

# Development of targeted therapies against FET oncogene sarcomas

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentlig försvaras i Hjärtats aula, Sahlgrenska Universitetssjukhuset, Vita stråket 12, den 19 september 2025, klockan 9.00

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## Avhandlingen baseras på följande delarbeten

- I. Safavi S, Järnum S, **Vannas C**, Udhane S, Jonasson E, Tesan Tomic T, Grundevik P, Fagman H, Hansson M, Kalender Z, Jauhiainen A, Dolatabadi S, Wessel Stratford E, Myklebost O, Eriksson M, Stenman G, Schneider Stock R, Ståhlberg A, Åman P. *HSP90 inhibition blocks ERBB3 and RET phosphorylation in myxoid/round cell liposarcoma and causes massive cell death in vitro and in vivo*. *Oncotarget* 2016; DOI: 10.18632/oncotarget.6336
- II. **Vannas C**, Andersson L, Dolatabadi S, Ranji P, Lindén M, Jonasson E, Ståhlberg A, Fagman H, Åman P. *Different HSP90 Inhibitors Exert Divergent Effect on Myxoid Liposarcoma In Vitro and In Vivo*. *Biomedicines* 2022; DOI: 10.3390/biomedicines10030624
- III. **Vannas C**, Tesan Tomic T, Jonasson E, Albatrok H, Andersson L, Lindén M, Grundevik P, Canfjorden V, Luna Santamaría M, Fagman H, Ståhlberg A, Åman P. *FUS::DDIT3-mediated PDGFRB signaling leads to pericyte recruitment and sensitivity to the tyrosine kinase inhibitor imatinib in myxoid liposarcoma*. Manuscript
- IV. **Vannas C**, Lindén M, Jonasson E, Canfjorden V, Albatrok H, Andersson L, Ranji P, Gustafsson A, Myklebost O, Fagman H, Åman P, Ståhlberg A. *Combined BRD4 and HDAC inhibition synergistically enhances anti-tumor activity in FET sarcoma models*. Manuscript.
- V. **Vannas C**, Escobar M, Tanyasiová M, Kindeberg Sederblad M, Nyström J, Österlund T, Wennergren D, Andersson D, Dalin M, Torinsson Naluai Å, Fagman H, Ståhlberg A. *The levels of circulating tumor DNA and inflammatory proteins depict the clinical response in a patient with metastatic undifferentiated pleomorphic sarcoma, a case report*. Manuscript submitted.

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Göteborgs universitet, Sverige, 2025

## Abstract

FET oncogene sarcomas are fusion-driven malignancies characterized by gene fusions involving one of the genes *FUS*, *EWSR1* or *TAF15*, fused to a transcription factor partner. FET oncogene sarcomas comprise more than ten different sarcoma entities, with myxoid liposarcoma (MLS) and Ewing sarcoma (EWS) being the most prevalent. Current treatments for advanced disease in MLS and EWS rely on chemotherapy, but outcomes remain poor. New therapies and improved methods to assess treatment efficacy are urgently needed. The aim of this project was to explore potential targeted therapies in preclinical models of MLS and EWS.

Initially, we analyzed receptor tyrosine kinase (RTK) signaling in MLS and tested the efficacy of targeted RTK inhibitors. Overall, they showed limited therapeutic benefit, likely due to compensatory crosstalk between different RTKs facilitated by the chaperone protein HSP90. We subsequently evaluated the HSP90 inhibitor 17-DMAG in both MLS cell lines and a patient-derived xenograft (PDX) model of MLS, observing potent anti-tumor effect. Various HSP90 inhibitors then demonstrated comparable efficacy *in vitro*, while the *in vivo* effects varied significantly between inhibitors. Next, we investigated tumor vessel formation in MLS and found that the tumor vasculature was enriched with pericytes. Additionally, we observed increased PDGFB-PDGFRB signaling, suggesting the presence of an autocrine loop that may influence both cell survival and vascular architecture. Targeting PDGFRB with the multi-RTK inhibitor imatinib caused tumor regression *in vivo*, though it did not noticeably alter the vascular morphology. We then pursued another treatment strategy targeting epigenetic dysregulation caused by the FET fusion oncoproteins. Combined inhibition of BRD4 and histone deacetylases, both epigenetic proteins, resulted in synergistic effects *in vitro* and significant tumor regression *in vivo*. Finally, we explored the use of circulating tumor DNA and inflammatory protein profiles as informative blood-based biomarkers for treatment monitoring. We demonstrated that simultaneous ctDNA and inflammatory protein quantification can be used to monitor treatment response and provide complementary tumor-related data in a patient with metastatic undifferentiated pleomorphic sarcoma.

In conclusion, our findings add to the understanding of dysregulated signaling pathways in FET oncogene sarcomas and potential targeted therapies to be further evaluated in clinical trials. Furthermore, incorporating quantification of novel blood-based biomarkers may enhance the precision and adaptability of future clinical trials, ultimately improving patient outcomes through real-time response assessment.

**Keywords:** Myxoid liposarcoma, Ewing sarcoma, FET fusion oncogenes, precision medicine, tyrosine kinase inhibitors, angiogenesis, epigenetic drugs, liquid biopsy, circulating tumor DNA