UNIVERSITÀ DEGLI STUDI DI UDINE

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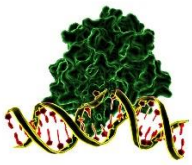
ADVERTISEMENT PhD POSITION AVAILABLE
Laboratory of Molecular Biology and DNA repair, Department of Medicine, University of Udine, Italy



PhD Project Title: Structural and functional characterization of Ovarian Cancer-related onco-miRNA containing G4-structures to identify novel anticancer drugs

Beginning: November 2024
Duration: 3-years
Net Salary: 1310 €/month
Applications: May 2024
Selections and interviews dates: June-July 2024

About the job

There is a vacancy for one PhD candidate in the G. Tell's Lab of Molecular Biology and DNA repair at The Department of Medicine at the University of Udine, Italy.
The PhD candidate will work on the structural and functional characterization of non-canonical activities of some proteins of the Base Excision Repair pathway in coping with processing of onco-miRNA containing G-quadruplex structures with relevance for Ovarian cancer.
Tell's Lab home page: Gianluca Tell | People@UniUd
and hiips://gianlucatell.wixsite.com/labtell

The project focuses on Apurinic/apyrimidinic endodeoxyribonuclease 1 (APE1), an essential enzyme of the BER pathway that operates to maintain genome stability which is considered a prognostic and predictive factor in OC cancers. APE1 regulates oncomiRs maturation, decay and sorting in extracellular vesicles in cancer cells and identified a miR-signature regulated by APE1 characterized by the presence of rG4 structures. These promising findings suggest novel unexplored APE1 mechanisms potentially involved in regulating cancer cell chemoresistance. Since combined chemotherapy using DNA-damaging agents and inhibitors of DNA-repair enzymes represents a promising direction in promoting synthetic lethality, this project will identify small molecules acting as effective tools for the development of new antitumor agents.

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This project will lead to:

1. Identify and functionally characterize prognostic rG4-oncomiR in OC regulated by APE1;
2. The biophysical, structural and functional characterization of the effects of 8-oxoG and AP-sites in the selected rG4-oncomiRNAs to identify small molecules interfering with the selected APE1/rG4-oncomiR as potential novel therapeutic bullets.

These goals will be pursued by combining biochemical/biophysical and structural approaches also using Nuclear Magnetic Resonance (NMR) spectroscopy techniques, along with investigations on immortalized cell lines and PDOs from Ovarian cancer models, as promising non-animal models for drug screening.

The Expected results are to characterize novel APE1 functions associated with oncomiRs regulation with relevance in OC. Small molecules will be identified to specifically inhibit the interaction between APE1 and rG4-miR. Indeed, this Project will push ahead with current studies on APE1 by integrating various molecular approaches and multilevel network analyses to develop unexplored anticancer drugs, leading to the development of novel in vitro cancer models and the identification of new targets for designing personalized novel approaches in cancer therapy.

A training period of up to 6-months abroad in an international Lab is foreseen during the PhD Program.

Reference papers

1. **The Apurinic/Apyrimidinic Endodeoxyribonuclease 1 is an RNA G-quadruplex binding protein and regulates miR-92b expression in cancer cells.** Bellina A., Malfatti M.C., Salgado G., Fleming A.M., Antoniali G., Gualandi N., La Manna S., Marasco D., Dessi E., Burrows C.J., Tell G. ***BioRxiv*** doi10.1101/2024.02.22.581538 (submitted to ***Proc. Natl. Acad. Sci.***, PNAS- 2023-17861)
2. **The DNA-repair protein APE1 participates with hnRNPA2B1 to motif-enriched and prognostic miRNA secretion** Mangiapane G., Notarangelo M., Canarutto G., Fabbiano F., Dalla E., Degrassi M, Antoniali G.,Gualandi N.,De Sanctis V., Piazza S., D'Agostino V.G., Tell G. ***BioRxiv*** doi:10.1101/2024.02.02.57856 (In Press **Oncogene**, ONC-2023-02419)
3. **Mammalian APE1 controls miRNA processing and its interactome is linked to cancer RNA metabolism**. Antoniali G, Serra F, Lirussi L, Tanaka M, D'Ambrosio C, Zhang S, Radovic S, Dalla E, Ciani Y, Scaloni A, Li M, Piazza S, Tell G. ***Nat Commun.*** 2017 Oct 6;8(1):797. doi: 10.1038/s41467-017-00842-8.
4. **APE1 controls DICER1 expression in NSCLC through miR-33a and miR-130b.** Antoniali G, Dalla E, Mangiapane G, Zhao X, Jing X, Cheng Y, De Sanctis V, Ayyildiz D, Piazza S, Li M, Tell G. ***Cell Mol Life Sci.*** 2022 Jul 25;79(8):446. doi: 10.1007/s00018-022-04443-7
5. **Clinical Significance of Apurinic/Apyrimidinic Endodeoxyribonuclease 1 and MicroRNA Axis in Hepatocellular Carcinoma.** Mangiapane G, Pascut D, Dalla E, Antoniali G, Degrassi M, Crocè LS, De Sanctis V, Piazza S, Canarutto G, Tiribelli C, Tell G. ***J Clin Transl Hepatol.*** 2023 Nov 28;11(6):1291-1307. doi: 10.14218/JCTH.2022.00179..
6. **Revisiting Two Decades of Research Focused on Targeting APE1 for Cancer Therapy: The Pros and Cons**. Malfatti MC, Bellina A, Antoniali G, Tell G. ***Cells.*** 2023 Jul 20;12(14):1895. doi: 10.3390/cells12141895.
7. **Inhibitors of the apurinic/apyrimidinic endonuclease 1 (APE1)/nucleophosmin (NPM1) interaction that display anti-tumor properties.** Poletto M, Malfatti MC, Dorjsuren D, Scognamiglio PL, Marasco D, Vascotto C, Jadhav A, Maloney DJ, Wilson DM 3rd, Simeonov A, Tell G. ***Mol Carcinog.*** 2016 May;55(5):688-704. doi: 10.1002/mc.22313.
8. **Small molecule inhibitors of hnRNPA2B1-RNA interactions reveal a predictable sorting of RNA subsets into extracellular vesicles** Corsi J, Peroni D, Belli R, Lassandro M, Sidarovich V, Adami V, Grosskreutz J, Fabbiano F, Grossmann D, Hermann A, Tell G, Basso M, D'Agostino VG ***BioRxiv*** **doi:** hiips://doi.org/10.1101/2024.02.05.578546

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