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POSTER 9: Identification of leukemic stem cells of chronic myeloid leukemia in a new mouse model

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Chronic myeloid leukemia (CML) is a disease that is thought to arise when a hematopoietic stem cell (HSC) acquires the *BCR::ABL1* fusion oncogene. Expression of *BCR::ABL1* leads to a pathological proliferation of granulocytes, which, left untreated, can be fatal. The development of tyrosine kinase inhibitors (TKIs) has revolutionized treatment of the disease. However, CML is not "cured" as more than 50% of patients relapse when treatment is stopped due to the persistence of TKI leukemic stem cells (LSCs). The identification and characterization of LSCs as well as the mechanisms of their persistence remain poorly studied due to a lack of relevant models.

Our objective is to characterize the LSCs that lead to CML relapse. We thus created a novel mouse model, *Pdzk1ip1*-CreERTg/+ TRE-*BCR-ABL1*Tg/+ *R26*rtTA-GFP/Tom, which enables inducible expression of a *BCR::ABL1* transgene within a fraction of HSCs. The differential expression of fluorescent markers enables the tracking of normal versus BCR::ABL1+ cells. Unlike existing models, our model recapitulates the chronic phase of human CML, permitting the study of LSCs.

The characterization of our in vivo model showed the development of a pathology which recapitulates the main characteristics of the human disease: an increase in the number of platelets and white blood cells in the circulating blood, splenomegaly and a long chronic phase with a good animal survival. Our model provides the ability to track Tom+ GFP+ leukemic cells throughout hematopoiesis as well as non-diseased Tom+ GFP- cells.

We harvested Tom+ GFP+ leukemic cells from the bone marrow of these mice in order to transplant them into previously conditioned congenic mice. The transplanted mice developed clinical symptoms similar to the leukemic donor mice with in particular a high level of platelets and splenomegaly. In addition, all hematopoietic compartments were colonized by Tom+ GFP+ leukemic cells.

In order to assess the impact of treatment in our model, we performed *in vitro* proliferation tests with four TKIs commonly used in therapy in order to identify the most effective dose to inhibit the proliferation of leukemic cells in vivo.

The identification and characterization of LSCs may reveal novel therapeutic strategies that "cure" CML. Such treatments would benefit patients and reduce the socioeconomic burden by eliminating the need for lifelong TKI treatment.