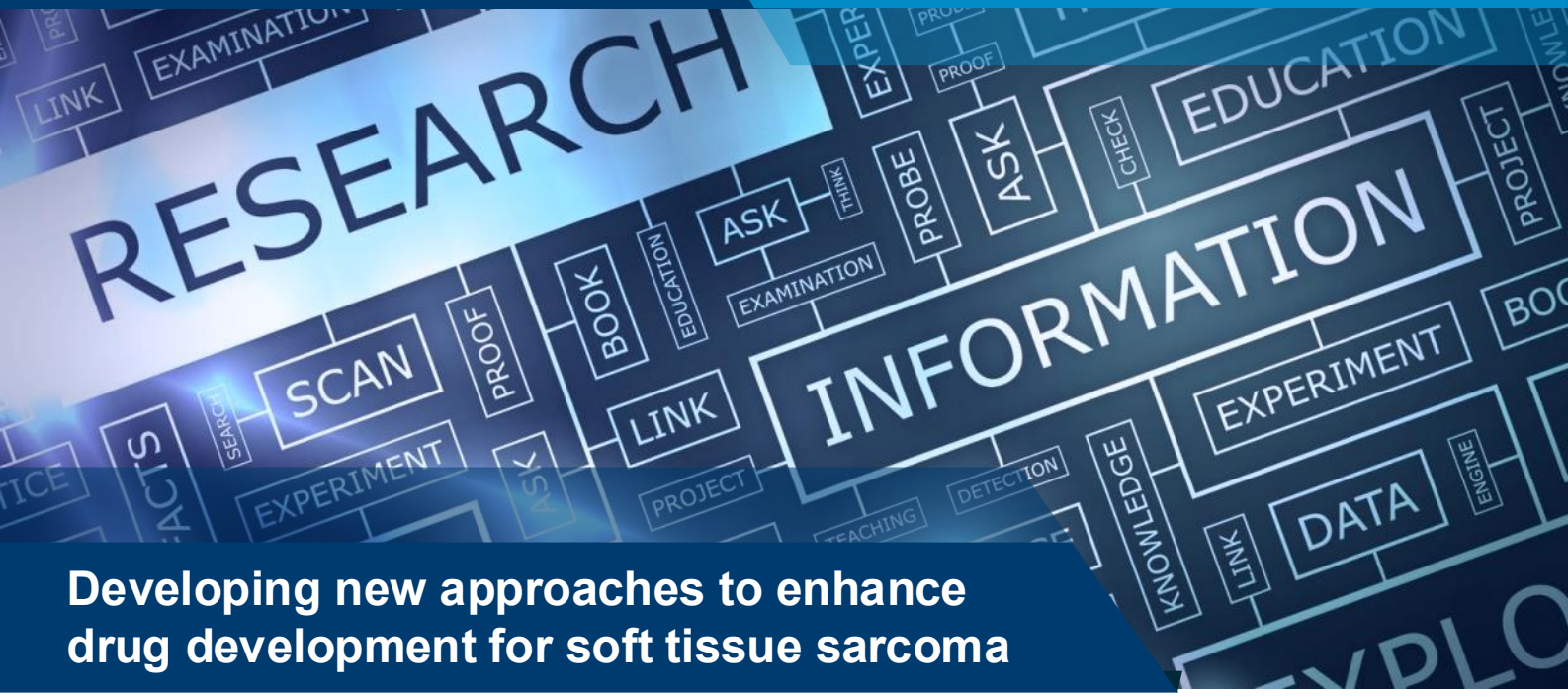
CHIEF SCIENTIST OFFICE

CODE: TCS/22/12

RESEARCH PROJECT BRIEFING



Developing new approaches to enhance drug development for soft tissue sarcoma

AIMS

Undifferentiated pleomorphic sarcoma (UPS) is a rare type of cancer without a clear genetic cause and with limited treatment options. Our aim was to discover new promising therapeutic interventions for UPS and develop new models and platforms for further drug studies.

KEY FINDINGS

- Patient genomic data can be used to construct targeted drug screens in rare cancers without clear genomic driver alterations.
- Trametinib (MEK inhibitor) and infigratinib (FGFR inhibitor) combination shows efficacy in preclinical models of UPS and should be investigated further.
- Tumour slices cut from UPS tumours are a novel viable model for validation of drug efficacy.
- The novel microfluidics platform designed by ScreenIn3D can be used to conduct drug studies on primary cells derived from tumour samples.
- Fresh patient material taken at surgery can be used for drug screening.

WHAT DID THE STUDY INVOLVE?

