

Magda Bienko

Personal Journey
Science
ERC

Forum Ambrosetti, Milano 2024



Ph.D.
Biochemistry

Postdoc
Systems Biology

Assistant Professor/ Group leader

Group leader

2006



2011



2015



Svedberg Prize 2019



humantechnopole.it



2022





$\sim 2\,000\,000\ \mu\text{m}$

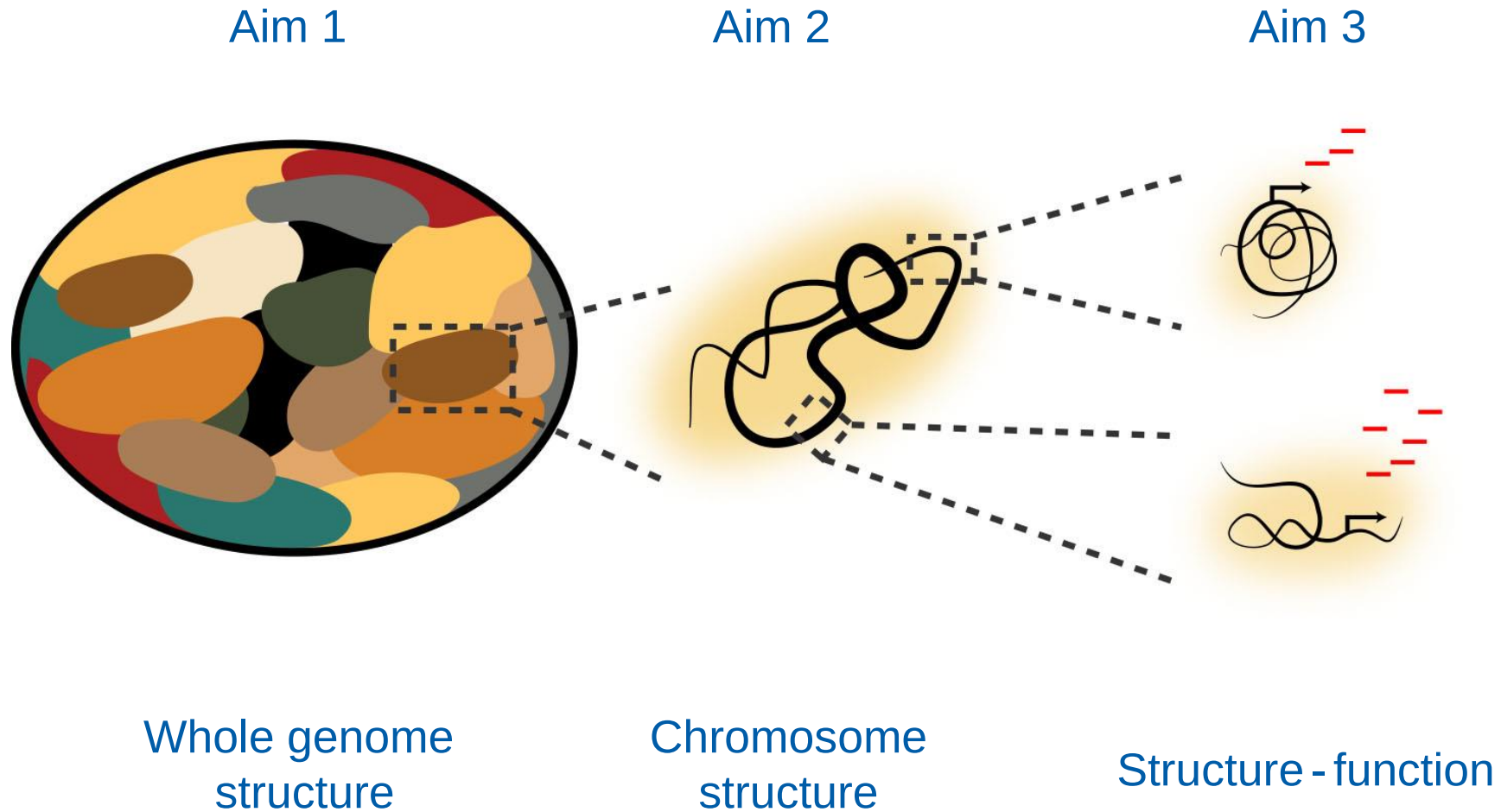


$\sim 10\ \mu\text{m}$

How is our genome arranged in 3D?



