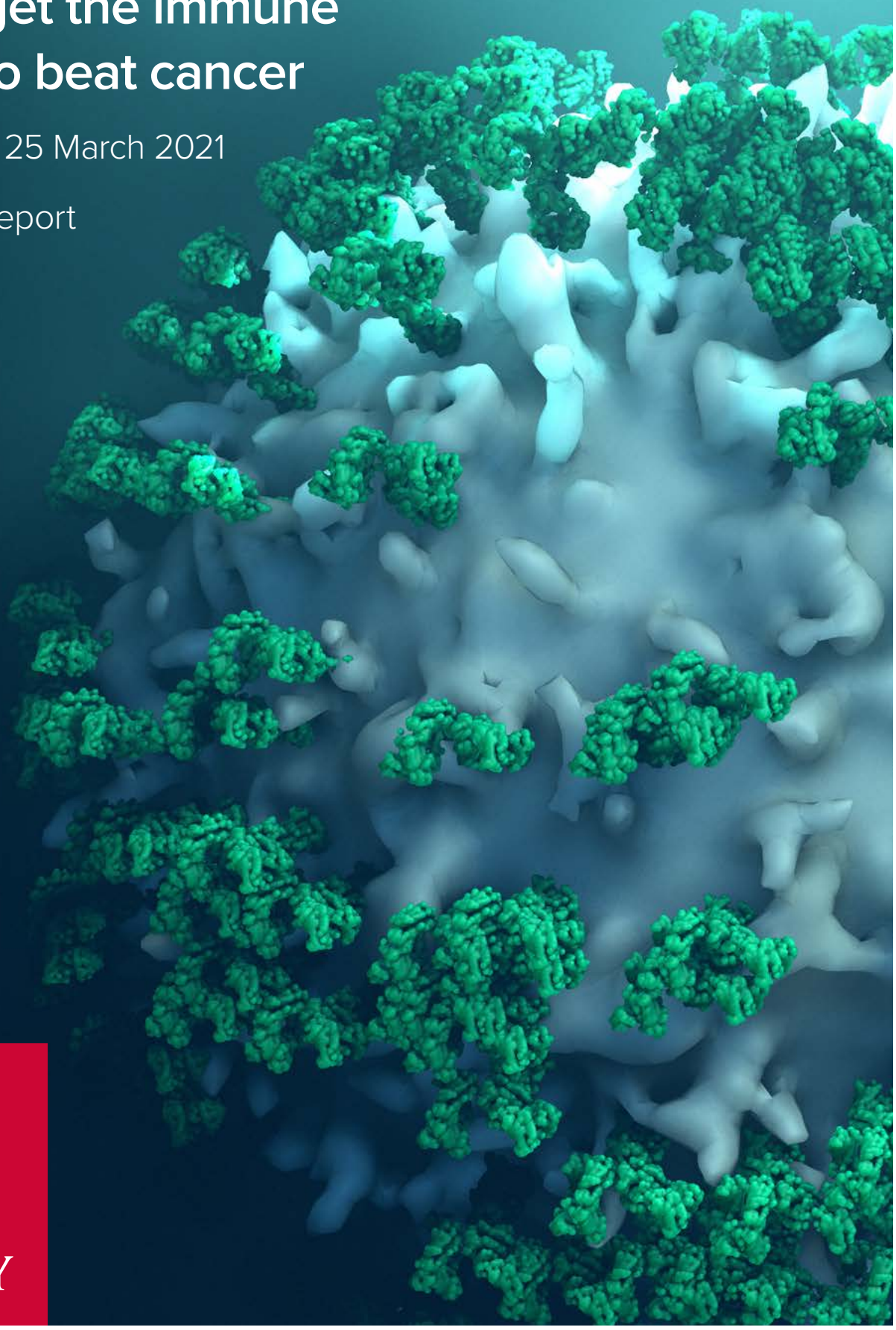
Part of the conference series
Breakthrough science and technologies
Transforming our future

