CHIEF SCIENTIST OFFICE

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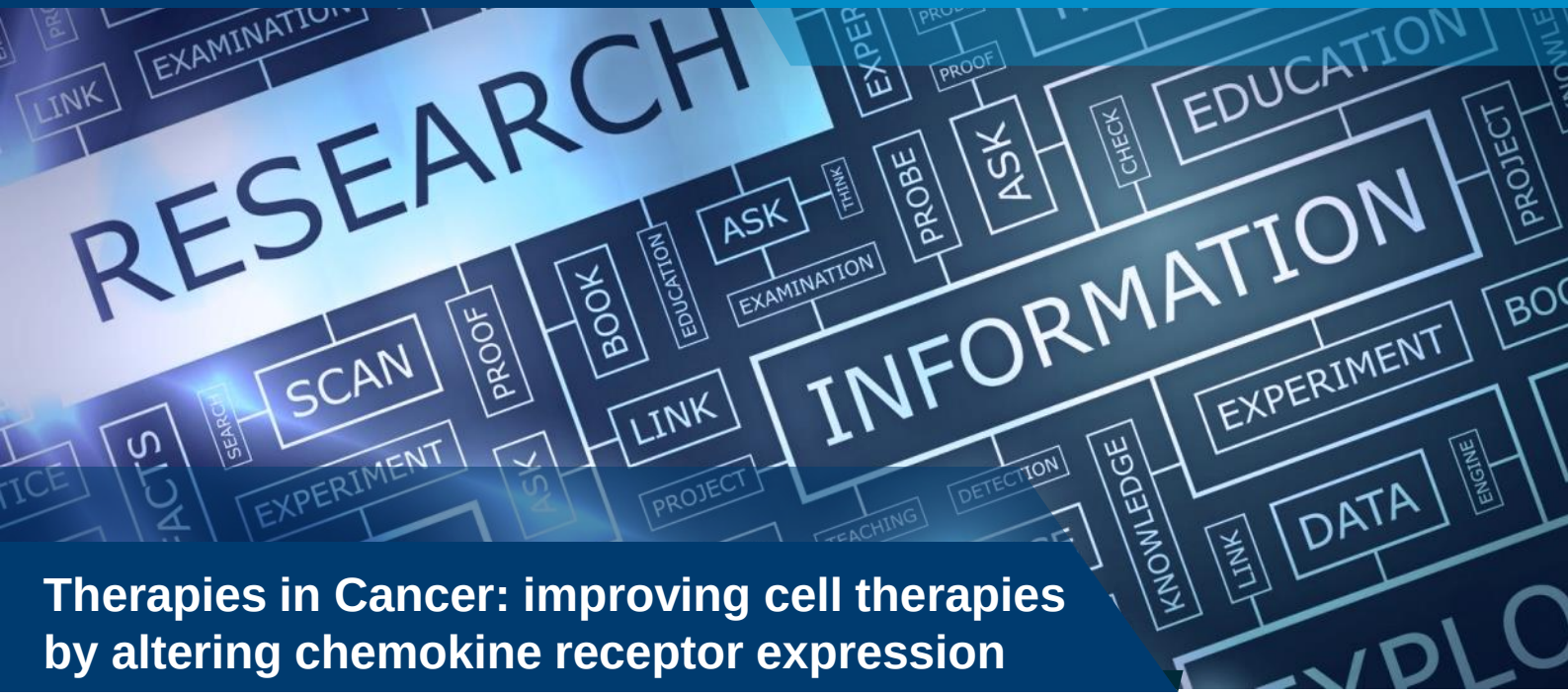
RESEARCH PROJECT BRIEFING



Therapies in Cancer: improving cell therapies by altering chemokine receptor expression

AIMS

Our bodies' immune cells are directed to sites of cancerous growth by small molecules called chemokines. We aimed to manipulate the interactions between immune cells and chemokines so they could target tumours more effectively. We aimed to do this by increasing the chemokine receptors (proteins which recognise the chemokines) on immune cells (NK cells and T cells) to see if the cells targeted the cancer better, which could be used to **improve cell-based cancer treatments.**

KEY FINDINGS

- We successfully modified blood stem cells to produce increased levels of CCR2, a receptor which recognises CCL2 (a chemokine highly expressed by most tumours). Cells which express such receptors should therefore migrate towards these tumours.
- We were able to turn these high CCR2 stem cells into NK cells, a kind of immune cell that targets cancer cells, to see whether CCR2-high NK cells migrate to tumours more effectively than normal NK cells..
- Unfortunately, the transformation process into NK cells reduced the expression of CCR2 back to what was seen with normal, unmodified cells.
- We next developed a cancer model using cancer cells that were changed to make high levels of chemokine CCL27 so that T cells with the right receptor would find and kill these modified cancer cells in the mouse.
- We then successfully modified T cells to make CCR10, the receptor for CCL27.
- These T cells were able to recognise and kill the CCL27-high cancer cells effectively.
- **This is important preliminary work to establish a pre-clinical model for cell therapies for cancer.**

WHAT DID THE STUDY INVOLVE?

