

Mesenteric fibrosis in small intestinal neuroendocrine tumours (SI-NETs): pathogenesis and therapeutic targets

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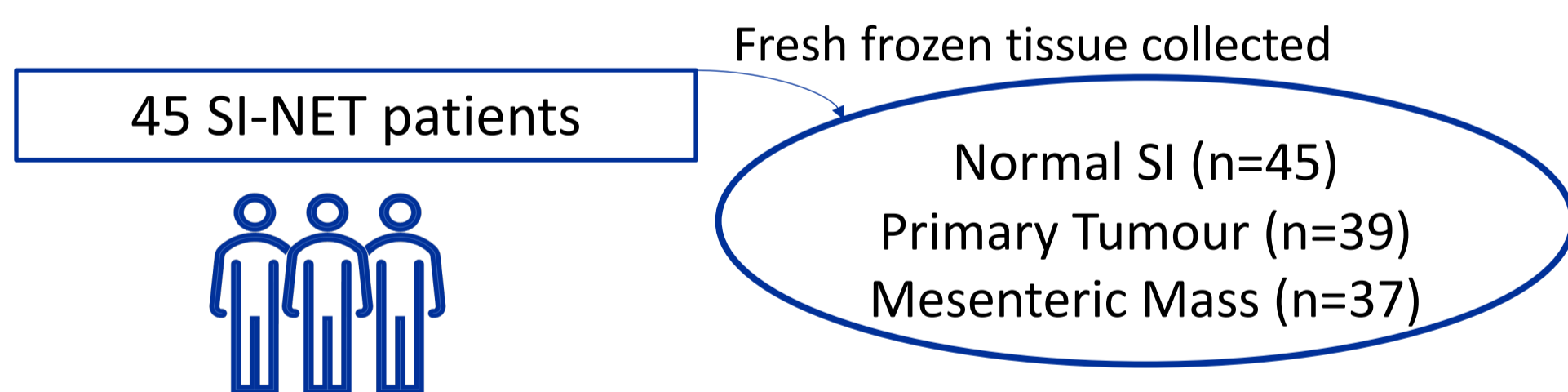
Background:

- Mesenteric fibrosis (MF) affects up to 50% of SI-NETs patients
- Poor understanding of MF pathophysiology limits treatment development and biomarker identification

Aim: improve the understanding of MF and identify useful diagnostic and predictive molecular markers.

Methods:

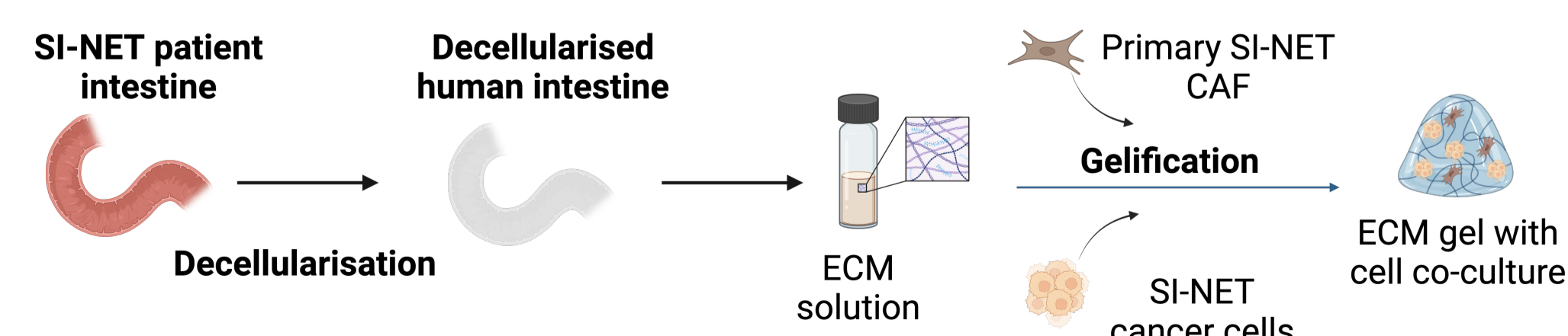
Transcriptomic and epigenetic analysis



Histological, radiological and surgical assessments for **fibrosis scoring**: None (n=3), Minimal (n=7), Mild (n=19), Severe (n=16)

