St. Anna Kinderkrebsforschung
CHILDREN'S CANCER RESEARCH INSTITUTE

Press Release

Austrian Science Fund FWF promotes St. Anna CCRI project: A SAGA on how to make childhood cancer vulnerable

(Vienna, 10.8.2022) **To find vulnerabilities of cancers that are driven by MYC, a protein known for its potential to induce tumor growth, is the goal of a new project funded by the Austrian Science Fund FWF. Davide Seruggia from St. Anna Children's Cancer Research Institute (St. Anna CCRI) and colleagues aim to deactivate this key cancer regulator by targeting components of SAGA, a protein complex tightly linked to MYC. Since pediatric leukemia and neuroblastoma, two of the most common childhood cancers are known to be driven by MYC, establishing new strategies to interrupt its activity in cancer cells is of utmost importance.**

Several types of cancers depend on the oncogenic protein MYC, which is a transcription factor – i.e. a protein that helps to turn specific genes "on" or "off" by binding to nearby DNA. MYC is directly involved in the control of cell cycle and proliferation and its gene *MYC,* a so-called proto-oncogene, has normal functions in the regulation of cell growth, but can cause cancer if overly activated. Despite enormous efforts, strategies to inhibit MYC in the context of cancer are still in their infancy.

In this FWF-funded Stand Alone Project, St. Anna CCRI's pediatric leukemia group led by Davide Seruggia aims at inactivating the oncogenic activity of MYC by targeting SAGA, a large protein complex comprising 20 components and linked to MYC expression and activity. "In-depth characterization of key components of the human SAGA complex allows for identification of protein domains that are most relevant for the induction of cancer. Such domains could be used as potential targets for new drugs in the context of MYC-driven malignancies," explains Davide Seruggia, principal investigator of this project. Cooperation partners in this project are the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences (Austria) and Harvard Medical School (USA).

Addiction to MYC makes cancers vulnerable

Master transcription factors like MYC selectively activate or repress hundreds of genes, orchestrating gene expression programs that control cell identity, differentiation and even tumorigenesis. To execute these functions, transcription factors often rely on associated co-factors such as SAGA, a protein complex with modules that directly interact with MYC.
"The trigger for the submission of this project was preliminary data showing that when SAGA components TAF5L and TAF6L are depleted in mouse embryonic stem cells, binding of MYC at its target genes is impaired. We speculate that the same could apply to cancer cells, particularly to those which are MYC-addicted," comments Seruggia.

Some pediatric tumors are particularly MYC-addicted, such as pediatric B-cell derived acute lymphoblastic leukemia (B-ALL), pediatric acute myeloid leukemia (AML) or rare c-*MYC*-amplified neuroblastoma. They remain dependent on the activity of this oncogenic pathway and when its expression is turned off, tumors regress. This vulnerability renders MYC and associated co-factors a very attractive target in pediatric oncology.

A complex SAGA in three chapters

This project systematically investigates how components of the SAGA complex can be targeted to disable the MYC network in human cancer cells. To reach this goal, the researchers use a comprehensive three-step approach:

- Step one is the generation of vulnerability maps of SAGA in MYC-driven cancers by performing precise genetic screening of all 20 SAGA components down to the nucleotide resolution, referred to as dense in situ mutagenesis.
- Step two focuses on the chromatin function of SAGA by studying how mutations affect gene expression and MYC loading on chromatin, giving new insights into the function of individual SAGA components.
- Step three aims to elucidate the hierarchies and dependencies in SAGA assembly. Proteomics will be used to investigate strategies to perturb the assembly of the SAGA complex. This step includes tests, whether small molecules can be used to prevent SAGA assembly, and could thus be of use as potential compounds against MYC-driven cancers.

Davide Seruggia compares his methodological approach with the work of a car mechanic: "We screen for genetic mutations in all 20 parts of a car engine. We expect to identify at least one or two engine parts that are particularly promising. We also study the performance of such ''engine'' and see what happens if we remove each of the 20 mechanical parts individually. And finally we will look at how this big machine of proteins comes together and how the assembly of the engine can be blocked."
"The best possible outcome of this project is the identification of a suitable component of the SAGA complex, specifically a protein domain within this target, to lay the foundation for a drug development process," Davide Seruggia adds.

Funding
Harnessing vulnerabilities at SAGA in MYC-driven cancer
Austrian Science Fund FWF, Stand-Alone Research Grant
Principal Investigator: Davide Seruggia, PhD

About Davide Seruggia
In 2021 Davide Seruggia, PhD, joined St. Anna Children's Cancer Research Institute as a Principal Investigator and CeMM as Adjunct Principal Investigator, supported by an ERC Starting Grant. He graduated in Biotechnology at the University of Milano-Bicocca, Italy, and obtained a PhD in Molecular and Cellular Biology at the CNB-CSIC in Madrid, where he studied non-coding regulatory DNA sequences in the mouse. During his postdoc with Stuart H. Orkin at the Boston Children's Hospital and Harvard Medical School, he trained in hematology, epigenetics and genomics. In 2019, he was promoted to Instructor in Pediatrics at Harvard Medical School and attracted funding from the WES Foundation and Pedals for Pediatrics to investigate non-coding sequence variation in pediatric leukemia.
Among others, Seruggia has first-authored publications in high-ranked journals such as *Nature Genetics* and *Molecular Cell*. He received several fellowships, awards and grants, among others the Young Investigator Award of the International Society for Transgenic Technologies (ISTT).

Photo
Davide Seruggia, PhD

About St. Anna Children's Cancer Research Institute, St. Anna CCRI
St. Anna CCRI is an internationally renowned multidisciplinary research institution with the aim to develop and optimize diagnostic, prognostic, and therapeutic strategies for the treatment of children and

adolescents with cancer. To achieve this goal, it combines basic research with translational and clinical research and focus on the specific characteristics of childhood tumor diseases in order to provide young patients with the best possible and most innovative therapies. Dedicated research groups in the fields of tumor genomics and epigenomics, immunology, molecular biology, cell biology, bioinformatics and clinical research are working together to harmonize scientific findings with the clinical needs of physicians to ultimately improve the wellbeing of our patients.
www.ccri.at www.kinderkrebsforschung.at

About the Austrian Science Fund FWF
The Austrian Science Fund FWF is Austria's central funding organization for basic research. The purpose of the FWF is to support the ongoing development of Austrian science and basic research at a high international level. In this way, the FWF makes a significant contribution to cultural development, to the advancement of our knowledge-based society, and thus to the creation of value and wealth in Austria. The FWF stand-alone program is open for researchers of any discipline who are working in Austria with the aim to fund individual high quality research in the area of non-profit oriented scholarly/scientific research.

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