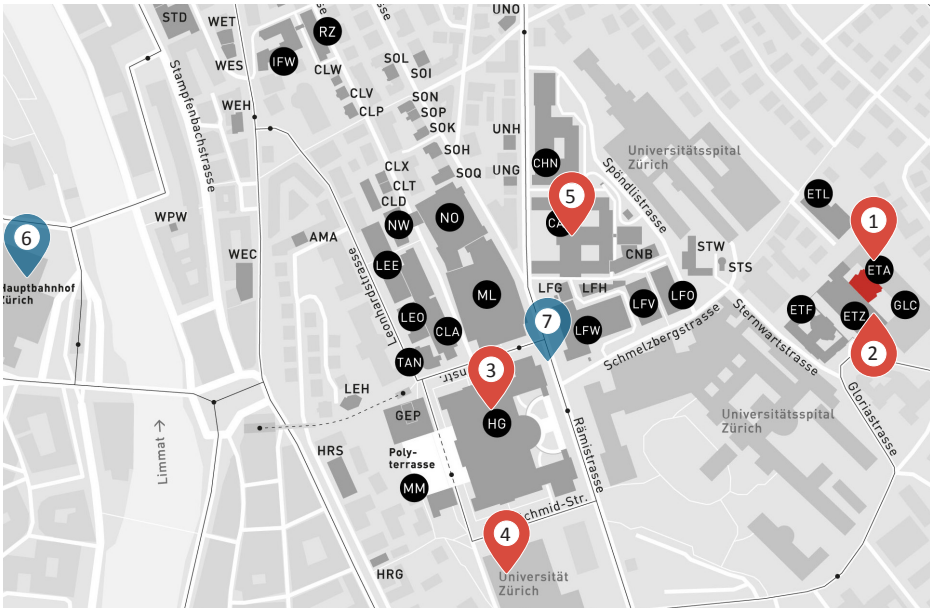
The symposium offers keynote lectures from leaders in the field, short and flash talks, poster sessions with an award for the best poster, and a workshop "Challenges for the field of epigenetics".

To continue the symposium's tradition to combine science and art, an art competition is organized during the symposium. Art pieces created by attendees on the theme of epigenetic inheritance are exhibited in the foyer of the ETA building and the best piece will be rewarded with a prize.
We also offer a public viewing of an art movie on transgenerational trauma "The war in me" ("Der Krieg in mir") in the presence of the movie producer, Sebastian Heinzel.

I hope that you'll enjoy the symposium, and find it inspiring for your research and your thinking about the biology of heredity. I wish you a great and productive time in Zurich and warmly thank you for participating.

Isabelle Mansuy

VENUE



1. Epigenetic Inheritance Symposium, ETH Zurich, ETA F 5, Gloriastrasse 39, 8006 Zurich
2. Coffee and Lunch Breaks, Poster Sessions, ETH Zurich, ETZ Foyer, Gloriastrasse 35, 8006 Zurich
3. Terrace Dinner, ETH Zurich, HG K 30.5, Rämistrasse 101, 8092 Zurich (upon registration only)
4. Movie viewing, University Zurich, building KO2 (Kino im Museum), Karl-Schmid-Strasse 4, 8006 Zürich
5. Workshop, ETH Zurich, Food & Lab, CAB H 41, Universitätsstr. 6, 8092 Zurich (upon registration only)
6. Zürich HB / Zurich Main Station
7. PubliBike Station

Direction for Public Transportation

Tram Nr. 10	From Zurich Main Station to ETH/Universitätsspital	Ticket: Zone 110
Tram Nr. 6	From Zurich Main Station to Voltastrasse	Ticket: Zone 110

PROGRAM

Wednesday 27.08.2025

07:45 – 08:45	Registration
Introduction	
08:45 – 09:00	Isabelle Mansuy, Professor in Neuroepigenetics, University and ETH Zurich
Session 1	**Epidemiological evidence and animal models I** Chair: Maria Dimitriu
09:00 – 09:40	New models to study the epigenetic impacts of environmental challenge Amanda Fisher, University of Oxford, United Kingdom
09:40 – 10:20	Human studies on gene environment interplay underlying mental disorders: Current status on possible transgenerational impact of traumatic stress via epigenetics Bart Rutten, Maastricht University, The Netherlands
10:20 – 11:00	*Coffee Break - ETZ Foyer, Floor E*
11:00 – 11:30	Differential microRNAs and metabolites in the breast milk of mothers with adverse experiences correlate with offspring temperament Ali Jawaid, PORT Polish Center for Technology Development, Poland
11:30 – 11:55	The missing heritability of autism: Is epigenetic inheritance playing a role? Jill Escher, Escher Fund for Autism, USA
11:55 – 12:05 5-min Flash talks	Vincent Fischer, ETH Zurich, Switzerland Chronic stress response induced long-term non-genetic changes in fathers and predicts offspring phenotype Leo Steg, University Zurich and ETH Zurich, Switzerland From sperm to embryo: Allele-resolved evidence for miRNA-mediated effects on the maternal transcriptome
12:05 – 13:30	*Lunch Break - ETZ Foyer, Floor E*
Session 2	**Transmission mechanisms I** Chair: Leo Steg
13:30 – 14:10	Passage of epigenetic information through the mammalian germline *** The EMBO Lecture *** Petra Hajkova, MRC Laboratory of Medical Sciences, United Kingdom

Session 2	Transmission mechanisms I (continued) Chair: Leo Steg
14:10 – 14:50	Maternal diabetes programs sexually dimorphic early-onset cardiovascular dysfunction in metabolically healthy offspring Qiaolin Deng, Karolinska Institute, Sweden
14:50 – 16:20	*Coffee Break and Poster Session I - ETZ Foyer, Floor E*
16:20 – 17:00	Long-read sequencing to resolve gene cluster (epi)genetics Lucia Daxinger, Leiden University Medical Center, The Netherlands
18:00 – 22:00	Terrace Dinner at ETH Dozentenfoyer (upon registration only)

Thursday 28.08.2025

08:30 – 09:00	Registration

Session 3	Transmission mechanisms II Chair: Theresa Schöpp
09:00 – 09:40	Epigenetic transmission of trauma-inducible glucocorticoid signalling within the male germline Katharina Gapp, ETH Zurich, Switzerland
09:40 – 10:20	Epigenetic programming in the parental germlines and epigenetic inheritance Satoshi Namekawa, University of California Davis, USA
10:20 – 11:00	*Coffee Break - ETZ Foyer, Floor E*
11:00 – 11:40	Small RNAs in male reproduction: spermatogenesis, sperm maturation and paternal influence Pei-Hsuan Wu, University of Geneva, Switzerland
11:40 – 12:00 5-min Flash talks	Ramji K. Bhandari, University of Missouri, USA Reversal of environmentally induced transgenerational epimutations in the germline and soma Sarah Cohen-Woods, Flinders University, Australia Footsteps of our fathers: sperm DNA methylation and early-life stress in men Magdalena Gomółka, Port Polish Center For Technology Development, Poland The role of lipid metabolism and circulating miRNAs in the intergenerational transmision of the effects of parental adverse childhood experiences Haojiang Lu, Karolinska Institute, Sweden Epigenetic transgenerational germline inheritance of polycystic ovary syndrome
12:00 – 13:30	*Lunch Break - ETZ Foyer, Floor E*

Thursday 28.08.2025 (continued)

Session 4	Epidemiological evidence and animal models II
	Chair: Leonardo Zingler Herrero
13:30 – 14:10	Maternal metabolic health and fertility: caring about mother's and daughter's oocyte Jo Leroy, University of Antwerp, Belgium
14:10 – 14:25	Understanding the metabolo-epigenetic rules underlying environmental epigenetic alterations Patrick Allard, University of California, Los Angeles (UCLA), USA
14:25 – 15:50	*Coffee Break and Poster Session II - ETZ Foyer, Floor E*
15:50 – 16:30 Online	The molecular mechanisms and biological impacts of epigenetic transgenerational inheritance Michael Skinner , Washington State University, USA
17:00 – 19:00	Movie "The War in Me" at the cinema in the KO2 museum (free, registration required)

Friday 29.08.2025

Session 5	Methodologies
	Chair: Anna Chamot
09:00 – 09:40 Online	Mechanism of epigenetic reprogramming in the human germ line Mitinori Saitou, Kyoto University, Japan
09:40 – 10:00 5-min Flash talks	Shiori Minabe, Iwate Medical University, Japan Mapping the human epigenetic landscape across three generations: A DNA methylation resource from TMM BirThree Stacy Rousse, Inrae France Transmission of DNA methylation: genetic or epigenetic? A transgenerational case study in quails Matthias Ronald Schaefer, Medical University of Vienna, Austria Copy number determination of small RNAs in mature mouse sperm involved in the intergenerational inheritance of metabolic syndromes Mariano Stornaiuolo, University Of Naples Federico II, Italy Sperm-derived lipids as epigenetic drivers of intergenerational inheritance: Shaping early embryonic development and disease susceptibility
10:00 – 10:30	*Coffee Break - ETZ Foyer, Floor E*

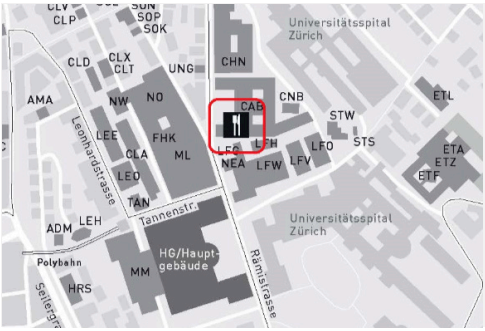
Friday 29.08.2025 (continued)

Session 6	Impact on society and evolution
	Chair: Eduardo Caceres
10:30 – 11:10	Social adversity as a strategic research site for social sciences and epigenetics Michel Dubois, University of Sorbonne, France
11:10 – 11:25	Samuli Laasanen, University of Turku, Finland Intergenerational effects of paternal HFD on germline RNAs and metabolic health can be altered by obesity treatment
11:25 – 11:40 5-min Flash talks	Alexander Murashov, Louisiana State University, USA Inherited metabolic imprints—or the mitochondrial memory of lifestyle? Mahesh Rachamalla, University of Saskatchewan Canada Transgenerational neurotoxicity of arsenic in zebrafish: Mechanistic insights into cogni tive deficits and epigenetic alterations Sarah Stucchi, Fondazione Human Technopole, Italy The impact of chemical exposures across generations: Integrating human epidemiology with in vitro modelling and causal models of epigenetic inheritance
11:40 – 12:00	Poster & Art prize / Closing

Workshop «Challenges for the field of epigenetic inheritance»

12:30 – 14:00	*Lunch - food&lab (CAB)*
14:00 – 15:30	Part I
15:30 – 16:00	*Coffee Break - food&lab (CAB)*
16:00 – 17:00	Part II

Moderated by Katharina Gapp, ETH Zurich, Switzerland
Rodrigo G Arzate-Mejia, University Zurich and ETH Zurich, Switzerland



Workshop

ETH Zurich
Food & Lab
Building CAB H 41
Universitätsstrasse 6
8092 Zurich

ABSTRACTS

New models to study the epigenetic impacts of environmental challenge

Amanda Fisher | University of Oxford, United Kingdom

We have developed new mouse models to image the impacts of environmental challenge. These rely on the expression of luciferase enzymes, non-disruptively integrated into genes of interest, that enable changes in gene expression to be longitudinally monitored in living animals using whole-body imaging. Using this approach we have been able to show that dietary regimes applied during pregnancy alter the epigenetic profiles and phenotypes of offspring. Careful examination of these reporter mice show that changes in DNA methylation and miRNAs expression likely underpin these effects. Similar models, applied to progressively track the expression of Utrophin and Dystrophin genes during development, implicate signalling pathways as useful targets for ameliorating conditions such as duchenne muscular dystrophy. Finally, to develop a better understanding of how signalling and diet interact, we developed luciferase reporters for Cyp1a1, a specific downstream target of aryl hydrocarbon receptor (Ahr). We will describe our current studies and future plans to generate autonomous bioluminescent reporters of AhR activity, as critical sensors of environmental change.

Human studies on gene environment interplay underlying mental disorders: Current status on possible transgenerational impact of traumatic stress via epigenetics

Bart Rutten | Maastricht University, The Netherlands

Exposure to psychological trauma is one of the most important and prevalent risk factors for mental and physical ill-health. While exposure to psychological trauma occurs in a large proportion of the general population, the majority of individuals does not develop overt signs or symptoms of ill-health, suggesting strong inter-individual differences in trauma susceptibility. Recent progress in epidemiological studies in the field of mental health has supported the notion that multiple environmental exposures co-exert their impact on mental and physical health, and work from our team has yielded a validated cumulative scores for the impact of environmental exposures, i.e. the so-called exposome, on a certain phenotypes, here schizophrenia. The biological mechanisms underlying differential susceptibility to the effects of environmental exposures on health are largely unknown, albeit that genetic and epigenetic variations have been proposed to moderate (and mediate) the relationship between exposures and the susceptibility to develop mental ill-health. At the molecular biological level, evidence indicates that exposure to shocking events (and related psychological trauma) can indeed affect gene expression and epigenetic profiles of exposed individuals and may even have biological and behavioral consequences on one or more generation of offspring of exposed individuals, in addition to the impact on well-being and behavior in the exposed individuals themselves. To date, (non-human) animal studies have provided quite robust evidence for this notion, while evidence from human studies is scarce. In the current presentation, our epidemiological human studies on gene-environment interactions in mental health (including the exposome score for schizophrenia) as well as longitudinal studies on epigenetic alterations in relation to exposures such as psychological trauma are presented and discussed. In addition, we will present our recently conducted review of the literature of human epidemiological studies on trans- and intergenerational epigenetic effects of trauma exposure. Taken together, the findings of these studies suggest that epigenetic regulation of several key physiological processes mediates the impact of psychological trauma on human health, while the current state of evidence on inter- and transgenerational transmission of the impact of psychological trauma in humans is hampered by the paucity of the performed studies and the complexities in research designs inherent in the subject of study. An outlook as well as critical reflection on these findings and their relevance for our biopsychosocial understanding of health and illness in a lifespan perspective will be provided.

Differential microRNAs and metabolites in the breast milk of mothers with adverse childhood experiences correlate with offspring temperament

Ali Jawaid | Lukasiewicz Research Network- PORT Polish Center for Technology Development, Poland

Adverse childhood experiences (ACE) can strongly impact the physical and mental health of individuals. Recent evidence further suggests that children born to mothers with a history of ACE are at an increased risk for behavioral and metabolic perturbations. In this study, we investigated the impact of maternal ACE on small RNAs and fatty acids (FAs) in the breast milk from a cohort of Polish mothers (n=103) and ascertained their association with early temperament of their children. Small RNA sequencing followed by qPCR assays were performed to compare small RNAs in the milk from lactating mothers with high vs. low ACE. Additionally, milk from mothers with high vs. low ACE were compared on the short-, middle-, and long-chain FAs content. Our study revealed distinct microRNA and FA signatures of ACE in human breast milk; with increased expression of miR-142-3p, miR-142-5p, and miR-223-3p and reduced levels of middle chain FAs (MCFAs) in the breast milk of mothers with high ACE. Furthermore, a positive correlation was observed between the milk expression of miR-142-3p, miR-142-5p, and miR-223-3p and the ACE score in the mothers. Finally, milk expression of miR-142-5p and MCFAs correlated with infant temperament at the age of 5 and 12 months. The observed associations were not confounded by symptoms indicative of postpartum depression in the mothers. In conclusion, this study newly reveals changes in milk miRNAs and FAs as potential signatures of ACE in humans and highlights their potential as predictors of intergenerational transmission of the effects of ACE.

