ISSUE 37 | SPRING 2023

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 SPRING 2023 ISSUE OF OUTLOOK

Since our last newsletter the charity has gone through a significant change in the way we fund research by becoming a member of the AMRC. This is an exciting change which brings a wealth of benefits for the charity. AMRC membership is the hallmark of quality research funding. To be accepted into membership, the ICVI had to demonstrate that we follow the AMRC's rigorous standards in peer review, enabling us to ensure the research we fund is of the highest quality.

Importantly for our small charity, membership of the AMRC also helps our research money go further. This means that in future the ICVI will only pay the direct research costs of clinical research with no overhead charge. This will save us many thousands which will now be spent on direct research costs to universities in the UK who are successful in applying to us for money.

One thing that hasn't changed though is that all of the research undertaken by those we fund is informed by Professor Dalgleish's research interests. In this issue one of the winners of our first ever call for funding, Dr Peter Smith, explains how his project could have important implications for patients whose cancer is currently resistant to treatment, including those with pancreatic cancer.

If you've ever wondered how traditional vaccines such as the ones given in childhood relate to the cancer vaccines which we fund research into, Professor Dalgleish has written a fascinating history of vaccines in which he answers that very question.

As ever we are so grateful to all of our fundraisers who continue to work hard to support our research, we value you and your hard work so very much and we really do try to ensure that every pound raised is spent wisely on research.

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ICVI Institute for Cancer Vaccines & Immunotherapy
Changing Lives Through Research

Christmas Appeal

Thank you very much to those of you who donated to Professor Dalgleish's Christmas appeal. £6,911 was raised and this will support an exciting new project for ovarian cancer patients which we are funding at Imperial College. The amount raised was much lower than usual and we feel that this may have been due to the Royal Mail strikes over the Christmas period.

Christmas Cards

Thank you to everyone who purchased, we made £790 profit on our sales and a further £946 in donations.

New Tribute Fund – Catriona Stephanie McLeod

We were very moved to hear from Catriona's sister Caroline recently. Catriona, who was known as Catt, sadly died from breast cancer in January.

Caroline has decided to set up a Tribute Fund to honour Catt. Catt believed that using the body's own response system, combined with a healthy diet and lifestyle and mindfulness was going to be the first port of call for treatment in the future.

Immunotherapy treatment was not an option for Catt until much later on and sadly she didn't get the opportunity to benefit from it herself, however she would be pleased to know that efforts are being made to make it more accessible in the future by supporting the ICVI.

Caroline said, "Catt initially appeared to be in the clear after treatment, but sadly this was not the case; however she showed an astonishingly positive attitude to dealing with her illness, she was determined to fight it with everything she could and continue to live a fulfilling life." Catt was a wonderful daughter, sister, friend and mother – she left behind her 14 year old daughter Morgan and her son Lachlan who was just turning 13; she adored them both and would have dearly loved to have had more time with them."

Catriona McLeod

Thank you so much to Catriona's family and friends for thinking of our charity at such an incredibly painful time. If you would like to donate to Catriona's tribute fund please visit https://icvi.org.uk/funds/the-catriona-stephanie-mcleod-tribute-fund/ where you can read beautiful tributes to Catriona and donate.

If anyone would like to set up a tribute fund for their loved one, please contact abi@icvi.org.uk

ICVI Wine Club

Our wine club is doing really well! The brainchild of supporter George Bouwens, it is now in its third year and has raised £2,182 for the Lucy Sands Tribute Fund so far. The process is smooth and we've had lots of good feedback about the quality of the wine too.

You can order a one-off case of 12 bottles of delicious wine for delivery the following month (deliveries March, June, Sept & December) or sign up to receive a case each quarter.

The next delivery will be in June 2023. Please get in touch if you would like to receive a case. Payment of £165 for the case of 12 bottles needs to be sent by the end of May.

If you would like to join or need any more information before you decide please email abi@icvi.org.uk

Text **CANCER10** to **70191** to donate **£10** Text **CANCER20** to **70191** to donate **£20** Text **HIGH5** to **70970** to donate **£5**

Garden Art

Loyal supporter Serena Aldous once again kindly held open garden events in support of the ICVI throughout the summer. This year she enhanced the experience even more by harnessing the talent and generosity of local Buckinghamshire artist Peter Keegan. Peter kindly offered art classes in Serena's beautiful garden in Steeple Claydon. A huge £1,641.22 was raised of which £900 was a donation from Peter and the rest donations from visitors.

