



RESEARCH

INFORMATION

## The use of JAK inhibitors as a novel treatment for colon cancer



### AIMS

- Chemotherapy is widely used to treat colon cancer, but it is not targeted and often does not work well for all patients. Our previous study has evidenced that JAK/STAT3 pathway (a molecular pathway in cells that regulates survival and growth) plays a key role in treatment resistance, making it a promising target for new therapies.
- This project looked at whether adding JAK inhibitors (Janus kinase inhibitors, a type of targeted drug commonly used to treat inflammatory conditions) to chemotherapy could improve treatment response in colon cancer. It also explored how the tumour microenvironment (the cells and tissue surrounding cancer cells) affects how well treatment works.



### KEY FINDINGS

- Adding JAK inhibitors (Fedratinib and AZD1480) to chemotherapy improved treatment response in colorectal cancer cell lines and patient-derived organoids (mini tumour models grown from patient tissue in the laboratory).



- Fibroblast (connective tissue cells involved in tissue repair and scarring) reduced how well treatment worked, including chemotherapy alone and chemotherapy plus JAK inhibitors.
- Macrophages (a type of immune cell) did not significantly change treatment response in the models used in this study.
- The results support STAT3 signalling as an important pathway that may help explain treatment resistance and could be a future treatment target.
- Spatial transcriptomic analysis, a method that allows an understanding of where genes of interest are expressed within a tissue sample, identified higher pSTAT3 (the activated form of STAT3) was linked to changes in immune responses and pathways involved in tumour spreading and metastasis.
- The study identified Cyclin D3, a protein that helps regulate cell growth and division, as a possible prognostic biomarker, which may help predict outcomes in colorectal cancer and should be tested further in larger patient groups.



## WHAT DID THE STUDY INVOLVE?

This was an early-stage preclinical study designed to support future clinical research. It combined several types of experiments to test treatment response and understand the biology behind it.

The study involved laboratory-based approaches:

- Testing standard-of-care chemotherapy alone and in combination with JAK inhibitors in colorectal cancer cell lines with different genetic mutations;
- Testing the same treatment combinations in patient-derived organoids (PDOs), which are three-dimensional mini tumour models grown from surgical resection samples;
- Developing co-culture models that included cancer cells together with fibroblasts or macrophages to study how the tumour environment affects treatment response;



- Using spatial transcriptomic analysis (GeoMx DSP) to show how gene activity differs in different parts of the tumour tissue, especially in relation to the activation of STAT3 (pSTAT3 levels);
- Blocking STAT3 pathway in colon cancer cells and analysing gene changes using RNA sequencing to identify possible downstream biomarkers;
- Testing cyclin D3 in patient tumour samples using immunohistochemistry (to detect protein levels in tissue) to evaluate whether it could predict patient outcomes in colorectal cancer;
- Public involvement: findings from the project were shared with the Glasgow Colorectal PPIE Group. Their feedback is helping us plan future communication and follow-on research in ways that are clear, relevant, and meaningful to patients and the public.



## WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

This study found early evidence that JAK inhibitors may help chemotherapy work better in colorectal cancer models. It also showed that tissue-supporting cells in the tumour microenvironment, especially fibroblasts, can reduce treatment effectiveness.

- In both colorectal cancer cell lines and patient-derived organoids, adding JAK inhibitors to chemotherapy increased cancer cell killing compared with chemotherapy alone.
  - What this means: JAK inhibitors may help make cancer cells more sensitive to chemotherapy.
- When fibroblasts were added to the models, treatment worked less well for both chemotherapy alone and chemotherapy plus JAK inhibitor.
  - What this means: Fibroblasts may induce treatment resistance and could be a potential target for future combination treatment approaches.
- Adding macrophages alone did not significantly change treatment response in the models used.



- What this means: In our experimental settings, macrophages by themselves may have less direct effect on treatment response.
- Spatial transcriptomic analysis showed that higher pSTAT3 expression (more activated STAT3 signalling) was linked to stronger immune/inflammatory pathway activity in both tumour and stroma (surrounding support tissue, including fibroblasts), and pathways linked to tumour metastasis.
- What this means: STAT3 may also affect how cancer cells interact with surrounding stromal and immune cells, which may influence the response to treatment.
- When STAT3 was switched off in cancer cells, RNA sequencing analysis identified Cyclin D3 as a possible downstream marker linked to cell growth. In a pilot patient tissue study (consist of 195 cases), higher Cyclin D3 showed a trend towards poorer cancer-specific survival, but this was not statistically significant.
- What this means: Cyclin D3 is a promising prognostic biomarker candidate, but it needs to be tested in larger patient groups.

What this study adds to the field:

- Provided early evidence that JAK inhibitors may improve chemotherapy response in colorectal cancer.
- Demonstrated fibroblasts in the tumour microenvironment may reduce treatment response, highlighting the importance of considering microenvironment context for treatment decisions.
- This project combines spatial analysis and mechanistic studies, giving a more complete picture of how STAT3 may influence chemotherapy resistance.
- Identified cyclin D3 as a candidate biomarker for further clinical studies.



## WHAT IMPACT COULD THE FINDINGS HAVE?

### Patients

- Provide evidence to support the development of a new treatment approach to improve chemotherapy response in colorectal cancer
- Highlights the importance of the tumour microenvironment, especially in stroma-rich colorectal cancer, that may be less likely to respond to standard chemotherapy.
- Identified potential biomarkers (eg: pSTAT3 or cyclin D3) in stroma-rich colorectal cancer.