GENOMIS (ERC Starting Grant)



Excerpts from ERC Reviewers' comments 1/2

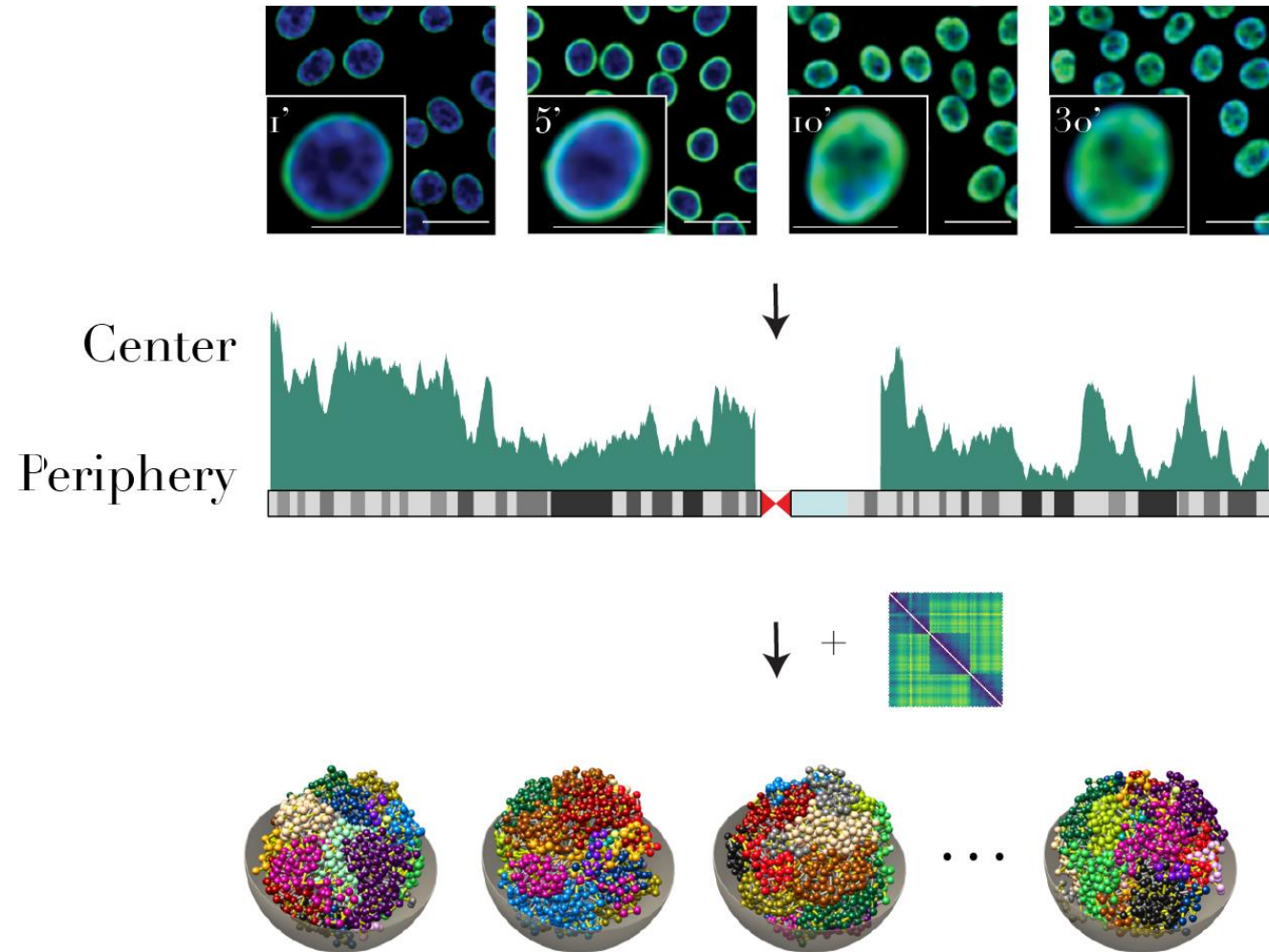
- *The technical edge of this project is to go **beyond the limits of existing technologies** to study genome organisation, by **combining in a novel and unique way**: mapping genomic loci by sequencing of nuclei gradually digested by nucleases (new method termed GPSeq), HiC methods and microscopy (FISH) methods at high resolution.*