Huge thanks to Serena for all her hard work now and over the years and also of course to Peter for his very generous contribution. Serena and Peter are hoping to repeat their success this summer. If you would like to join the fun, please visit www.peterkeegan.com

Art class taught by Peter Keegan in Serena's beautiful Buckinghamshire garden

Fundraising Flowers

More garden related fundraising came to us via Liz Sands, another loyal supporter who once again kindly sold cut flowers from her garden last summer, raising the substantial sum of £543 towards the Lucy Sands Tribute Fund. Blooming wonderful work Liz!

Sami's Marathon

We are very proud of Sami Mason who finally (following cancellations due to Covid) ran the London Marathon for us in October in memory of his father. Sami raised just over £3,000 for the charity which is wonderful. Thank you to Sami for all your hard work training and fundraising!

Sami at the finish line'

Jackie pre dive

Golf Club Update

In our last issue we reported on Caroline Bouwens' tenure as Ladies' Captain of Tidworth Golf Club last year. We are delighted that Caroline raised £4,674.06 through various fundraising efforts. This includes member and friend Jackie Agate who raised £1,488 of the final total with her brave sky dive. Thank you very much Caroline, Jackie and all of the members who supported this incredible fundraising. The total has been added to the Lucy Sands Tribute Fund.

All change at the ICVI

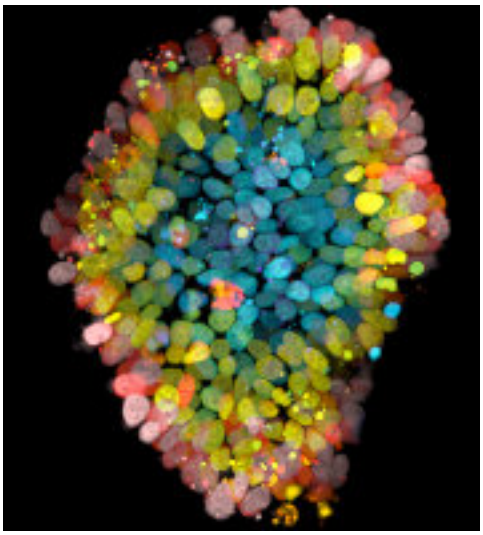
Last year we announced that we are delighted now to be a member of the AMRC (Association for Medical Research Charities). As Professor Dalgleish explained in the Christmas appeal letter, this is a big and important step for the charity and will hopefully lead to a higher profile for our work.

We have completed our first ever call for funding round and were delighted to be able to fund three very important projects, the first of which we feature in this newsletter.

Ovarian Cancer Trial update

We are delighted to announce that our ovarian cancer clinical study (funded before we gained AMRC membership) is now well underway. We are in the process of agreeing our collaboration with the UCL clinical trials unit which will allow us to study immune responses in ovarian cancer patients with the intention of finding prognostic and functional immune 'markers' suitable for therapeutic exploitation.

Our experiments in the laboratory have identified bacterial and vitamin derived metabolites capable of enhancing the ability of chemotherapy to kill ovarian tumour cells. These metabolites include the short chain fatty acid butyrate, calcitriol and retinoic acid. We shall identify whether these metabolites are present in ovarian cancer patients and, if so, whether their presence and abundance correlate with patient survival and markers indicative of anti-tumour immune responses.



New Research Project

We are delighted to be funding the below project which was one of three winners of our first ever call for funding. Following a strict peer review process we awarded £250,000 to Dr Peter Smith of St George's University of London to fund this project which we hope will have positive implications for patients with cancers which are resistant to chemotherapies. Peter explains below:

Immune Checkpoint Blockade (ICB) is an innovative treatment that uses medications known as immune checkpoint inhibitors to address several types of cancer. Specifically, these medications can help the body's immune system recognize and attack cancerous cells. ICB has dramatically improved treatment for some cancer patients, particularly those with melanoma or lung cancer. However, many patients are non-responsive to ICB and some cancers such as pancreatic cancer are largely resistant.

Cytotoxic T-lymphocytes (CTL) represent one of several types of cells of the immune system that have the capacity to directly kill other cells. Tumours 'switch off' these CTL using checkpoint molecules to hijack the CTL and allow themselves to grow. ICB prevents tumours from switching off CTL, so that CTL can kill tumour cells and sometimes eradicate tumours completely.

