PHYSICIAN SCIENTIST
LA MEDICINA INCONTRA LA RICERCA
promosso da: AIRC Fondazione CARIPLO | con il supporto di: SEMM European School of Molecular Medicine, UNIVERSITÀ DEGLI STUDI DI MILANO

2026 Physician Scientist Call

AVAILABLE POSITIONS

Principal Investigator	**TRIVELLIN GIAMPAOLO**
Institute of Affiliation	Università Humanitas
Title of the proposed project:	Modeling PAM variants in ACTH-secreting pituitary tumors using human organoids
Short description of the project	Pituitary neuroendocrine tumors (PitNETs), although usually benign, can cause substantial morbidity through hormone hypersecretion and local mass effects. ACTH-secreting PitNETs lead to Cushing's disease (CD), a severe endocrine disorder with substantial unmet clinical need. Our lab identified loss-of-function variants in PAM, a multifunctional secretory-granule protein, in functioning PitNETs, including pediatric CD. Preliminary data support the hypothesis that altered PAM function contributes to pituitary hypersecretion and tumorigenesis. The aim of this PhD project is to develop a human induced pluripotent stem cell (hiPSC)-derived hypothalamic-pituitary organoid model to investigate five PAM variants associated with CD and located in distinct functional regions: c.-133T>C (5'UTR), p.Tyr200Ter and p.Val244Ala (PHM domain), p.His778fs (PAL domain), and p.Leu856Pro (transmembrane domain). Each variant will be introduced by CRISPR-Cas9 into two well-characterized iPSC lines, one male and one female, generating isogenic mutant and wild-type controls. Edited lines will be molecularly and cytogenetycally validated, differentiated into hypothalamic-pituitary organoids, and followed at multiple time points from early pituitary commitment (d40) to endocrine cell maturation (d100/200). Since corticotrophs represent the default differentiation pathway for pituitary progenitors in this system, the model is particularly well suited to assess their development, ACTH secretion, and tumorigenic potential. The organoid system preserves the hypothalamic-pituitary interaction regulating hormone secretion and allows evaluation of both pituitary and hypothalamic effects of PAM dysfunction. Readouts will include single-cell RNA sequencing, immunofluorescence for pituitary and hypothalamic markers, ELISA for basal and stimulated hormone secretion, and assessment of proliferation/progenitor signatures. Results will be integrated with ongoing AtT-20 cell line analyses and PamPomc-cKO mouse studies, providing a human, sex-specific platform to define how PAM variants perturb corticotroph physiology and predispose to corticotroph PitNETs. The student will spend 20% of the PhD on clinical duties, potentially within the Endocrinology and Metabolism Disease Specialty Program of the Humanitas Research Hospital, subject to the required agreement.
Main research area for the project	Genomic Medicine
5 keywords for the project	Normal stem cells – Hormones - Neuroendocrine cancers – Organoids - Transcriptome/Transcriptomics

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promosso da: AIRC Fondazione CARIPLO | con il supporto di: SIEMM Società Italiana di Endocrinologia Molecolare | UNIVERSITÀ DEGLI STUDI DI MILANO

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LAB INFO	
Main topic/s of the lab	Neuroendocrinology and oncological endocrinology
Short description of the lab activity	The hosting laboratory focuses on translational endocrinology, with a specific emphasis on neuroendocrinology and oncological endocrinology. The group investigates the genetic and molecular mechanisms underlying PitNETs and rare disorders of hypothalamic-pituitary development, integrating patient-derived observations with mechanistic disease models. Current research activities include: a) the identification and functional characterization of genetic variants predisposing to PitNETs, b) the study of pituitary hormone hypersecretion and tumorigenesis using CRISPR-Cas9-edited cell lines and mouse models, c) the immunohistochemical and molecular profiling of human PitNET specimens, and d) the generation of hiPSC-based hypothalamic-pituitary organoids to model pituitary developmental and neoplastic disorders. The lab has established expertise in genome editing, iPSC culture, validation of engineered clones, differentiation into hypothalamic-pituitary organoids, quantitative PCR, immunofluorescence, hormone secretion assays, and transcriptomic approaches. The group has already generated and validated isogenic iPSC models for SOX3-related X-linked hypopituitarism and differentiated male and female iPSC lines into hypothalamic-pituitary organoids. This platform is now being extended to other pituitary diseases, including GPR101 duplications associated with X-linked acrogigantism, and will support the proposed PAM project. The laboratory is embedded within the Humanitas research and clinical environment, providing access to endocrine, neurosurgical, pathology, imaging, genomics, cytogenetics, stem cell, and bioinformatics expertise. The PhD student will be trained in human stem cell models, CRISPR-Cas9 editing, pituitary organoid differentiation, single-cell transcriptomics, confocal imaging, hormone assays, data interpretation, research integrity, scientific writing, and presentation of results at national and international meetings. The group currently includes the PI and postdoctoral researchers with complementary expertise in pituitary biology, genome editing, chromatin biology, iPSC culture, and organoid differentiation. The group interacts closely with the Pituitary Unit coordinated by Prof. Andrea Lania.
Recent bibliography	Duplications disrupt chromatin architecture and rewire GPR101-enhancer communication in X-linked acrogigantism. AM J HUM GENET 2022 Apr; 109: 553 Germline loss-of-function PAM variants are enriched in subjects with pituitary hypersecretion. FRONT ENDOCRINOL 2023; 14: 1166076 Chromatin conformation capture in the clinic: 4C-seq/HiC distinguishes pathogenic from neutral duplications at the GPR101 locus. GENOME MED 2024 Sep; 16: 112 Distinguishing benign from pathogenic duplications involving GPR101 and VGLL1-adjacent enhancers in the clinical setting

	with the bioinformatic tool POSTRE. NPJ GENOM MED 2026 Jan; 11: 12 Diverse SOX3 genetic variants and their associated phenotypic spectrum in human disease. Endocr Rev 2026 Apr;
Group composition	Three members in total, including the PI and two post-docs
Institutional page link	https://www.hunimed.eu/member/giampaolo-trivellin/