The missing heritability of autism: Is epigenetic inheritance playing a role?

Jill Escher | Escher Fund for Autism, USA

As autism prevalence continues to rise, both advocates and government leaders are pressing for answers about risk factors. However, despite three decades of research to uncover genetic and environmental factors contributing to autism risk, the vast majority of cases, about 80%, remain idiopathic. Because autism is strongly heritable — based on high rates of twin concordance and sibling recurrence -- the field has largely assumed that the majority of autism risk lies in normally harmless common variants, even though autism GWAS investigations have largely come up empty. The presentation provides an alternative hypothesis for autism's strong heritability — that certain forms of toxicant-induced perturbation of parental germ cells can increase risk for transcriptional error during offspring early neurodevelopment, and ultimately, to brain and behavioral phenotypes associated with autism. Parental history of procedures under modern halogenated anesthesia serves as a model for this under-appreciated epigenetic inheritance paradigm.

*** The EMBO Lecture ***

Passage of epigenetic information through the mammalian germline

Petra Hajkova, MRC Laboratory of Medical Sciences, United Kingdom

Using mouse embryonic development as an experimental model, our long term interest is how epigenetic information is propagated during development and erased in the context of the germ line (zygotic and germline reprogramming). My laboratory has contributed fundamental insights regarding the mechanisms of global DNA demethylation, the connection to chromatin remodelling and the role of Tet enzymes in both zygotic and germline reprogramming events (Amouroux et al, Nat Cell Biol 2016, Hill et al, Nature 2018, Huang et al, Nature 2021). One of our core research interests is the epigenetic resetting that occurs in the gonadal foetal germ cells. In the course of this process, post-migratory primordial germ cells (PGCs) undergo a near complete erasure of DNA methylation, reshape their repressive histone modification and profoundly change their nuclear morphology and chromatin 3D structure. I will present our latest results addressing the molecular regulation at this epigenetically naïve state and our understanding of the potential mechanistic links between the germline epigenetic resetting and the meiotic competence.

Maternal diabetes programs sexually dimorphic early-onset cardiovascular dysfunction in metabolically healthy offspring

Qiaolin Deng | Karolinska Institute, Sweden

The incidence of cardiovascular disease (CVD) in young individuals is increasing. This alarming trend underscores the need to identify at-risk groups for preventive measures. Emerging evidence suggests that maternal diabetes increases the risk for metabolic diseases and early-onset CVDs in their offspring. However, the evidence is largely observational, limited by confounding factors and lacks crucial mechanistic insight. Here, we combined experimental, epidemiological and clinical approaches to disentangle the effects of maternal diabetes on offspring metabolism and endothelial function. In mice, we found that maternal hyperglycemia induces early-onset endothelial dysfunction specifically in male offspring, independent of metabolic disease. In humans, a case-control study and an epidemiological study confirmed elevated risk of early-onset endothelial dysfunction and related CVDs in metabolically healthy sons of mothers with type 1-diabetes. Our findings identify an underrecognized risk group for early-onset CVDs and emphasize the importance of maternal conditions in shaping the cardiovascular health of future generations.

Long-read sequencing to resolve gene cluster (epi)genetics

Lucia Daxinger | Leiden University Medical Center, The Netherlands

Metastable epialleles represent genomic loci where epigenetic states are established during early development and stably maintained, contributing to phenotypic variation independent of DNA sequence. Traditional bulk epigenetic assays often obscure the heterogeneity and allele-specific methylation patterns intrinsic to these loci. Single-molecule approaches, leveraging long-read sequencing technologies that simultaneously detect native DNA methylation and structural variation, now make it possible to examine these regions at unprecedented resolution. Here, I will highlight how we employ single-molecule methodologies to resolve these complex patterns and identify and characterize new putative metastable epialleles.

Epigenetic transmission of trauma-inducible glucocorticoid signalling within the male germline

Katharina Gapp | ETH Zurich, Switzerland

A host of studies have implicated disregulated corticosteroid levels in intergenerational effects relevant to neuropsychiatric phenotypes. While so far much emphasis has been put on dissecting non-coding RNA in the male germline as a mediator of these effects, it has become clear that they are not the sole transmitting signal. I will present an in depth analysis of stress hormone receptors in the male germline and early embryo focusing on their putative role in shaping chromatin in response to stress across generations. We will put our findings in perspective of a murine model of stress and its intergenerational phenotypic alterations and propose a novel mechanistic basis for intergenerational transmission of the effects of stress.

Epigenetic programming in the parental germlines and epigenetic inheritance

Satoshi Namekawa | University of California Davis, USA

A central question in the field of epigenetic inheritance is when and how heritable epigenetic states are established in parental germlines. In the male germline, progressive and dynamic chromatin remodeling leads to formation of haploid spermatids. Together with genome-wide changes in gene expression, we showed that the mitosis-to-meiosis transition accompanies the dynamic reorganization of epigenetic modifications. We are currently seeking to address how epigenetic regulation during spermatogenesis leads to the formation of functional gametes in ways that impact the next generation. In the female germline, reproductive lifespan is defined by long-lived, non-growing oocytes (NGOs) that comprise the ovarian reserve. We found that mouse NGOs possess abundant histone modifications that both underlie maintenance of the ovarian reserve and prime the epigenome of growing oocytes for early embryogenesis. Importantly, the Polycomb Repressive Complex 1 (PRC1) -driven epigenetic state of NGOs provides a bluerint for subsequent generation of a PRC2-catalyzed H3K27 trimethylation profile in growing oocytes that is characterized by broad domains and DNA methylation-independent imprints that are transmitted to the embryo.

Thus, Polycomb complexes play pivotal roles in priming the NGO epigenome for oocyte growth and early embryogenesis. Our research is uncovering epigenetic programming in the parental germlines that underlies epigenetic inheritance.

Small RNAs in male reproduction: spermatogenesis, sperm maturation and paternal influence

Pei-Hsuan Wu | University of Geneva, Switzerland

PIWI-interacting RNAs (piRNAs) are the most abundant small RNAs in the animal germline and are specialized for ensuring reproductive success in a wide range of animals. In mice and rats, piRNAs are uniquely required for and enriched in the male germline. Their crucial role in male fertility and spermatogenesis has been firmly established through decades of research and dozens of piRNA mouse mutants. However, an unexpected paternal phenotype observed in two mouse mutant lines carrying independent deletions of piRNA-producing loci on chromosome 6 and chromosome 18, respectively, raised new questions about piRNA functions. Embryos fertilized by mutant sperm lacking respective subpopulations of pachytene piRNAs developed poorly. Many of these embryos were delayed or arrested at various pre-implantation stages, suggesting a post-fertilization role of sperm-derived piRNAs. Using the pi6 mouse model, we investigated how transcriptome alterations in paternal mutant embryos led to this developmental phenotype. Our data revealed a specific and consistent disturbance in the typically highly coordinated timing of maternal transcript clearance and zygotic transcript production in one- and two-cell paternal mutant embryos. Notably, transcripts encoding proteins with mitochondrial localization were disproportionately affected. Together, our results suggest that a combinatorial effect of imbalanced maternal-zygotic transcript regulation and impaired mitochondrial function underlies the reduced developmental robustness of paternal mutant embryos. We propose that sperm-derived pachytene piRNAs impact embryonic fitness not by acting as binary switches but as fine-tuning modulators of embryonic transcriptome, thereby influencing early developmental robustness in mice.

Maternal metabolic health and fertility: caring about mother's and daughter's oocyte

Jo Leroy | University of Antwerp, Belgium

Disturbed maternal metabolic health, linked to eg. obesity and diabetes, drastically hampers fertility. More and more research confirms the central role that oocyte quality plays in this subfertility problem, as the female gamete is very sensitive to alterations in its micro-environment. Metabolic stress conditions are often characterized by upregulated lipolysis and together with fat rich diets this may induce lipotoxicity at the follicular level. This provokes oxidative stress and mitochondrial dysfunctions. We showed that such mitochondrial dysfunctions may alter the genome wide methylation patterns in the subsequent embryos and thus may alter metabolic programming. Embryos that do survive have a lower potential to induce the pregnancy recognition in the uterus. In strategically designed obese (outbred) mouse models we found that an obesogenic diet has the potential to almost double the oocyte lipid content after already 24h of feeding. Mitochondrial morphological abnormalities only became apparent after 6 weeks on the diet and granulosa cell transcriptome responses were multiphasic, depending on the duration of feeding. A very recent project from our research team focused on mitochondrial morphological features in primordial and primary follicles in adult mice. We could clearly confirm the negative impact of obesity on these dormant or freshly activated follicles. This may partly explain why obese mice that were submitted to a diet normalization preconception care intervention for 6 weeks displayed improved oocyte features, however, some mitochondrial morphological aberrations clearly stayed apparent. Finally, an intergenerational study indicated for the first time that there may be an additive negative effect of the maternal obesogenic background on the impact of the offspring high fat/high sugar diet on mature oocyte mitochondrial features. However, this was not translated in reduced mitochondrial function. For sure, much more research is needed on how the maternal health around conception can shape the newly formed embryo and the health of the next generation.

The molecular mechanisms and biological impacts of epigenetic transgenerational inheritance

Michael Skinner | Washington State University, USA

Epigenetic transgenerational effects of environmental factors such as toxicants, diet and stress significantly amplify the biological impacts and health hazards of these exposures, as well as influence future generations. One of the most sensitive periods to exposure is during fetal gonadal sex determination when the germ line is undergoing epigenetic programming and DNA methylation alterations. Previous studies have shown that toxicants (e.g., Glyphosate, DDT, Vinclozolin) can transgenerationally increase in adults the onset of disease such as infertility, prostate, ovary and kidney disease, cancers and obesity. Interestingly, these effects are transgenerational (F1, F2, F3 and all further generations) due to a permanent (imprinted-like) altered epimutations in the germline. The transgenerational epigenetic mechanism involves the actions of an environmental compound at the time of sex determination to permanently alter the epigenetic (e.g., DNA methylation) programming of the germline that then alters the embryo stem cells to alter all epigenomes of all developing somatic cells and organs to induce disease susceptibility and development transgenerationally. In addition to DNA methylation, alterations in sperm ncRNAs and histone modifications and retention have also been observed. A variety of different environmental compounds have been shown to induce this epigenetic transgenerational inheritance of disease, including: fungicide vinclozolin, plastics BPA and phthalates, pesticides, DDT, dioxin, hydrocarbons and herbicides like atrazine and glyphosate. Interestingly, exposure specific epigenetic alterations were observed between the specific toxicants. Recently we have identified in human's epigenetic biomarkers for parental germ cell transmission of offspring disease states such as infertility, autism, and arthritis. These epigenetic biomarkers can be used in preventative medicine. The suggestion that environmental exposures (e.g., toxicants) can reprogram the germline to induce epigenetic transgenerational inheritance of disease is a novel non-genetic paradigm in disease etiology, toxicology, and evolutionary biology that needs to be considered in the future.

Mechanism of epigenetic reprogramming in the human germ line

Mitinori Saitou | Kyoto University, Japan

The germ-cell lineage ensures the creation of new individuals, perpetuating/diversifying the genetic and epigenetic information across the generations. We have been investigating the mechanism for germ-cell development, and have shown that mouse embryonic stem cells (mESCs)/induced pluripotent stem cells (miPSCs) are induced into primordial germ cell-like cells (mPGCLCs) with a robust capacity for both spermatogenesis and oogenesis and for contributing to offspring. These works have served as a basis for elucidating key mechanisms during germ-cell development such as epigenetic reprogramming, sex determination, meiotic entry, and nucleome programming. By investigating the development of cynomolgus monkeys as a primate model, we have defined a developmental coordinate of pluripotency among mice, monkeys, and humans, identified the origin of the primate germ-cell lineage in the amnion, and have elucidated the X-chromosome dosage compensation program in primates. Accordingly, we have succeeded in inducing human iPSCs (hiPSCs) into human PGCLCs (hPGCLCs) and elucidated the mechanism of human germ-cell specification, demonstrating that the mechanisms for germ-cell specification are evolutionarily divergent in many aspects between humans and mice. Furthermore, we have demonstrated an ex vivo reconstitution of fetal oocyte development in humans and monkeys, and an in vitro induction of fetal meiotic oocytes from ESCs in monkeys. More recently, we have established a robust strategy for inducing epigenetic reprogramming and differentiation of hPGCLCs into mitotic pro-spermatogonia or oogonia, coupled with their extensive amplification (˜>1010-fold). These studies have established a foundation for human in vitro gametogenesis. Here, I will discuss our latest findings on the mechanism of epigenetic reprogramming in the human germ line.

Social adversity as a strategic research site for social sciences and epigenetics

Michel Dubois | University of Sorbonne, France

After briefly reviewing current knowledge on the public circulation of epigenetics, this presentation will turn to the reasons why social scientists should treat social adversity as a strategic interface with the life sciences. I argue that social adversity—conceived as the cumulative effects of chronic stress, deprivation, and marginalization—offers a particularly productive site for interdisciplinary collaboration. Epigenetic studies of early-life adversity or "social defeat" provide a unique opportunity for sociologists to explore how social experiences become biologically embedded. Drawing on recent multidisciplinary research initiatives, we will reflect not only on the insights generated through such collaborations, but also on the methodological and epistemological challenges they pose.

POSTERS

Posters marked with * were selected for short or flash talks

*P1 Allard P. Understanding the metabolo-epigenetic rules underlying environmental epigenetic alterations

P2 Berezenko A et al. Not all eggs are the same: Maternal RNA variability in the face of heat stress

P3 Buchbut R (...) and Zaidan H. Social isolation in adolescence alters offspring social behavior and germline Crhr1/miR-34c expression: a four-generation study

P4 Cardamone F et al. Chromatin landscape at cis-regulatory elements orchestrates cell fate decisions in early embryogenesis

*P5 Chakraborty S, Anand S and Bhandari RK. Reversal of environmentally induced transgenerational epimutations in the germline and soma

*P6 Cohen-Woods S et al. Footsteps of our fathers: Sperm DNA methylation and early-life stress in men

P7 Eynard SE et al. Modelling genetic and epigenetic selection signatures from pool sequencing

P8 Farooq S et al. Paternal epigenetic association with infant birthweight and transmission of epigenetic signatures

P9 Feudjio O et al. Epigenetics and alternative splicing: Unraveling gene regulation during spermatogenesis

*P10 Fischer V et al. Chronic stress response induces long-term non-genetic changes in fathers and predicts offspring phenotype

P11 Fratini F et al. From linear genetic determinism to complex epigenetic responsibility: an urgent paradigm shift in the increasing pandemic of neurodevelopment spectrum disorders

*P12 Gomółka M et al. The role of lipid metabolism and circulating miRNAs in the intergenerational transmission of the effects of parental adverse childhood experiences

P13 Gozzo A. Embryonic metabolism is controlled by paternal Argonaute proteins and sperm-borne mitochondrial small RNA

P14 Iashvili N. Multimodal assessment of cardiac interoception: Behavioral and electrophysiological evidence in healthy adults

P15 Islam S. Tet-assisted SMRT sequencing for strand-specific detection of 5mC

P16 Ivanova I et al. Investigating germline effects of paternal trauma on offspring behavior

P17 Iversen J. Exposure to childhood maltreatment is associated with specific epigenetic patterns in sperm

P18 Javadinia Seyed A et al. Cancer epigenetics: From laboratory studies and clinical trials to precision medicine

P19 Karami K et al. Using the transmissibility model to demonstrate transgenerational transmission of environmental effects in quails

P20 Kishida T and Mazda O. Epigenetic inheritance of allergic predisposition in mice

*P21 König L (...) and Schaefer MR. Copy number determination of small RNAs in mature mouse sperm involved in the intergenerational inheritance of metabolic syndromes

*P22 Laasanen S et al. Intergenerational effects of paternal HFD on germline RNAs and metabolic health can be altered by obesity treatment

P23 Lai WS. Environmental maternal effect and intergenerational inheritance

P24 Le Cléac'h J et al. Epigenetic evidence of stress-driven aging in monozygotic twins

P25 Longster R, Frei S et al. The long-term effects of short-term stress

*P26 Lu H et al. Epigenetic transgenerational germline inheritance of polycystic ovary syndrome

*P27 Minabe S et al. Mapping the human epigenetic landscape across three generations: A DNA methylation resource from TMM BirThree

*P28 Murashov A et al. Inherited metabolic imprints–or the mitochondrial memory of lifestyle?