Unfortunately ICB alone is often insufficient to reinvigorate CTL for various reasons – damaged CTL in cancer patients being one - and other approaches are needed. Methods are in development but they will be expensive and potentially toxic for patients.

The approach we are interested in involves 'priming' CTL so that they're ready to respond to ICB and are more able to persistently attack tumours during ICB treatment. Recently metabolites derived from our diets or the good bacteria in our gut have been found to improve ICB immunotherapy. These include a fatty acid called butyrate and an active metabolite of vitamin D called calcitriol.

This funding will allow us to study the ability of metabolites to prime CTL and improve CTL responses. The presence of these metabolites will be measured in the serum of cancer patients with ICB resistant tumours or undertaking ICB immunotherapy.

The research has three main aims:

1. Do butyrate and calcitriol improve CTL function?
2. How do they induce effectiveness of CTL?
3. Are butyrate and calcitriol present in the serum of cancer patients? Are they associated with immune function and the effectiveness of ICB in these patients?

Implications for Cancer Patients

This research will tell us whether butyrate and calcitriol have potential as immunotherapies with ICB. Understanding how they work will allow us to predict which patients might benefit from their use. Associating the presence of butyrate and calcitriol with patients' ability to respond to ICB will allow us to assess the merit of using them to treat patients. Calcitriol and/or butyrate can be administered orally at home rather than in a hospital setting and are inexpensive and non-toxic.

If proven, this project could provide a viable treatment option for patients who may not otherwise benefit from ICB.

Update from Professor Dalgleish

How do cancer vaccines relate to early vaccines?

This year is the 200th anniversary of the death of Edward Jenner, who is widely accredited with the birth of vaccination. I thought it would be interesting to talk about how the fundamentals of vaccination and research into it over the years since Jenner's discovery have been very relevant to our work in the ICVI over the last twenty years. Jenner's vaccine and other early vaccines are related to cancer vaccines in the sense that they both aim to stimulate the immune system to recognise and fight off a disease. However, the mechanisms by which they achieve this goal are quite different.

Jenner is widely recognised as the father of vaccination, with not only one of our wings at St George's being named after him (he trained here), but also the National Vaccine Institute, known as the Jenner Institute in Oxford.

I found it very interesting that Jenner's major role in the development of vaccines was not related to his background. He was an eminent biologist and a Fellow of the Royal Society for his work on bird behaviour. It was this eminence that launched his challenge experiment worldwide, which ended up with smallpox coming under worldwide control.

Smallpox was an incredibly infectious disease which was very mutilating and there was no effective treatment. However, it had been known from at least the 1400s, and possibly thousands of years earlier in China, that a tiny dose of the disease vesicle, when injected under the skin, could protect from serious smallpox. A Dorset farmer called Mr Jesty had made the observation that none of his milkmaids ever contracted smallpox, although they did all get infected with cowpox, which was a very mild disease. Mr Jesty decided in 1774 to test the hypothesis that cowpox could protect against smallpox by variolating or injecting a small amount of cowpox under the skin of his family and children and he then noted that none of them developed smallpox, although non-variolated fellow people in the village did. What Jenner did was to do a challenge experiment with a young man given attenuated (weakened) pox virus, possibly the same cowpox technique, to a young boy and then to inject live smallpox as a challenge. Fortunately, the boy did not contract the disease and due to Jenner's eminence he was able to broadcast this fact throughout the country, Europe and then to America, where the practice was adopted. In our current era, where evidence other than a randomised controlled trial is needed to get anything done, this is really quite extraordinary. However, the good news was that this approach was to lead to the total eradication of smallpox by 1980.

This approach of using an attenuated version of an agent that would cause severe disease was then taken up by Louis Pasteur who was the first to make laboratory derived vaccines, passaging agents through cultures and using the effect of attenuation to make them less infective in order to develop vaccines. His first vaccine was for a cholera-like illness, which was successful in chickens, and he used the approach in many other diseases, such as anthrax, as well as developing a vaccine for rabies, to be given post exposure.

This approach of taking an agent and culturing it until it becomes very non-pathogenic is the approach taken by Calmette and Guerin, two French scientists who developed the BCG vaccine for Tuberculosis, which has played such a major role in the ICVI vaccine programme, both in basic research and in the clinic.