RNA and DNA extracted for **RNA sequencing, DNA methylation arrays**

3D in vitro models



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Cell viability in extracellular matrix (ECM) gels was assessed using PrestoBlue assay. **Histological analysis** was performed using Haematoxylin and Eosin stains

Results:

Transcriptomic and epigenetic analysis

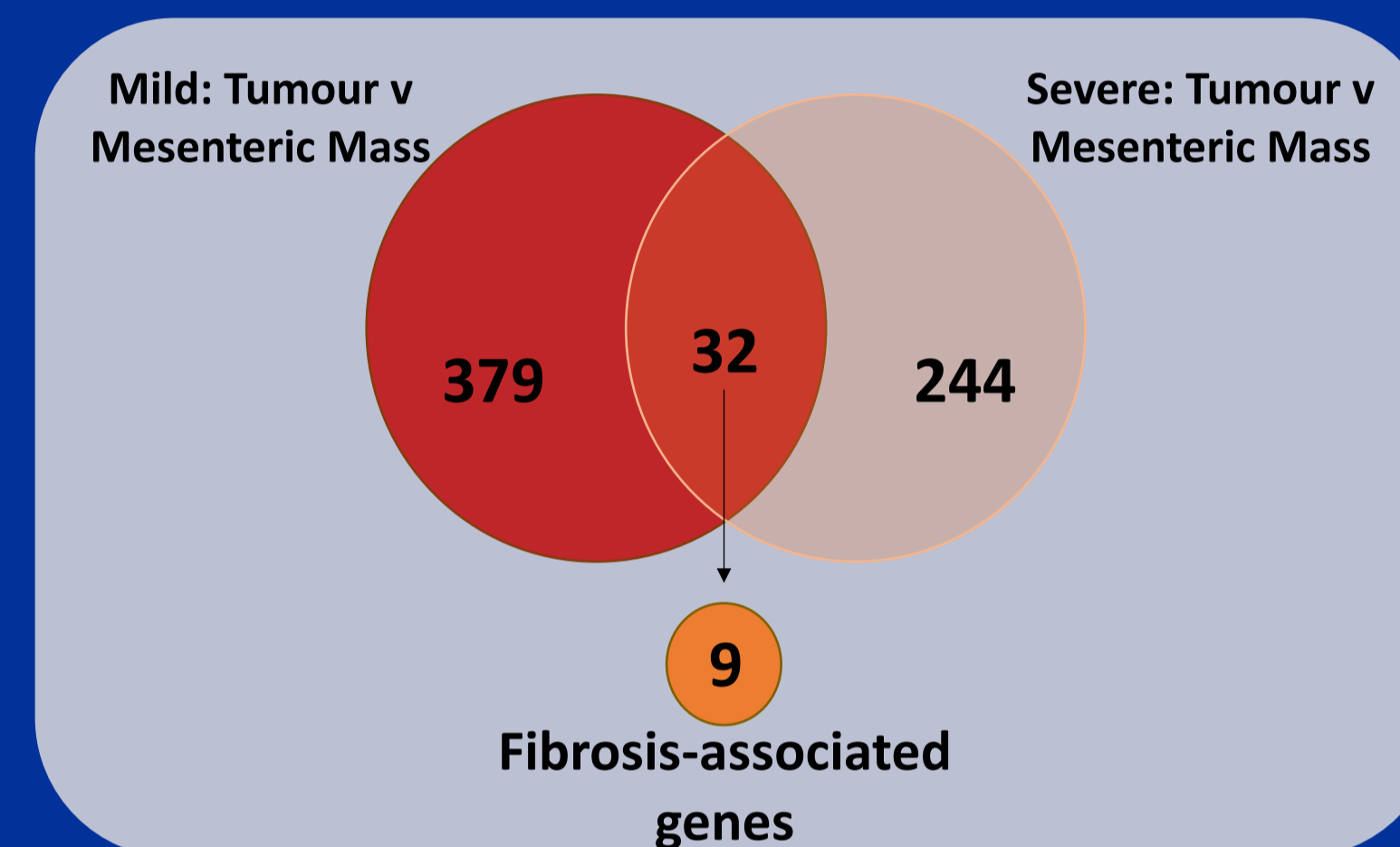


Figure 1. Transcriptomic and epigenetic analysis highlights fibrosis-associated genes significantly altered in SI-NET patients with MF. Mesenteric mass tissues in patients with mild or severe MF have an overlap of 9 fibrosis-associated genes which have significantly altered expression and methylation (p-val<0.05).

