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DISSERTATION TITLE: *Precision medicine for the treatment of a highly malignant and resistant type of liposarcoma*

In this study we have tried to find new treatment options for rare cancers by targeting specific mechanisms through detailed analysis of the cancer's genome and by identifying therapeutically active compounds using a drug-sensitivity screen. Our aim was to identify personalized treatment strategies based on a case-study of a patient with a highly aggressive and metastatic type of liposarcoma. Liposarcoma, a soft-tissue cancer resembling fat tissue, belongs to one of 50 different subtypes of sarcoma, a rare cancer with a prevalence of only 1% of all cancers. Because rare cancers have limited commercial potential, industry shows little interest, and there has been very little therapeutic progress the last decades. However, personalized cancer medicine holds the potential of finding novel treatment strategies for patients who do not have any other options.

The patient had an exceptionally long and daunting disease history, initially treated with several chemotherapeutic drugs and had several rounds of surgery, however without any improvement. The patient also received therapy targeting the gene products of two genes commonly found amplified in liposarcoma, *MDM2* and *CDK4*, to which the patient also did not respond. We have sequenced, using next-generation sequencing methods, several metastatic tumors of the patient with the aim to identify genetic anomalies that could explain the aggressive and metastatic nature of the tumor and potentially offer a weakness that could be therapeutically exploited. We identified amplification of the *FRS2* gene, which was an indication that certain mechanisms could be targeted for the treatment of liposarcoma. The gene product of *FRS2* is known to be an important constituent of the FGFR signaling pathway, involved especially during development and for maintaining a wide range of vital functions in humans. It is not surprising that this pathway is commonly found affected in various cancers.

Although no therapeutic drugs are available that could target *FRS2* directly, our strategy was to inhibit the signaling pathway in which FRS2 is involved in by using FGFR inhibitors. In this study we have compared the potential of two FGFR inhibitors, NVP-BGJ398 and LY2874455, in a patient derived cell line and xenograft mouse model. We observed growth inhibition of tumor cells using either one of the FGFR inhibitors. However, NVP-BGJ398 showed less potency and the growth inhibition turned out to be

reversible upon withdrawal of the drug treatment. This finding was of particular significance, considering the potential risk of disease relapse. However, we found that LY2874455 had not only a much greater inhibitory and clinical potential than NVP-BGJ398, but also inhibited tumor growth irreversibly.

We also used a drug-sensitivity screen with 349 active compounds to obtain a detailed picture of potential vulnerabilities of the tumors to individual drugs. Instead of looking for drugs that could specifically target the products of certain genomic anomalies, we employed a complementary approach and observed the response of tumor cells to a wide range of different drugs, which did not only confirm resistance of the tumor to almost all drugs tested, but also identified APO866 (FK866) among a list of 6 potential drugs that could be employed for the treatment of liposarcoma.

We showed the potential of genomic sequencing and drug-sensitivity screens for personalized therapy through the identification of novel therapeutic targets in the treatment of not only rare cancers such as sarcoma, but also for highly aggressive and resistant tumors.