P29 Nagni R et al. From pluripotency to germ cells and back: Modeling intergenerational epigenetic dynamics in a dish

P30 Nickel T (...) and Bhandari RK. Epigenetic aging of the liver due to direct and ancestral exposure to Bisphenol A

*P31 Rachamalla M and Niyogi S. Transgenerational neurotoxicity of Arsenic in zebrafish: Mechanistic insights into cognitive deficits and epigenetic alterations

*P32 Rousse S et al. Transmission of DNA methylation: genetic or epigenetic? A transgenerational case study in quails

P33 Saleh A. The biophysical mechanism underlying epigenetically inherited stress response/unpredictability learning

*P34 Samavat MS (...) and Stornaiuolo M. Sperm-derived lipids as epigenetic drivers of intergenerational inheritance: Shaping early empbryonic development and disease susceptibility

P35 Scherer Fernandez B and Scherer Fernandez J. Imagery rehearsal therapy and self-talk in trauma-exposed active-duty soldiers in Ukraine: A randomized controlled trial

P36 Schöpp T, Arzate R and Mansuy I. From germline to soma with Parse: Matched high-resolution transcriptomes with single-cell precision across tissues

P37 Schroeder R, Diniz E and Fischer A. Circulating miRNAs in neurodegenerative and neuropsychiatric diseases: A systematic review and meta-analysis

*P38 Steg L et al. From sperm to embryo: Allele-resolved evidence for miRNA-mediated effects on the maternal transcriptome

*P39 Stucchi S et al. The impact of chemical exposures across generations: Integrating human epidemiology with in vitro modelling and causal models of epigenetic inheritance

P40 Walters B. KDM6A loss in the mammalian paternal germline alters COMPASS-mediated histone methylation and predisposes offspring to cancer

P41 Wasson JA. Social regulation of intergenerational signaling via a defined chemosensory pathway

P42 Zaidan H et al. Non-coding RNA changes in adolescent stress-exposed female rats and their offspring

P43 Zhao A et al. Maternal type 1 diabetes programs sex-dimorphic liver-associated metabolic dysfunction in offspring

POSTER ABSTRACTS

Posters marked with * were selected for short or flash talks

*P1 Understanding the metabolo-epigenetic rules underlying environmental epigenetic alterations

Patrick Allard | University of California Los Angeles, USA

The overarching goal of our research is to understand how environmental cues trigger a deregulation of the epigenome that can resist epigenetic reprogramming in germ cells and therefore can become heritable. We will focus our presentation mainly on the model epigenetic toxicant inorganic arsenic (iAs). Inorganic arsenic (iAs) is a model epigenetic toxicant owing to its impact on global DNA hypomethylation coinciding with a reduction in the levels of the universal methyl donor SAM, used towards DNA and histone methylation. iAs is also a chemical with well-established transgenerational epigenetic inheritance effects, producing heritable reproductive and metabolic dysfunctions and neurobehavioral outcomes for multiple generations. However, iAs shows remarkable complexity in its epigenetic impact since even in the context of global DNA hypomethylation, some loci show hypermethylation and the effect on histone methylation are non-uniform with many methylated histone marks showing increases while others show a decrease. It is unclear how iAs causes such varied epigenetic effects and how these effects are maintained during developmental reprogramming. Here, we will present our most recent data linking comprehensive metabolic, epigenetic, and gene expression datasets that allow us to determine the key drivers behind DNA and histone locus-specific methylation events in response to arsenic exposure.

P2 Not all eggs are the same: Maternal RNA variability in the face of heat stress

Anastasiia Berezenko, Dragan Stajic, Simone Oberhaensli, Irene Adrian-Kalchhauser | University of Bern, Switzerland

Epigenetic inheritance - the inheritance of genome activity and accessibility states without changes in the underlying DNA sequence – has been observed across the tree of life. It is postulated to facilitate adaptation to rapidly changing environmental conditions, thereby promoting population evolution and survival.
Among the various molecular mechanisms mediating epigenetic inheritance, we study maternally provided RNA. Deposited directly into the oocyte, it orchestrates early embryonic development before the transition from maternal to zygotic control (MZT). Importantly, maternal RNA also exhibits variable components, e.g., in Ciona intestinalis [Sato A, et al. BMC Ecol Evo 2024], Neogobius melanostomus [Adrian-Kalchhauser I, et al. BMC Evol Biol 2018], or Drosophila melanogaster [Petkova MD, et al. Current Biology 2014]. We hypothesize that variability in maternal RNA, and thus among offspring, is a) inducible, e.g., increased under stressful or novel conditions, and b) affects offspring phenotypes. Together, this would allow for between-offspring diversification under stressful conditions and support population survival through a bet-hedging approach. We therefore aimed to determine the extent of maternal RNA variability in zebrafish oocytes under optimal versus heat-stressed conditions. Using single-egg RNA sequencing, we investigate the impact of heat shock on maternal RNA composition immediately after heat shock, at multiple recovery time points, and in downstream generations. We find a multi-layered response that includes directional effects (e.g., heat-shock genes), between-mother variability, and an effect of treatment on between-offspring variability on a global and a gene-specific scale. Together, our results support that diversification should be considered alongside directional effects when studying epigenetic inheritance. We therefore hope our findings will inspire investigations into aspects of variability and changes thereof in the context of epigenetic inheritance.

P3 Social isolation in adolescence alters offspring social behavior and germline Crhr1/miR-34c expression: a four-generation study

Rachel Buchbut, Ilya Dobrovinsky, Muntaha Karakra, Revital Eyzenberg, Hiba Zaidan, Inna Gaisler-Salomon
University of Haifa Israel

Social stress, particularly during adolescence, has long-term behavioral and physiological consequences. The impact of stress in peri-adolescent rodents on germline epigenetic and offspring phenotypes and offspring phenotypes has mostly been studied in males. Specifically, the impact of pre-reproductive social stress in adolescent female rodents on oocyte microRNA and subsequent offspring phenotypes remains largely unexamined. We exposed adolescent female rats (F0) to Social Isolation (SI) stress, and mated their male F1 and F2 offspring with naïve females to produce the F2 and F3 generations. A separate group of rats was exposed to metabolic stress, i.e., Food and Water Deprivation (FWD), to control for non-social stress effects. In exposed females, both SI and FWD induced anxiety-like behavior and elevated Crhr1 mRNA expression in the nucleus accumbens, but SI alone caused depression-like behavior, and increased blood corticosterone, BDNF and oxytocin as well as hypothalamic oxytocin receptor expression. Pre-reproductive SI in F0 females sex-dependently altered social recognition and brain Crhr1 expression in F1 and F2 offspring. No SI-induced effects were observed in F3. Notably, while SI stress had no impact on maternal care, it uniquely impacted miR-34c expression in oocytes of exposed females and in sperm of their stress-naïve F1 offspring. These findings highlight the direct and transgenerational impact of the social environment during adolescence on germline, brain transcriptional patterns and behavioral phenotypes, and support the role of miR-34-c in transgenerational transmission of social stress.

P4 Chromatin landscape at cis-regulatory elements orchestrates cell fate decisions in early embryogenesis

Francesco Cardamone, Annamaria Piva, Eva Löser, Bastian Eichenberger, Mari Carmen Romero-Mulero, Fides Zenk, Emily J Shields, Nina Cabezas-Wallscheid, Roberto Bonasio, Guido Tiana, Yinxiu Zhan, Nicola Iovino
Max Planck Institute, University of Freiburg, CIBSS, Germany; IRCCS, INFN, Italy; EPFL Lausanne and ETH Zurich, Switzerland; University of Pennsylvania, Perelman School of Medicine, USA

The establishment of germ layers during early development is crucial for body formation. The Drosophila zygote serves as a model for investigating these transitions in relation to the chromatin landscape. However, the cellular heterogeneity of the blastoderm embryo poses a challenge for gaining mechanistic insights. Using 10x Multiome, we simultaneously analyzed the in vivo epigenomic and transcriptomic states of wild-type, E(z)-, and CBP-depleted embryos during zygotic genome activation at single-cell resolution. We found that pre-zygotic H3K27me3 safeguards tissue-specific gene expression by modulating cis-regulatory elements. Furthermore, we demonstrate that CBP is essential for cell fate specification functioning as a transcriptional activator by stabilizing transcriptional factors binding at key developmental genes. Surprisingly, while CBP depletion leads to transcriptional arrest, chromatin accessibility continues to progress independently through the retention of stalled RNA Polymerase II. Our study reveals fundamental principles of chromatin-mediated gene regulation essential for establishing and maintaining cellular identities during early embryogenesis.

*P5 Reversal of environmentally induced transgenerational epimutations in the germline and soma

Sourav Chakraborty, Santosh Anand, Ramji K. Bhandari | University of Missouri, USA

Epigenetic inheritance of environmentally and lifestyle-induced phenotypes has been demonstrated in many model organisms in a laboratory setting, suggesting that current generations could be harboring ancestral environmental/diet exposure-induced molecular memories or future generations may carry such memories due to exposure of the current generation. It is essential to develop strategies to correct transgenerational abnormalities before they are transferred to offspring via germline transmission or to block the heritable pathways leading to the abnormal health phenotype before they induce the disease.

*P5 Continued
Nevertheless, such strategies are yet to be developed. As a proof of concept, using medaka fish as an aquatic model organism of human health, we investigated whether the environmentally induced transgenerational non-alcoholic fatty liver disease (NAFLD) can be reversed by epigenetic modifier treatments. Ancestral bisphenol A (BPA) exposure caused transgenerational NAFLD leading to nonalcoholic steatohepatitis (NASH) at F2 generation, which persisted for five generations. DNA methylation profile of the F0&F1 paternal sperm predicted the DNA methylation and transcriptional landscape of the F2 offspring liver revealing distinct pathways associated with NAFLD. A treatment of the diseased fish with a weak epigenetic modifier resulted in: 1) A reversal of NAFLD phenotype to normal, 2) Correction of the majority of BPA-induced DMRs, irrespective of their methylation status, and 3) restoration of transcriptional network comparable to that in untreated controls. The present results suggest that low-concentration nutritional epigenetic modifiers may be useful for correcting EDC-induced transgenerational epimutations in parental germline and liver injury in offspring. Results open avenues for further research towards understanding the role of epigenetic landscape in metabolic health and disease and the mitigation of this multifactorial metabolic disease in humans.

*P6 Footsteps of our fathers: sperm DNA methylation and early-life stress in men
Sarah Cohen-Woods, T Trebilco, S Antoniades, R Laattoe, W Song, J Perrott, S Wong, H Newman, A Bowshall, N Kamal, W Ledger, A Storr | Flinders University and University of New South Wales, Australia
Childhood stress affects both individuals throughout their lives, and their children. The mechanism of this intergenerational transmission has been suggested to be epigenetic. Whilst evidence for pre-conception stress induced inter- and transgenerational epigenetic changes are reported in rodents, a mechanism in humans has not been established. Only gametes can transmit genetic information across generations, and investigation is humans is necessary. The aim of this study is to investigate DNA methylation in sperm DNA in relation to early-life stress exposures of men. Sixty-four men recruited from Flinders Fertility clinic (mean age=35.6, stdev=5.2) completed in-depth psychological questionnaires including childhood stress (CTQ). Excess sperm from the in-vitro fertilization (IVF) treatment underwent swim-up and was pelleted, snap-frozen, and transferred to -80C storage. DNA was extracted from the sperm pellets, and DNA methylation measured with the Infinium MethylationEpic BeadChip (Illumina), controlling for age, body mass index, and sperm concentration and motility. Reduced DNA methylation at one cg site was genome-wide signficant ($p<5x10-8$) with elevated childhood maltreatment at the genome-wide significance level, within the LOXL2 gene, an epigenetic regulator. A further 107 CpG sites yielded p-values at the suggestive level ($p<5x10-5$), but showed no enrichment in gene ontology networks. This study is one of the largest studies to date that correlates early-life stress with sperm DNA methylation. We present some evidence for dysregulated DNA methylation. If this translates to dysregulated systems in the next generation needs to be investigated; the FEEL cohort is unique with potential to recontact participants to follow-up findings in children.

P7 Modelling genetic and epigenetic selection signatures from pool sequencing
Sonia E Eynard, Kossi-Julien Kowou, Cécile Donnadieu, Loïc Flatres-Grall, Carole Iampietro, Sandrine Lagarrigue, Sophie Leroux, Joanna Lledo, Marie-José Mercat, Juliette Riquet, Céline Vandecasteele, Frédérique Pitel, Bertrand Servin | INRAE, AXIOM, Alliance R&D, IFIP-Institut du porc, France
Natural or artificial selection drives genome evolution but what is the effect of selection on epigenetic marks through time? In the context of animal production it appears crucial to be able to integrate factors driven by the environment in our standard selection models, especially knowing the challenges that we now face: adaptation to climate change, evolution of breeding conditions, animal resilience, health, welfare, reduced resource use and environmental impact. Livestock species, bred under controlled conditions, traced throughout history for many generations and of large census population size, offer a unique opportunity to describe the evolutionary trajectory of genetic and epigenetic patterns over time. In this study, we analysed sperm coming from 15 generations of selection for a sino-european pig breed.

P7 Continued
Both genetics and epigenetics information were obtained through Oxford Nanopore Technology (ONT) sequencing, providing about 8 millions genetic variants and about 20 millions CpGs sites with high coverage (>30X). Using a model of Hidden Markov Models for the evolution of allele frequencies we identified genetic regions for signature of selection in the breed. In addition, we identified differentially methylated regions across generations. We are now developing a statistical framework to analyse the evolution patterns of CpGs islands, with the aim to identify selection signatures on epigenetic marks. We aim to correlate genetic and epigenetic selection signatures to identify regions where epigenetic changes are driven by genetic changes or independent of them, the latter revealing epigenetic inheritance associated with selection. This study will contribute to a better understanding of the evolution of epigenetic marks throughout time and its relationship with selection. Our results will contribute to a more accurate accounting for environmental variation in selection decisions.

