

outlook

THE NEWSLETTER FOR SUPPORTERS OF THE INSTITUTE FOR CANCER VACCINES & IMMUNOTHERAPY (ICVI)

FROM THE CHAIRMAN



Sir Harry Cotterell Bt OBE
Chair of Trustees

WELCOME TO OUR AUTUMN 2021 ISSUE OF OUTLOOK

As I write the UK is taking ever bolder steps out of the restrictions imposed by the pandemic. Professor Dalgleish and his team continue to work extremely hard to ensure that our research continues apace. We say goodbye and thank you to one of our team, Dr Jonathan Caron, who is moving back to France to take up a new position. His recently published paper “How to train your dragon: harnessing Gamma Delta T Cells, Antiviral Functions and Trained Immunity in a Pandemic Era” is summarised in our research section of this issue. If you would like to see the full paper please look at the news section of our website.

Our last issue told of the research being undertaken by our current PhD students, Alex and Issy. Alex has also recently had a paper published, “Cheap and Commonplace: Making the Case for BCG and Gamma Delta T Cells in COVID-19”. This is also summarised in this issue and the full paper is available on our website. Congratulations Alex, and again please check our website for the paper.

I was fascinated to read the piece from one of our research team, Dr Peter Smith. He writes about the latest research on how our diets may affect our chances of getting cancer.

On the fundraising side, I was delighted to hear that the Spiers siblings decided to walk a marathon along the Thames in memory of their mother Helen, raising over £2,800 for the ICVI. We were delighted that longstanding supporter Liz Sands raised more funds in memory of her daughter Lucy by growing and selling flowers for us. The Sands family and friends have worked tirelessly over the years and Lucy’s tribute fund now stands at over £122,000, an incredible achievement from Lucy’s family and friends.

Likewise Serena Aldous who has long been a great supporter of our work in memory of her son Mark, continued her fundraising via her open garden event which is featured in this issue. Thank you Serena for everything you do for us.

PHONE ISSUES

We are sorry to say that we are having problems with our landline at present which means that email is the best way to contact us.

Thames Walk

Huge thanks to Alistair, Joanna, Andy and Laura Spiers who raised an impressive £2,827 for the ICVI in memory of their mother Helen. Congratulations Spiers family for managing to avoid all of those lovely river pubs on your 26 mile route and raising such a wonderful amount towards our research.



Blooming Fundraising

Liz Sands has had a busy summer raising funds for us. Selling a mixture of flowers from her beautiful garden, sunflowers from the field and home-grown tomatoes, she hopes to raise £400 for the ICVI. Liz was grateful to her local village community in Brewood for their support. We are very grateful to Liz for her hard work and a wonderful resulting donation.



Serena's Garden

Loyal supporter Serena Aldous has for many years held open garden events to raise funds for the ICVI, raising thousands of pounds in memory of her son Mark.

Serena sent us this beautiful photo and said; "It was the 100th birthday of this dear lady!!! She was utterly amazing and went all round the garden -wheeled!! The happiness it gave us ALL. I am also putting a cheque in the post for £1,003:50 - a lot of this was collected with small openings, an honesty box and people enjoying a peaceful wander in small numbers- very therapeutic."

Thank you so much Serena for all your hard work for us.

Feel good Christmas Shopping

Use EasyFundraising for all your online shopping and a proportion of each sale will be donated to the ICVI. It's simple to use and it's free, with over 3,700 retailers taking part. www.easyfundraising.org.uk/causes/icvi/



UPDATE FROM PROFESSOR DALGLEISH

Highlights of this period are that our study which mixed the drug IMM-101 with standard immunotherapy (Nivolumab) have given a better response rate than the standard treatment alone, and as good a response as the standard combination therapy (Ipilimumab and Nivolumab) without the significant increased toxicity associated with this.

We published a paper last year highlighting the importance of sequencing 2 chemotherapy drugs, showing that correct sequencing was more effective than giving both together. It would appear that this is just as relevant to immunotherapy as a separate study confirms that IMM-101 has to be given before or with immunotherapy and not after it.

