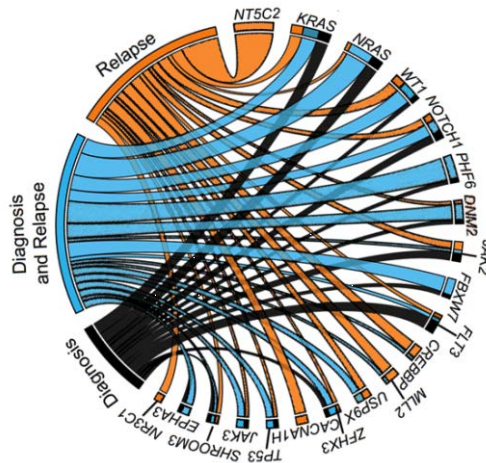




Genetics and mechanisms of relapse and resistance in acute lymphoblastic leukemia



Relapse acute lymphoblastic leukemia (ALL) is associated with chemotherapy resistance and poor prognosis. Persistent leukemia initiating cells with increased self-renewal capacity, clonal heterogeneity and selection of resistance-driving genetic alterations have been proposed as drivers of leukemia relapse. Gain of function mutations in the 5'-Nucleotidase, Cytosolic II (NT5C2) gene are selectively present in relapsed ALL and confer resistance to chemotherapy with 6-mercaptopurine (6-MP). Yet, the specific mechanisms mediating constitutive activation of NT5C2 and the role of these mutations as drivers of clonal evolution during leukemia initiation and disease progression remain unknown. Here we used a combination of structure function and crystallographic analyses to uncover new intramolecular mechanisms of NT5C2 regulation specifically targeted by relapsed leukemia-associated mutations. In addition, using an *in vivo* leukemia model we have explored the role and mechanisms of NT5C2 mutations in clonal evolution during tumor initiation, disease progression and relapse. These results have important implications for monitoring of leukemia relapse driving clones and for the development of targeted therapies for the treatment of relapsed disease

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Host: Dr. John Dick

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Time: 2PM

Place: Donnelly Centre, 160 College St
Red Seminar Room