P8 Paternal epigenetic association with infant birthweight and transmission of epigenetic signatures
Saad Farooq, Zehra Jamil, Asad Ali | The Aga khan University, Pakistan
Low birthweight infants are at increased risk of mortality and chronic conditions in later life. The concept of Paternal Origins of Health and Disease (POHaD) focuses on the significance of paternal health in embryonic development, offspring growth and long term health outcomes. There is a lack of evidence regarding paternal contributions to birthweight through epigenetic mechanisms. We explored the association of paternal epigenetic signatures with children's birthweight and potential biological pathways involved. This exploratory study also aimed to analyze the DNA methylation and Gene expression differences in full-term low birthweight (FT-LBWs) compared with those in normal birthweight infants (FT-NBWs) whose parents had no medical complications and were nonsmokers. Cord blood, placenta and parents' blood samples were collected from 100 families, DNA and RNA isolation were performed. Genome-wide DNA methylation analysis was performed using Illumina's MethylationEPICv2 BeadChip array which targets ~935,000 CpG sites. RNA seq was performed and Differentially Expressed Genes (DEGs) were identified. Weighted gene co-expression network analysis (WGCNA) was utilized to build a gene co-expression network, the most significant module and its hub genes were identified. The gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were performed. Gene set enrichment analysis performed on RNA seq data in both parents and infants revealed pathways that appeared to be significantly associated with ribosome and ribosome biogenesis in eukaryote, suggesting its possible role in development. Enrichment analysis performed on the gene modules most correlated with birthweight identified few interesting hub genes in father and infant. We could not find any significant association between father methylome and infant birthweight. However, investigating methylation sites present on DEGs may give us an understanding of DNA methylation in regulating genes responsible for birthweight.

P9 Epigenetics and alternative splicing: Unraveling gene regulation during spermatogenesis
Olivier Feudjio, Manon Coulée, Marion Crespo, Delphine Pflieger, Julie Cocquet | Adlin Science, Université Paris Cité, EDyP laboratory - CEA Grenoble, France
The regulation of gene expression in eukaryotic cells involves various mechanisms, including dynamic histone post-translational modifications, DNA methylation, and alternative splicing (Zhang Y. et al. 2021; Jones PA et al., 2013). Epigenetic marks have been suggested to act in a combinatorial way to regulate splicing (Agirre et al., 2021). Spermatogenesis is a differentiation process that includes the mitotic proliferation of spermatogonia, meiotic division of spermatocytes and post-meiotic spermatid differentiation. This process is characterized by one of the highest transcriptome and proteome complexity (Soumillon M. et al., 2013), as well as dynamic chromatin remodeling (Vara et al., 2019). It therefore serves as an ideal model to study the interplay between epigenetic marks and alternative splicing. It is also particularly relevant to better understand the causes of male infertility since splicing factors and RNA-binding proteins (RBPs) are essential

P9 Continued
for male fertility and the dysregulation of splicing in some spermatogenic genes results in male infertility (Tao et al., 2024). This project investigated the relationship between alternative splicing and epigenetic modifications by analyzing RNA-seq and ChIP-seq data from spermatogenic cells with bioinformatic tools. Studying alternative splicing during spermatogenesis revealed its dynamic nature, with the mitosis-to-meiosis transition showing the most splicing events and the meiosis II to post-meiosis transition the fewest. Studying epigenetic regulation of splicing showed that histone marks like H3K79me2 and H3K36me3 were linked to spliced exons, while H3K27me3 and H3K9me3 were associated with retained introns during the mitosis-to-meiosis transition. In male germ cells, conditional Dot1l knockout, which reduces H3K79 methylation, has been linked to hypo-spermatogenesis, gene deregulation, and altered chromatin organization (Blanco et al., 2023). However, its effect on alternative splicing during spermatogenesis remained unexplored. Since differentially spliced exons in leukemia cells are enriched in this PTM (Li et al., 2018), I also investigated the impact of Dot1l knockout on alternative splicing. Surprisingly, knocking out Dot1l did not result in significant splicing deregulation in spermatogenic cells. Splicing during spermatogenesis, especially at the mitosis-to-meiosis transition, is associated with epigenetic marks. H3K79me2 and H3K36me3 are linked to spliced exons, while H3K27me3 and H3K9me3 are associated with retained introns. Interestingly, knocking out Dot1l, which reduces H3K79 methylation, did not significantly affect splicing. This suggests that H3K79 methylation primarily influences gene expression and chromatin structure rather than splicing directly. Understanding these mechanisms could also provide insights into diseases like cancer and neurodegeneration, where splicing defects and epigenetic changes are also involved. Support Financier: ANR CHROMATOZOA (to J. Cocquet), ANR CHROMACYL (to D.Pflieger and J. Cocquet), CIFRE N°2022-0803, ADLIN Science (to M. Crespo)

*P10 Chronic stress response induces long-term non-genetic changes in fathers and predicts offspring phenotype
Vincent Fischer, Miriam Kretschmer, Iryna Ivanova, Philipp Kohling, Selina Frei, Pierre-Luc Germain, Katharina Gap | ETH Zurich, Switzerland
While moderate levels of stress are fundamental for an organism's survival, excessive or repeated stress can have detrimental effects on brain function, behavior, and an increased risk for developing neuropsychiatric diseases. Behavior is influenced by hormones, including glucocorticoids, that are secreted upon stress. Chronic stress can impact the release of those hormones and change brain properties, such as gene expression and morphology. However, research shows animals are not equally affected by the same stress. The consequences of persistent stress and varying responsiveness to it are not only constrained to the perturbed generation, but also can extend to the next generation through epigenetic mechanisms. Here, we demonstrate that chronic stress disrupts hormonal levels, the behavior, the sperm epigenome, and gene expression in the hippocampus of stressed mice. Furthermore, we report altered physiological, behavioral, and molecular phenotypes in the offspring, induced by paternal stress, which cannot be explained by genetics.

P11 From linear genetic determinism to complex epigenetic responsibility: an urgent paradigm shift in the increasing pandemic of neurodevelopment spectrum disorders
Federica Fratini, Annamaria Porru, Ernesto Burgio, Daniela Lucangeli | Italian National Health Institute, University of Padova Italy; European Cancer and Environment Research Institute, Belgium
Neurodevelopmental disorders (NDD) impairs synaptogenesis and neural network formation mainly affecting the prefrontal cortex and the amygdala, thus influencing social, cognitive, emotional, language, learning, memory, motor, or executive functioning skills. NDD have long been considered primarily genetic in origin. However, the striking and persistent rise in their prevalence over recent decades, joined with the high rates of comorbidity across several psychiatric disorders, and most importantly, advances in the understanding of epigenetics mechanism and inheritance, supported by the huge development of -omics sciences, have resulted in a fundamental paradigm shift from linearity to complexity, from nodes to edges.

P11 Continued

A neuro-bio-psycho-social approach aim to model the relationships and regulatory logic within the genome, recognizing that a change in one gene or an epigenetic mark (a „node“) is often significant because of how it alters its interaction („edge“) with other regulatory elements or genes, thereby perturbing the entire network. In the scientific understanding of neurodevelopmental conditions there is strong evidence that genetic factors cannot be the unique determinants, rather epigenetic mechanism serve as crucial interaction's mediators in a complex dynamic interplay of genetic predisposition, neurobiological pathways and environmental influences. This perspective fundamentally shifts the understanding of multi-comorbidity from a chance of co-occurrence to a manifestation of shared neurodevelopmental vulnerabilities. The „spectrum“ concept, now central to NDD classification, represents a fundamental shift in psychiatric nosology, emphasizing the continuum of symptoms and functional impacts and encouraging clinicians to think dimensionally. Not only we now need to consider the complexity of the feed-back loop interactions among many different molecules involved in any cellular pathway (nuclei acids, proteins, lipids, metabolites), but of this complex network - which represents a huge challenge for deep learning and AI based bioinformatics - we now understand that more than nodes, are fundamental the dynamics of the edges and the communication strategies of molecular transports, like the increasing field of investigation represented by the small extracellular vesicles. This amazing structural dynamics is shaped by the lifespan continuous interchange with environmental factors, it is mirrored in the epigenome and it is potentially inherited for three generations. Besides the serious impact of chemical and physical transformations of our environment; cultural and structural forms of systemic social violence and injustice (poverty, wars, gender discrimination, racism, alcohol-drug-device addictions, employment-instability, hate-speech and violent content perfusion by TV, social media and video games, etc.) determine high psychological-emotional-physical stress or traumas. Environmental factors and childhood trauma interact with genetic predispositions to influence the onset and severity of neurodevelopmental spectrum disorders and mood spectrum disorders, which both represent a growing significant public health challenges and social responsibility for the present and future generations. In our study we aim to examines the evolving scientific understanding of these globally alarming conditions and the impact of “educational intervention” to take advantage of epigenetic reversibility especially for children. Emerging scientific evidence of the positive effects of educational best practise over NDD supports the concept that epigenetics and epigenetic inheritance become a new concept not only in biology and medicine but also in education, which bridges internal brain mechanisms and external environmental factors, giving to all involved stakeholders at the same time huge responsibilities and possibilities. In synthesis, the science of complexity, and in particular epigenetic inheritance, asks for a focus on the working structure of the interaction network between intervening players, abandoning the search for a specific culprit.

*P12 The role of lipid metabolism and circulating miRNAs in the intergenerational transmission of the effects of parental adverse childhood experiences

Magdalena Gomółka, Weronika Tomaszewska, Sandra Binias, Regina Nadalinska, Ali Jawaid | Łukasiewicz Research Network PORT, Nencki Institute of Experimental Biology PAS, Poland

Childhood trauma is an important risk factor for psychiatric and physical ailments during adulthood. Emerging evidence suggests that some of its behavioural and metabolic symptoms are transmissible across generations. Intergenerational transmission of the effects of trauma is postulated to involve changes in germline non-coding RNAs. However, it is unclear how childhood trauma affects ncRNAs in the gametes. Circulating ncRNAs, such as miRNAs, majorly carried by lipid-associated factors in the body fluids, appear as important candidates for carrying the trauma effects to the gametes for intergenerational transmission. Synergizing investigation in a mouse model of ACE induced via unpredictable maternal separation and unpredictable maternal stress (MSUS) and cross-injection studies, we hypothesize that lipid-associated miRNAs communicate the effects of ACE to the germline for intergenerational transmission. Intergenerational behavioral and metabolic phenotyping was performed, supplemented with small RNA sequencing followed by qPCR. Cross-injections of lipid-associated carriers into the tail vein of mice performed.

*P12 Continued
Offspring of both MSUS- and HFD-exposed male mice showed impaired glucose tolerance, depressive-like behaviour and anxiety. Cross-injections from MSUS into CTRL mice prolonged the offspring latency to enter open arms in Elevated Plus Maze test. Cross-injections from MSUS into CTRL mice recapitulated the offspring metabolic phenotype associated with MSUS in Glucose tolerance test. Cross-injections from VE mice into MSUS mice partially mitigated the metabolic MSUS phenotype. Injections of MSUS-material is sufficient and necessary to induce the intergenerational metabolic phenotype associated with MSUS while lipid-modifying interventions can potentially alter the intergenerational metabolic MSUS phenotype. This research provides proof-of-concept for a role of lipids and circulating miRNAs in communicating the effects of ACE to the germline for intergenerational sequelae.

P13 Embryonic metabolism is controlled by paternal Argonaute proteins and sperm-borne mitochondrial small RNA
Alessandro Gozzo | Linköping University, Sweden
The paternal germline serves as a repository of intricate genetic information, contributing to shaping the development and fitness of the offspring. Beyond transmitting genomic DNA, spermatozoa also carry small non-coding RNAs (sncRNAs). These undergo notable shifts during spermatogenesis, resulting in a highly specific mature sperm sncRNAs profile. Among these, mitochondrial-derived small non-coding RNAs (mitosRNAs) represent a poorly understood class yet are abundant in the male gonads. We characterize Drosophila sperm mitosRNAs, finding the majority mapping to piRNAs, exhibiting similar lengths and nucleotide biases. Previously, we showed the plasticity of sperm mitosRNAs in response to diet. Using RNA interference experiments we now prove Piwi and Aubergine involvement in the biogenesis of mitosRNA and finally, find mitosRNA to be involved in the intergenerational metabolic reprogramming of the early embryos.

P14 Multimodal assessment of cardiac interoception: Behavioral and electrophysiological evidence in healthy adults
Nino Iashvili | National Research University Higher School of Economics, Russia
This study investigates cardiac interoception through a multimodal framework that integrates behavioral and neurophysiological measures. Eighteen healthy adults completed three interoception tasks—the Heartbeat Counting Task (HCT), Button-Press Task (BPT), and Auditory Feedback Task (AFT)—during simultaneous electrocardiography (ECG) and electroencephalography (EEG) recording. HCT accuracy was significantly higher than BPT ($p = 0.005$), with strong correlation between the two ($r = 0.66$, $p = 0.003$), supporting their convergent validity. EEG-derived heartbeat-evoked potentials (HEPs) were amplified in high-performing individuals, particularly over frontal-central regions. Task performance was further modulated by individual biological variables such as sex and fat mass. Beyond validating these interoceptive tasks, the findings offer insights into how bodily self-awareness interacts with stress regulation systems. While interoceptive sensitivity has not been traditionally classified as an epigenetic trait, growing evidence suggests it may influence, and be influenced by, stress-responsive systems—such as the HPA axis and autonomic nervous system—which are themselves subject to epigenetic modulation. Thus, interoception may serve as an embodied interface where lived experiences become biologically embedded. Importantly, such embodiment does not occur in isolation. Cultural norms around emotion, body awareness, and caregiving shape the development of interoceptive abilities and may either reinforce or buffer stress-related epigenetic changes. This suggests that interoception is a culturally sensitive mediator between environment and biology—one that co-regulates emotional resilience, psychosomatic health, and potentially transmits adaptive or dysregulated stress patterns across generations. These findings support a broader view of emotion regulation as both a biologically grounded and socially shaped process.

P15 Tet-assisted SMRT sequencing for strand-specific detection of 5mC

Shariful Islam | LMU München, Germany

DNA methylation at CpG dinucleotides is a key epigenetic mark in mammals, playing a crucial role in regulating gene expression. While bisulfite sequencing (BS) is the gold standard for methylation analysis, it cannot capture long-range, single-molecule modifications. To study the inheritance of DNA methylation and local crosstalk between neighboring CpGs at single-molecule resolution, long-read sequencing is essential. However, understanding the faithful transmission of 5mC during DNA replication requires the use of strand-specific detection methods. Current technologies fall short: Nanopore reads strands randomly, and SMRT sequencing assumes symmetric methylation to infer 5mC levels. To overcome these limitations, we developed a Tet-assisted, strand-resolved methylation detection strategy using SMRT sequencing. A high-performance engineered Tet enzyme (hpTet) enhances the kinetic signal of 5mC, enabling sensitive detection. We trained a convolutional neural network (CNN) to distinguish unmodified from fully methylated CpGs at single-base, strand-specific resolution. This approach provides unprecedented insight into DNA methylation inheritance and local methylation dynamics.

P16 Investigating germline effects of paternal trauma on offspring behavior

Iryna Ivanova, Selina Frei, Rosie Longster, Vincent Fischer, Miriam Kretschmer, Pierre-Luc Germain, Katharina Gapp | ETH Zurich, Switzerland

Depression and anxiety disorders run in families, but in few cases we understand the biological underpinnings. Many studies indicate molecular alterations in sperm and oocytes, the cells that form the next generation in a first place, alongside parents passing on risk through behaviors affected by environmental exposure. A range of prior studies showed that excessive stress induces intergenerational behavioral effects, leading to increased disease risk in the progeny. Our data from a mouse model showed that even a single traumatic event in fathers induces changes in anxiety associated behavior in the progeny. This study investigated whether anxiety phenotype persists after a traumatic event and whether these changes increase the likelihood of anxiety in offspring, as well as whether these changes could be reversible. To test this, mature sperm from stressed fathers was incubated with a Proteolysis Targeting Chimera (PROTAC) to deplete the glucocorticoid receptor (GR), a major player in the stress reaction, and then used to generate offspring via IVF. The aim of this project was to identify changes in offspring behavior and gene expression in early embryo due to a single traumatic stress, and the interaction with the depletion of the GR. Our results provide preliminary but important insights into how traumatic stress impacts the offspring generation, while dissecting the role of the GR.