In another study we published last year we showed that non responders to a vaccine had significantly higher inflammatory markers than responders. This suggests that anti-inflammatories could play an important role in improving responses to immunotherapy.

We have focused on how two drugs, LDN and CBD, exert significant anti-inflammatory activity in cancer and have shown that they alone and in combination, enhance the response to chemotherapy. This can allow the chemotherapy to be effective at half the normal dose and hence avoid significant toxicity.

We now plan to look at the effect on immunotherapy as I have noted exceptional disease control when IMM-101 and LDN is given with or without CBD in a number of tumour types.

A clinical study using standard treatment with or without IMM-101 and LDN/CBD across several tumour types is the next logical step and we are exploring how this may be funded.

The ICVI funded group was the first to describe how LDN prevents the production of a substance called IL-6 which is recognised to drive cancer progression. As it is also a major factor associated with COVID-19 demise and death. We have tried it in 3 cases of long COVID, 2 of whom had suffered for over a year. All complained of severe fatigue, inability to concentrate and do anything (brain fog), muscle pains and severe shortage of breath

at night. All 3 patients have had a complete resolution of their symptoms. Interestingly, in one patient, symptoms started to return on stopping daily treatment which suggests that the use of LDN may be needed for some months to return completely to normal.

PROFESSOR DALGLEISH

NEW WAYS TO DONATE

AMAZON SMILE

We are registered with Amazon Smile, which means that Amazon will donate 0.5% of your purchases to the ICVI. Simply type Amazon Smile into the Amazon search box and you will be asked to search for the ICVI.



PUBLISHED PAPER SUMMARIES

HOW TO TRAIN YOUR DRAGON: harnessing Gamma Delta T Cells, Antiviral Functions and Trained Immunity in a Pandemic Era

Jonathan Caron, Laura Ridgely, Mark Bodman-Smith

This review, published recently in *Frontiers in Immunology* by members of the ICVI funded team explains how we think the cells we study in treating cancer might also play a role in the body's defence against SARCoV2, the virus causing COVID19. Mycobacterial preparations (such as IMM-101 and BCG) currently and previously used by Professor Dalgleish to treat his cancer patients could also provide some extra protection against Covid-19, particularly new variants which might be resistant to current vaccinations.

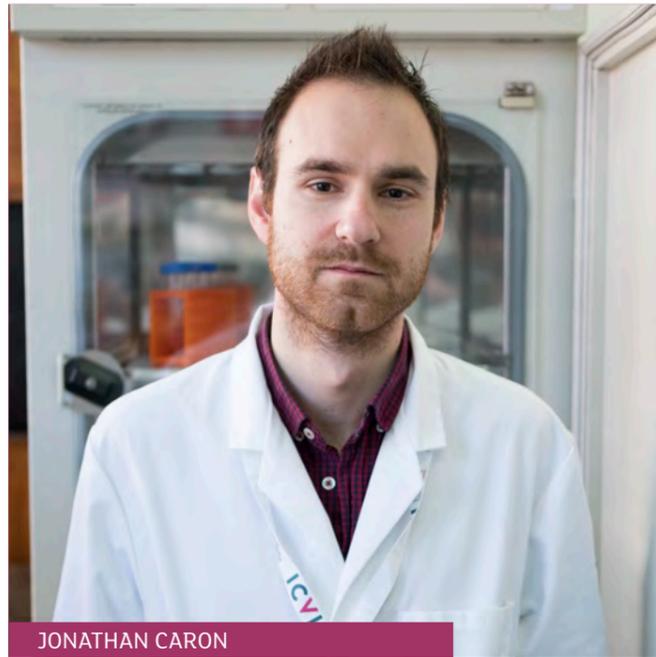
We have done a lot of work in recent years on Gamma Delta T cells. We know that these cells are activated by the mycobacterial preparations that Prof Dalgleish is using clinically to treat melanoma, and we believe them to be a powerful cancer killer. We have published a number of papers showing this to be the case and that mycobacteria can stimulate them to expand and kill tumour cells that we grow in the laboratory.