- *As witness of Dr Bienko's ability to be a **creative independent thinker** serves the fact that she was brave enough to be the first biologist joining Alexander van Oudenaarden's lab. Further evidence hereof is the **highly interdisciplinary team** that she has formed as a PI and the **very strong (and again interdisciplinary) collaborations** she already established.*

Excerpts from ERC Reviewers' comments 2/2

- *Unfortunately, both major methods proposed here are **flawed**. The GPSeq method is **unlikely to have the sensitivity** expected by the applicant. Given a diffusion coefficient of on the order of 30-50 $\mu\text{m}^2/\text{s}$, a restriction enzyme molecule will only take a few seconds to diffuse across the nucleus making suggested time-courses to control the depth of entry into the nucleus **implausible**. In addition, given the known heterogeneity in positioning amongst individual cells, it is **unlikely that consistent digestion profiles will be generated**.*

Never give up!

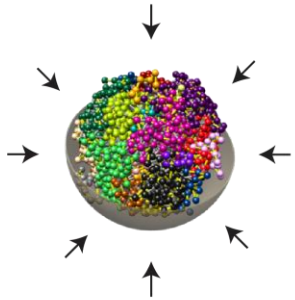


Girelli et al., *Nat Biotechnol* 2020

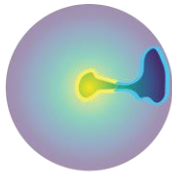
RADIALIS (ERC Consolidator Grant)