Cell therapies shown great promise in the treatment of some cancers i.e. lymphoma/leukaemia. However, this success hasn't translated well into the treatment of solid tumours. We believe that, in part, this is due to failure of the cells to target properly to the tumour site. To tackle this, we exploited the chemokine system. This is a complex network of secreted proteins (chemokines), detected by chemokine receptors (CKRs) on the surface of immune cells. This process directs cells towards areas of damage, infection and cancer. By altering immune cells to over-produce CKRs, we hoped to develop a proof of concept **that improved targeting increased killing of solid tumours**. To achieve this, we took two approaches:

1. Using a process called 'viral transduction' to introduce new genes to blood stem cells. The virus integrates into the cell's genetic blueprint and permanently incorporates genes of interest into the cells. We introduced the genes for the CKR CCR2. The modified stem cells were then differentiated into NK cells, immune cells known to be important in the fight against cancer.
2. Using a method known as 'mRNA transfection' to introduce a CKR to another important immune cell (T-cell) for targeting cancer cells. We used mRNA for making a T cell express CCR10 as well as modifying a melanoma cancer cell line to make the matching chemokine (CCL27), so that we can test whether the cells can find and kill the tumour cells.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

For approach i), we showed that we can successfully use viral transduction to make stem cells display increased amounts of CCR2 on their surface. We also showed that at this stage these cells maintained the genes which class them as stem cells and allow them to transform into any cell in the body. However, when we came to transform them into our cells of interest (cancer-fighting NK cells) we found that the process of transformation resulted in a loss of the ability to make more CCR2 (Figure 1). Consequently, our original aim of developing a method to improve targeting of cell therapies using this approach may not be possible without further investigation.

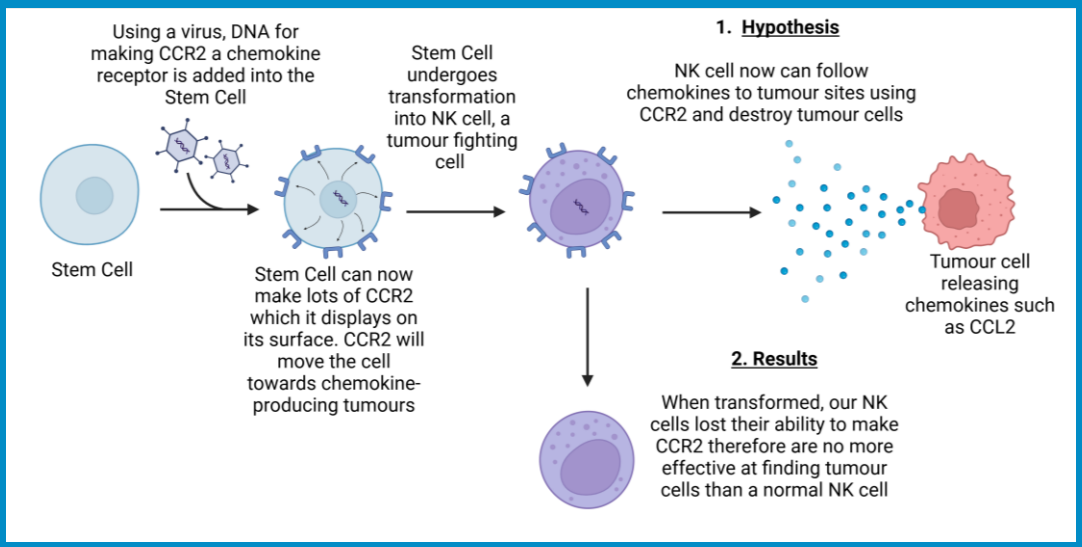


Figure 1: Stem cells demonstrate enhanced CCR2 expression after viral transduction but lose this when being turned into NKCs

