2023
LOUIS-JEANTET SYMPOSIUM

Transcription and beyond

FONDATION
LOUIS-JEANTET

PROGRAMME

Louis-Jeantet Prize Winners' Day 2023

08:15 – 08:50 **Registration and welcome coffee**

08:50 – 08:55 **Antoine Geissbühler,** Dean of the Faculty of Medicine, University of Geneva
Opening

08:55 – 09:00 **Denis Duboule,** President of the Board of Trustees of the Louis-Jeantet Foundation
Welcome

SESSION 1

Chairperson: **Patrick Cramer,** Max Planck Institute for Multidisciplinary Sciences, Göttingen, Germany

9.00 – 9.30 **Ana Pombo,** Max Delbrück Centre for Molecular Medicine, Berlin, Germany
Specialization of 3D genome structure in different cell types and states

9.30 – 10.00 **Maria-Pia Cosma,** Centre for Genomic Regulation (CRG), Barcelona, Spain
Transcription-mediated supercoiling shapes 3D chromatin structure and looping

10.00 – 10.30 **Ibrahim Cissé,** Max Planck Institute of Immunobiology & Epigenetics, Freiburg, Germany
Super-resolution imaging of transcription in living cells

10:30 – 11:00 **COFFEE BREAK**

11.00 – 11.30 **Karen Adelman,** Harvard Medical School, Boston, USA
Gene control at coding and non-coding RNA loci

11.30 – 12.00 **Torben Heick Jensen,** Aarhus University, Denmark
Nuclear sorting of RNA

12:00 – 13:30 **LUNCH**

SESSION 2

Chairperson: **Richard Treisman,** The Francis Crick Institute, London, UK

13.30 – 14.00 **Elena Conti,** Max Planck Institute of Biochemistry, Martinsried, Germany
To degrade or not to degrade: molecular mechanisms of mRNA homeostasis

14.00 – 14.30 **Martijn Luijsterburg,** Leiden University Medical Center, The Netherlands
Molecular mechanisms in transcription-coupled DNA repair

14.30 – 15.00 **Maria Carmo-Fonseca,** Instituto de Medicina Molecular, Lisbon, Portugal
Intriguing Frontiers: Exploring Unresolved Questions on Co-transcriptional Splicing

15.00 – 15.30 **COFFEE BREAK**

15.30 – 16.00 **Lori Passmore,** MRC Laboratory of Molecular Biology, Cambridge, UK
Molecular insights into mRNA 3'-end processing and transcription termination

16.00 – 16:30 **Jesper Svejstrup,** University of Copenhagen, Denmark
Distinct pathways for removal of defective RNA polymerase II transcription complexes at a promoter-proximal pause checkpoint

16.30 – 16:40 **Patrick Cramer and Richard Treisman**
CONCLUDING REMARKS

ORGANISING COMMITTEE

Patrick Cramer
2021 Louis-Jeantet prize-winner

Richard Treisman
2002 Louis-Jeantet prize-winner

THE LOUIS-JEANTET SYMPOSIUM

Held for the first time in 2012, the Louis-Jeantet Symposium has been chaired every year by two former Louis-Jeantet prize winners who, together with speakers specialized in the same area, report on the progress of their research and discuss the challenges on the latest developments. These events offer a unique opportunity for Master students, PhD students and post-docs to meet with other scientists and create networking opportunities. Over the years, a wide range of medical and biomedical research topics such as cancer, stem cells, immunity, developmental biology, and mRNA biology were discussed.

THE LOUIS-JEANTET FOUNDATION

Founded in 1983 and established in Geneva, the Louis-Jeantet Foundation seeks to further the cause of medicine by encouraging innovative projects, both in fundamental and in clinical medicine. It is one of the leading European foundation in its field of activity.

Each year since 1986 the Louis-Jeantet Prize for Medicine and the Jeantet-Collen Prize for Translational Medicine, recognize cutting-edge researchers who are active in the European Council member countries. These prizes do not reward a completed work but serve to ensure the continuation of promising projects. Research is encouraged in all aspects of life sciences which relate to human health.

Strongly attached to its home town, the Louis-Jeantet Foundation provides annual funds to the Faculty of Medicine of the University of Geneva in support of local biomedical research. These subsidies allow the Faculty to finance full professorial and tenure track positions.