Novel biology

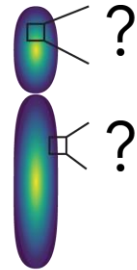
Forces



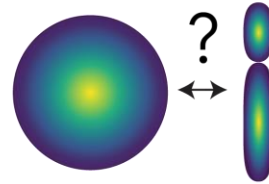
New karyotypes



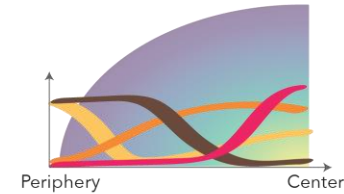
Mitotic chromosome structure



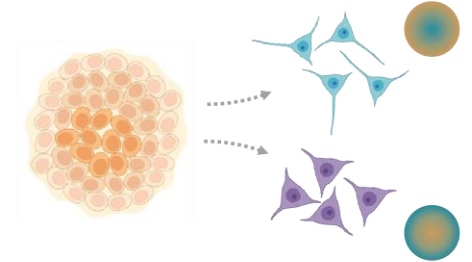
Chromatin (de)condensation



Atlas of nuclear RNAs and proteins along radius

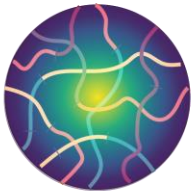


New TF biology and cell fate specification

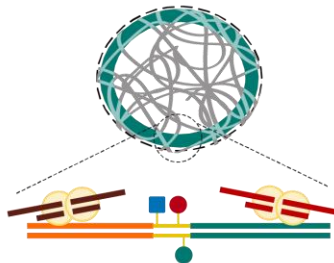


Novel technologies

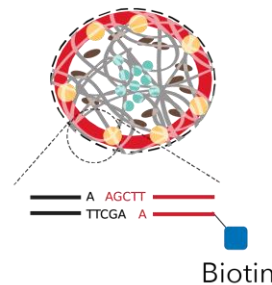
GP-C



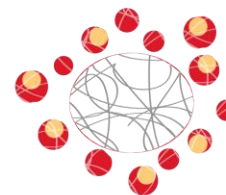
Radial RADICL-seq



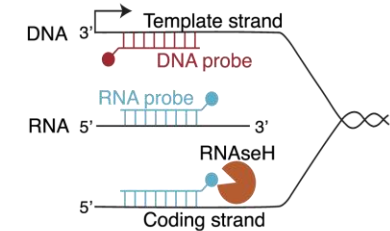
GPSpec



Chrom-peel



DNA - RNA FISH



Excerpts from ERC Reviewers' comments 1/3

*This is a fantastic proposal. The potential to produce knowledge that may **change current thinking** about the 3D genome and gene expression regulation is very high. Sophisticated methods are likely to advance knowledge on genome organization at the single cell level and during mitosis, and*

...

*She is internationally recognised by her **high-quality** work which takes an **original orthogonal approach**, and **uniquely** contributes to the European position in 4D-Nucleome research.*

Excerpts from ERC Reviewers' comments 2/3

*The PI already demonstrated the **ground-breaking research** in her publications, and the scope of the research that cover **multiple disciplines is the proof for creative and independent thinking.***

*The proposal is **brimming with interesting conceptual ideas and highly original approaches** that focus on the 3D organisation of the genome, both in interphase nuclei and in mitotic chromosomes. Certainly, **the applicant is not following mainstream ideas and techniques, but relies on her own concepts and approaches***

*From the proposal it is clear that the applicant is **extremely creative, and has many highly original ideas.***

Excerpts from ERC Reviewers' comments 3/3

(...) will hopefully **revolutionize the CRISPR-based cellular programming** by introducing into host DNA sequence the segments of the predefined GC content to guide the spatial location of selected DNA loci. This will allow to **manipulate gene expression by the non-coding regions DNA sequence modifications, without actually changing gene coding sequence and/or regulatory DNA regions.** That will provide the useful exploitation of so-called DNA junk sequence.

It's all about the team



Alessandra Alberta Albertini
Technician



Carlos Jimenez
Postdoctoral Researcher



Emily Georgiades
Postdoctoral Researcher



Giulia Della Chiara
Senior Staff Scientist



Giulia Peveri
Postdoctoral Researcher



Ilaria Castiglioni
Senior Technician



Lorenzo Salviati
Postdoctoral Researcher



Mohit Virdi
PhD student



Simona Pedrotti
Senior Technician



Britta Bouwman
Research Specialist



Emma Inns
Lab Coordinator



Erik Wernersson
Senior Researcher



Wing Hin Yip
PhD student



Jinxin Chen
PhD student



Kaja Harton
PhD student



Konstantinos Georgiadis
Postdoctoral Researcher
(shared with Foukakis lab)



Linxuan Zhao
PhD student (incoming)



Quentin Verron
Postdoctoral Researcher



Sen Li
Postdoctoral Researcher
(shared with Foukakis lab)



Wenjing Kang
Postdoctoral Researcher



Xiaoze Li-Wang
Research Specialist

Stay tuned!

The technical edge of this project is to go beyond the limits of existing technologies to study genome organisation, by combining in a novel and unique way: mapping genomic loci by sequencing of nuclei gradually digested by nucleases (new method termed GPSeq), HiC methods and microscopy (FISH) methods at high resolution.

She has demonstrated the ability to propose and conduct excellent research, she has very strongly proven creative independent thinking, and her achievements have clearly gone beyond the state of the art.

The objectives are ambitious and beyond the state of the art, including novel concepts and approaches/developments across disciplines.

As witness of Dr Bienko's ability to be a creative independent thinker serves the fact that she was brave enough to be the first biologist joining Alexander van Oudenaarden's lab. Perhaps not unrelated, most of van Oudenaarden's work now focuses on biology. Further evidence hereof is the highly interdisciplinary team that she has formed as a PI and the very strong (and again interdisciplinary) collaborations she already established.

Following her very successful PhD in DNA repair in Frankfurt, the PI continued her work on DNA breaks as a postdoc at MIT and Utrecht, and developed early techniques for establishing chromatin territories, which she has followed up since starting her lab at the Karolinska with innovative microscopy by FISH, including deconvolution and other imaging software. The development of radial sequencing (GPseq) completes the package. A string of fellowships and awards culminated in the Svedberg prize normally awarded to much more senior researchers in Sweden.

