BIOGRAPHICAL SKETCH

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NAME: Attya Omer Javed

eRA COMMONS USER NAME (credential, e.g., agency login): N/A

POSITION TITLE/CONTACT: Project Leader

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Ecole Pratique des Hautes Etudes / Université Paris Sciences et Lettres, Paris	MS	06/2013	Science and Technology
Université Paris-Saclay, Paris *Joint with* Whitehead Institute for Biomedical Research, Cambridge	PHD	12/2017	Cellular and Molecular Physiopathology
San Raffaele - Telethon Institute for Gene Therapy, Milan	Postdoctoral Fellow	01/2019	Stem cell biology, Gene therapy, Chemotherapy-free conditioning

A. Personal Statement

I have served as a Project Leader at the San Raffaele Telethon Institute for Gene Therapy (SR-TIGET) since January 2025, where my research focuses on developing next-generation gene therapy strategies. My work addresses one of the major limitations of hematopoietic stem cell transplantation (HSCT): the reliance on toxic conditioning regimens to enable efficient donor cell engraftment.
To overcome this barrier, my research program aims to redefine how hematopoietic stem cell (HSC) engraftment and niche accessibility are achieved. Specifically, my objectives are twofold.

First, I seek t**o identify the key molecular determinants governing HSC engraftment and egress**. By leveraging optimized genome-wide gain- and loss-of-function *in vivo* screening platforms in HSCs, my team is uncovering critical regulators of these processes. These insights inform the development of innovative mobilization strategies and the engineering of HSCs with a transient competitive advantage during engraftment.

Second, we aim to **establish a mobilization-based, non-genotoxic conditioning paradigm**. By exploiting the temporary niche depletion induced by clinically relevant ane novel mobilizers, we are developing conditioning regimens that avoid chemotherapy or irradiation. By integrating cell-surface profiling data with mobilizer-resistant variants generated through directed evolution, we actively tilt the competitive balance between endogenous and infused HSCs in favor of the latter.

This research program pioneers innovative approaches that enhance HSC mobilization and engraftment while eliminating the need for toxic conditioning. By addressing fundamental biological mechanisms and translating them into therapeutic strategies, my work has the potential to transform HSCT practice and significantly improve patient outcomes across hematological, metabolic, and immune disorders.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2013 - 2013	Graduate Student, Institut Curie, Orsay
2022 - 2017	PhD student, Université Paris-Saclay, Paris *Joint with* Whitehead Institute for Biomedical Research, Cambridge
2018 - 2018	Post-doctoral Fellow, Whitehead Institute for Biomedical Research, Cambridge
2019 - 2024	Post-doctoral Fellow, San Raffaele - Telethon Institute for Gene Therapy, Milan
2025 -	Project Leader, San Raffaele - Telethon Institute for Gene Therapy, Milan

Other Experience and Professional Memberships

2015 -	Member; International Society for Stem Cell Research
2022 -	Member; American Society of Gene & Cell Therapy
2023 -	Member; American Society for Hematology
2023 -	Member, Abstract reviewer; European Hematology Association
2024 -	Member, Abstract reviewer; European Society of Gene & Cell Therapy

Awards

2013	PhD scholarship - French Ministry of National Education, Higher Education and Research
2015	Fulbright Scholarship
2015	Boehringer Ingelheim Fonds Fellowship
2022	MSCA Postdoctoral Fellowships
2022	Top Italian Women Scientist
2022	Under 40 in Hematology
2025	Nature Inspiring Women in Science Award – Scientific achievement; Runner up

Grants as PI

2024	ASH Global Research Award (2 years)
2024	EHA Junior Research Grant (3 years)
2025	FIS Starting Grant (3 years)
2026	ERC starting grant (5 years)

C. Contributions to Science

I specialize in the genome engineering of pluripotent stem cells and primary hematopoietic stem cells, leveraging this expertise to drive technological innovation, develop disease models, and devise therapeutic strategies.
My dissertation work focused on modeling microcephaly using pluripotent stem cells, genome engineering, and brain organoids. First, I studied the role of KNL1, a key component of the mitotic machinery, in human neural development and disease. While most of the mutated genes found in microcephaly patients encode a cell division related protein, presumably important in all tissues, only the brain is impacted. To get insight into the brain-specific phenomenon, I introduced a point mutation in human embryonic stem cells that has been identified in microcephalic patient. As opposed to neural progenitors, no changes in KNL1 expression, cell proliferation or genomic integrities were found in mutated astrocytes, neurons, neural crest cells or fibroblast, demonstrating a cell specific role of KNL1 in neural progenitors to control the human brain size. This distinct phenotype has never been reported and could provide a new paradigm to microcephaly understanding (*first co-author).