Immuno-oncology: How to get the immune system to beat cancer

Held on 24 – 25 March 2021

Conference report



THE ROYAL SOCIETY

Introduction

On 24 and 25 March 2021, the Royal Society hosted an online conference on Immuno-oncology: How to get the immune system to beat cancer. This meeting, supported by AstraZeneca, forms part of the Royal Society's Transforming our Future series. The Transforming our Future meetings are unique, high-level events that address scientific and technical challenges of the next decade and bring together leading experts from the wider scientific community, including, academia, industry, government, and charities. The meetings are organised with the support of the Royal Society Science, Industry and Translation Committee.

The conference series is organised through the Royal Society's Science and Industry programme which demonstrates the Society's commitment to integrate science and industry across its activities, promote science and its value, build relationships and foster translation.

The programme was organised by Dr Susan Galbraith (AstraZeneca), Professor Sir Roy Anderson FMedSci FRS (Imperial College London), and Professor Luke O'Neill FRS (Trinity College Dublin). The first day focused on cell therapy approaches and recent immuno-oncology breakthroughs including the role of the microbiome, personalised cancer vaccines and oncolytic viruses. The second day explored the current barriers and pitfalls in immuno-oncology leading to a panel discussion that concentrated on solving the issues of cost and regulations for new therapeutics.

This report is not a verbatim record, but a summary of the discussions that took place during the day and the key points raised. Comments and recommendations reflect the views and opinions of the speakers and not necessarily those of the Royal Society.

Executive summary

Every two minutes, someone in the UK is diagnosed with cancer. Year on year, the cancer incidence rate continues to grow, with a projected increase of approximately 62% by 2040, resulting in over 27 million additional worldwide cancer cases per year. Traditionally, cancer has been treated using methods such as chemotherapy and radiotherapy. However, some cancers don't respond well to traditional therapies, and others recur.

Immuno-oncology could help provide a solution to these problems by harnessing the body's immune system to eradicate cancer and prevent its recurrence. This conference focused on recent advances in immuno-oncology, providing updates to current research into new therapeutics and outlining key issues that would need to be overcome to implement new technologies.

Key points taken from the conference included:

- There has been a large benefit to some patients receiving immuno-oncology treatment who have shown an increase in survival rates. However, not all patients respond to these therapies, so more research is needed to find a broader range of therapeutic solutions.
- Current cell therapies use an autologous, personalised approach to treating patients, however, research into allogenic off the shelf therapies is expanding, allowing the possibility of a more general treatment approach to a wider patient population.
- Recent breakthroughs and developments in cancer immunotherapy in the fields of gut and tumour microbiome biology, cancer vaccines, and oncolytic viruses, are providing an even wider range of possible treatment options for patients with cancer.
- Next generation sequencing has allowed for rapid progress to be made in predicting tumour biomarkers allowing for accelerated development of personalised cellular therapies.
- Immuno-oncology treatments are expensive per patient, but this cost is largely justified due to the high failure rate in the pipeline and lack of revenue overall. Costs are predicted to decrease as more is discovered around the implementation of these new therapies.

"The immuno-oncology revolution has changed the outcome for patients with a variety of different cancers, but there is still work to be done for patients who are not responding to treatments"

Dr Susan Galbraith FMedSci, AstaZeneca

"The recent immuno-oncology technologies and advances are remarkable and rquire large scale research and investment to develop"

Professor Luke O'Neill, Trinity College Dublin

"Immuno-oncology therapies work well for a few, but not for most – an extrodinary puzzle which needs to be solved"

Professor Sir Roy Anderson, Imperial College London

KEYNOTE

The evolution of immuno-oncology: an industrial perspective

Dr Klaus Urbahns, Merck KGaA, outlined the key therapeutic modalities that industry is examining, highlighting their potential, the current limitations, and recent successes.

