DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

40° Cycle

Project proposal for a PhD scholarship (with no financial support from Sapienza)

Title of the research: Investigating the role of a new ATM-ATG4 axis in oxidative stress response dysfunctions of Ataxia-Telangiectasia cells

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Summary

Ataxia-telangiectasia (A-T) is a childhood disease with an incident of 1:40,000–1:200,000 live births in worldwide each year(OMIM:208900). The identification of ATM as the gene whose mutations are responsible for A-T pathogenesis, gave impulse to extensive research to determine the functions of its multifaceted protein product. ATM is recently emerging as an important component of the oxidative stress response and autophagy regulator in the cytoplasm, beyond the well-characterized role of this protein in DNA damage response (DDR) in the nucleus. Even if the role of the loss of the ATM-dependent DDR in the pathogenesis of A-T has been well characterized, the significance of the role of ATM as modulator of oxidative stress and autophagy in the development of this disease is still largely obscure. Our preliminary data identified a new signalling pathway that connects ATM signalling to the autophagic signalling, sustaining the expression of the autophagic gene ATG4C. Of note, ATG4C expression in AT cells is able to rescue some AT defects, like cell growth and sensitivity to oxidative stress. More interestingly, recent evidences suggested a central role of different ATG4 isoforms in neuroprotection. Based on our previous studies and compelling preliminary data, we planned to investigate more deeply the role of ATM-ATG4 axis in AT progression. On the other hand, we are developing an **in vivo** zebrafish-based A-T model, in collaboration with Prof.Gabellini (University of PISA) to future testing of autophagy as possible therapeutic target for patients affected by this pathology. We strongly believe that this project could open the opportunity to lead the way towards drug screening and the identification of novel therapeutic approaches for A-T treatment.

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Pertinent Publications of the proponent (last 5 years)

1-**Stagni V**, Kaminari A, Contadini C, Barilà D, Sessa RL, Sideratou Z, Vlahopoulos SA, Tsiourvas D. A Triphenylphosphonium-Functionalized Delivery System for an ATM Kinase Inhibitor That Ameliorates Doxorubicin Resistance in Breast Carcinoma Mammospheres. Cancers (Basel). 2023 Feb 25;15(5):1474. doi: 10.3390/cancers15051474.*corresponding

2-Asteriti IA, Polverino F, **Stagni V**, Sterbini V, Ascanelli C, Naso FD, Mastrangelo A, Rosa A, Paiardini A, Lindon C, Guarguaglini G. AurkA nuclear localization is promoted by TPX2 and counteracted by protein degradation. Life Sci Alliance. 2023 Feb 16;6(5):e202201726. doi: 10.26508/lsa.202201726. Print 2023 May.

3-Ansari MSZ, **Stagni V**, Iuzzolino A, Rotili D, Mai A, Del Bufalo D, Lavia P, Degrassi F, Trisciuoglio D. Pharmacological targeting of CBP/p300 drives a redox/autophagy axis leading to senescence-induced growth arrest in non-small cell lung cancer cells Cancer Gene Ther. 2023 Jan;30(1):124-136. doi: 10.1038/s41417-022-00524-8.

4-Ourhzif EM, Ricelli A, **Stagni V**, Cirigliano A, Rinaldi T, Bouissane L, Saso L, Chalard P, Troin Y, Khouili M, Akssira M. Antifungal and Cytotoxic Activity of Diterpenes and Bisnorsesquiterpenoides from the Latex of *Euphorbia resinifera* Berg. Molecules. 2022 Aug 16;27(16):5234. doi: 10.3390/molecules27165234.

5-**Stagni V***, Orecchia S, Mignini L, Beji S, Antonioni A, Caggiano C, Barilà D, Bielli P, Sette C. Cancers (Basel). DNA Damage Regulates the Functions of the RNA Binding Protein Sam68 through ATM-Dependent Phosphorylation. 2022 Aug 9;14(16):3847*corresponding