Ana Pombo
Max Delbrück Centre for Molecular Medicine, Berlin, Germany

Specialization of 3D genome structure in different cell types and states

The three-dimensional (3D) structure of chromosomes is important for gene regulation and cell function. Understanding how 3D genome structure varies between cell types, in development and disease, promises to enhance the interpretation of genome sequence and to accelerate the discovery of disease target genes. To explore 3D genome structure variation in different stages of development, from blastocysts to highly specialised cells of the brain, we applied Genome Architecture Mapping (Winick-Ng et al 2021 Nature; Loof et al 2022 Biorxiv). We found extensive cell-type specialisation of 3D chromatin contacts, such as extensive reorganisation of topological domains (TADs) and eu/heterochromatic compartments. We also discovered large scale decondensation events, or 'melting', of long genes when most highly expressed, many of which with roles in neurodevelopment and neurodegeneration. Through integration of 3D genome structure with single-cell expression and single-cell chromatin accessibility, we find cell-type specific hubs of contacts containing genes associated with specialised cellular functions, such as addiction and synaptic plasticity in dopaminergic and glutamatergic neurons, respectively. Our recent work explores advantages of GAM relative to ligation-based conformation capture methods (Beagrie et al 2023 Nat Methods), differences in 3D genome structure between parental chromosomes, and the effects of environmental insults, such as addiction drugs or sleep deprivation, and mutations in chromatin remodellers on the complex 3D genome structures of brain cells, and their long-term impact in gene deregulation.

Biography

Ana Pombo studies 3D genome folding and gene expression in development and disease. After her DPhil at University of Oxford, UK, Ana received a Royal Society Dorothy Hodgkin Fellowship and started her independent lab at the MRC London Institute for Medical Sciences. In 2013, she moved to the Berlin Institute of Medical Systems Biology (BIMSB) of the Max Delbrück Center in Berlin, Germany, where she serves as Deputy Director. Ana received the Robert Feulgen Prize, and was elected member of EMBO and the European Academy of Sciences. She has pioneered Genome Architecture Mapping (GAM) to map 3D genome structure.

https://www.mdc-berlin.de/pombo

Maria-Pia Cosma
Centre for Genomic Regulation (CRG), Barcelona, Spain

Transcription-mediated supercoiling shapes 3D chromatin structure and looping

Dissecting the 3D-chromatin organization in cell physiology is a key area of investigation. By using quantitative super-resolution nanoscopy, we identified a novel chromatin fiber assembly and its relation with naïve pluripotency. Nucleosomes are arranged in groups of various sizes, the nucleosome clutches, which control gene function. We recently visualized the structure of cohesin-mediated loops in human cells and discovered that transcriptional-dependent supercoiling controls loop formation and 3D-genome organization. Furthermore, by combining imaging and genomic approaches, we designed MiOS, a powerful integrated strategy to model the folding of key pluripotency genes at nucleosome resolution. Overall, super-resolution microscopy combined with genomic and modeling methods allowed us to dissect the functional role of transcription-mediated supercoiling and the nucleosome level structure of genes, which ultimately are key features controlling gene activity.

Biography

Maria-Pia Cosma received her PhD in Cellular and Molecular Genetics in 2000. She held a junior PI position at TIGEM in Naples and became a EMBO Young Investigator in 2003.Since 2010 she is a senior PI and ICREA Research Professor at the CRG in Barcelona where she is now a program co-coordinator. She received numerous awards including the Marie Curie Excellence Award in 2005; the Order of Merit of the Italian Republic in 2007; the Barcelona City Prize in 2015; and the EIC National Champion in 2021. She is EMBO Member since 2010. The laboratory uses different approaches ranging from the nanoscale imaging of the chromatin to complex systems such as tissue regeneration.

https://www.crg.eu/maria_pia_cosma

10:00 – 10:30

Ibrahim Cissé
Max Planck Institute of Immunobiology & Epigenetics, Freiburg, Germany

Super-resolution imaging of transcription in living cells

We will discuss the latest efforts in our laboratory to develop highly sensitive methods of microscopy, to go directly inside living cells and uncover the behavior of single biomolecules as they effect their function in transcription. Transcription is the first step in gene expression regulation, during which genetic information on DNA is decoded into RNA transcripts. Methodologically, the so-called live cell single molecule and super-resolution techniques – that break the optical diffraction limit– are revealing with unprecedented spatial and temporal resolutions, novel emergent phenomena inside the living cells. We will discuss our recent discoveries on highly dynamic biomolecular clustering, and phase transitions in vivo. These discoveries are challenging the 'textbook view' on how our genome (DNA) is decoded in living cell.