For many years, researchers have been trying to selectively kill cancer cells during the process of DNA replication by the constant stimulus for proliferation through growth hormone signaling. Targeted medicines interfering at this point have been remarkably successful for the last 50 years. The only way for cancer cells to escape the impending attack of the immune system is to develop a tumour microenvironment which creates tolerance, reduces immunity, and escapes immune control. Rather than directly attacking the tumour, immuno-oncology sets out to activate and enhance the immune system, bolstering its response to cancer.

Check point receptors

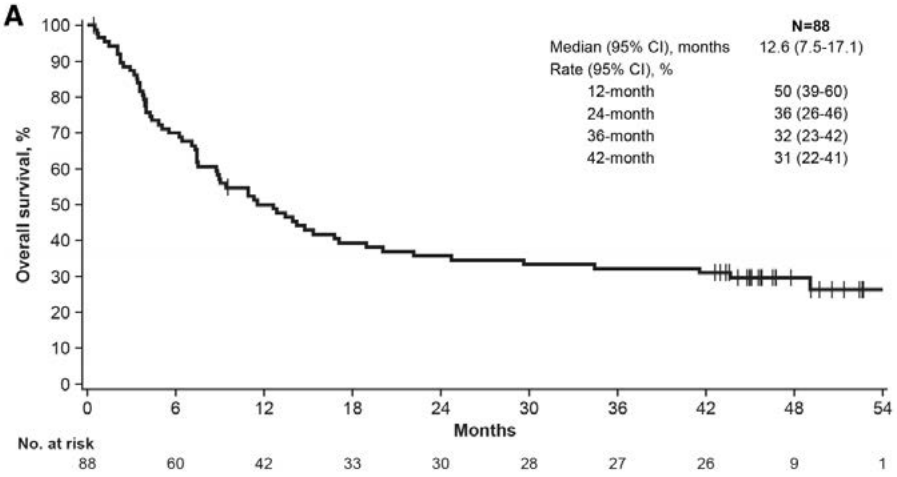
There are many check point receptors – the most extensively studied is the programmed cell death receptor (PD-1), and its ligand PDL1, which can also be expressed on the surface of tumour cells. PDL1 binds to the PD-1 expressed on the membrane of cytotoxic T-cells, which creates an immune dampening signal, eventually resulting in the cancer cell evading the immune response.
A PDL1-specific antibody developed by Merck, Avelumab, not only seeks to disrupt the interaction between PD-1 and PDL1, but also readily activates and attracts Natural Killer cells to the site of action. Avelumab therefore acts as an agent activating both active and innate immunity.

Clinical trials of Avelumab (Figure 1) used Merkel Cell Carcinoma as a target as it was known there was an abundance of T-cells ready to be activated at the site of the cancer. Seven consecutive doses of the PDL1 antibody were given to the first patient showing a complete response, making this patient the first to leave the hospice in its history.

FIGURE 1

Overall survival: Merkel Cell Carcinoma

Percentage overall survival of 88 patients treated with Avelumab. The death rate seems to tail off, suggesting long term effects for almost 20% of patients four years into the trial.



Combining the PDL1 antibody with another inhibitory drug, Axitinib, showed an almost doubling effect on progression-free survival time compared to standard of care for patients who expressed PDL1 in their tumours. There was also a significant clinical effect for Avelumab in the maintenance setting for advanced metastatic urothelial cancer. However, this is not the only check-point inhibitor on the market, with 72 other FDA approved checkpoint inhibitors being competitively implemented. It should be noted that there could be significant financial gains for checkpoint inhibitors, with predictions that these drugs may become some of the most profitable in pharmaceutical history.

Small molecules

Combination therapy hopes to extend patient survival beyond the current standard of care, transforming some cancer types into more manageable diseases. Small molecules can be well-suited partners to antibody check-point blockers. In contrast to antibodies, they penetrate tissue tumours deeply and can easily be administered by mouth allowing for more flexible dosing. Flexible dosing allows for implementation of drug holidays: a period when toxicities and patient side effects would previously have been intolerable.