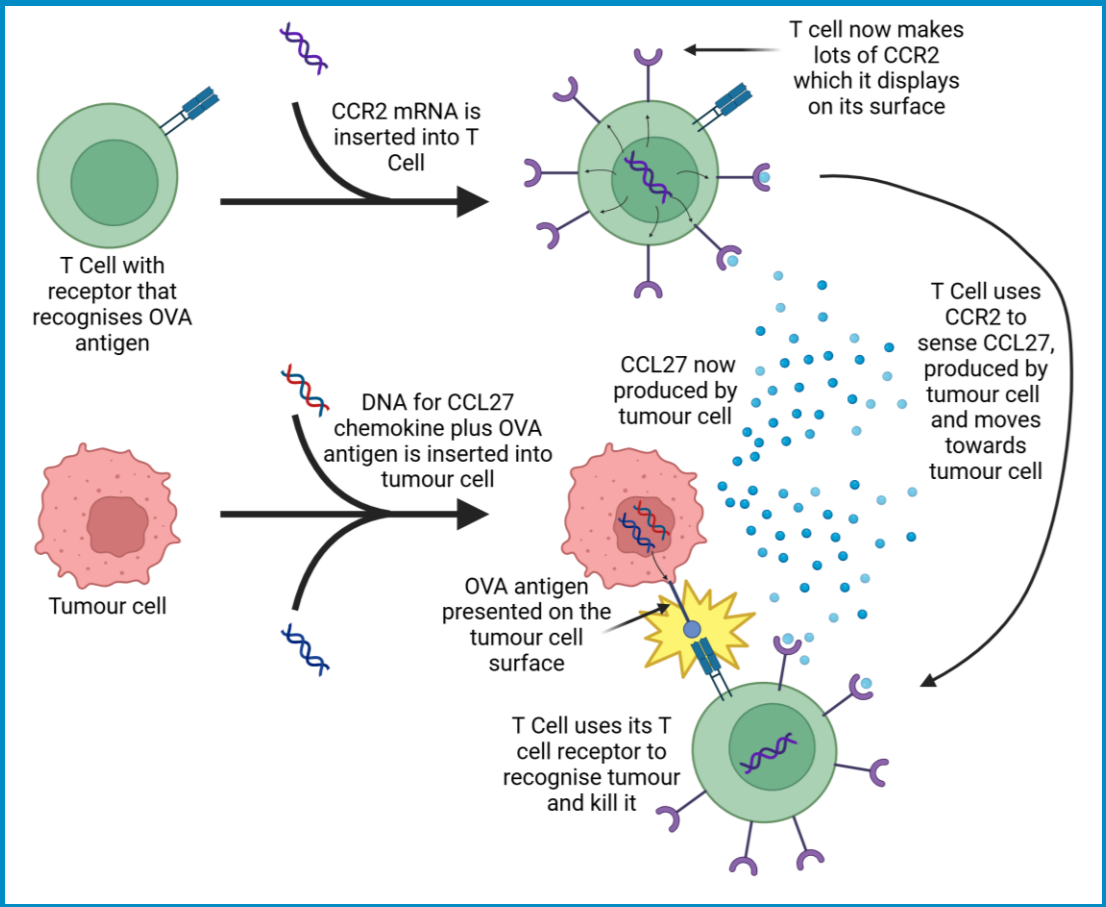
For approach ii), we successfully modified a melanoma cancer cell line to produce a chemokine (CCL27) plus a molecular "flag" on the cell surface which T cells can use to recognise cells which need to be killed). Our flag is an antigen called OVA.

We then modified OVA-specific T cells to produce CCR10, the receptor which recognises CCL27. Our hypothesis was that the cancer-fighting T-cell now had a way to detect CCL27 being made from the cancer and, therefore, move towards it in order to kill it - like a sniffer dog following a scent. As the cancer also had an OVA "flag", the modified T cells should recognise it as a target for killing.

We tested whether the genetic modification to produce CCR10 affected the T-Cells' ability to kill the cancer cells and found that they were equally as effective as the unmodified T-Cells.

While these data are preliminary, we can now make use of these established methods to show whether enhanced CKR expression improves immune cell targeting and killing of cancer in a mouse model of cancer. Additionally, these methods can be employed for most combinations of tumour cell and tumour-responsive immune cell, and any combination of chemokine and CKR, making for a powerful tool kit for determining the effectiveness of this approach to enhancing cancer cell therapies.

Figure 2: T-cells can be effectively transfected with CKRs (CCR10) without losing their cancer-killing properties.



WHAT IMPACT COULD THE FINDINGS HAVE?

- Despite cell therapies showing significant success in the treatment of blood cancers, solid tumours remain largely resistant to this approach.
- We investigated two new ways of manipulating the chemokine system in this study to better target solid tumours; (1) stably introducing a chemokine receptor into stem cells which were then turned into non-specific cancer-targeting immune cells (NK cells), (2) introducing a chemokine receptor to T cells which target a cancer cell line which has an OVA flag.
- While the former approach requires further investigation, the latter produced significant expression of the desired receptor amongst treated cells.
- We also established methods for producing cancer cell lines that can make any chemokine required, as well as a protein known to elicit an immune response (OVA).
- Using these established techniques in combination, we can develop models for improving targeted, tumour specific cell therapies for cancer with follow-on funding.

HOW WILL THE OUTCOMES BE DISSEMINATED?

- A short publication is planned for submission to a scientific journal, though further work is required before work is of publication quality, including taking the work into mouse models of cancer.
- Additionally, key aspects of this work will be carried forward into related ongoing projects in the group and with commercial collaborators.

CONCLUSION

We have developed several key technologies in this study that will improve understanding of immune cell modification to drive more effective targeting of solid tumours. We established a means of creating chemokine-expressing cancer cell lines that also express an OVA antigen recognised by some T cells), as well as a method for inducing chemokine receptor expression to T cells quickly and without the need for further genetic manipulation. This means we can now effectively investigate any combination of chemokine/receptor and tumour/tumour-targeting immune cell. With this, we can determine the best way of getting cancer targeting cells to the tumour and provide proof of concept for improved clinical cell therapies as a result.

RESEARCH TEAM & CONTACT

Professor Gerard Graham
Sir Graeme Davies Building.
120 University Place
Glasgow G12 8TA

gerard.graham@glasgow.ac.uk

0141 330 3982

Additional Information

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