Biography

Ibrahim Cissé is currently Director in Max Planck Gesellschaft, heading the Department of Biological Physics at the Max Planck Institute of Immunobiology & Epigenetics in Freiburg, Germany. Prior to this he was Professor of Physics at the California Institute of Technology (Caltech), and before, an Associate Professor with Tenure in Physics (& Biology by courtesy) at the Massachusetts Institute of Technology (MIT). He received his Bachelor in Physics in 2004 from North Carolina Central University, and his Ph.D. in Physics from the University of Illinois at Urbana-Champaign in December 2009. He moved to Paris from 2010 to 2012, where he was a Post-doctoral Fellow at Ecole Normale Supérieure. He moved back to the US in 2013, as a Research Specialist at the HHMI's Janelia Research Campus before joining MIT in 2014 as a junior faculty. His research on single molecule and super-resolution imaging has been recognized through many honors including being named a Pew Biomedical Scholar, an NIH Director's New Innovator awardee, Science News "SN10 Scientists To Watch", a Vilcek Prize for Creative Promise in Biomedicine, and a MacArthur Fellow.

www.ie-freiburg.mpg.de

Karen Adelman
Harvard Medical School, Boston, USA

Gene control at coding and non-coding RNA loci

The transition of RNA polymerase II (Pol II) from initiation to productive elongation is a central, regulated step in metazoan gene expression. At many genes, Pol II pauses stably in early elongation, remaining engaged with a short nascent RNA for many minutes while awaiting signals for release into the gene body. However, this paused Pol II can be actively targeted for premature termination, which releases the polymerase and a short, non-productive RNA, effectively short-circuiting the process of gene expression.
I will discuss our recent work investigating the balance between productive elongation vs. premature termination of Pol II near gene promoters and enhancers. Further, I will discuss the factors that modulate this balance in response to signaling from the environment, or during development.

Biography

Dr. Karen Adelman is the Edward S. Harkness Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School. She is also a Member of the Gene Regulation Observatory at the Broad Institute, and the Ludwig Cancer Center at Harvard Medical School. The Adelman lab pioneered genomic studies of RNA polymerase II (RNAPII) transcription. Her work revealed that pausing of RNAPII in early elongation is a central regulatory step in metazoan gene expression. Ongoing work probes the interplay between transcription, RNA processing and chromatin modifying machineries to elucidate the determinants of mature mRNA formation in health and disease.

https://adelman.hms.harvard.edu/

11:30 – 12:00

Torben Heick Jensen
Department of Molecular Biology and Genetics, Aarhus University, Aarhus, Denmark

Nuclear sorting of RNA

Mammalian genomes are promiscuously transcribed, demanding efficient nuclear sorting of RNA. On the degradative side of the sorting process, the RNA exosome is a central ribonuclease. In the nucleoplasm, it is assisted by its adaptors the Nuclear EXosome Targeting (NEXT) complex and the PolyA eXosome Targeting (PAXT) connection. Via an association between a basic patch of the RNA-binding ARS2 protein and an acidic short linear motif (SLiM) of the ZC3H18 protein, NEXT/exosome is recruited to capped and short unadenylated transcripts. Similarly, PAXT provides exosome access to short adenylated substrates through the association of ARS2 with an acidic SLiM of the core PAXT component ZFC3H1.
Conspiciously, the basic patch of ARS2 also binds an acidic SLiM of the transcription restriction factor ZC3H4. This interaction recruits the ZC3H4/WDR82 dimer to chromatin to elicit RNAPII termination. ZC3H4 in turn directly connects to the ZCCHC8 component of the NEXT complex, hereby facilitating rapid degradation of the nascent RNA. Finally, ARS2 also interacts with SLiM-containing RNA maturation factors, FLASH and PHAX.
Overall, this positions ARS2 centrally in the nuclear RNA sorting process at the nexus of transcription termination, RNA processing and decay. Putative mechanisms and implications will be discussed.

