ImmunoTools *special* Award 2019

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Harnessing the power of the immune system to fight obesity associated cancer

Background

Obesity is a global health epidemic with the number of overweight and obese children and adults increasing rapidly. The World Health Organisation estimated in 2016 more than 1.9 billion adults aged 18 years and older were overweight. Of these, over 650 million adults were obese. Another cause of grave concern is the increasing incidence of childhood obesity, with approximately 1 in 4 children classified as overweight or obese in Ireland alone. Therefore, a large proportion of our global population are at great risk of developing one of a plethora of obesity-associated diseases such as diabetes, cancer or heart disease. Therefore, examining novel ways to treat and prevent these diseases is of the utmost importance.

One such obesity associated disease is the obesity associated cancer, oesophageal adenocarcinoma (OAC). Rates of OAC are increasing rapidly and in parallel with the worldwide obesity epidemic. OAC patients face dismal 5-year survival rates of <20% and a paucity of treatment options. Over 70% of such patients do not respond to first line treatment with chemoradio therapy, and are in urgent need of improved therapeutic options. We propose that immunotherapy would improve outcomes for this patient cohort.

Numerous studies have linked better patient outcomes with the level of infiltration of anti-cancer immune cells in solid tumours, particularly natural killer (NK) and T cells. NK cells are crucial immune cells in the eradication of solid tumours. However, our group have previously reported that NK cells are recruited to the visceral adipose tissue (VAT) instead of tumour, where they undergo increased levels of apoptosis and functional

alteration. We propose that this occurs at the cost of effective anti-tumour immunity in these patients and that they would benefit from therapies that can redirect NK cells toward the tumour.

The chemokine system governs immune cell movement and our group has also reported dysregulated chemokine production in the VAT of OAC patients. It is this dysregulated chemokine production that is resulting in the erroneous recruitment of crucial anti-tumour T cells and NK cells to VAT as opposed to the tumour. We believe identification and targeting of the key chemokine(s) guiding this migration may hold the key to halting NK cell migration to the VAT in OAC and prevent their depletion. Furthermore, such a therapeutic could give NK cells a chance to migrate to the tumour, where they can contribute to tumour eradication and better outcomes for OAC patients. We propose that chemokine

Objective: To determine whether chemokine-targeted therapies can also enhance the efficacy of NK cell-based therapies for OAC and other obesity-associated cancers.

Methodology

First, it is important to phenotype NK cells in the setting of OAC blood, VAT and tumour to elucidate where the most potent anti-tumour immune cells are located.

- Determination by flow cytometry of:
    - Markers of NK maturation: CD56, CD3, CD27, CD11b, adhesion (CD49d, CD54, CD62L)
    - Markers of activation CD69
    - Determination of Intracellular cytokine production TNFa, IFNy.

In addition to endogenous NK cells, the NK cell line NK-92 is of interest due to its potential therapeutic applications.

- To support the growth and stimulation of NK92 in culture the following cytokines will be utilized:
    - rh cytokines IL-2, IL-12, IL-15
- ELISA will be carried out to examine levels of :
    - IP-10 (CXCL10)
    - MCP-2 (CCL-8)

Expected outcome

At a time when the obesity epidemic shows no signs of abating, our research aims to explore novel ways to utilise the immune system to help treat the escalating numbers of patients with obesity-associated cancer. These ImmunoTools reagents will help part of the research to design of the next generation of cellular based immuno therapies and provide insights into utilising chemokine-targeted therapies to maximise their efficacy.

Reagents: **ImmunoTools** reagents helpful in conducting the above-mentioned studies.

ImmunoTools *special* AWARD for **Eimear Mylod** includes 25 reagents

FITC - conjugated anti-human	CD56
PE - conjugated anti-human	CD27, CD49d, CD69, TNFa, IFNy
PerCP- conjugated anti-human	CD3
APC- conjugated anti-human	CD11b, CD54, CD62L
Recombinant human cytokines	IL-2, IL-12, IL-15
human ELISA-set (for one 96 plate)	IP-10 (CXCL10) and MCP-2 (CCL-8).

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