3D in vitro models

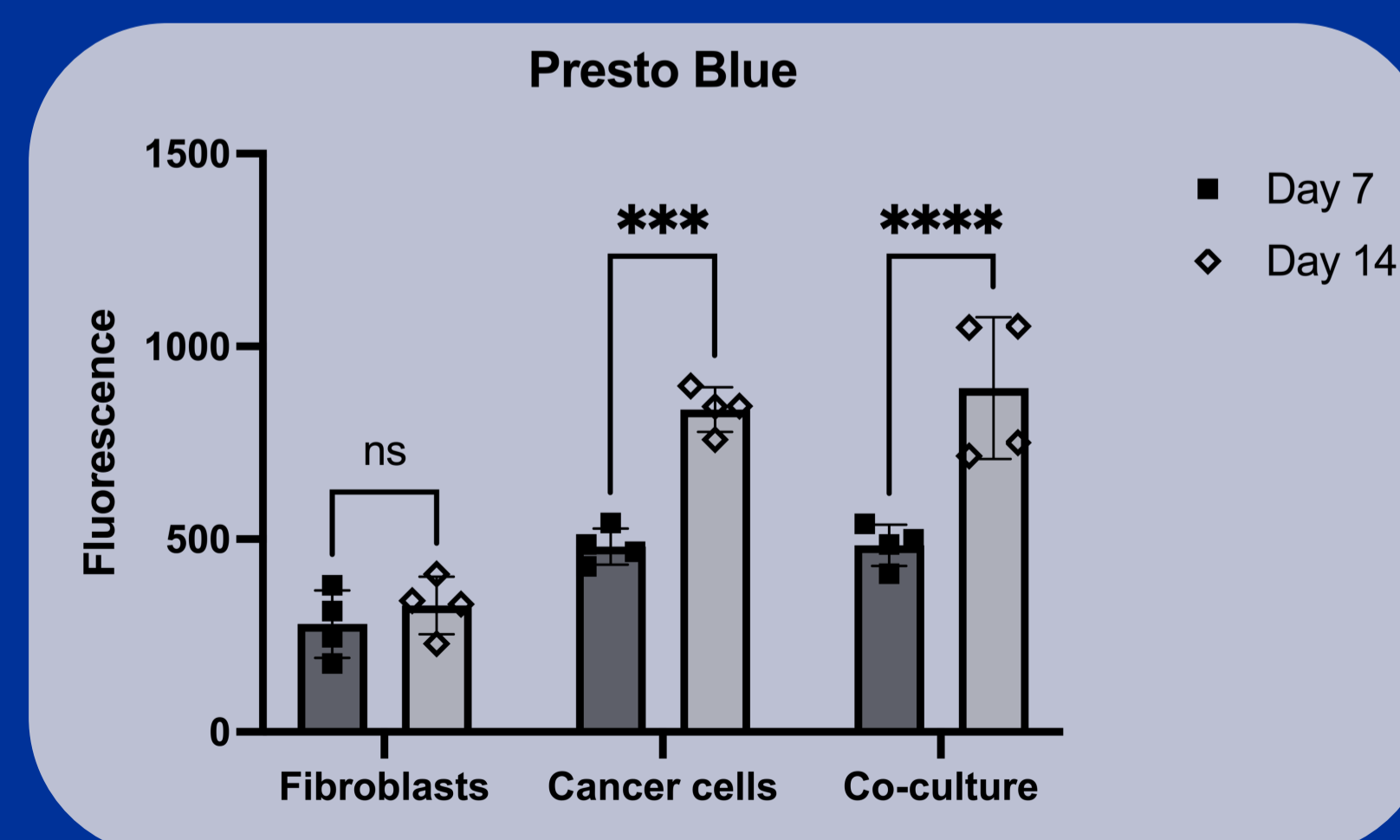


Figure 2. Cell viability of primary SI-NET fibroblasts and cancer cells in ECM gels. Cell viability was assessed at days 7 and 14 of culture in mono- or co-cultures (n=3). Cancer cells and co-cultures had significant increase in viability.