P17 Exposure to childhood maltreatment is associated with specific epigenetic patterns in sperm

Jo Iversen | University of Copenhagen, Denmark

Childhood maltreatment exposure (CME) increases the risk of adverse long-term health outcomes in affected individuals. Animal studies further suggest that CME-induced epigenetic changes in the germ line may influence the health and behavior of the next generation. We examined the relationship between early life stress and the sperm epigenome in men with a history of CME. Paternal CME was assessed using the Trauma and Distress Scale (TADS), and sperm epigenomic features were profiled in participants from the FinnBrain Birth Cohort Study. Small RNA sequencing (small RNA-seq) was used to characterize sperm-borne small non-coding RNAs (sncRNAs), and DNA methylation (DNAme) was analyzed using reduced-representation bisulfite sequencing (RRBS-seq). The study design was a nested case-control study, which included high-TADS (≥39) and low-TADS (≤10) males (n = 25 vs. n = 30 for DNAme; n = 14 vs. n = 16 for small RNA-seq). We identified three genomic regions with differential DNA methylation between high and low-TADS, and 68 small RNAs—including tRNA-derived small RNAs (tsRNAs) and microRNAs (miRNAs)—with altered abundance in high-TADS individuals (false discovery rate, FDR < 0.5). Notably, differential methylation was observed near the CRTC1 and GBX2 genes, both implicated in brain development. These findings add to the growing evidence that early life stress leaves molecular signatures in the paternal germ line, supporting a potential role for sperm epigenetic variation in shaping offspring neurodevelopment.

P18 Cancer epigenetics: From laboratory studies and clinical trials to precision medicine

Alireza Seyed Javadinia | Sabzevar University of Medical Sciences, Iran

Epigenetic dysregulation plays a central role in the initiation, progression, and recurrence of cancer. Unlike genetic mutations, epigenetic alterations—such as DNA methylation, histone modifications, and non-coding RNA expression—are reversible and represent promising therapeutic targets. This review highlights recent advances in understanding the epigenetic landscape of cancer and the clinical translation of epigenetic therapies. Several epigenetic drugs, including DNA methyltransferase and histone deacetylase inhibitors, have received regulatory approval, particularly for hematological malignancies. However, their efficacy in solid tumors remains limited, prompting the development of combination regimens and next-generation agents, such as BET and EZH2 inhibitors. Integration of multi-omics approaches with artificial intelligence is accelerating the discovery of predictive biomarkers and enabling personalized epigenetic treatment strategies. Despite significant progress, challenges persist in translating preclinical findings into durable clinical responses. Future research must focus on refining biomarker-guided therapies, elucidating resistance mechanisms, and optimizing combinatorial approaches to fully harness the potential of epigenetic precision oncology.

P19 Using the transmissibility model to demonstrate transgenerational transmission of environmental effects in quails

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Non-genetic information, such as epigenetic modifications, can modulate gene expression and influence phenotypic outcomes. Additionally, these modifications can be transmitted across generations, contributing to transgenerational phenotypic variation independent of changes in the DNA sequence. The present study aimed to demonstrate the vertical transmission of environmental effects. We used an experimental design in quails with two epilines: a control line and a treatment line (Epi-/Epi+). Females in the Epi+ line were fed a genistein-supplemented diet. Reproduction of these lines was then conducted in a mirrored mating design over three generations, with a total of 1,566 animals phenotyped. We used the transmissibility model with environment with fixed effects of rearing condition, sex, generation, age at the time of measurement and direct effect of the genistein (on the animal, embryo and germ cells). We added to the model the random effect of the transmissible potential of the animal, which transmissibility matrix contains sire and dam path coefficients of transmission. These coefficients have to be estimated conversely to the genetic model where they are fixed to 0.5, and, moreover an additional covariance (r) for offspring of genistein-fed dams which is then transmitted to next generations via sires and dams. In the transmissibility model with environment, the proportion of transmitted variance of body weights varied from 0.36 (at 1 week) to 0.73 (at 7 weeks). The covariance (r) was significantly different from zero for body weight traits, indicating a transgenerational transmission of genistein's effects. This value corresponded to a high correlation at one week (0.44) but low for other body weight traits (lower than 0.02). The findings demonstrated the transgenerational transmission of environmental effects induced by genistein on body weight traits in quails, indicating that environmental factors can potentially influence multiple generations. Using these results may enhance the effectiveness of genetic selection by accelerating the response to selection for traits of interest, which is crucial for accelerating adaptation to environmental challenges. This work was funded by the European Union's Horizon 2020 research and innovation program under grant agreement N°101000236 (GEroNIMO). This project is part of EuroFAANG (https://eurofaang.eu).

P20 Epigenetic inheritance of allergic predisposition in mice

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Allergy is induced in postnatal mammals by repetitive exposure to an allergen. Epidemiological studies suggest that children whose parent(s) have allergic diseases show a higher incidence of developing allergies. We examined whether induction of anaphylaxis in adolescent male mice resulted in allergic predisposition of their offsprings. Male mice aged 5-week-old were sensitized and challenged with an antigen to develop

P20 Continued
anaphylaxis, followed by mating with unimmunized female mice. The F1 mice manifested significant anaphylactic symptoms after they received a low-dose sensitization/challenge with the allergen, although the same sensitization/challenge regimen failed to cause anaphylaxis in normal control mice. We identified some miRNAs that were significantly overexpressed in anaphylactic male mice, and found that transduction of these miRNAs into fertilized eggs resulted in generation of mice displaying the similar anaphylaxis-prone phenotype. These findings strongly suggest epigenetic inheritance of allergic susceptibility from male to offsprings, and molecular mechanism underlying the transmission.

*P21 Copy number determination of small RNAs in mature mouse sperm involved in the intergenerational inheritance of metabolic syndromes

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Mammalian spermatocytes harbor a variety of RNAs that are mostly degradation products of abundant non-coding RNAs, including ribosomal RNA-derived small RNAs (rsRNAs) and tRNA-derived RNAs (tDRs). Notably, tDRs have been implicated in the inheritance of paternally acquired traits, primarily in rodents. Direct experimental proof for this notion comes from the manipulation of fertilized murine oocytes through microinjection of small RNA preparations resulting in an impact on specific metabolic pathways that were measurable in the offspring. How exactly these paternally transmitted small RNAs could function mechanistically in the fertilized oocyte remains to be understood. Since nothing is known about how many small RNA molecules would be required for functional impact in the developing zygote, we aimed to determine absolute copy numbers of specific small RNAs contained in a single murine spermatocyte. Using hybridization-based methods that avoid amplification-induced biases, we report here average copy numbers for specific tDRs and rsRNAs in single mouse spermatocytes. These results should allow approximation of how many rRNA- and tRNA-derived RNAs will enter an oocyte in the physiological context of fertilization. The reported numbers underscore the need for a better understanding of the quantitative nature of the biological system that is being manipulated using small RNAs, and to be cautious when arriving at conclusions as to the effect of introducing unphysiological numbers of molecules into a biological system.

*P22 Intergenerational effects of paternal HFD on germline RNAs and metabolic health can be altered by obesity treatment

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Growing evidence shows that father's metabolic disorders and other acquired conditions can be transmitted to the offspring via sperm-mediated epigenetic mechanisms, such as small non-coding RNAs. Taking into consideration the increasing prevalence of obesity and associated metabolic disorders, this poses a huge risk for the health of the following generations as the preventability of the harmful epigenetic inheritance remains unknown. Here we performed multigenerational diet studies in mice to investigate if the epigenetic transmission of father's high-fat diet (HFD)-induced metabolic disorder to the offspring can be prevented by treating the father's obesity with a healthy diet. We show that HFD-induced changes in sperm tsRNAs and piRNAs were reversed back to control levels with the diet intervention. Surprisingly, the sperm RNAs were also normalized with a metformin treatment despite not reversing the metabolic syndrome completely like the diet intervention did. In F1 offspring, the father's HFD-induced obesity and diet intervention caused highly variable metabolic alterations as well as transcriptomic changes in liver and epididymal white adipose tissue. Furthermore, father's HFD induced changes in F1 sperm small RNAs and round spermatid mRNAs, which were all largely prevented with father's diet intervention. Some influences of the F0 diet intervention were still observed in F2 metabolism and sperm small RNAs. Together, our results suggest that inter- and transgenerational effects of paternal HFD are complex but can be altered by different obesity treatment strategies, and that germline RNAs are responsive to these exposures in three generations while not explaining all of the observed intergenerational effects.

P23 Environmental maternal effect and intergenerational inheritance

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Auanema freiburgense is a free-living nematode characterized by three distinct sexual morphs: male, female and hermaphrodite. A key aspect of its biology is the ability of the mothers to sense environmental cues. Social signals mediated by crowding, for example, are a major determinant of the sexual morphs in their offspring. Under optimal growth conditions, A. freiburgense mothers primarily produce offspring that develop into either male or female worms. However, when experiencing stress, such as food scarcity or overpopulation, this nematode secretes specific pheromones to the environment. Mothers that sense these signals via neural receptors, shift to the production of starvation-resistant larvae, which later develop as self-fertilizing adults. My research aims to elucidate how environmental cues sensed by the mother influence intergenerational sex determination. We found there are at least three different types of environmental signals - crowding, heat and starvation- that can trigger sexual morph determination in the F1 generation. A maternally produced hormone, dafachronic acid, has been implicated in the production of female offspring. Thus, the intergenerational transmission of this hormone influences the development of either female or hermaphrodite offspring. Indeed, artificial supplementation of dafachronic acid to the offspring of stressed mothers, or the inhibition of the maternal production of dafachronic acid is sufficient to change F1 sex determination. Beyond its fundamental biological insights in A. freiburgense, this research may reveal common mechanisms to other environmentally-induced phenotypic plasticity models, such as those found in Daphnia or in agriculturally important insect pests.

P24 Epigenetic evidence of stress-driven aging in monozygotic twins

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Early life adversity (ELA), particularly psychosocial environmental (PSE) stress, is a major contributor to long-term health disparities and increases the risk of non-communicable diseases in adulthood. These outcomes are thought to result from complex interactions between genetic predispositions and environmental exposures, leading to immune, endocrine, and epigenetic dysregulation. However, the molecular mechanisms by which PSE impacts immune function remain poorly understood. In the ImmunoTwin study, we examined the effects of PSE on the whole blood epigenome in 28 pairs of monozygotic twins discordant for life experiences. A detailed psychosocial assessment was used to derive a PSE score for each twin. Within each pair, the individual with the higher PSE score was assigned to the "divergent" category, and the other to the "control." DNA methylation (DNAme) profiling was conducted using the Illumina Infinium EPICv2 BeadChip arrays. We calculated epigenetic age and age acceleration using established second and third generation epigenetic clocks: PhenoAge, GrimAge, and DunedinPACE. Across twin pairs, a positive correlation was observed between differences in PSE scores and differences in epigenetic age acceleration. Although the overall group comparison between divergent and control individuals did not show significant differences, stratified analysis by sex revealed that divergent males exhibited slower epigenetic aging compared to their control co-twins. These preliminary findings suggest that psychosocial stress may be biologically embedded through epigenetic modifications such as DNAme. Moreover, sex-specific effects may influence how PSE shapes biological aging trajectories. Our results support the use of DNAme a biomarker of stress exposure and underscore the utility of monozygotic twin designs in disentangling gene–environment interactions. The ImmunoTwin study aims to advance our understanding of the molecular basis of social health inequalities and inform future preventive strategies.

P25 The long-term effects of short-term stress

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Traumatic stress can negatively alter behaviour and increase the risk for neuropsychiatric diseases within and across generations. It is crucial to investigate the sustained impact of stress as well as the epigenetic mechanisms potentially mediating such effects to further understand the paternal heritability of stress-linked disorders. Acute stress describes a single, isolated challenge of the stress axis that normally subsides with the termination of the event. In this work we show that a return to baseline, even after a single acute inescapable foot shock (IFS) stressor is not guaranteed. While such a stressor typically doesn't alter the DNA sequence passed on to the offspring, it may impact the germ line epigenome. The sperm epigenome is established during spermatogenesis and consists of a specific set of stress-susceptible epigenetic marks including DNA methylation and chromatin accessibility. Spermatogenesis is impacted by transcription factors (TFs) such as the glucocorticoid receptor (GR). GR is the cellular messenger of the stress hormone cortisol/corticosterone and mediates the genomic response to stress. We report persistent hormonal and behavioural alterations up to 35 days post-IFS in male mice as well as their adult offspring. These are associated with early changes in embryonic gene expression as revealed by SMART-Seq of embryos derived from IFS- or control sperm and naive oocytes.

*P26 Epigenetic transgenerational germline inheritance of polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is a highly heritable disease with high androgen levels as its main feature, which manifests itself in reproductive, metabolic and psychiatric symptoms. Daughters of women with PCOS have a 5-fold higher risk of being diagnosed with PCOS and their sons are predisposed to abnormal metabolic traits. Previous research has shown that maternal obesity and hyperandrogenism contribute to the transgenerational inheritance of PCOS-like traits, along with transcriptomic alterations in the germ cells. This study aims to determine whether genetic or epigenetic marks in germ cells alone can mediate this transmission across the generations. To model PCOS, female mice (F0 donors) were exposed to dihydrotestosterone (DHT) or vehicle from peri-pubertal age, some F0 donors received additional exercise or treatment with an androgen receptor blocker (flutamide). Six weeks later, oocytes from donors were retrieved and subjected to in vitro fertilization (IVF) and healthy surrogacy to generate first-generation (F1) offspring. Similarly, second-generation (F2) offspring was obtained using IVF with either F1 sperm or oocytes. To identify underlying molecular mechanisms of the germline inheritance, the transcriptomic profile of female germline oocytes (F0, F1 and F2) and the transcriptomic and methylation profiles of F1 and F2 sperm were investigated. The DHT-exposed F0 donors developed PCOS-like reproductive and metabolic phenotypes. While the metabolic disturbances were prevented by both exercise and flutamide treatment, the reproductive alterations were prevented only by flutamide but not by exercise. F1 offspring from DHT-exposed donors showed only mild metabolic abnormalities, while F2 males and females from female and male germ lines, respectively, showed marked metabolic abnormalities, including heavier subcutaneous fat depot, hypertrophic adipocytes and liver steatosis. Remarkably, donor exercise prior to IVF prevented the inheritance of these abnormalities in the F2-DHT lineages, suggesting a promising role for exercise in the management of PCOS-associated metabolic alterations across generations. Investigation of the role of genetic and epigenetic mechanisms in germ cells that contribute to the inheritance of the PCOS-like phenotype is ongoing. However, transcriptomic analysis of F0 oocytes revealed alterations in PCOS-related signaling pathways in the DHT lineage, while F1 and F2 oocytes from the male germline indicated disturbances in neurotransmitter activity. Together with methylation analysis of F2 sperm, we hope to determine how the transcriptome and methylome of germ cells contribute to metabolic alteration across generations and how exercise prior to IVF prevents such inheritance.