Biography

Torben Heick Jensen (THJ) is a Professor at Aarhus University (AU), Department of Molecular Biology and Genetics (MBG). He obtained his PhD in 1997 at MBG, AU and conducted postdoctoral work in 1998-2001 with Nobel Laureate Prof. Michael Rosbash HHMI, Brandeis University, USA. The research group of THJ is a central player within the RNA biogenesis/turnover field with focus on identifying eukaryotic RNA termination, maturation and turnover systems; their factor compositions, substrate specificities and regulatory capacities. The group also investigates how these complexes interrelate/compete with RNA export complexes and how gene expression regulation at the RNA level impacts cellular differentiation and disease processes.

http://www.mrnp.dk/
http://mbg.au.dk/thj/

Elena Conti

Max Planck Institute of Biochemistry, Martinsried, Germany

To degrade or not to degrade: molecular mechanisms of mRNA homeostasis

In eukaryotes, the transcription of protein-coding genes is coupled to processing mechanisms that modify the transcripts and coat them with proteins, leading to the formation of messenger ribonucleoprotein complexes (mRNPs). If all biogenesis steps occur correctly, the resulting mature mRNPs are transported through nuclear pore complexes by export factors. However, disruptions or errors in essentially any step of the biogenesis process can give rise to malformed mRNPs, which are then retained in the nucleus and eliminated by nuclear quality control pathways. A large proportion of Pol II transcription indeed terminates before reaching the end of gene, resulting in degradation of the incomplete transcripts, primarily via the action of the RNA-degrading exosome. A crucial question is, how do the quality control and decay machineries recognize aberrant mRNAs/mRNPs and degrade them? Conversely, what features do mature, correctly packaged nuclear mRNPs possess that enable them to evade degradation? Over the years, we have been employing biochemical and structural approaches to unravel the fundamental questions surrounding these complex processes, which are crucial to maintain cellular mRNA homeostasis. The talk will focus on our recent data at the crossroads of mRNA biogenesis, quality control and degradation.

Biography

Elena Conti, PhD, is an Italian biochemist and structural biologist who has been serving as a Director at the Max Planck Institute of Biochemistry in Munich, Germany, since 2007. Conti is a globally renowned authority in the study of protein-RNA complexes. Her group made major contributions to our understanding of the molecular mechanisms that govern cellular RNA homeostasis, with a particular emphasis on RNA surveillance and degradation. She is an elected member of EMBO, the Accademia dei Lincei (IT) and the Royal Society (UK). In recognition of her work, Conti received numerous awards, including the Louis Jeantet Prize in 2014.

https://www.biochem.mpg.de/conti

14:00 – 14:30

Martijn Luijsterburg
Leiden University Medical Center, The Netherlands

Molecular mechanisms in transcription-coupled DNA repair

For transcription-coupled DNA repair (TCR), RNA polymerase II (Pol II) must transition from a transcriptionally active to an arrested state that allows for removal of DNA lesions. This transition requires site-specific ubiquitylation of Pol II by the CRL4CSA ubiquitin ligase, a process that is facilitated by ELOF1 in an unknown way. Using cryo-EM, biochemical assays, and cell biology approaches, we show that ELOF1 serves as an adaptor to stably position UVSSA and CRL4CSA on arrested Pol II, leading to ligase neddylation and activation of Pol II ubiquitylation. In the presence of ELOF1, a TFIIS-like element in UVSSA gets ordered and extends through the Pol II pore towards the polymerase active site where it prevents Pol II reactivation by TFIIS. These results provide the molecular basis underlying the transition of Pol II from a transcriptionally active to an arrested state that allows for DNA repair.

Biography

Martijn Luijsterburg is a molecular biologist, group leader and associate professor at the Leiden University Medical Center, the Netherlands. His group investigates mechanisms in transcription-coupled DNA repair using genome-wide genetics, genomics and proteomic approaches. He was elected EMBO young investigator (in 2021) and received an ERC consolidator grant and NWO-VICI grant for his work. The goal of his lab is to increase our fundamental knowledge about how cells deal with obstacles caused by DNA damage during transcription, and to understand how – if this process fails – this can cause human diseases. Martijn is advisor for Cockayne syndrome support groups in the Netherlands, the UK and the US.

https://www.luijsterburglab.org/

Maria Carmo-Fonseca

Instituto de Medicina Molecular, Lisbon, Portugal

Intriguing Frontiers: Exploring Unresolved Questions on Co-transcriptional Splicing