### Policy

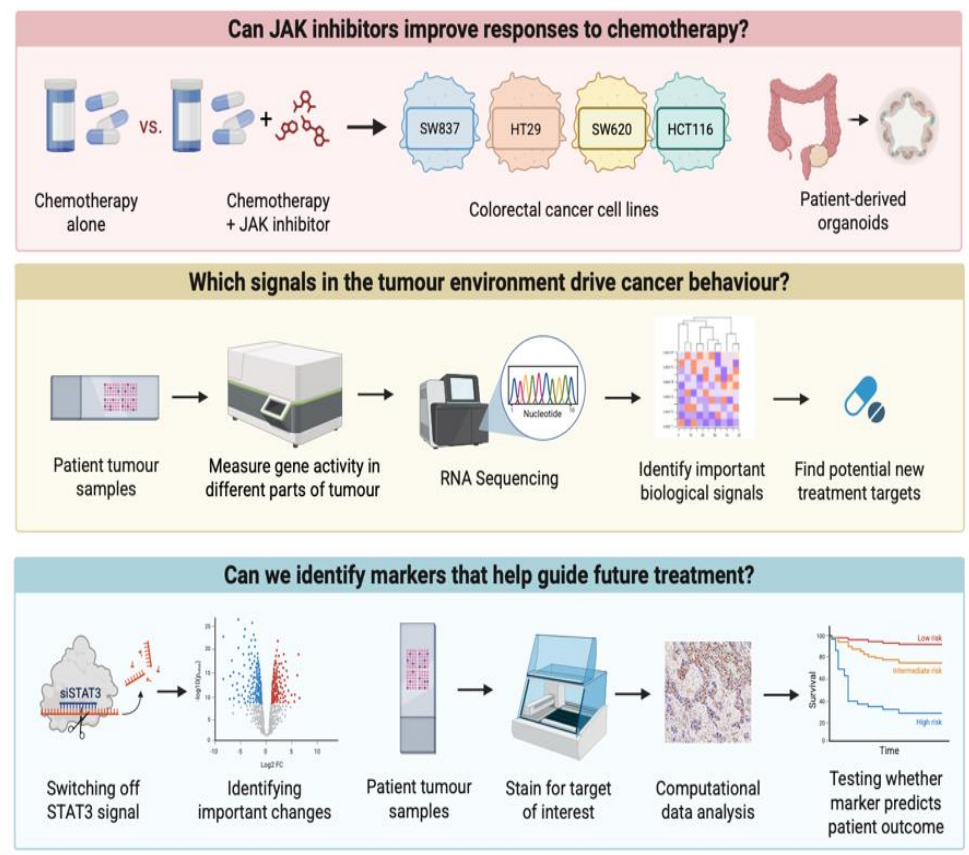
- The project is currently preclinical, so there is no direct policy impact yet.
- If follow-on animal studies are successful, the findings could help build the evidence base for future clinical trials to evaluate this treatment approach in stroma-rich colorectal cancer.

### Practice

- No immediate change to clinical practice at this stage.
- Provides a stronger scientific basis for:
  - testing JAK inhibitor plus chemotherapy in animal models which may help guide future clinical study design;
  - including tumour microenvironment components (such as stromal context) in translational research;
  - assessing candidate biomarkers (eg: pSTAT3 or cyclin D3) for future translational studies and early-phase clinical trial design.



This project investigated whether adding JAK inhibitors to chemotherapy could improve treatment responses in colorectal cancer. It also identified potential new treatment targets and biomarkers that may help predict patient outcomes and support more personalised treatment approaches in the future. Together, these findings provide a foundation for developing more effective treatments for colorectal cancer patients.



## HOW WILL THE OUTCOMES BE DISSEMINATED?

### Dissemination plan

- **Peer-reviewed publications:** Key findings will be prepared for submission to peer-reviewed journals. Planned manuscripts include:
  - *JAK Inhibition Enhances Chemotherapy Response in Stroma-Rich Colorectal Cancer*
  - *Cyclin D3 as a Candidate Prognostic Marker in Stroma-Rich Colorectal Cancer*
- **Conference presentations:** Findings will be presented at national and international cancer research meetings, including the British Association for Cancer Research (BACR) or the

European Association for Cancer Research (EACR) annual conferences, to disseminate results, obtain expert feedback, and support future collaborations.

- **Patient and public involvement:** Findings have been shared with the Glasgow Colorectal PPIE Group. We will continue working with this group to make future communication and follow-on studies patient-centred and accessible.
- **Public-facing dissemination:** We have also appointed a social media communications officer (4 hours per week) to support public-facing dissemination of our research. This role will develop lay summaries and short posts for platforms such as Instagram and LinkedIn, create short films for our website, and help establish a YouTube channel with short videos explaining the impact of our research in clear, accessible language for the public.

### Next steps

- Based on the preliminary findings from this grant, we will apply for further funding to support the next stage of this research.
- Test combined chemotherapy with JAK inhibitor in orthotopic mouse models (more clinically relevant animal models).
- Further investigate how fibroblasts reduce treatment response and whether targeting these cells could improve treatment effectiveness.
- Validate cyclin D3 as a prognostic marker in a larger colorectal cancer patient tissue cohort (n=787) and examine its relationship with STAT3 activation and the tumour microenvironment.
- Use the results to support future planning of a clinical trial for combining JAK inhibitor with chemotherapy in stroma-rich colon cancer (if the results from mouse models are positive).



## CONCLUSION

This project provides preclinical evidence that targeting the JAK/STAT pathway may improve chemotherapy response in colorectal cancer. It also shows that fibroblasts may reduce treatment effectiveness, highlighting the importance of tumour microenvironment context. In addition, the study identified cyclin D3 as a potential prognostic biomarker for colorectal cancer. Together, these findings provide a strong foundation for next stage of work, including animal studies and future biomarker-guided translational research, with the longer-term aim of clinical translation.



## RESEARCH TEAM & CONTACT



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