*P27 Mapping the human epigenetic landscape across three generations: A DNA methylation resource from TMM BirThree

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Transgenerational epigenetic inheritance, predicted by the Developmental Origins of Health and Disease (DOHaD) theory to influence long-term health and disease risk, has been demonstrated in rodent models but not in humans. To address this gap, we established a comprehensive DNA methylation resource derived from 158 three-generation Japanese families. The dataset integrates genome-wide methylation profiles with extensive clinical and lifestyle data, including dietary records, medication use, standardized psychosocial questionnaires, and socioeconomic status. Using targeted bisulfite sequencing, we profiled > 1 million CpG sites across the genome, covering the promoter and gene body regions of > 22,000 annotated genes, in 938 adult peripheral blood and 155 neonatal cord blood samples. To demonstrate the utility of this resource, we performed a representative analysis focusing on the intergenerational impact of maternal and grandmaternal pre-pregnancy smoking, suggesting potential transgenerational transmission of environmental effects in humans. We identified persistent methylation marks in neonates associated with ancestral smoking history, suggesting the potential transgenerational transmission of environmental effects in humans. This multigenerational epigenomic resource provides a valuable foundation for future studies on intergenerational epigenetic mechanisms and their role in shaping human health trajectories.

*P28 Inherited metabolic imprints—or the mitochondrial memory of lifestyle?

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Parental diet leaves durable molecular marks on offspring physiology, but the mechanisms of inheritance remain unresolved. Using a Drosophila model, we investigated how paternal Western diet (WD) exposures affect brain bioenergetics, gene expression, and behavior in the next generation. Our data show that ancestral exposure to WD impairs mitochondrial respiration and induces widespread, sex- and lineage-specific shifts in the brain transcriptome and proteome of offspring. High-resolution respirometry (Oroboros O2k) in F1 brains revealed significant reductions in complex I- and complex II-supported respiration and ATP/O_2 ratios, consistent with impaired oxidative phosphorylation efficiency. Integrated multi-omics analysis identified concordant RNA and protein-level changes in mitochondrial ribosomal components and metabolic regulators, implicating core bioenergetic and neuronal processes. These molecular alterations co-occurred with reproducible behavioral phenotypes in offspring, including hyperphagia and impaired locomotor activity. Several affected targets are predicted or validated downstream of differentially expressed miRNAs such as miR-10, suggesting a role for post-transcriptional regulation in transgenerational brain programming. These findings define molecular correlates of inherited mitochondrial dysfunction and establish a framework for mechanistic studies of how parental nutritional history shapes offspring brain physiology.

P29 From pluripotency to germ cells and back: Modeling intergenerational epigenetic dynamics in a dish

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Whether and how the impact of environmental exposures can be inherited, with parental environments shaping phenotypes across generations independent of DNA sequence carried in gametes, is a fundamental question in biology, with far-reaching implications for human health. Despite evidence of such epigenetic inheritance in animals, the mechanisms and relevance to humans remain elusive due to lack of (i) multi-generational human data on environmental exposures with quantified health outcomes, and (ii) access to germ cells and tissues from exposed individuals to deduce and validate molecular mechanisms. To overcome this last challenge, we developed a hiPSC-derived in vitro system, to model epigenetic dynamics

P29 Continued
across generations. Starting from hiPSC, we differentiated human primordial germ cell-like cells (hPGCLC, model of F1 generation developing germline) and, for the first time, converted them back to the pluripotent state, namely human embryonic germ cell-like cells (hEGCLC, proxy model of F2 generation post-implantation epiblast). By scRNAseq and DNA methylation profiling, we confirmed hEGCLCs pluripotency and showed how the initial demethylation occurring in hPGCLCs is largely reversible, as hEGCLCs exhibit methylation levels comparable to hiPSCs (Stucchi et al., BioRxiv 2025). We were also able to recapitulate the behaviour of escapee regions, found by (Tang et al., Cell 2015), in primordial germ cells from aborted human fetuses as escaping the global wave of DNA demethylation and therefore pointed out as potential interesting candidates for epigenetic inheritance. For the first time, we also differentiated hEGCLC into cortical brain organoids (CBOs), proxy of F2 generation fetal cortex. Altogether, this new in vitro model represents a highly tractable system to study epigenetics transitions and dynamics in humans. We are now exposing this model to widespread and hazardous compounds at epidemiologically relevant concentrations, to evaluate their impact on primordial germ cells epigenome and the inheritance of these epigenetic modifications and their potential neurodevelopment effects. Overall, this project will contribute to shed light on the impact of environmentally induced, epigenetically inherited changes on human development, providing scientific evidence to guide the reduction of adverse effects on present and future generations resulting from widespread environmental exposures.

P30 Epigenetic aging of the liver due to direct and ancestral exposure to Bisphenol A
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The aging process is characterized by a decline in bodily function and resiliency, leading to increased sensitivity to aging-related diseases. Chemicals in the diet and environment can alter the mechanisms underlying aging process, thereby accelerating or decelerating aging process It is not clearly understood if environmentally induced transgenerational inheritance results in acceleration of epigenetic aging in the metabolic organs. This study examined transgenerational epigenetic, transcriptional, and metabolomic signatures associated with accelerated aging of the liver and tested whether such age-related epigenetic alterations are reversible. We treated medaka fish embryos with BPA (10 ug/L) from 8 hours post-fertilization to 15 days post-fertilization stages overlapping with liver differentiation and raised them without BPA exposure thereafter. We performed transgenerational methylome, transcriptome, and metabolomic profiling of the livers at F2 and F4 generations. We also treated fish with vitamin C to understand if reversal of non-alcoholic fatty liver disease (NAFLD) accompanies the correction of epigenetic, transcriptomic, and metabolic alterations associated with aging. We found significant downregulation of key longevity genes: kl, sp1 apoeb, and egr1 accompanied by hypermethylation of their promoter in parental germline and the offspring liver. Proline, arginine, and tryptophan metabolism pathways were significantly altered. Vitamin C treatment reversed significant epigenomic and transcriptional alterations and restored the normal liver health. The present results show transgenerational epigenetic aging in the liver of female fish whose ancestors were exposed to BPA and the reversal of aging with Vitamin C. The potential for BPA to cause accelerated, heritable epigenetic aging has implications for human health and organisms at high risk of exposure to chemicals.

*P31 Transgenerational neurotoxicity of Arsenic in zebrafish: Mechanistic insights into cognitive deficits and epigenetic alterations
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Chronic exposure to arsenic is known to impair learning and memory functions; however, the underlying mechanisms and potential transgenerational inheritance of these cognitive deficits remain poorly understood. In this study, we first evaluated the effects of chronic dietary arsenic exposure on the cognitive performance of adult zebrafish and investigated the molecular pathways involved in arsenic-mediated neurotoxicity. Adult zebrafish were exposed to environmentally relevant concentrations of dietary arsenic (30, 60, and 100 µg/g dry weight as arsenite) for 60 days, and cognitive performance was assessed using a latent learning maze paradigm. Arsenic exposure, particularly at medium and high doses, significantly impaired

*P31 Continued
cognitive performance, accompanied by increased arsenic accumulation, elevated dopamine levels, and oxidative stress in the brain. Gene expression analyses revealed significant alterations in dopaminergic signaling pathways, including changes in the expression of dopamine receptors, tyrosine hydroxylase, monoamine oxidase, brain-derived neurotrophic factor (BDNF), and ectonucleotidases critical for learning and memory. Building on these findings, we further investigated the inter- and transgenerational inheritance of arsenic-induced cognitive deficits and associated epigenetic modifications. Adult zebrafish (F0) exposed to dietary arsenic for 90 days were crossed with unexposed partners to generate F1 progeny through maternal and paternal lineages, and subsequently, F2 progeny were generated from F1 crosses. Ancestral arsenic exposure led to cognitive impairments in both F1 and F2 generations, with maternal lineage effects evident at lower exposure levels compared to paternal lineage. These cognitive deficits were associated with persistent oxidative stress, dopaminergic dysregulation, and downregulation of cognition-related genes (Drd1, MAO, BDNF) across generations. DNA methylation analysis revealed hypermethylation of the promoter regions of these genes, suggesting an epigenetic basis for the observed transgenerational neurotoxicity. Collectively, these findings demonstrate that chronic dietary arsenic exposure not only impairs cognitive function through oxidative stress and dopaminergic disruption but also that these neurotoxic effects can be epigenetically inherited across multiple generations.

*P32 Transmission of DNA methylation: genetic or epigenetic? A transgenerational case study in quails
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Part of the environmental story of individuals lies within their DNA methylation (DNAm). Variations in the environment can trigger changes at the DNAm level and translate to phenotypic variability, even in the progeny of the individuals directly impacted. However, the amount of environmental information transmitted between generations via epigenetic phenomena is hardly quantifiable. The present study analyses DNAm from Reduced Representation Bisulfite Sequencing (RRBS) data for 1267 quails (Coturnix japonica) within 3 successive generations following an environmental modification. Among 112,561 dinucleotides CG (CpG) used, we estimated an average heritability of DNAm of 0.24. After a sub-selection of 40 CpG sites showing high heritability and a significant difference in methylation between two epilines, we conducted methylation Quantitative Trait Loci (metQTL) analysis at those sites in order to shed light on the origin of the high heritability of those sites: genetic or epigenetic?

P33 The biophysical mechanism underlying epigenetically inherited stress response/unpredictability learning
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Stressful behavior is transferred epigenetically. Here we study the biophysical mechanism of such epigenetic inheritance. Mice were exposed to varying protocols of tone-shock fear conditioning: a predictable group exposed to repetitions of consistent pairs of tone-shock; an unpredictable group exposed to tone and shocks in a random order; a naive group exposed to home cage conditions. After two weeks, all groups were exposed to the tone only for three days. The unpredictable group exhibited significantly higher freezing than both control and predictable groups on all three days, pointing to an enhanced fear response and reduced extinction. This enhanced response was accompanied by reduced pots-burst after-hyperpolarization (AHP) amplitude in pyramidal neurons of the anterior insula. In the other hand, both unpredictable and predictable stress showed lower AHP amplitude in the Basolateral amygdala. Subjects of the three groups were paired for breeding, and first-generation offspring were exposed to one tone-mild shock pair followed by three days of tone-alone exposure. Offspring of both predictable and unpredictable subjects exhibited significantly higher freezing levels than offspring of naïve parents, with significantly higher responsiveness in offspring of the unpredictable group. Additionally, offspring of the unpredictable group were born with lower AHP amplitude in the anterior insula neurons. These results indicate that experiencing unpredictable stress can alter the neuronal properties of the insula's neurons and the behavioral response to fear.

*P34 Sperm-derived lipids as epigenetic drivers of intergenerational inheritance: shaping early embryonic development and disease susceptibility

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Currently, paternal contributions to embryo development and offspring phenotypic variability (including intergenerational transmission of metabolic traits and susceptibility to disease) have been ascribed exclusively to paternally inherited allelic variants. Nowadays, a plethora of epigenetic signals have been shown to contribute to paternal inheritance. Epigenetic signals so far identified include methyl groups covalently added to cytosines of the parental genome, post-translational modifications of histones that remain associated with sperm chromosomes and are delivered to the oocyte, and regulatory RNA molecules released from sperm into the oocyte at fertilization. Along with nucleic acids, the sperm also contributes metabolomic components to the zygote, such as lipids, carbohydrates, and amino acids. These metabolites, particularly those endowed with modulatory activities, could influence zygotic gene expression and embryonic development and thus might act as epigenetic signals. Here, we propose that the sperm lipidome might act as an additional carrier of epigenetic information, potentially affecting the embryo's development. Lean or obese male mice are isotopically labeled by drinking $^{2}H_2O$- or $U^{13}C$-glucose-enriched water to allow integration of the isotopes into sperm metabolites. Labeled males are then mated with unlabeled, lean females, and preimplantation embryos (zygotes, morulae, blastocysts) are collected. Sperm and embryos are analyzed by mass spectrometry to detect isotopically labeled paternal metabolites transferred into the oocyte and assess the impact of paternal diet on the composition and profile of the transferred lipid species. Our findings reveal a previously underappreciated contribution of the paternal sperm lipidome to early embryonic development and shed light on a new molecular vehicle involved in intergenerational transmission of metabolic traits.

P35 Imagery rehearsal therapy and self-talk in trauma-exposed active-duty soldiers in Ukraine: A randomized controlled trial

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It is estimated that 100,000 Ukrainian soldiers have died as a result of the Russian invasion of Ukraine on February 24, 2022. The majority of the one million Ukrainian active-duty soldiers are experiencing ongoing extended exposure to combat and war-related stress. Common manifestations of this ongoing stress likely include acute stress disorder (ASD), depression, nightmares, intrusive thoughts, and poor sleep quality, although the prevalence of these symptoms is unknown. In low-resource and high-conflict environments, structured, short-term interventions may offer viable treatment alternatives. Some soldiers with severe symptoms are provided brief respite care from combat at psychiatric facilities around Ukraine. This study investigated the efficacy of a brief protocol combining Imagery Rehearsal Therapy (IRT) and Self-Talk Rehearsal Therapy (SRT) in mitigating traumas-related symptoms among these soldiers while they were temporarily removed from combat in the psychiatry department. 50 trauma-exposed active soldiers were randomly assigned to either an intervention group (IRT+SRT, n=25) or a control group receiving standard care (n=25). The treatment group participated in three 2-hour sessions over 10 days, including trauma narrative reframing, structured guided imagery, positive self-talk exercises, and progressive muscle relaxation. Pre- and post-intervention assessments included the Trauma Symptom Checklist-40 (TSC-40), PTSD Symptom Scale–Self-Report (PSS-SR), Beck Depression Inventory (BDI), Pittsburgh Sleep Quality Index (PSQI), Nightmare Frequency Questionnaire (NFQ), Intrusive Thoughts Frequency Questionnaire (ITFQ), and a brief Imagery Rehearsal Therapy (IRT) and Self Rehearsal Therapy (SRT) familiarity form. The intervention group demonstrated significant improvements across multiple symptom domains compared to controls. Notably, symptom severity (TSC-40) and imagery rehearsal therapy clinical risk scores significantly declined ($p = 0.00457$), especially in the ability to "Imagine" showing a strong effect ($p= 0.0101$). Self-talk scores improved significantly in the treatment group (3.39 to 4.50, $p = 0.000043$), with no meaningful change in controls. Key gains included better familiarity, calm application, and mood regulation. Functional disability on the (questionnaire) decreased in the treatment group in the Work section ($p = 0.0218$) and Social Life

P35 Continued
aspect (p = 0.0053). Sleep quality improved significantly in the treatment group (p < 0.05), especially in sleep disturbance (p = 0.0075), and depressive symptoms, including reduced anhedonia ("Pleasure"), also improved (p = 0.0006). Irritability increased significantly in both the treatment (p = 0.0283) and control (p = 0.0214), possibly due to the war symptoms. These findings suggest the intervention group effectively reduced trauma-related symptoms, enhanced coping mechanisms, and improved daily functioning. The results of this randomized controlled trial provide strong evidence that IRT coupled with SRT significantly improve psychological resilience and functional outcomes in Ukrainian active-duty soldiers with trauma. We believe this is the first study using these techniques with active-duty soldiers who remain in combat. Participants in the treatment group experienced marked reductions in trauma-related symptoms, depressive features, and functional impairment, alongside significant improvements in self-regulation skills such as imagery ability and self-talk. These consistent improvements across multiple validated measures, supported by robust p-values, highlight the clinical relevance and potential of this low-cost, non-pharmacologic intervention as an effective tool for distressing symptom reduction in soldiers who are in active combat.