These unique cells seem to be able to detect 'danger signals' which can be expressed on the surface of cells when they are in distress. These 'danger signals' are expressed on a wide range of tumour cells and are one recognition path by which Gamma Delta T Cells can see the tumour. Perhaps unsurprisingly these signals are also expressed on virally infected cells.

There are many reports of Gamma Delta T Cells being one of the first responding cells in a number of respiratory viral infections including 'flu and the first SARS virus which arose in the early

2000s. We thought that this interesting cell type might also have a role to play in the control of SARCoV2; our review goes on to provide evidence of this. 'Training Dragons' refers to the powerful killing capacity of the Gamma Delta T Cell and also the fact that this population may need 'training' to see its target. Mycobacteria seem to have the ability to train Gamma Delta T Cells. This could be of great importance as the current vaccines for COVID19 are very specific and the appearance of new variants might diminish the protective response generated. The recognition of 'danger signals' does not rely on the specific proteins seen in traditional vaccination and so this approach might offer additional broad protection.

One ICVI PhD project, in collaboration with Public Health England, is designed to show the anti-tumour effect of stimulating Gamma Delta T Cells happening in a 'real life-mimicking' model system. In the light of the current pandemic, much of the work at PHE has been moved to investigate COVID19 and we have been for-



JONATHAN CARON

tunate to look at the role of Gamma Delta T Cells in this devastating disease. These studies are very preliminary but we have seen profound changes in this cell population in response to BCG, a mycobacterial preparation, and to SARCoV2 infection. This suggests that these cells may play a role in the disease.

With a disease which is ravaging the health and economy of most of the world, Gamma Delta T Cells might be yet another weapon in our armoury which can be brought to bear on COVID.

For the full paper please look at the news section of our website.

CHEAP AND COMMONPLACE: Making the Case for BCG and Gamma Delta T Cells in COVID-19

Alexandra L. Morrison, Sally Sharpe, Andrew D. White and Mark Bodman-Smith

Antigen-specific vaccines developed for the COVID-19 pandemic demonstrate a remarkable achievement and are currently being used in high income countries with much success. However, new SARS-CoV-2 variants are threatening this success via mutations that lessen the efficacy of antigen-specific antibodies. One simple approach to assisting with this issue is focusing on strategies that build on the non-specific protection afforded by the innate immune response. The BCG vaccine has been shown to provide broad protection beyond tuberculosis disease, including against respiratory viruses, and ongoing studies are investigating its efficacy as a tool against SARS-CoV-2. Gamma delta T cells, particularly the Vd2 subtype, undergo rapid expansion after BCG vaccination due to MHC-independent mechanisms. Consequently, Gamma delta T cells can produce diverse defences against virally infected cells, including direct cytotoxicity, death receptor ligands, and pro-inflammatory cytokines. They can also assist in stimulating the adaptive immune system. BCG is affordable, commonplace and non-specific, and therefore could be a useful tool to initiate innate protection against new SARS-CoV-2 variants. However, considerations must also be made to BCG vaccine supply and the prioritization of countries where it is most needed to combat tuberculosis first and foremost.



ALEX MORRISON

HOW CAN YOUR DIET AFFECT YOUR CHANCES OF GETTING CANCER?

Dr Peter Smith – ICVI funded researcher at St George’s University of London

As a senior post doctoral researcher in cancer immunotherapy I have been studying the latest research which looks at the incredible impact the health of your gut can have on your risk of developing cancer.

We all know that the way we live affects our risk of developing cancer. Cancers with the highest incidence have strong environmental causes. Exposing ourselves to carcinogens from smoking, processed food or ultra violet light heightens our risk of cancer.

