Internship Opportunity for Master's Student March -July 2025 (M/F)

Investigating Auranofin resistance in ovarian cancer cell model A2780

Presentation of the École Supérieure de Physique et de Chimie Industrielles de la Ville de Paris (ESPCI Paris - PSL)

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Since its creation, ESPCI has never ceased to mobilize its forces and skills to address major societal issues and defend the importance of science at the service of society. The environment, solidarity, health, access, and openness to knowledge are issues that ESPCI has committed to taking into account in its daily life while contributing to its progress.
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Project Description:

Cancer cells exhibit a high concentration of Reactive Oxygen Species (ROS) due to several factors, such as oncogenic activation and increased metabolism [1]. Persistent oxidative stress is harnessed to drive cancer progression, as ROS act as signaling molecules in processes such as proliferation, migration, differentiation, and angiogenesis. Because ROS can cause irreversible oxidation of macromolecules above a certain threshold, cancer cells over-activate antioxidant response mechanisms to maintain the concentration just below that threshold, yet high enough to allow cancer to progress. The aberrant redox homeostasis of cancer cells is highly sensitive to impairment of antioxidant activity. NRF2 is a transcription factor that is upregulated in several types of cancer [2–4] and plays a central role in regulating genes involved in redox homeostasis, drug, and xenobiotic detoxification. NRF2 regulates the thioredoxin (TRX) antioxidant system, whose main enzyme is thioredoxin reductase (TRXR). TRXR is targeted by various chemotherapeutic molecules, including several metal-based compounds.

Auranofin (AF) is a gold-based molecule that primarily targets TRXR, leading to an increase in ROS and subsequent cell death. We have characterized the effects of AF in the A2780 ovarian cancer cell line following 24 hours of treatment, using a redox proteomic approach. Our findings show that NRF2 is overactivated by the treatment, endoplasmic reticulum (ER) stress is induced along with activation of the Unfolded Protein Response (UPR), while significant cysteine redox alterations were not observed [5]. We are currently working on characterizing an A2780 cell line with increased resistance to AF treatment (A2780/AF-R) to investigate the molecular mechanisms underlying its greater tolerance compared to the parental sensitive cell line (A2780WT). We have found that the resistant cells do not exhibit the same NRF2 activation response as the sensitive cells, but they show upregulation of some ATP-binding cassette (ABC) proteins, which are known to be involved in xenobiotic influx/efflux. In A2780/AF-R cells, we also observed downregulation of the retinoic acid transporters CRABP1 and CRABP2, along with morphological differences between the sensitive and resistant cells.

The project aims to develop these proteomic observations further through molecular biology techniques. Specifically, to validate the role of CRABP1 and CRABP2 in drug resistance, siRNA silencing and cell viability experiments will be performed. The different NRF2 activation levels will be explored by examining the possible involvement of the identified upregulated ABC proteins in drug efflux in resistant cells. A comparative study on gold accumulation will be conducted between A2780WT and A2780/AF-R cells. A proteomic comparison based on data

from the comparative characterization will serve as a starting point to characterize an AF-resistant A2780 cell line with higher tolerance, allowing us to evaluate the aggressiveness and migration associated with AF-induced resistance.

The project also aims to optimize the redox proteomic workflow currently used in the laboratory to enhance analysis robustness. This optimization will facilitate the analysis of cysteine redox PTMs in resistant and sensitive cells upon AF treatment at early time points. As the cysteine redox proteomics field continues to evolve, reliable analysis will help us understand redox reactions in cancer cells when treated with AF.

Bibliography

1.Singh, R. & Manna, P. P. Reactive oxygen species in cancer progression and its role in therapeutics. *Explor. Med.* **3**, 43–57 (2022).
2.Konstantinopoulos, P. A. *et al.* Keap1 mutations and Nrf2 pathway activation in epithelial ovarian cancer. *Cancer Res.* **71**, 5081–5089 (2011).
3.Solis, L. M. *et al.* Nrf2 and Keap1 abnormalities in non-small cell lung carcinoma and association with clinicopathologic features. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **16**, 3743–3753 (2010).
4.Romero, R. *et al.* Keap1 loss promotes Kras-driven lung cancer and results in dependence on glutaminolysis. *Nat. Med.* **23**, 1362–1368 (2017).
5.Chiappetta, G. *et al.* Redox proteome analysis of auranofin exposed ovarian cancer cells (A2780). *Redox Biol.* **52**, 102294 (2022).

Job reporting structure

Supervision: Joelle VINH, Xhesika LIMAJ, Giovanni CHIAPPETTA

Position: At the SMBP interface of the collaborative scientific project, the candidate will be in charge of the project follow-up

About SMBP Laboratory (Biological Mass Spectrometry and Proteomics), CNRS-UAR2051 – ESPCI Paris PSL University

The SMBP Laboratory at ESPCI Paris is a leading research group dedicated to developing innovative analytical strategies for studying biological macromolecules, particularly proteins. Their expertise lies in proteomics, with a nationally recognized platform equipped with high-resolution mass spectrometry and nanochromatography instruments.

If you are a highly motivated individual with excellent communication and organizational skills, and a passion for scientific research, this position offers a unique opportunity to contribute to a scientific network at the SMBP Laboratory. Website: www.smbp.espci.fr

Techniques and Skills to be developed:

- Cell Culture Techniques: Including cell line maintenance, treatment application, and harvesting for proteomics analysis.
- Proteomics Workflows: Sample preparation for mass spectrometry, protein digestion, and peptide enrichment.
- Mass Spectrometry: Data acquisition and instrument (Orbitrap Eclipse Tribrid Mass spectrometer) handling, including sample loading and troubleshooting.
- Data Analysis and Interpretation: Using bioinformatics software (e.g., MaxQuant, Perseus, R) to analyze and visualize large datasets.
- Scientific Communication: Opportunity to present findings in lab meetings and contribute to drafting scientific reports or publications.

Required Profile

- Education: Currently enrolled in a Master's program in Molecular Biology, Biochemistry, Analytical Chemistry, or related fields.
- Technical Skills: Prior experience in cell culture is appreciated; knowledge of proteomics, mass spectrometry, or bioinformatics is a plus but not mandatory.
- Soft Skills: Strong analytical skills, attention to detail, good organizational and communication abilities, and a collaborative mindset.

Recruitment Process

Category: Intern fellowship granted
Duration : 5-6 months

Starting date for the position: February-March 2025

Contact

Applications (CV, cover letter) should be emailed to Joelle Vinh. The position is open for applications. Please submit a tailored application in response to the November 25, 2025 advertisement. For more information, please contact Joelle Vinh joelle.vinh (at) espci.fr, or Giovanni.Chiappetta (at) espci.fr

Location

ESPCI Paris - 10 rue Vauquelin - 75005 PARIS

Métro ligne 7 (Place Monge/Censier Daubenton) - RER B (Luxembourg) - Bus 21, 27 & 47 - 3 Vélib' stations.