Cellular therapies

A less common therapeutic modality, but which is making significant advancements, are cellular therapies. In most cases these are leukocytes which must be obtained autologously[1]. Transfection of the isolated T-cells with chimeric T-cell receptors – combining antigen binding and T-cell activation functions – is then undertaken. The isolated cells are then reinjected into the patients with promising outcomes, particularly in children with acute lymphoblastic leukemia. There are currently 3 therapies on the market with 670 ongoing clinical trials, but unfortunately it has not yet been possible to demonstrate efficacy in solid tumours.

Despite remarkable progress for some patients who experience complete durable responses, unfortunately not all patients respond to cancer immunotherapies. However, it is encouraging to see how modern immuno-oncology has contributed to the progress made in reducing the death rate of many cancer types over the last couple of years.

> "The idea of immuno-oncology is that tumours are seen as a defect of the immune system which has failed to recognise the malignancy."
>
> Dr Klaus Urbahns, KGaA

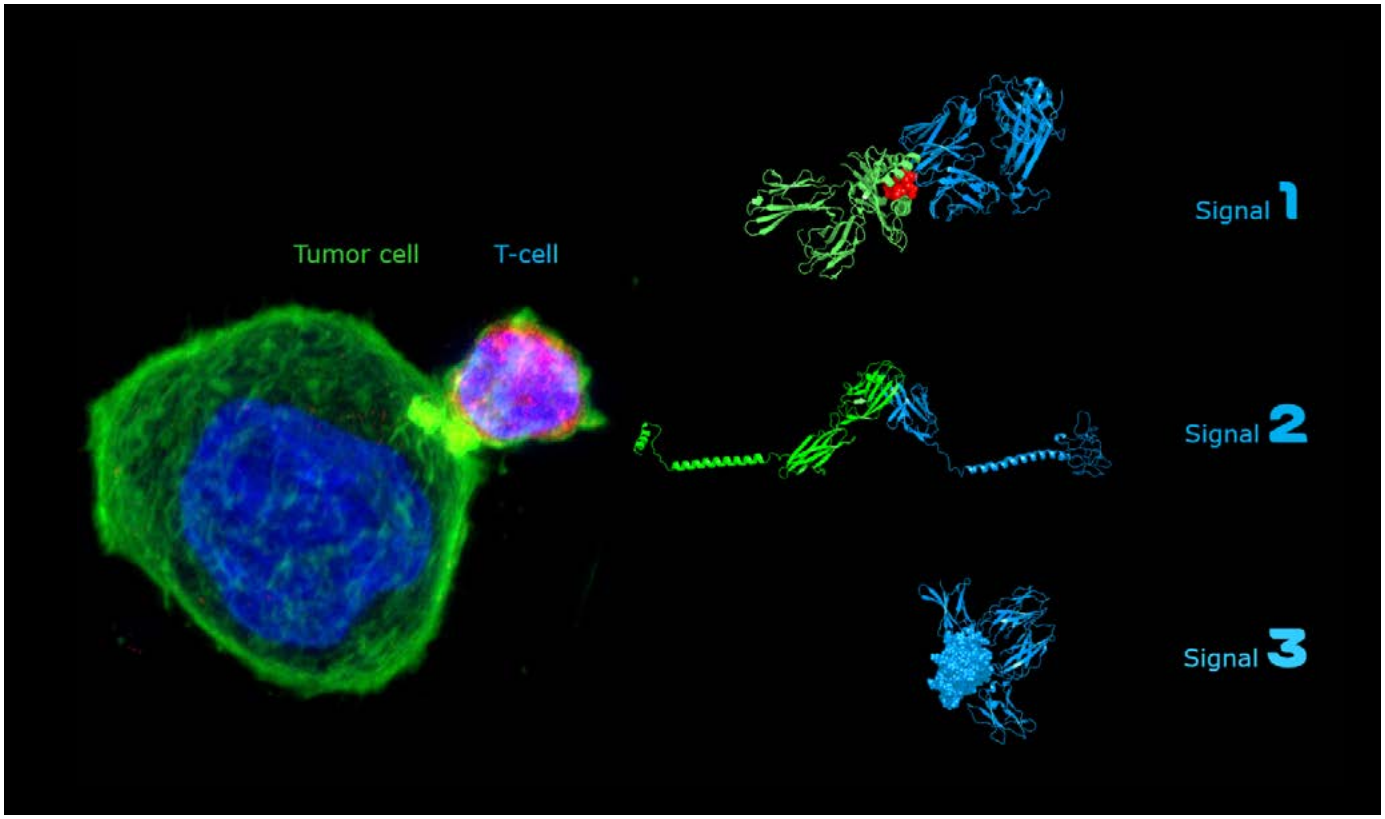
> "Rather than killing the tumour itself like targeted therapies, immuno-oncology sets out to break tolerance and re-activate the natural defences by harnessing the power of the immune cells."
>
> Dr Klaus Urbahns, KGaA