The way we live can also prevent or delay the onset of cancer and our diets have a vital role to play. It is important to avoid or limit foods that have been smoked, cured or salted for preservation or charred during cooking, all of which produces carcinogens, as well as saturated fats and sugar. Diets with a high fibre content from grains, fruits and vegetables are consistently associated with the prevention of cancer. Micronutrients (termed phytochemicals) found in different fruits, vegetables and plants also have immune, anti-inflammatory or anti-cancer properties. For example, the root vegetable turmeric contains a phytochemical called curcumin which reduces inflammation. Tomatoes contain a carotenoid called lycopene which can prevent tumours growing and help prevent cancer. Compounds such as those derived from garlic, have anti-inflammatory and immune modulatory properties and can kill tumour cells. Leaves used in green tea contain antioxidants called epigallocatechin gallate (EGCG) which can

influence parts of the immune system.

Whilst many different types of food are associated with either protection from, or increased risk of, cancer, it’s difficult to prove the anti-cancer effects of a given food due to the complex nature of our lifestyles and inherited traits. Even where research clearly shows the effects, the extent to which a particular food may help prevent or increase our risk of cancer is difficult to quantify. For these reasons most dietary advice is generalised and centres upon diets high in fibre and with varied fruit and vegetable intake whilst limiting foods with processed, preserved, containing high levels of fat or sugar.

This advice may change due to the development of ‘functional foods’, sometimes referred to as ‘nutriceuticals’, which consist of pharmacologic doses of the active components of foods associated with health and cancer prevention. Examples include the supplementation with high dose vitamin D which can be difficult to obtain from our diets alone, or



PETER SMITH

non-digestible dietary fibres to support gut health and immune stability. Combinations of the active components of functional foods are also in development in order to combine their cancer preventative properties.

The identification and use of these active components led to investigations to determine whether vitamins or phytochemicals such as curcumin, lycopene or EGCG might be effective not just to prevent cancer, but to treat it when it occurs. These agents have been used individually or in combination with established chemotherapy, however improved anti-tumour effects have rarely been ob-

served. The conclusion from these studies, that our diets can help prevent cancer but not treat it, became the established view but is now being challenged by the advent of cancer immunotherapy.

Cancer immunotherapy activates a patient’s immune system to target tumours for destruction. The success of immunotherapy has resulted in a revolution in how some cancers are treated, however immunotherapy doesn’t work for all patients and is largely ineffective for some types of cancer. Important studies investigating how cancer immunotherapy works may have shown why. These studies have revealed that patients who were successfully treated with immunotherapy were found to have different bacteria in their guts compared to patients in whom the therapy failed to work. There are about 13 trillion bacteria in our guts, collectively called the ‘gut microbiome’, which have profound effects on how our immune system functions. Bacteria capable of digesting dietary fibre are linked with the success of immunotherapy and patients with diets high in fibre are also more likely to respond to immunotherapy. In support of this are observations that the metabolic products of fibre fer-

menting gut bacteria are capable of activating our immune system. The use of antibiotics, which damages our gut microbiomes, is linked to the failure of immunotherapy. The use of probiotics, which are unlikely to replicate the complexity of our gut microbiomes, may also reduce the effectiveness of some types of immunotherapy. Patients who fail to respond to immunotherapy can become responders by ingesting the microbiomes (via colonoscopy) from responder patients.

Our diets influence the make-up of our gut microbiome, with diets high in fibre supporting populations of bacteria that are beneficial to cancer immunotherapy. Other components of our diets may also aid immunotherapy. These include vitamin D or the phytochemicals described above, which can prime our immune system and reduce the inflammation associated with poor immunotherapy responses. Although these functional foods can prevent but



not directly treat cancer, their ability to prime the immune system makes them powerful tools with the potential to improve the effectiveness of cancer Immunotherapy - however most remain untested in this setting. At the ICVI we are studying how combinations of these agents support anti-tumour immune responses with the aim of increasing the success of immunotherapy so that more patients can benefit.

OVARIAN CANCER TRIAL

Unfortunately, our last recruitment round was unable to find a suitable candidate to run this trial. We are hopeful that the next round will be more successful and we will continue to keep in touch with you about this.

DONATING - PLEASE HELP US FIGHT CANCER TODAY



To donate by card please visit www.icvi.org.uk or phone **020 7498 8263**

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