Splicing of pre-mRNAs is a fundamental process for gene expression in eukaryotic cells and its misregulation is a hallmark of many human diseases including cancer. Understanding the processes involved in splicing regulation is essential to deciphering disease mechanisms as well as to develop novel targeted treatments. Although the molecular mechanisms of the splicing reactions have been extensively characterized, the principles governing splicing regulation remain elusive. Proteins that bind to the pre-mRNA (RNA-binding proteins, RBPs) are the main influencers of splicing decisions. However, because most splicing occurs during transcription, the interaction of RBPs with pre-mRNA may be modulated by chromatin structure and transcriptional rates. Previous studies from our lab addressed the timing of intron excision relative to Pol II elongation. The results that we and others observed suggest that the rate at which splicing occurs is faster than expected from diffusion and RBP binding affinity alone. One possibility to explain why splicing can occur so rapidly is that Pol II assembles with splicing factors (RBPs) into local higher-order complexes that control the efficiency of the splicing process. However, not all splicing occurs immediately after transcription. What is the fate of unspliced pre-mRNAs detected in association with elongating Pol II? This unresolved question in co-transcriptional splicing will be discussed.

Biography

Maria Carmo-Fonseca is Professor at the University of Lisbon Medical School. She is a founder of the Institute of Molecular Medicine (iMM), a biomedical research institute affiliated with the University of Lisbon Medical School, where she currently serves as President. She was visiting Professor at Harvard Medical School (2011 to 2013). She is member of the European Molecular Biology Organization, the Portuguese Academy of Sciences, the Portuguese Academy of Medicine, and Academia Europaea, and she served as President of the RNA Society (2021-2022). She is scientific editor for the Journal of Cell Science and the RNA journal. Carmo-Fonseca received several prestigious national science awards, and serves in multiple national and international advisory committees.

Since her post-doc at EMBL Heidelberg, Carmo-Fonseca is interested in understanding the nuclear organization and dynamic regulation of pre-mRNA splicing. Her lab combines microscopy techniques and genome-wide methodologies to study the interplay between transcription and RNA processing.

https://imm.medicina.ulisboa.pt/investigation/laboratories/maria-carmo-fonseca-lab/#intro

Lori A Passmore
MRC Laboratory of Molecular Biology, Cambridge, UK

Molecular insights into mRNA 3'-end processing and transcription termination

Eukaryotic mRNAs must be processed before they can be exported from the nucleus as mature transcripts. 3'-end processing is carried out by the cleavage and polyadenylation specificity factor (CPSF; CPF in yeast). This involves endonucleolytic cleavage of the nascent pre-mRNA and addition of a poly(A) tail. Cleavage and polyadenylation define the 3' end of the transcript which is important for mRNA localization, translation and stability. In addition, CPF is required for efficient transcription termination. I will speak about our efforts to use structural biology and biochemical reconstitution to gain molecular insight into this process.

Biography

Lori A Passmore is a Group Leader at the MRC Laboratory of Molecular Biology in Cambridge UK. She uses an integrated approach combining structural, biochemical and functional studies, aiming to reconstitute multi-protein complexes and their activities, and to determine their high-resolution structures to understand their mechanisms. She works on protein complexes that add and remove poly(A) tails from mRNAs and complexes involved in DNA repair. She was elected a member of EMBO in 2018, received the RNA Society's Inaugural Elisa Izaurralde Award in 2020 and was elected a Fellow of the Royal Society in 2023.

http://www2.mrc-lmb.cam.ac.uk/groups/passmore/

16:00 – 16:30

Jesper Q. Svejstrup
University of Copenhagen, Denmark

Distinct pathways for removal of defective RNA polymerase II transcription complexes at a promoter-proximal pause checkpoint

Cells constantly experience and contend with 'transcription stress', i.e., the pausing, arrest, and/or backtracking of RNAPII during its journey across a gene. Such stress can be triggered by a number of different conditions, including DNA damage. Irrespective of cause, transcription stress has general and severe consequences for genome stability, and different pathways and factors have evolved to ensure that such stress is abated. We have described an evolutionarily conserved pathway, which allows RNAPII ubiquitylation and proteasomal degradation as a 'last resort' so that the consequences of impediments to transcript elongation can dealt with and genome instability avoided. Ubiquitylation of RNAPII is extremely tightly regulated, involving several distinct ubiquitin ligases in a multi-step process that is in turn 'proof-read' by specific ubiquitin proteases. In this talk, a new ubiquitin ligase required for dealing with regulated RNAPII pausing is described, which establishes evidence for a novel checkpoint mechanism that removes defective RNAPII complexes at promoter proximal pause sites.

