INSTITUTE OF CANCER RESEARCH
MEDICAL UNIVERSITY OF VIENNA

ICR – Cancer Lecture Series Seminar

„Restoring apoptosis through the inhibition of Mcl-1 “

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Tumor cells that harbor genetic mutations and are recognized as abnormal should be naturally eliminated but they maintain their existence by a combination of multiple activities - also known as the hallmarks of cancer [1]. One of these hallmarks is the evasion of apoptosis, the programmed cell death. The restoration of the apoptotic cascade in tumor cells has long been recognized as a promising way to treat cancer but the major members of this protein family, BCL2, MCL1, and BCL-xL have long remained elusive targets decades long for drug discovery. Recently the decade long efforts of the pharmaceutical industry have been rewarded by the identification of potent and selective inhibitors for some family members [2]. In spite of being a compelling target Mcl-1 has been considered "un-druggable" due to its high affinity for natural substrates and the largely hydrophobic nature of the interaction surface that has to be inhibited. We have conducted a fragment-based drug discovery program targeting the natural ligand binding site (so-called BH3 groove) of Mcl-1. This presentation will describe the structure-guided development of a non-selective, moderate affinity fragment into selective and potent Mcl-1 inhibitors [3] culminating in the clinical candidate S 64315 .

[1] D. Hanahan, R.A. Weinberg Cell, 2011, 144, 646.

[2] A. Ashkenazi, W.J. Fairbrother, J.D. Leverson, A.J. Souers Nature Reviews in Drug Discovery, 2017, 16, 273.

[3] A. Kotschy, Z. Szlávik, J. Murray et al. Nature, 2016, 538, 477.

Venue: Lecture Hall Container, Institute of Cancer Research (ICR), Borschkegasse 8a,1090 Vienna

Time: May 17th, 2019, 13.00

Host: Gergely Szakács