P36 From germline to soma with Parse: Matched high-resolution transcriptomes with single-cell precision across tissues
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Mechanistic studies of genome activity and regulation require precise knowledge of transcriptomic signatures in individual cells. Single-cell and single-nucleus RNA sequencing has transformed the ability to capture cell-specific transcriptomes and resolve them with precision that is unachievable by bulk RNA sequencing. However, such sequencing has limitations, including low coverage, high cost, and challenging experimental design, especially for tissues with complex and dense cellular organization such as the testis. We implemented a novel single-nucleus RNA sequencing method from Parse Biosciences, which enables the generation of high-resolution transcriptomic datasets from many samples in parallel. We isolated nuclei from flash-frozen tissues—testis, brain, and heart—from adult male mice and prepared a joint library to generate high-quality datasets that capture coding and non-coding RNAs. This approach allows consistent transcriptomic profiling at single-cell resolution across tissues, minimizing the number of experimental batches for optimized comparability, technical interoperability, and cost. It is expected to be highly valuable to assess systemic effects of exposures across cells and tissues, including the reproductive system, and add value to the field of epigenetic inheritance.

P37 Circulating miRNAs in neurodegenerative and neuropsychiatric diseases: A systematic review and meta-analysis
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Neurodegenerative and neuropsychiatric diseases impose a considerable burden on patients, caregivers and healthcare services on a global scale. An early diagnosis is crucial for effective treatment, highlighting the need for reliable biomarkers. Circulating microRNAs (miRNAs) are promising candidates for this purpose, as their expression profiles can serve as non-invasive indicators of pathological changes. The objective of this study was to identify differentially expressed miRNAs that could serve as potential biomarkers or drug targets for neurodegenerative and neuropsychiatric diseases. In order to achieve this objective, we conducted a systematic literature screening in PubMed, Scopus and Web of Science for case-control studies which investigated expression changes of in blood circulating miRNAs by using small RNA sequencing, followed by a meta-analysis and qPCR experiments. From 1474 discovered studies we included 30 into the meta-analysis with overall 1228 dysregulated miRNAs, leading to the identification of 51 significant commonly deregulated miRNAs across all diseases. A subsequent subgroup meta-analysis, focusing exclusively on Alzheimer's disease (AD) studies, revealed 13 differentially expressed miRNAs. We further characterized the 13 miRNAs bioinformatically, focusing on tissue expression, target genes, and disease context, and validated our findings with qPCR experiments. Notably, miR-21-5p exhibited not only interesting potential target genes, but also an up-regulation in human AD brains and in neurons and microglia from primary mouse

P37 Continued
cultures. The findings of this study suggest that it is possible to enhance the robustness of results obtained from RNA sequencing studies by applying a meta-analysis, facilitating the identification of miRNAs that are frequently deregulated across multiple datasets. Furthermore, we identified miR-21-5p as a promising biomarker or drug target for Alzheimer's disease.

*P38 From sperm to embryo: Allele-resolved evidence for miRNA-mediated effects on the maternal transcriptome

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Intergenerational epigenetic inheritance of diet-induced phenotypes has been well documented, yet the underlying molecular mechanisms remain poorly understood. A major limitation in embryo studies is the inability to distinguish between paternal and maternal genomes and transcripts in omic analyses. To overcome this, we used breedings between C57BL/6J and PWK/PhJ mice, generating hybrid offspring in which parental alleles can be separated based on single nucleotide polymorphisms. As a first step, we replicated previous findings demonstrating that paternal exposure to a low-protein diet (LPD) affects offspring body weight and the transcriptome in liver. We next investigated early development using single-embryo RNA sequencing of hybrid two-cell embryos, which allows allele-specific resolution of the transcriptome. Although both parental contributions were resolved, here we focus on the maternal transcriptome. We observed that paternal LPD exposure induces differential expression of maternal genes enriched in metabolic pathways. We combined these results with sperm small RNA sequencing from LPD-exposed fathers. This reveals a subset of sperm-derived microRNAs (miRNAs) that are altered by LPD, and whose targets are dysregulated within the maternal transcriptome of the embryo. Together, these findings provide mechanistic evidence that a paternal LPD modifies sperm miRNA composition, which in turn perturbs the maternal transcriptome during early stages of embryonic development. They highlight how epigenetic information can be transmitted from father to offspring and establishes a framework for allele-resolved analyses of intergenerational epigenetic inheritance.

*P39 The impact of chemical exposures across generations: Integrating human epidemiology with in vitro modelling and causal models of epigenetic inheritance

Sarah Stucchi, Nicolò Caporale, Riccardo Nagni, Gaja Matassa, Alessia Valenti, Cristina Cheroni, Manuel Lessi, Marco Tullio Rigoli, Benedetta Muda, Yoshiaki Nosaka, Ken Mizuta, Harry G Leitch, Mitinori Saitou, Giuseppe Testa | Fondazione Human Technopole, Italy

Whether and how the impact of environmental exposures can be inherited, with parental environments shaping phenotypes across generations independent of DNA sequence, is a fundamental question in biology with far-reaching implications for human health. Despite evidence of such epigenetic inheritance in animals, the mechanisms and relevance to humans remain elusive due to lack of (i) multi-generational human data on experimentally tractable environmental exposures with quantified health outcomes, and (ii) access to germ cells and tissues from exposed individuals to deduce and validate molecular mechanisms. Considering the paradigmatic case of the heritable impact of the exposure to endocrine disruptors (EDC), a widespread and hazardous class of chemicals that interfere with hormonal signaling causing a wide range of adverse health effects, including adverse neurodevelopmental outcomes, we are overcoming these challenging by leveraging (i) a unique multigenerational human cohort, SELMA (Tanner et al., Environ Int. 2020; Bornehag et al., Environ Int. 2021; Caporale et al., Science 2022), where we are measuring the parental prenatal (F1) exposure to EDC and relating it to quantified neurodevelopmental outcomes in their children (F2), (ii) an innovative in vitro system we recently developed (Stucchi et al., BioRxiv 2025) to model epigenetic dynamics across generations, thus making epigenetic inheritance tractable in humans. We converted human primordial germ cell-like cells (differentiated from hiPSC and model of F1 generation developing germline, (Sasaki et al., Cell Stem Cell 2015; Murase et al., Nature 2024) back to the pluripotent state, namely human embryonic germ cell-like cells (hEGCLC, proxy model of F2 generation post-implantation epiblast,

*P39 Continued
(Stucchi et al., BioRxiv 2025) and further differentiated these into cortical brain organoids (CBOs, model of F2 fetal cortex). By exposing this in vitro model to mixtures of EDCs at epidemiologically relevant concentrations derived from the SELMA cohort, we are profiling the transcriptome and epigenome of in vitro-derived gametes precursors, hEGCLC and CBOs to assess what transcriptomic and epigenetic changes are induced in the germline by the EDCs and which are inherited and maintained in the next generation and with what phenotypic consequences. We will then dissect the underlying mechanisms with precision epigenome editing (Policarpi, Dabin and Hackett, Bioessays 2021). Through the integration of multi-generational human cohorts with in vitro modelling, our design is set to deliver robust conclusions on one of the most debated questions in human biology and evolutionary theory alike. By defining the legacy of chemical exposure on human traits, this first-in-kind molecular atlas of epigenetic inheritance aims thus to constitute an intellectual vanguard for the way we articulate our collective responsibility to future generations, with far reaching implications for cultural discourse and environmental policy alike.

P40 KDM6A loss in the mammalian paternal germline alters COMPASS-mediated histone methylation and predisposes offspring to cancer
Benjamin Walters | Yale University, USA
Growing evidence indicates that sperm carry heritable epigenetic information, of which histone modifications represent a major component. However, how histone modifications in the paternal gametes influence offspring traits and health is not well understood in mammals. To robustly address this question, we generated mice harboring germline deletions of the X-linked histone modifier KDM6A and phenotyped genetically wild type male offspring (Kdm6a F1). Surprisingly, Kdm6a F1 mice develop normally but have significantly reduced lifespans and higher tumor burdens relative to control animals, suggesting that inherited epigenetic perturbations lower the threshold for malignant transformation. We found that a subset of genes previously associated with cancer initiation and progression is transcriptionally dysregulated in normal somatic tissue of Kdm6a F1 animals before the onset of cancer. To pinpoint the inherited epigenetic changes that may alter the gene regulatory state of these genes, we characterized KDM6A function in the paternal germline. In contrast to previous reports showing an association between KDM6A and enhancers in somatic tissues, we found that KDM6A widely and preferentially binds to promoters marked by active histone methylation modifications during a restricted developmental interval of spermatogenesis. KDM6A interacts with known (MLL3) and novel (SETD1) methyltransferases of the COMPASS complex at these promoters and KDM6A loss alters the deposition of H3K4me1 and H3K4me3. Ongoing work is aimed at determining if the same epigenetic lesions detected in the Kdm6a cKO male germline are present in normal somatic tissue and tumors of Kdm6a F1 mice and how affected genes may contribute to tumorigenesis. Our preliminary data provide support for the paternal germ line epigenome as a contributor to the large fraction of familial cancer risk that remains unexplained in humans.

P41 Social regulation of intergenerational signaling via a defined chemosensory pathway
Jadiel A Wasson | New York University, USA
Classically, inheritance was believed to be restricted to the passage of information from parent to progeny in the form of genetically encoded material. It has become appreciated that other types of information, including that which informs about the environment, can be passed between generations. However, the mechanisms behind how this information can be both passed on and interpreted by the embryo remain unknown. Recently, we have identified a previously unknown pathway for intergenerational communication that links neuronal responses to maternal provisioning in C. elegans. Here, a chemosensory signaling pathway responsive to social cues initiated in the mother alters the pool of maternally provided factors that modulates gene silencing in progeny. This intergenerational signal transmission depends on specific chemosensory neurons and neuronal FMRFamide (Phe-Met-Arg-Phe)–like peptides including FLP-21. Parental FLP-21 signaling dampens oxidative stress resistance and promotes the deposition of mRNAs for translational components in progeny, which, in turn, reduces gene silencing. Furthermore, overexpression

P41 Continued
of FLP-21 has the opposing effect on gene silencing in progeny suggesting that the levels of FLP-21 signaling in mothers influences embryonic stress phenotypes. Taken together, we hypothesize that loss of social cues in the parental environment represents an adverse environment that stimulates stress responses across generations. This work demonstrates how alterations to chemosensory signaling pathways can have long range consequences via changes in not only what mothers provide to their young, but also how resulting progeny modulate their gene expression changes in response to a challenge. Ultimately, this work will lead to a clearer understanding of the mechanisms involved in cross-generational signaling between mother and progeny.

P42 Non-coding RNA changes in adolescent stress-exposed female rats and their offspring

Hiba Zaidan, Jennifer Blaze, Magnus Kummerfeld, Katarzyna Winek, Hermona Soreq, Schahram Akbarian, Inna Gaisler-Salomon | University of Haifa, The Hebrew University of Jerusalem, Israel; Icahn School of Medicine at Mount Sinai, USA; Fritz Lipmann Institute, Germany

Pre-reproductive stress in adolescent female rats affects anxiogenic behavior as well as mRNA and microRNA (miRNA) expression in exposed rats and their offspring. Transfer RNAs (tRNAs), non-coding RNAs (ncRNAs) consisting of 70-90 nucleotides, were recently implicated in stress-related brain function and transgenerational information transfer. tRNAs may be cleaved into tRNA halves or fragmented into smaller tRNA fragments (tRFs), which play a role in regulating transcription and translation. This study examines whether chronic unpredictable stress (CUS) impacts tRNA halves and tRFs in the prefrontal cortex (PFC) of female rats and their neonate offspring, and explores sncRNA, specifically tRF and miRNA expression, in blood and germline. Adolescent female rats underwent CUS for 7 days. PFC was extracted 4 or 14 days later. A separate subset of CUS and Control females was bred with naïve males 14 days after CUS to produce the F1 generation. PFC samples were collected from neonate offspring and YAMAT-seq was performed to assess tRNA expression. In a subsequent experiment, blood and oocytes were extracted from CUS and Control adolescent female rats 14 days following the stress procedure, and sncRNAseq was performed to assess tRF and miRNA expression in blood and oocytes. RT-PCR was used in both experiments to verify expression changes. In PFC of CUS-exposed females, we found differences in the levels of tRNA isodecoders and tRFs 4 and 14 days after stress. In neonate F1 offspring, we found no change in tRNA isodecoders, but the same tRFs that were altered in directly-exposed females were also altered in their F1 offspring. A comparison between blood and oocyte samples from Control females revealed different expression patterns of tRFs and miRNAs, indicating that transcriptional regulation may differ in these tissues. Stress affected miRNA, but not tRF expression in blood. Specifically, miR-99a was decreased in blood of CUS-exposed females. Analysis of sncRNA expression in CUS and Control oocytes is ongoing; Preliminary RT-PCR analysis points to differential miRNA expression in stress-exposed oocytes. Combined with our previous findings, these data signify that stress affects both miRNA and tRNA/tRF expression in the brain, and that sncRNA changes in blood and oocytes may play a role in the intergenerational transfer of stress-related information.

P43 Maternal type 1 diabetes programs sex-dimorphic liver-associated metabolic dysfunction in offspring

Allan Zhao, Paulo Jannig, Hong Jiang, Valentina Clio Zingerle, Annika Blaufuss, Qiaolin Deng | Karolinska Institute, Stockholm University, Sweden

Growing evidence suggests that prenatal exposure to hyperglycemia of maternal T1D is associated with an increased risk of developing metabolic dysfunction, such as fatty liver disease. So far, whilst epidemiological studies have prevailed in highlighting the intergenerational effects, the mechanistic investigation remains largely limited. Here, we investigate the long-term consequences of maternal T1D on metabolic function of the offspring using an optimized streptozotocin-induced T1D model. After mating with healthy males, their offspring were followed longitudinally up to 52 weeks on chow diet with extensive metabolic

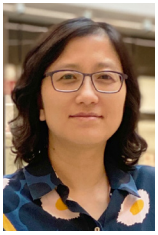
P43 Continued
phenotypic and molecular analyses. At 16 weeks of age, which corresponds to young adulthood in human, both male and female offspring of diabetic mothers (ODM) exhibited normal glucose tolerance, insulin sensitivity and body weight gain. However, only female ODM exhibited increased adiposity and signs of hepatic lipid accumulation when compared to control offspring (CO). These phenotypes aligned with transcriptomic alterations in liver and adipose tissue related to lipid metabolism. At 52 weeks, female ODM developed both glucose intolerance and insulin resistance, whereas the male ODM only developed insulin resistance. Interestingly, this was associated with clear transcriptomic alterations in the liver and visceral adipose tissue related to de novo lipogenesis and lipolysis predominantly in the female offspring. Surprisingly, when challenged with a 16-week long high-fat diet (HFD) starting from 6 weeks of age, ODM of both sexes gained less weight compared to CO, whilst the ODM and CO exposed to HFD had comparable glucose tolerance and whole-body metabolism. However, specifically female ODM exposed to HFD developed a hepatic fibrosis-like phenotype with corresponding transcriptomic alterations when compared to female CO exposed to HFD, indicating the importance of the liver as a central organ for development of metabolic dysfunction in ODM. To summarize, mild maternal T1D programs sex-dimorphic liver-related metabolic dysfunction in offspring which is exacerbated by a HFD challenge. Further studies are now ongoing to translate our experimental findings using epidemiological cohorts and clinical case-control studies.