Biography

Jesper Svejstrup is interested in RNAPII transcription and its coordination with other processes such as DNA repair. He received his PhD from Aarhus University and did postdoc work at Stanford, before starting his independent group at CRUK's Clare Hall Laboratories. In 2015, he joined the Francis Crick Institute, before returning to Denmark in 2020. Svejstrup is an honorary professor at UCL, Imperial College, and Aarhus University. He was elected to EMBO in 2003, to the Royal Society In 2009, to the Royal Danish Academy in 2016, and in 2018, to the UK's Academy of Medical Sciences. Svejstrup is recipient of consecutive ERC Advanced Grants and serves as member of ERC Council as vice-president for Life Sciences.

https://icmm.ku.dk/english/research-groups/svejstrup-group/

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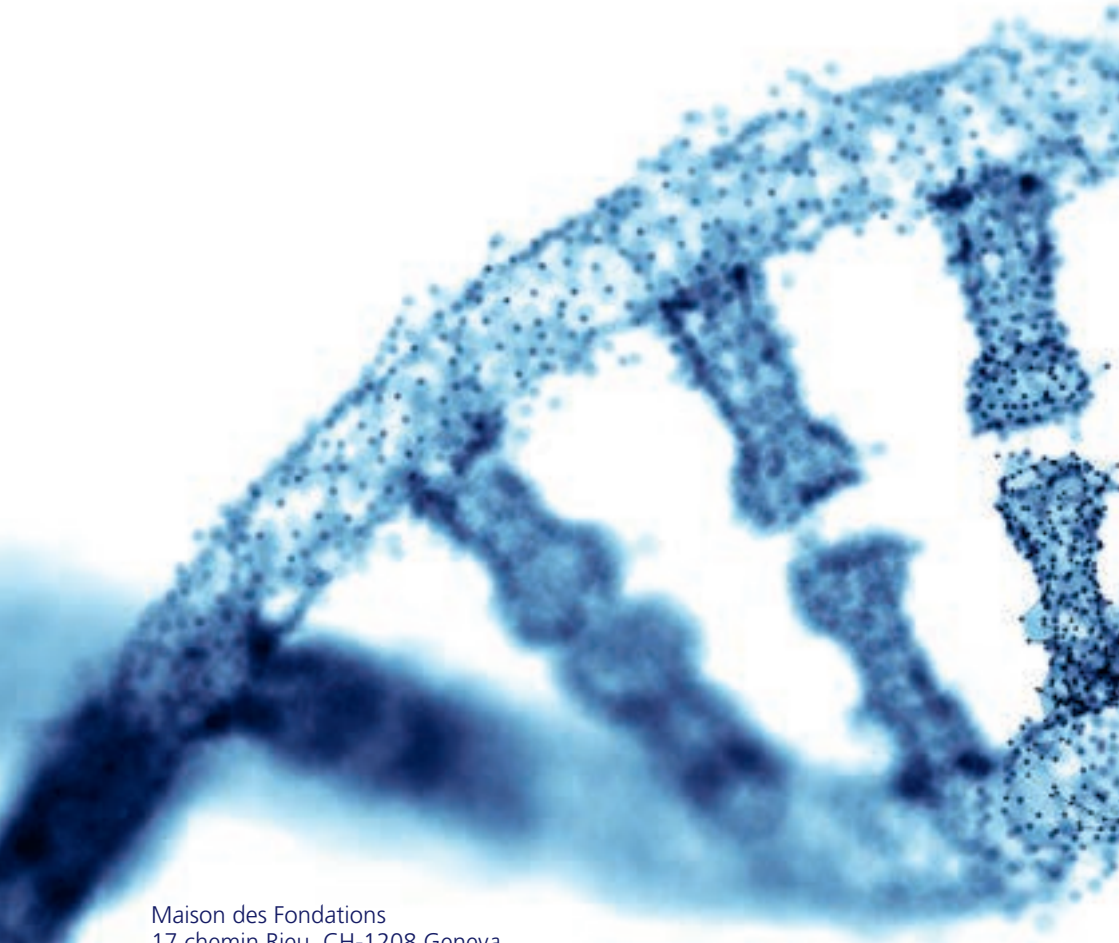

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