This is a fantastic proposal. The potential to produce knowledge that may change current thinking about the 3D genome and gene expression regulation is very high. Sophisticated methods are likely to advance knowledge on genome organization at the single cell level and during mitosis and explore the role of RNAs in genome radiality and the role of radiality in gene expression and in nuclear processes.

Dr. Bienko represents the great talent in Europe in the multidisciplinary field of 3D genome organisation. She has a great track record from her PhD, with several awards, and publications, and was recruited competitively to one of the best international centres in single cell and systems biology.

Her programme reflects an effort to advance her field of research from the technical and analytical aspects. Although less focused on a given biological model, this work reflects an international effort to produce the technologies, knowledge and human resources needed for understanding genome function.

The outcome(s) could potentially be significant and transformative.

The scientific track of PI is exceptional in her involvement in multiple research aims and interdisciplinary approaches.

The PI already demonstrated the ground-breaking research in her publications, and the scope of the research that cover multiple disciplines is the proof for creative and independent thinking.

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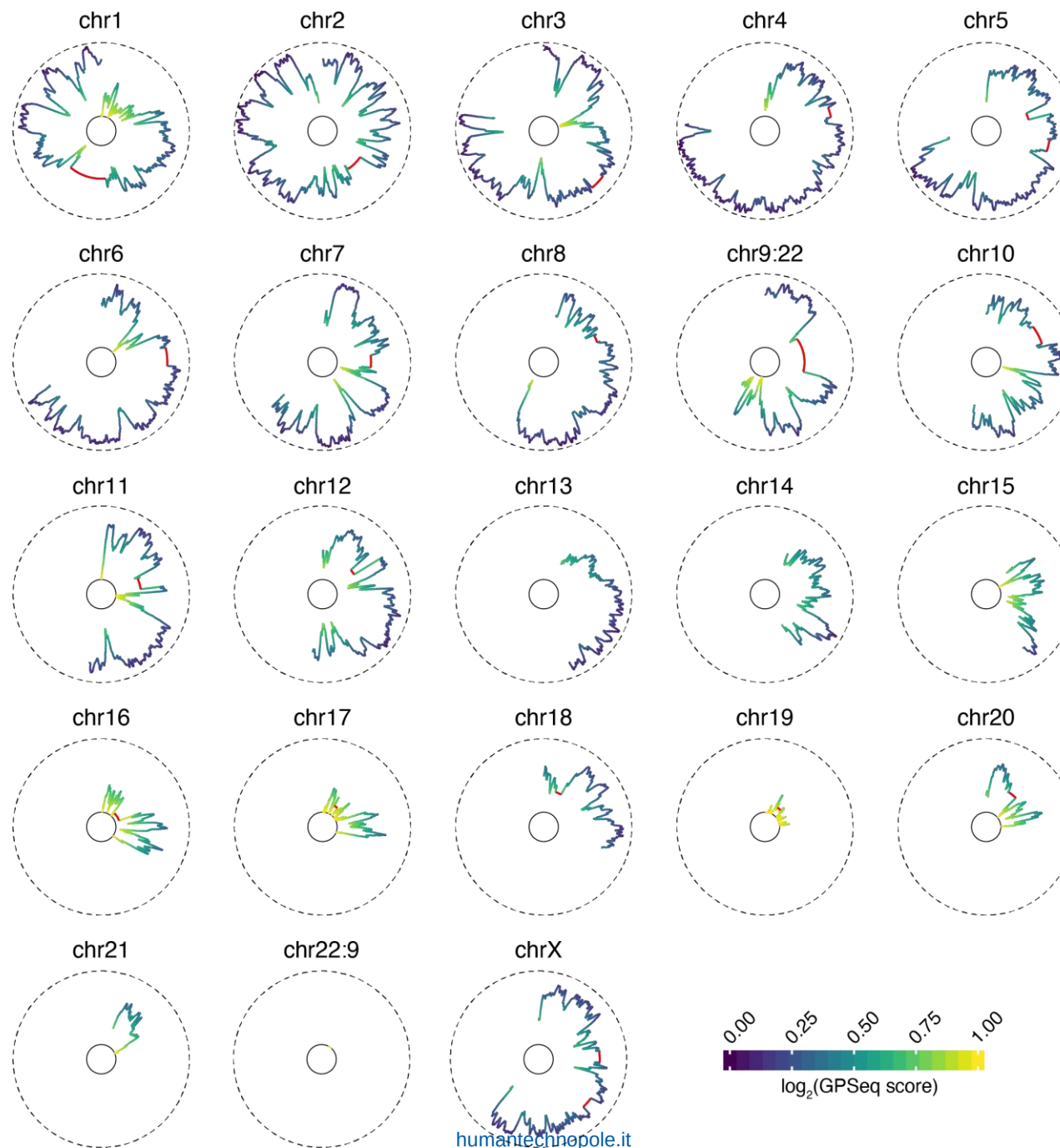
Ten most important publications are listed, only as PI, almost all of which are new methodologies mostly co-developed with her colleagues in Karolinska and in Milan following her recent move. While this is a prodigious record of achievement, her own group has yet to address a major biological question using this extensive methodology, though there can be little doubt this will happen in the near future.

