19 SEPT

4.30 P.M.
ROOM A102
POVO 1

MARTIN DISTEL

ST. ANNA CHILDREN´S CANCER RESEARCH INSTITUTE (CCRI)

MODELING EWING SARCOMA IN ZEBRAFISH

Ewing sarcoma is a pediatric bone and soft tissue tumor found in children and young adults with dismal outcome. The disease is driven by a fusion oncogene, EWS::FLI1 in the vast majority of cases, which acts as an aberrant transcription factor and epigenetic regulator. Unfortunately, the cell of origin of Ewing sarcoma remains elusive, hampering the development of faithful genetic animal models. Currently, mouse xenograft models are the gold standard for disease investigation and drug testing.
We explored the use of zebrafish for Ewing sarcoma modeling following two different strategies: xenotransplantation and genetic modeling. We successfully established zebrafish xenograft models and performed an automated drug screen, which revealed a specific vulnerability of Ewing sarcoma towards combined MCL-1 and BCL-XL inhibition. Furthermore, in an ongoing project we are trying to establish a genetic model of Ewing sarcoma. We observed that untargeted expression of EWS::FLI1 leads to tumor formation in zebrafish. Using specific regulatory elements and also optogenetic approaches for targeted expression of the oncogene, we are currently investigating, which regions and cell types are permissive for tumor formation to identify candidates for the so far unknown cell-of-origin of Ewing sarcoma. Surprisingly, aside from tumors, EWS::FLI1 can also induce ectopic fins in zebrafish. Comparing mechanisms leading to tumor versus fin formation may reveal novel therapeutic strategies for Ewing sarcoma.

CIBIO EXTERNAL SEMINAR

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