The technology of attenuating flu vaccines was stimulated by the Great Spanish flu of 1918. The initial vaccines centred around totally inactivated viruses, which also formed the basis of the first polio vaccine by Jonas Salk. The Spanish flu infected around 500 million people and killed 25-50 million, most of whom were fit adults and not the elderly, who were most at risk to later flu epidemics. It was therefore an obvious target for vaccination and many trials were started but no conclusion regarding effectiveness could be confirmed. However, the knowledge gained was used effectively against

another worldwide scourge, polio, and the first vaccine against this was developed by Jonas Salk who used a fully activated virus, who noted however that it did not prevent transmission. Another scientist followed the attenuated oral vaccine route, which eventually became the highly effective worldwide polio vaccine and this was developed by Albert Sabin.

Early vaccines as described above are designed to prevent infectious diseases by exposing the immune system to a harmless version of the pathogen, such as a weakened or inactivated virus or a piece of the pathogen (antigen) that the immune system can recognise and respond to. The immune system then mounts a response to the antigen, generating memory cells that can recognise and respond to the pathogen if it is encountered again in the future.

Cancer vaccines, on the other hand, are designed to treat cancer by stimulating the immune system to recognise and attack cancer cells. Unlike infectious diseases, cancer is not caused by an invading pathogen but rather by the body's own cells that have become abnormal and started to grow and divide uncontrollably. Therefore, cancer vaccines work by targeting specific proteins or antigens that are present on cancer cells but not on normal cells, and presenting them to the immune system to generate an immune response.

So while cancer vaccines and early vaccines share the common goal of stimulating the immune system to fight disease, they differ in their mechanisms of action and the diseases they target. Early vaccines were designed to prevent infectious diseases by exposing the immune system to a harmless version of the pathogen, while cancer vaccines aim to break the tolerance to tumour antigens which are very similar to normal antigens.

Over the last twenty years or more, due to ICVI funding, my team has been able to assess many different types of vaccines and witnessed unexpected phenomena. With regards to cancer vaccines the first and most important lesson learnt was not to target one or two specific antigens as the tumours will downregulate the expression of these antigens and escape any immune response of them. The second thing is that the best immune response in controlling cancer in our preclinical experiments is the non-specific T-cell responses, provided by agents like BCG, first developed as a TB vaccine.

Indeed, because of this we went on to use Mycobacterium vaccae and more recently IMM-101, the latter of which is heat killed. There is an interesting parallel here that the attenuated viruses were more effective against polio, as compared to heat killed viruses, but in the case of cancer vaccines it really appears to be the other way round, with the heat killed viruses providing a very strong immune response that can be boosted without losing efficacy. Indeed, with some of our vaccine models we have clear evidence of two vaccines being good, a third of no particular use and a fourth destroying any benefit from the first two.

The other thing that we noticed, especially from our early clinical trials, was that patients who did not respond to vaccines when similar patients had dramatic responses were found to be very low in Vitamin D levels. Restoring Vitamin D function just with oral supplementation could lead these patients to respond to the vaccine programme. Indeed, since we first noticed this it has been confirmed worldwide, not only for vaccines but also immunotherapy and chemotherapy.

Our core ICVI research programmes have shown us that correcting Vitamin D and stimulating the innate immune response with IMM-101 and inhibiting any chronic background inflammation with anti-inflammatories greatly increases the response to basically anything else, including radiotherapy and chemotherapy. I am very proud that Dr Alberto Fusi was recently able to confirm that priming with IMM-101 greatly increases the response to the current immunotherapy agents in melanoma and this obviously has to be expanded to the point of getting a license and rolling it out to all the other cancer types.

Our intensive research into what drives inflammation and hence cancer has led us to realise that **low dose Naltrexone (LDN) is one of the best anti-inflammatory agents for cancer known as it inhibits a growth factor called Interleukin-6, which is often known as cancer growth factor.** Interestingly it was the first factor to be identified in acute Covid infection. This could help explain why there are so many reports of long Covid responding to LDN and, indeed, people who have been on LDN having no recollection of being infected with Covid or, if they were, only being very mild. It is therefore a logical goal for future studies to prime with IMM-101, Vitamin D and use LDN as the background anti-inflammatory and combine this with any other standard treatment to enhance efficacy and reduce the side effect profile, as we have published last year where we show that priming with LDN can allow the same effectiveness with half the normal dose of chemotherapy across several tumour types.

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One hour of research undertaken by the whole of the research team costs £400 and £2,000 per patient per year for a trial (this is an average cost, including salaries, consumables and supervision)

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