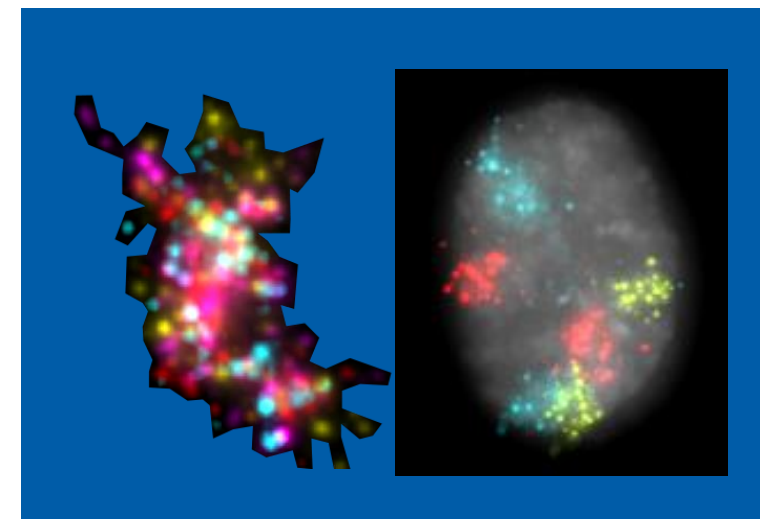
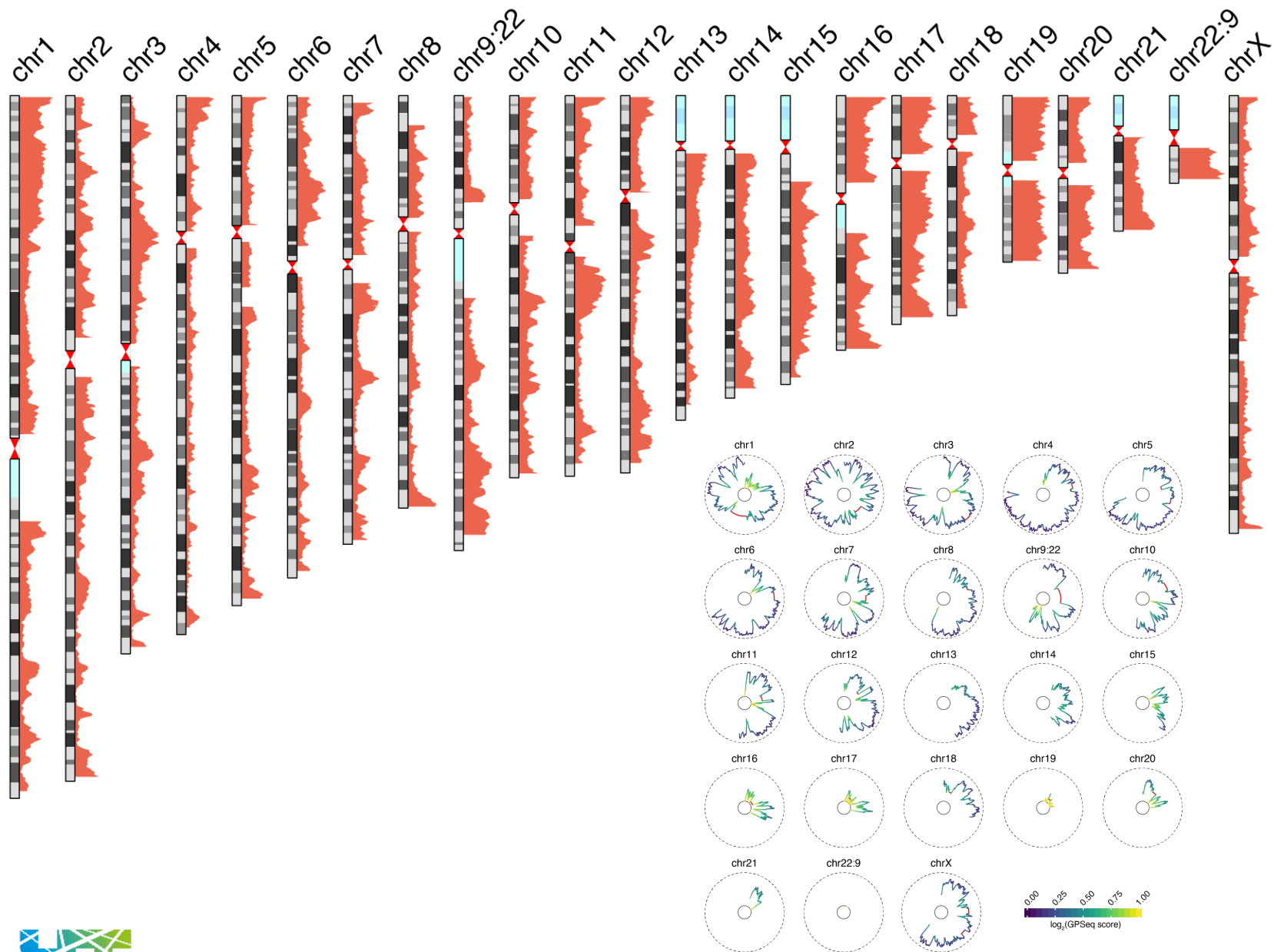
She is internationally recognised by her high-quality work which takes an original orthogonal approach, and uniquely contributes to the European position in 4D-Nucleome research.