> Microcephaly modeling of kinetochore mutation reveals a brain-specific phenotype. **Attya Omer Javed***, Yun Li*, Julien Muffat*, Kuan-Chung Su, Malkiel Cohen, Tenzin Lungjangwa, Raaji Alagappan, Patrick Aubourg, Iain Cheeseman and Rudolf Jaenisch; *First co-author; Cell Reports, doi: 10.1016/j.celrep.2018.09.032

Genetic mutations are not the only cause linked to microcephaly. ZIKA virus has received a lot of attention, especially since the epidemy. It was reported that the virus could infect the nervous system of fetuses through maternal infection, leading to a child born with microcephaly. Yet, how ZIKA virus reaches the fetal neural

progenitor is subject to debates. We first established a robust and efficient protocol for the rapid production of microglia-like cells from human induced pluripotent stem (iPS) cells using defined serum-free culture conditions. Prior to this study, bona fide microglia had not been derived from cultured human pluripotent stem cells, opening new avenues for disease modeling, drug testing, and studies on cell transplantation. I contributed by discussing/performing few experiments and revising the manuscript.

> Efficient derivation of microglia-like cells from human pluripotent stem cells. Julien Muffat, Yun Li, Bingbing Yuan, Maisam Mitalipova, **Attya Omer**, Sean Corcoran, Grisilda Bakiasi, Li-Huei Tsai, Patrick Aubourg, Richard M Ransohoff, Rudolf Jaenisch; Nature Medicine, doi: 10.1038/nm.4189

We then complemented the canonical organoids model, by Lancaster, with ZIKA virus infected microglia and suggested an unconventional hypothesis. We proposed that the microglia act like a viral reservoir and travels from the maternal vasculature to the embryo and could cause infection of the fetal brain (*first co-author).

> Human induced pluripotent stem cell-derived glial cells and neural progenitors display divergent responses to Zika and dengue infections. Julien Muffat*, Yun Li*, **Attya Omer*,** Ann Durbin, Irene Bosch, Grisilda Bakiasi, Edward Richards, Aaron Meyer, Lee Gehrke, Rudolf Jaenisch; *First co-author; PNAS, doi: 10.1073/pnas.1719266115

Finally, we established a cerebral organoid model displaying surface folding and showed that infection with Zika virus impairs cortical growth and folding. Our study provided new insights into the mechanisms regulating the structure and organization of the human cortex. I contributed by discussing/performing few experiments and revising the manuscript.

> Induction of expansion and folding in human cerebral organoids. Yun Li, Julien Muffat, **Attya Omer**, Irene Bosch, Madeline A. Lancaster, Mriganka Sur, Lee Gehrke, Juergen A. Knoblich, Rudolf Jaenisch; Cell Stem Cell, doi:10.1016/j.stem.2016.11.017

To identify ZIKV host genes and potential molecular targets for therapies, we used a genome-wide CRISPR-Cas9 knockout screen in human neural progenitors. The screen identified host factors involved in heparan sulfation, endocytosis, endoplasmic reticulum processing, Golgi function, and interferon activity. Our findings provided insights into host-dependent mechanisms for ZIKV infection in the highly vulnerable human neural progenitor cells and proposed potential molecular avenues for therapeutic solutions (*first co-author).

> Genome-wide CRISPR screen for Zika virus resistance in human neural cells. Yun Li*, Julien Muffat*, **Attya Omer Javed*,** Tim Wang, Ann F. Durbin, Irene Bosch, Eric S. Lander, Lee Gehrke, David M. Sabatini, Rudolf Jaenisch; *First co-author; PNAS, doi:10.1073/pnas.1900867116

Parallel to my focus on neurodevelopment, I participated in the establishment of a mesofluidic platform technology to study gut-liver-cerebral interactions in the context of Parkinson's disease. It connects microphysiological systems (MPS) of the primary human gut and liver with a human induced pluripotent stem cell-derived cerebral MPS in a systemically circulated common culture medium containing CD4+ regulatory T and T helper 17 cells, allowing to parse out how genetic, immune and environmental factors contribute to neurodegenerative diseases. I contributed by discussing the experimental plan and performing few experiments.

> Engineered Human Physiomimetic Model Integrating Microphysiological Systems of the Gut, Liver and Brain for studies of Neurodegenerative Diseases. Martin Trapecar, Emile Wogram, Devon Svoboda, Catherine Communal, **Attya Omer Javed**, Tenzin Lungjangwa, …, David Trumper, Rudolf Jaenisch, Linda G. Griffith; Science Advances; doi: 10.1126/sciadv.abd1707

After my PhD, I decided to redirect my research and apply my expertise in human disease modeling towards challenges in hematopoietic stem/progenitor cell therapies. I therefore joined the laboratory of Prof. Naldini, where I embarked on projects addressing obstacles in gene therapy, which enriched my skill set in cellular and genetic biotherapies and built upon my earlier experience. One of the pivotal projects I delved into focused on alternatives to traditional chemotherapy.