Results:

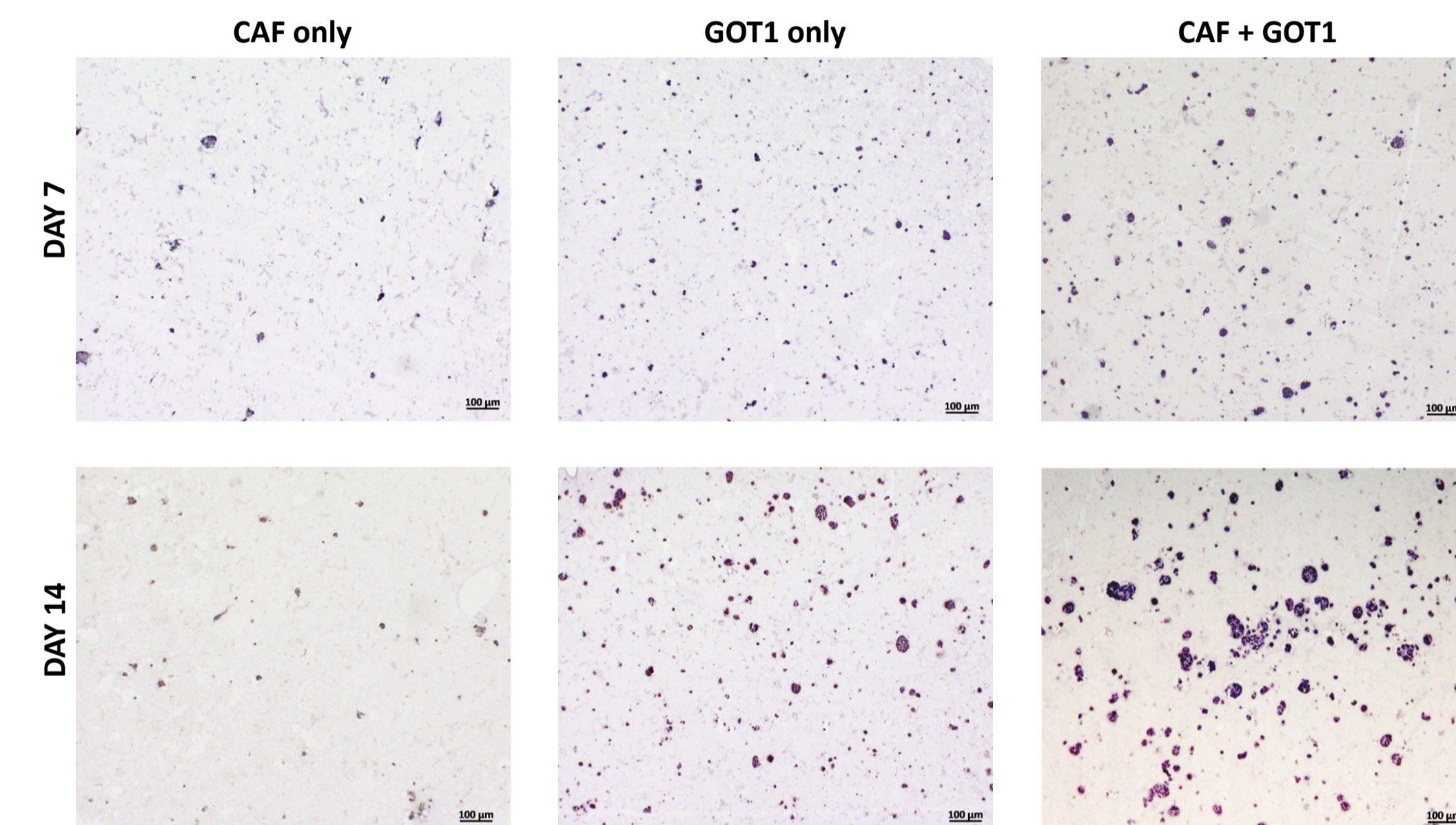


Figure 3. Histological analysis of primary SI-NET fibroblasts and cancer cells in ECM gels. At day 7 and 14, gels were fixed and embedded. Haematoxylin and eosin stainings showed increase in cell population in cancer cell monocultures and in co-cultures.

Conclusions and Future work:

- Mesenteric mass has a significantly altered methylation profile causing transcriptomic changes in fibrosis-related genes of SI-NET patients with MF. Targets will be further investigated *in vitro*.
- Human intestine ECM gels provide a good platform for studying the interactions between SI-NET cancer cells and cancer-associated fibroblasts.