Of mice and men

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The use of carefully chosen animal models often underlies crucial medical advances. A perfect example is provided by the recent demonstration that a known drug, imatinib, can be used to treat a rare but highly aggressive type of lymphoma. The work was largely undertaken in the group of Lukas Kenner at the Ludwig Boltzmann Institute for Cancer Research and the Medical University of Vienna with the support of Karoline Kollmann and Veronika Sexl at the University of Veterinary Medicine, Vienna, together with a number of national and international collaborators. The findings are published in the current issue of the prestigious journal *Nature Medicine*.

So-called Anaplastic Large Cell Lymphoma (ALCL) is even less attractive in real life than it is on paper. It is a highly aggressive type of lymphoma that generally occurs in children and young adults and that

has to date proven extremely difficult to treat. It has long been known that ALCL patients frequently show a genetic alteration (a translocation) that causes expression of nucleophosmin-anaplastic lymphoma kinase (NPM-ALK), a gene known to be capable of giving rise to cancer. But how the NPM-ALK gene works has to date remained largely a matter of conjecture.

Working in a mouse model for lymphoma, Karoline Kollmann in Veronika Sexl's group at the University of Veterinary Medicine, Vienna and colleagues in the Ludwig Boltzmann Institute for Cancer Research and the Medical University of Vienna were able to show that the development of lymphoma is absolutely dependent on the "Platelet derived growth factor receptor B" (PDGFRB), a protein already associated with the growth of other types of tumour. They demonstrated that the effect was direct, with NPM-ALK stimulating the production of the transcription factors JUN and JUNB, which bind to and activate the PDGFRB promoter. And importantly they were able to show that inhibition of PDGFRB with the drug imatinib was able to extend dramatically the survival of mice with this kind of lymphoma.

In human patients, ALCL is traditionally treated with crizotinib, a drug that directly inhibits the NPM-ALK protein. The major problem is that the patients tend to relapse and their chances of survival are extremely poor. Based on the results from the imatinib tests in mice it seemed conceivable that the use of this drug might improve the prognosis of patients who do not or no longer respond to crizotinib therapy. The scientists obtained ethical approval and informed consent to attempt imatinib treatment of an ALCL patient who had not responded to conventional chemotherapy and had relapsed after transplantation of stem cells. Remarkably, the patient improved immediately upon imatinib treatment: after ten days he was in complete remission and he is still alive – and again working – 22 months later.

The idea of inhibiting PDGFRB in ALCL is novel and potentially of great therapeutic importance. Kollmann is naturally extremely excited by the implications of the results. "The patient had essentially run out of options and would have died a long time ago. But thanks to the indications from our mouse work that inhibiting PDGFRB could prevent growth of this type of tumour he is still alive. This new type of therapy could significantly prolong patient survival."

Intriguingly, the researchers have also found that PDGRFB is also present in ALCL patients without the translocation that leads to NPM-ALK expression. Whether the PDGRFB protein is required for the development of tumours in such patients is not yet clear but it is possible that a combined crizotinib / imatinib therapy might be more widely applicable, providing hope for patients suffering from other types of lymphoma.

More information: The paper "Identification of PDGFR blockade as a rational and highly effective therapy for NPM-ALK driven lymphomas" by Daniela Laimer, Helmut Dolznig, Karoline Kollmann, Paul W. Vesely, Michaela Schlederer, Olaf Merkel, Ana-Iris Schiefer, Melanie R. Hassler, Susi Heider, Lena Amenitsch, Christiane Thallinger, Philipp B. Staber, Ingrid Simonitsch-Klupp, Matthias Artaker, Sabine Lagger, Stefano Pileri, Pier Paolo Piccaluga, Peter Valent, Katia Messana, Indira Landra, Thomas Weichhart, Sylvia Knapp, Medhat Shehata, Maria Todaro, Veronika Sexl, Gerald Höfler, Roberto Piva, Enzo Medico, Bruce A. Riggeri, Mangeng Cheng, Robert Eferl, Gerda Egger, Josef M. Penninger, Ulrich Jaeger, Richard Moriggl, Giorgio Inghirami and Lukas Kenner is published in the current issue of "*Nature Medicine*". The first four authors contributed equally to the work.

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