1 Obtaining tissues or cells from the same individual.

FIGURE 2

A T-cell killing a tumour cell

In order to actually proceed to 'execution', the T-cell requires 3 subsequent signals. A T-cell receptor/MHC-interaction (signal 1), a checkpoint interaction (signal 2) and a supportive signal mediated by interleukins (signal 3). It is the mechanistic and clinical understanding of signal 2, which sparked the recent revolution in immuno-oncology.



KEYNOTE

Chromosomal instability and immune evasion in cancer evolution

Professor Charles Swanton FMedSci FRS, The Francis Crick Institute, outlined how cancer genetic diversity limits an effective immune response, as well as the role of clonal neoantigens as therapeutic targets to mitigate resistance and treatment failure.

TRACERx is a clinical programme to understand how cancers evolve over space and time in solid tumours of the lung and kidney. The primary aim of the study is to understand cancer from diagnosis to reoccurrence and death, with extensive tumour sampling to help distinguish between cancer subclones which can spread, and those that cannot. The goal of the study was to determine whether cancers with the most diverse evolutionary history have the worst clinical outcomes compared to cancers with relatively little genetic heterogeneity. For the first 100 patients in the lung TRACERx programme, single nucleotide variations were not associated with poor clinical outcome, however tumours with more cell-to-cell variation in their chromosome content, termed chromosomal instability, were associated with poorer clinical outcome.

Chromosomal Instability

Chromosomal instability was associated with metastatic dissemination of kidney cancer, whereas DNA point mutations did not show a link to metastatic dissemination. Chromosomal instability is thought to cause the loss of tumour suppressor genes on two key chromosomes, 14q and 9p, allowing the tumour to spread to distant organ sites and cause premature death. The timing of 14q and 9p loss appeared to be associated with different outcomes:

- Early loss of 14q and 9p led to rapid tumour dissemination across multiple organ and anatomical sites with early death.
- Later loss of 14q and 9p resulted in slower pace of metastasis, often to single sites of disease and a prolonged disease course over years.
- Tumours with no evidence of loss of 14q and 9p do not appear to result in metastatic disease.

The above suggests that cancer evolution is more deterministic than expected and understanding early chromosomal changes could allow for the prediction of the future physical impacts of cancer.

Cell intrinsic mechanisms of immune evasion

Across the patients of Lung Cancer TRACERx study, tumours could be defined as immune hot, where there is a high presence of immune cells, or immune cold, where there is very little evidence for the presence of immune cells. Three mechanisms of immune evasion in both immune hot and immune cold tumours were presented, driven by chromosomal instability.