She has demonstrated fully her capacity to develop the proposed research, technology development and its application to cell type specific and interference systems to characterise radial genome positioning.

The proposal is brimming with interesting conceptual ideas and highly original approaches that focus on the 3D organisation of the genome, both in interphase nuclei and in mitotic chromosomes. Certainly, the applicant is not following mainstream ideas and techniques but relies on her own concepts and approaches.

From the proposal it is clear that the applicant is extremely creative and has many highly original ideas.





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From the proposal it is clear that the applicant is **extremely creative and has many highly original ideas.**

Unfortunately, both major methods proposed here are flawed. The GPSeq method is unlikely to have the sensitivity expected by the applicant. The preliminary data does not alleviate this concern. The method is based on the controlled diffusion of restriction enzymes through the nuclear space to probe the radial location of genome regions. Given a diffusion coefficient of on the order of $30\text{-}50\mu\text{m}^2/\text{s}$, a restriction enzyme molecule will only take a few seconds to diffuse across the nucleus making suggested time-courses to control the depth of entry into the nucleus implausible. In addition, given the known heterogeneity in positioning amongst individual cells, it is unlikely that consistent digestion profiles will be generated. Finally, it is not clear how differences in nuclear shape and volume would affect the interpretation of the data. The author's preliminary data demonstrating differences between the gene dense and poor chromosomes 18 and 19 are not a correct validation of the method as the observed differences are likely due to differences in chromatin structure rather than position.



Thank you.

Fondazione Human Technopole
Palazzo Italia
Viale Rita Levi-Montalcini, 1 - 20157 Milan, Italy

humantechnopole.it