- Targeted drug screening based on genomic analysis in tumour-derived UPS models in novel microfluidic devices.
- Validation of devices on the high-throughput ImageXpress imaging platform which allows quantification of cell death metrics following acquisition of high-resolution images.
- Collection and optimisation of fresh patient material taken at surgery for drug screening.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

Targeted drug screening based on genomic analysis identified sensitivity of UPS models to the MEK inhibitor trametinib. The combination of trametinib and the FGF receptor inhibitor infigratinib significantly reduce the viability of UPS tumour slices compared to untreated control and both monotherapies. This was validated in a novel tissue slice model (Figure 1). The microfluidic device designed by ScreenIn3D (Figure 2) allows higher throughput for drug screening, enabling a high number of replicates per drug treatment using very small patient-derived samples. We demonstrate that it can be used to study drug responses in small sarcoma spheroids. Data shows that trabectedin reduced UPS spheroid viability even at low concentrations (Figure 2).

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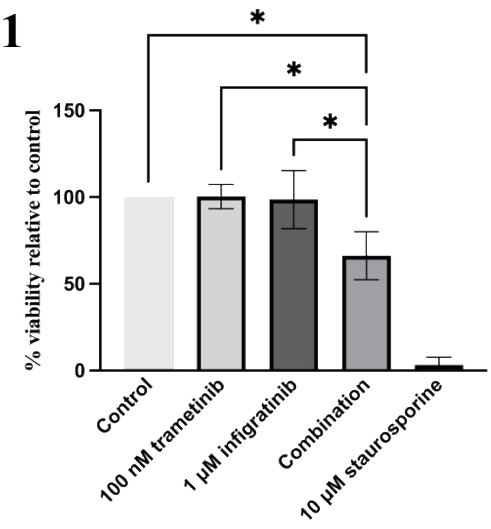

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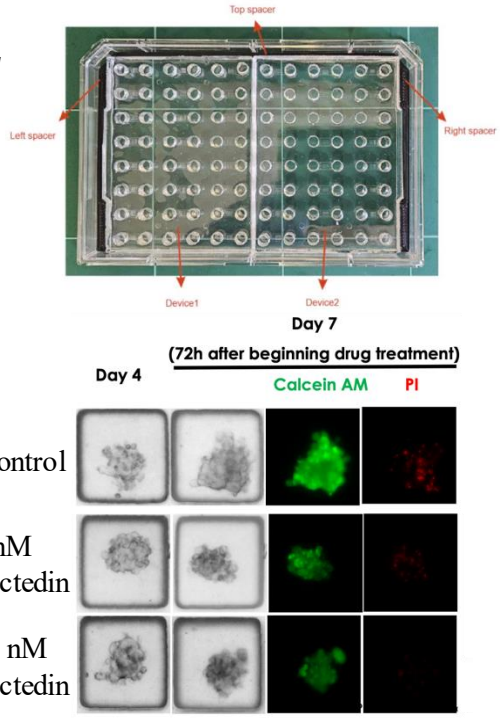

Figure 1 shows the effect of treatment with trametinib, infigratinib and their combination on tumour slice viability. The 10 µM staurosporine treatment was used as a positive control to show induction of cell death. The error bars represent the standard deviation from the mean (n=4). The results were analysed using a one-way ANOVA with Tukey's multiple comparisons test (*$p<0.05$).

Figure 2 shows the microfluidic device and representative images of UPS spheroids at day 4 (left column) and day 7 (second column from the left) after seeding them into the ScreenIn3D microfluidic devices. Calcein AM and PI staining show viable and dead cells, respectively.

WHAT IMPACT COULD THE FINDINGS HAVE?

- The synergy between trametinib and infigratinib identified in the preclinical UPS models could be translated into the clinical practice should either of the drugs or their combination show efficacy in clinical trials.
- The approach of using genomic data to formulate targeted drug screens in rare cancers, which often have limited treatment options, could lead do novel therapies being offered to patients.
- The novel microfluidic device can be used for drug and phenotypic studies of samples with limited amount of starting material.

HOW WILL THE OUTCOMES BE DISSEMINATED?

The patient sequencing data and drug screens that identified the synergy of trametinib and infigratinib in preclinical UPS models has been published doi: 10.1002/1878-0261.70059.

The validation of the novel microfluidic device will be described in a research article submitted to the SLAS Discovery journal.

The results were presented at EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics. Barcelona, Oct 2024 and to a Sarcoma Patient Advocate Day at the Institute of Genetics & Cancer, Nov 2024.

CONCLUSION

Genomic data obtained from patient samples can be used to inform targeted drug screen in rare forms of cancer without a clear targetable driver alteration. Using this approach, trametinib and infigratinib were found to be synergistic in preclinical models of UPS. The novel microfluidic device validated in collaboration with ScreenIn3D company can be used to conduct drug screens on small amounts of starting material.

RESEARCH TEAM & CONTACT

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Additional Information

The project was completed as planned on the 28th of February 2025