SPEAKERS

(In alphabetical order)

Lucia Daxinger, Leiden University Medical Center, The Netherlands

Lucia Daxinger received her PhD in Molecular Genetics from the University of Vienna in 2008, studying RNA-directed DNA methylation under Dr. Marjori Matzke at the Gregor Mendel Institute for Molecular Plant Sciences. Intrigued by the conservation of epigenetic silencing factors across organisms, she transitioned from plants to mammals. In 2009, she was awarded an Erwin Schroedinger Postdoctoral Fellowship from the Austrian Science Fund and joined Prof. Emma Whitelaw's lab in Australia, where she identified epigenetic factors in mammals and their role in paternal effects. Inspired by the link between epigenetic regulators and human diseases, she secured a LUMC Fellowship in 2014 and an NWO-VIDI grant in 2018, becoming a group leader at the Department of Human Genetics. Lucia's research focusses on understanding how epigenetic mechanisms contribute to phenotypic variation by defining how epigenetic regulators function in modifying chromatin state. Her lab has been developing approaches to leverage advanced single-cell and long-read singlemolecule sequencing techniques to uncover cell type-specific epigenetic and transcriptional variation in in-vivo models. She aims to increase our understanding of the molecular mechanisms that control phenotypic variation and variable disease susceptibility and identify the repertoire of genomic loci where even subtle disruption to epigenetic state influences (disease) phenotype (i.e., metastable epialleles).



Qialon Deng, Karolinska Institute, Sweden

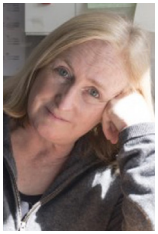
Qiaolin Deng completed her undergraduate study in Shanghai Medical College, Fudan University from 1996-2001. She later moved to Sweden and earned her Ph.D degree in Medical Science at Karolinska Institutet in 2010, focusing on neurodevelopmental biology. From 2011 to 2014, she was funded by the Swedish Medical Research Council and joined Rickard Sandberg's lab at the Ludwig Institute for Cancer Research, where she significantly contributed to the development of Smart-seq and Smart-seq2 single-cell RNA sequencing technologies. She applied single-cell sequencing technology to study preimplantation embryonic development in mouse and human embryos and pioneered in identifying random monoallelic expression of autosomal genes. From 2015, Qiaolin established her independent research group at Karolinska Institutet and currently holds the Associate Professor position at Karolinska Institutet and Stockholm University. Her research is focused on understanding gene regulation of pluripotency transition, germ cell fate specification, as well as dynamics of X-chromosome activity. Moreover, her lab is interested in intergenerational transmission of disease via the germline or developmental programing. Her lab has been/are funded by several prestigious grants including Swedish Society for Medical Research, Swedish Medical Research Council, Wallenberg Foundation in Medicine among others.

Michel Dubois, University of Sorbonne, France

Michel Dubois is a sociologist at the French National Centre for Scientific Research (CNRS). He currently serves as director of the Groupe d'étude des méthodes de l'analyse sociologique de la sorbonne (GEMASS), a social science research laboratory in Paris. Previously, he was deputy director of the CNRS international research unit Epigenetics, Data and Politics based in Los Angeles. Among his recent publications : Michel Dubois, Catherine Guaspare, (with S.Louvel), „Epigenetics and Society: Epigenetics in the French Press", in Grunaud C., Maury S. (eds), Epigenetics in Ecology and Evolution, ISTE Wiley, 2025, 291-310 ; Michel Dubois, „'Changing our genes': the public image of epigenetics and gene editing in France", in Bauer W. M., Schiele B. (eds), Science Communication: Taking a Step Back to Move Forward, CNRS Editions, 2023, 41-56 ; Michel Dubois, Catherine Guaspare, „From Cellular Memory to the Memory of Trauma: Social epigenetics and its public circulation", Social science information, 2020, 144-183.

Jill Escher, The Escher Fund for Autism, USA

Jill Escher is an autism research philanthropist through the Escher Fund for Autism, focusing on questions of toxicant exposures that may affect the genomic and epigenomic integrity of germ cells. She is president of the National Council on Severe Autism, past president of Autism Society San Francisco Bay Area, and co-chair of the Germ Cell special interest group of the Environmental Mutagenesis and Genomics Society. Her work has been published in Environmental Epigenetics, Environmental and Molecular Mutagenesis, Journal of Autism and Developmental Disorders, Biology of Reproduction and Autism Research. She is an outspoken autism research advocate who has been featured in The Free Press, Tablet Magazine, National Public Radio, and New York Times, among others. Jill is a provider of affordable housing for adults with autism and related developmental disorders, and sponsors more than 70 informational and recreational events per year for the San Francisco Bay Area autism community. A former lawyer, she is a graduate of the UC Berkeley School of Law and Stanford University. She and her husband have two adult children with severe, nonverbal forms of autism. Please learn more at jillescher.com.



Amanda Fisher, University of Oxford, United Kingdom

Amanda Fisher is a cell biologist and Whitley Professor of Biochemistry at the University of Oxford. She previously worked for many years at the MRC Laboratory of Medical Sciences at Imperial College London, as well as in France and America. She is interested in how cell identity is transmitted as cell divide, and the epigenetic mechanisms underpinning cellular differentiation and reprogramming. Fisher was awarded the EMBO gold medal in 2002, appointed a Fellow of the Royal Society in 2014 and received an International Helmholz Fellowship in 2015.

Katharina Gapp, ETH Zurich, Switzerland

Katharina Gapp is an Assistant Professor at the Institute for Neuroscience at ETH Zürich, Switzerland. Over the past 15 years, her research has focused on the impact of paternal stress on offspring phenotype and the mechanisms mediating non-genetic information transfer across generations. During her PhD in the lab of Isabelle Mansuy at the Brain Research Institute of ETH Zürich, she made a groundbreaking discovery identifying sperm RNA as a key vector for transmitting the behavioral and metabolic effects of early life stress across generations in mice. This pioneering work helped establish a new field of RNA-mediated inheritance of environmentally induced traits in mammals. Following her doctoral work, she continued her research as a postdoctoral fellow in the lab of Eric Miska at the University of Cambridge and the Sanger Institute in the UK, where she further explored the role of non-coding RNAs. Her research has been published in numerous prestigious scientific journals and has earned her significant recognition, including the PRIMA grant from the Swiss National Science Foundation, an ERC Starting Grant (now funded by Switzerland) and most recently a Human Frontiers Science Programme grant. Currently, her team's research centers on nuclear receptors and the development of novel translational tools to modulate their function. These tools are applied to investigate disease mechanisms and promote health, reflecting her ongoing commitment to advancing biomedical science through innovative and impactful research.

Petra Hajkova, MRC Laboratory of Medical Sciences & Imperial College London, United Kingdom

Petra Hajkova is a senior group leader and the Deputy Director at the MRC Laboratory of Medical Sciences (LMS), and a Professor of Developmental Epigenetics at Imperial College London. Following her undergraduate studies at the Charles University in Prague, Petra moved to Berlin, where she carried out her PhD work on regulation of developmental DNA methylation in the Max Planck Institute for Molecular Genetics. In 2002 Petra joined Azim Surani's laboratory at the Gurdon Institute in Cambridge, UK to investigate the processes of epigenetic reprogramming in vivo; and following this very successful postdoctoral work, established her own laboratory at the MRC LMS in 2009. Her group has been using genetic and biochemical approaches to understand the basis of epigenetic reprogramming and germ cell development, unravelling how epigenetic information is transmitted, erased and re-instated in the course of mammalian lifecycles. Petra was appointed an EMBO young investigator, awarded the prestigious Mary Lyon medal by the Genetics Society and the Cheryl Tickle Medal of the British Society of Developmental Biology. Petra is an elected EMBO member and an elected Fellow of the UK Academy of Medical Sciences.

Pei-Hsuan Wu, University of Geneva, Switzerland

Pei-Hsuan Wu is an Assistant Professor in the Department of Genetic Medicine and Development at the University of Geneva in Geneva, Switzerland. Her research focuses on the molecular mechanisms underlying male reproduction driven by small non-coding RNAs. In particular, her lab investigates PIWI-interacting RNAs—also known as "piRNAs"—in spermatogenesis, sperm function, and intergenerational inheritance. Dr. Wu earned her Bachelor's degree in biology from Boston University in the US. Following her undergraduate studies, she worked as a research technician in Bruce Spiegelman's lab at Harvard Medical School, studying transcriptional regulation in metabolism. She completed her Ph.D. in Richard Carthew's lab at Northwestern University, where she investigated small RNA-mediated gene silencing using fly genetics and biochemistry. Dr. Wu then conducted postdoctoral training in Phillip Zamore's lab at the RNA Therapeutics Institute at the UMass Chan Medical School. There, her research using mouse models contributed to our understanding of mammalian piRNA function. In 2022, supported by a PRIMA career starting grant from the Swiss National Science Foundation, Dr. Wu established her independent research group at the University of Geneva. She is an active member of the Swiss RNA community through the NCCR RNA & Disease network and the European male reproduction network via the COST Action ANDRONET.

Ali Jawaid, Łukasiewicz Research Network – PORT Polish Center for Technology Development, Poland

Dr. Ali Jawaid is a physician-scientist with expertise in both clinical and basic neuroscience. He earned his medical degree from Aga Khan University (Karachi, Pakistan) and pursued clinical and research training in Neuropsychiatry at Baylor College of Medicine (Houston, TX, USA). He later completed an MD-PhD in Neuroscience at UZH/ETH (Zurich, Switzerland) under the mentorship of Prof. Isabelle Mansuy. Dr. Jawaidcurrently leads the Laboratory for Translational Research in Neuropsychiatric Disorders (TREND Lab) at the Lukasiewicz Research Network – PORT Polish Center for Technology Development. His lab focuses on understanding the interplay between non-coding RNAs and metabolic factors in the long-term effects of childhood trauma, with a particular emphasis on metabolic interventions to mitigate neuropsychiatric symptoms. In addition, Dr. Jawaid is a FENS-Kavli Network of Excellence (FKNE) scholar, an exclusive network of outstanding early- and mid-career neuroscientists in Europe. FKNE fosters scientific collaboration, promotes advocacy for neuroscience research, and provides mentorship opportunities for young researchers in the field.

Jo Leroy, University of Antwerp, Belgium

Jo Leroy graduated with a Master's degree in Veterinary Medicine from the University of Ghent in July 2001, achieving Magna cum laude and receiving the Faculty of Veterinary Medicine's distinction award. He subsequently secured an IWT grant for his PhD at the same university, focusing on metabolic changes in high-producing dairy cows and their impact on oocyte and embryo quality. Jo joined the Department of Veterinary Sciences of Antwerp University as a doctoral assistant, taking on a significant teaching role. Promoted to full professor in 2018, he currently teaches physiology, pathophysiology, husbandry, propedeutics, and veterinary public health. He also leads the on-campus large animal facility, De Ark, and has chaired task forces for educational visitation rounds. Jo's research focuses on the impact of maternal health on fertility, oocyte and embryo quality, and postnatal health, utilizing innovative in vitro and ex vivo models across species. Beyond academia, he founded the Camelid Immunisation Facility, providing expert services to biotech companies, and actively contributes to ethical committees on animal experiments.

Satoshi Namekawa, University of California Davis, USA

Dr. Satoshi H. Namekawa received his Ph.D. from the Tokyo University of Science in 2005 and completed postdoctoral training in the laboratory of Dr. Jeannie T. Lee at Massachusetts General Hospital and Harvard Medical School in 2009. He was then appointed to the faculty at Cincinnati Children's Hospital Medical Center. Dr. Namekawa's research focuses on epigenetic mechanisms that establish the cellular identities of male and female germlines and regulate critical developmental transitions. His laboratory pioneered the concept of epigenetic priming and identified chromatin-based mechanisms that drive germ cell differentiation. His research is uncovering meiosis as a global epigenetic reprogramming process. He received the Basil O'Connor Starter Scholar Research Award from the March of Dimes Foundation in 2011 and the New Investigator Award from the Society for the Study of Reproduction in 2015. In 2020, he was recruited to the University of California, Davis, as a tenured full professor. He served as a standing member of the NIH Molecular Genetics (MG) Study Section from 2020 to 2024 and chaired the MAYosis Seminar Series in 2023 and 2024.

Bart P.F. Rutten, Maastricht University, The Netherlands

Bart P.F. Rutten, Professor of Psychiatry at Maastricht University, is a leader in translational neuroscience, focusing on gene-environment interactions and neuroepigenetics in mental disorders. He chairs the Department of Psychiatry and Neuropsychology and coordinates the Horizon Europe Youth-GEMS project on youth mental health trajectories. Rutten co-founded the Center for Integrative Neuroscience (CIN), blending clinical practice with research in psychotrauma and neuropsychiatry. A graduate with honors in medicine from Maastricht University and KU Leuven, he earned his Ph.D. on neuronal loss in aging and Alzheimer's disease. His work integrates human studies, molecular biology, and animal models to explore conditions like psychosis, PTSD, and dementia. Rutten leads multinational projects, including the largest study on gene-environment interactions in schizophrenia and epigenetic research on trauma resilience. Awarded VENI and VIDI grants from NWO and EU funding for projects like EU-GEI and Youth-GEMS, he contributes to the Psychiatric Genomics Consortium. Rutten disseminates his findings through publications, including Neuroepigenetics and Mental Illness, and unique initiatives like an exposition on transgenerational trauma. His work bridges clinical practice and neuroscience, advancing mental health research.

Mitinori Saitou, Kyoto University, Japan

Mitinori Saitou received his M.D. and Ph.D. (under Prof. Shoichiro Tsukita) from the Kyoto University, and performed his postdoctoral work at the Wellcome Trust/Cancer Research UK Gurdon Institute (with Prof. Azim Surani). He was appointed team leader at the RIKEN Center for Developmental Biology in 2003. He was appointed Professor at the Kyoto University Graduate School of Medicine in 2009, and Director of the JST ERATO program in 2011. He was appointed Professor at the Kyoto University Institute for Advanced Study (KUIAS) and Director of Institute for the Advanced Study of Human Biology (ASHBi) in 2018. He was appointed program officer of the JST FOREST program in 2023. His work focuses on the mechanism and reconstitution in vitro of germ cell development in mice, non-human primates including great apes, and humans.

Michael Skinner, Washington State University, USA

Dr. Michael Skinner is a professor in the School of Biological Sciences at Washington State University, Pullman Washington, USA. He did his B.S. in chemistry at Reed College in Portland Oregon, his Ph.D. in biochemistry / chemistry at Washington State University (WSU) and his Postdoctoral Fellowship at the C.H. Best Institute at the University of Toronto, Canada. He has been on the faculty of Vanderbilt University and the University of California at San Francisco. He is the Founding Director of the Center for Reproductive Biology at WSU and University of Idaho, which is the largest reproduction biology center in the world, with over 100 faculty. Dr. Skinner's current research has demonstrated the ability of environmental exposures (e.g., toxicants) promote the epigenetic transgenerational inheritance (non-genetic form of inheritance) of disease phenotypes due to abnormal germ line epigenetic programming in gonadal development. Dr. Skinner has over 400 peer reviewed publications and has given over 400 invited symposia, plenary lectures and university seminars. Dr. Skinner is the Editor-in-Chief of the Encyclopedia of Reproduction and the Oxford publishing journal Environmental Epigenetics. He has done Ted talks and had documentaries done on his research with BBC Horizon, PBS Nova, Smithsonian, and France ARTE. Dr. Skinner has also founded several biotechnology companies.

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