Welcome to a guest lecture in cancer drug development

Speaker: **Assoc. Professor Yousef Najajreh, Al-Quds University, East Jerusalem**

Title: **Design, Synthesis, and Biological Evaluation of Pyrimidine and Pyrazine. Derivatives for Modulation of Kinase Activity**

Host: **Professor Bjørn Tore Gjertsen, K2**

Place: **BBB, Auditorium 4**

Time: **Tuesday 14th October, at 14.30**

NB! The campus bus Realfagbygget/HIB->BBB (normal schedule: 14.20) will be up here just in time. For the way back we refer you to buses #12 (15.34/15.49/16.04/16.19) and #21 (15.42/16.12)

Design, Synthesis, and Biological Evaluation of Pyrimidine and Pyrazine Derivatives for Modulation of Kinase Activity

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The formation t(9;22) of the chimaeric bcr/abl fusion gene which encodes for the unregulated and constitutively active BCR/ABL fusion protein. BCR/ABL, non-receptor tyrosine kinase, was identified as the initial inducer of multiple downstream signaling of the leukemogensis in blood cells. So far all BCR/ABL inhibitors in clinical use, including Imatinib, Nilotonib, Dasatinib, and the recently approved Ponatinib are ATP competitors that occupy ATP-binding cleft or closely binding regions. However, one major drawback beside undesired side effects including cardiotoxicity, accelerated atherosclerosis and myocardial infarction, is the irresponsiveness of patients to first and second generation TKIs due to resistance associated with Abl kinase domain mutations. To overcome those drawbacks, we aim at targeting leukemia cancer cells with novel molecular entities that bind selectively to distinct binding sites other than ATP-cleft. The discovery that N-terminal myristated is involved in the autoregulation of unmutated ABL through a “capping” and docking mechanism ending in the insertion of N-myristate moiety into a hydrophobic “myristoyl binding pocket” (MBP), residing in the kinase domain, paved the way for exploring the possibility of inhibiting the chimaeric BCR/ABL by targeting MBP.
Using advanced computational chemistry techniques including molecular docking and estimations of all free energy components sets of myristate and pyrimidine analogues were designed. Those were synthesize, purified and characterized. The compounds were assessed for their ability to modulate BCR-ABL activity in Ba/F3, murine B lymphocytes cells transfected with BCR-ABL, in a cell-based autophosphorylation assay. The anticlonigenicity potential of the newly synthesized compounds was evaluated. Few myristate and pyrimidine derivatives were identified as allosteric modulators for BCR/ABL. Additionally, some of the potent derivatives were BCR/ABL in CML blast crisis K562 cells, Jurkat – Ph- ALL control cells; SupB15 – Ph+ ALL cells; BV173 – Ph+ lymphatic blast crisis. The second part of the presentation will focus on recent endeavors for exploring pyrimidine- and pyrazine-cored derivatives kinase inhibitors.

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