Tutor: Prof. Alfonso De Simone, Dipartimento di Farmacia, Unviersità di Napoli Federico II

Co-Tutor: Dr. Alessia Ruggiero, Istituto di Biostrutture e Bioimmagini, CNR

PROJECT TITLE Targeting KRAS isoforms in cancer

Project description (max 300 words**)**

KRAS is the most frequently mutated oncogene in human cancer. Pathologies driven by KRAS mutations are associated with poor response to standard-of-care treatments. The KRAS gene encodes for a small GTPase regulating cellular pathways involved in signal for growth, proliferation, and differentiation, and existing in two splice variants. The ambitious aim of this project is to generate a comprehensive biomolecular and structural characterisation of KRAS isoforms, to elucidate the effect of its pathological cancer mutations. We will ultimately address the effect that currently known molecular inhibitors in clinical trials have on different variants of KRAS to establish a platform to facilitate drug discovery against this protein.

The project will impact Cancer Research by shedding light on primary structural aspects of KRAS isoforms and their involvement in cancer development. The impact of a similar result would directly propagate into translational applications where patient-derived models (PDX) can be tested specifically against KRAS isoforms to support the development of personalized medicine.

REFERENCES

Punekar, S.R., V. Velcheti, B.G. Neel and K.K. Wong, *The current state of the art and future trends in RAS-targeted cancer therapies.* Nat Rev Clin Oncol, 2022. **19**(10): p. 637-655.

Simanshu, D.K., D.V. Nissley and F. McCormick, *RAS Proteins and Their Regulators in Human Disease.* Cell, 2017. **170**(1): p. 17-33.

Tsai, F.D., M.S. Lopes, M. Zhou, H. Court, O. Ponce, J.J. Fiordalisi, J.J. Gierut, A.D. Cox, K.M. Haigis and M.R. Philips, *K-Ras4A splice variant is widely expressed in cancer and uses a hybrid membrane-targeting motif.* Proc Natl Acad Sci U S A, 2015. **112**(3): p. 779-84.

Ambrogio, C., J. Kohler, Z.W. Zhou, H. Wang, R. Paranal, J. Li, M. Capelletti, C. Caffarra, S. Li, Q. Lv, S. Gondi, J.C. Hunter, J. Lu, R. Chiarle, D. Santamaria, K.D. Westover and P.A. Janne, *KRAS Dimerization Impacts MEK Inhibitor Sensitivity and Oncogenic Activity of Mutant KRAS.* Cell, 2018. **172**(4): p. 857-868 e15.

FUNDS 000005_AIRC_ID_30556_De_Simone