Patients selected for gene therapy are first treated with mobilization drugs allowing the egress of HSCs from the bone marrow to the circulation. These primitive cells are then harvested from the patient, genetically corrected *ex-vivo* and infused back to the patient. However, before the administration of corrected cells, patients go through chemotherapy treatment to make space in the bone marrow, necessary for the engraftment of corrected cells. The chemotherapy and subsequent effect are dreaded by patients and are associated with severe long-term toxicity, thus constraining considerably the broader application of gene therapy. In our recently published work that I led as first author, we showed that mobilization drugs substantially, albeit transiently, deplete the bone marrow niches by orchestrating the egress of hematopoietic stem cells toward the circulation, creating a window of opportunity for seamless engraftment of corrected cells, bypassing altogether genotoxic conditioning. The mobilization-based conditioning encourages the eventual disposal of conventional genotoxic conditioning and should provide a transformative strategy greatly minimizing toxicity of current treatments, ameliorating patients' outcome, and paving the way to a broader use of HSCT (*first author).

> Mobilization-based chemotherapy-free engraftment of gene-edited human hematopoietic stem cells. Attya Omer-Javed, Gabriele Pedrazzani, Luisa Albano, Sherash Ghaus, Claire Latroche, Maura Manzi, Samuele Ferrari, Martina Fiumara, Aurelien Jacob, Valentina Vavassori, Alessandro Nonis, Daniele Canarutto, Luigi Naldini; First author ; Cell; doi: 10.1016/j.cell.2022.04.039

Besides my focus on HSC fitness and genotoxic-free conditioning, I also worked on emerging editing systems, particularly base and prime editors. In this collaborative project, we conceived and executed complex genomics and transcriptomics experiments that allowed to discover genotoxicity concerns of these novel tools and to devise strategies mitigating them in human HSCs. Moreover, we were among the first to provide evidence of efficient prime editing in human HSCs *ex vivo*. This recent publication provides a solid base for this proposal, provides platforms for safer and more effective genome manipulation (Second co-author).

> Genotoxic effects of base and prime editing in human hematopoietic stem cells. Martina Fiumara, Samuele Ferrari, Attya Omer-Javed#, Stefano Beretta#, Luisa Albano, Daniele Canarutto, Angelica Varesi, Chiara Gaddoni, Chiara Brombin, Federica Cugnata, Erika Zonari, Matteo Maria Naldini, Matteo Barcella, Bernhard Gentner, Ivan Merelli, Luigi Naldini. #Second co-author; Nature Biotechnology, doi: 10.1038/s41587-023-01915-4

Having been privileged to gain extensive research experience from leading experts in the field, my journey from the detailed investigations into neurodevelopment to groundbreaking work in HSC therapies has instilled in me a comprehensive understanding of the intricacies of cellular and genetic research. Throughout my research journey, I have not only employed existing methodologies but have also been at the forefront of establishing new protocols and models. Furthermore, my publications in high-impact journals validate the significance and rigor of the work I've accomplished. In reflection, my diverse research experiences, deep understanding of the field, and my ability to collaborate with experts, uniquely position me to lead the proposed research project.

A full list of my published work can be found at My Bibliography (NCBI):

https://www.ncbi.nlm.nih.gov/myncbi/attya.omer%20javed.1/bibliography/public/

1. **Research monographs and educational papers (Reviews and Commentaries)**

1) Editing of Hematopoietic Stem Cells: Hopes and Hurdles Toward Clinical Translation. Samuele Ferrari, Valentina Vavassori, Daniele Canarutto, Aurelien Jacob, Maria Carmina Castiello, Attya Omer Javed, Pietro Genovese; Gene Frontiers in genome editing; doi: 10.3389/fgeed.2021.618378
2) Mobilisation-based Engraftment of Hematopoietic Stem Cells: a New Perspective for Chemotherapy-free Gene Therapy and Transplantation. Daniele Canarutto*, **Attya Omer-Javed*;#,** Gabriele Pedrazzani, Samuele Ferrari, Luigi Naldini; *First co-author; # Corresponding author; British Medical Bulletin; doi: 10.1093/bmb/ldad017

2. **Patents.**

1) Methods for haematopoietic stem cell transplantation.

Inventors: Attya Omer-Javed, Gabriele Pedrazzani, Luigi Naldini

2) Targeted base editing for gene correction of WHIM syndrome.
   Inventors: Samuele Ferrari, Martina Fiumara, Attya Omer-Javed, Daniele Canarutto, Anna Villa, Luigi Naldini

D. Academic supervision

M.S students:
Grisilda Bakiasi (2015 - 2016)
Camilla Manzi (2024 - 2025)
Giada Volpi (2025 -)

Ph.D students:
Maura Manzi (2019 - 2021)
Gabriele Pedrazzani (2021 – 2024)

Postdoctoral Fellows:
Paolo Marchi (2022-2023, now postdoctoral fellow at University College London)
Gabriele Pedrazzani (2024 - 2025, now project leader at Università degli Studi di Torino, Turin)