Immune hot tumours

- HLA loss of heterozygosity (LOH) – the disruption of the ability for tumour cells to present neoantigens[2]. HLA loss occurs in 40% of tumours as a later event in the evolution of the tumour suggesting the pressure to evade immune evasion is a relatively late event in tumour evolution. Cancer subclones lose HLA, and as a result, cannot be recognised and escape T cell mediated cell death. There is evidence for selection for loss of HLA in the subclone that metastasises to the brain of cancer patients so it is thought there may be an obligate requirement for HLA loss for metastatic potential from the primary tumour.
- There is also evidence for antigen presentation machinery disruption brought about by chromosomal instability. These appear to be mutually exclusive with HLA LOH events. Therefore, a tumour requires immune evasion via HLA LOH or through antigen presentation machinery mutations.

Immune cold tumours

- Where there is a low presence of immune cells, there is a significant increase in the loss of neoantigens some of which are truncal (ie early in their evolution) in nature. It is thought that in the evolutionary history of the tumour, there were neoantigens presenting themselves to the immune system, which in turn resulted in identification and predation of tumour by the immune system. As a result, only the cancer cells that had lost neoantigens through chromosomal instability avoided predation by the immune system, surviving immune surveillance.

2 Antigens specifically expressed by tumours, subsequently allowing for the tumour to be recognised by the immune system.

Clonal mutations in tumour cells

Professor Charles Sawnton's team have found that clonal/truncal mutations found in tumour cells are potent forces of attraction for immune attack. These truncal mutations are the most potent predictors of clinical outcomes in immune therapy treated patients. In contrast, branch mutations did not predict clinical outcome. Therefore, truncal mutations are thought to most optimally guide immune surveillance and optimal targets for check point inhibitor therapy blockade.

In UV light induced murine tumour models, evidence suggests the more diverse the tumour, the more immuno-suppressive the environment around the tumour becomes, and the less able the mouse immune system is to combat the evolving cancer.

Professor Swanton's team are now applying these insights to patients where phase 1 clinical trials are currently being undertaken and T-cells are being extracted from tumours that recognise and target multiple clonal neoantigens, which will then be expanded and given back to patients to try and fight cancer.

> "A mentor said to me a few years back 'Do you seriously believe by understanding evolution you will be able to beat cancer evolution given that it had had 4 billion years to evolve?' And I said I didn't know, but we would give it our best attempt"
>
> Professor Charles Swanton FMedSci FRS,
> The Francis Crick Institute

Session 1:
Cell therapy approaches

Programming cells through genetic engineering – advancing cell therapy innovation

Dr Jo Brewer, Adaptimmune, discussed how they are looking to move from individual patient manufacturing towards 'off-the-shelf' allogeneic alternatives to enable deeper product understanding and greater consistency of cell therapies.

Cell therapy is a rapidly developing field in immuno-oncology. CAR-T[3] products were among the first cell therapies to be approved. There are currently three CD19 CAR-T products targeting blood cancers on the market, with further adoptive cell therapies making good clinical progress for solid tumours. Current cell therapies, including CAR-T products, are utilising autologous techniques: a process that is expensive, time consuming, and patient specific. However, allogenic techniques – taking cells from a source other than the patient – avoid these issues and could provide a solution for a much wider patient population.

The recent explosion in cell modification techniques, through viral vectors and specific genetic editing, coupled with the ever-expanding knowledge of the human genome, provides a powerful toolkit for drug developers to improve on current therapies.

For cell therapies, maintaining a fine balance is key to success. Techniques used to increase the efficacy of a cell therapy can often result in greater toxicity to the patient. Ensuring therapies focus the immune system on the desired target is something of concern and still needs to be further understood.

Autologous Therapies

Firstly, the patient undergoes leukapheresis – a procedure to separate and collect white blood cells from the blood. Specific cells are then chosen for genetic modification to generate the final product, which is then re-infused into the patient.

Allogenic therapies

For allogenic therapies, the patient is not involved in the manufacturing of the required cells and the product can be shipped to the patient on demand. Allogenic therapy falls into two categories:

- Healthy donor – a healthy donor is taken for leukapheresis treatment. Extracted cells are healthier than those from cancer patients. These cells are then genetically modified to recognise the cancer, prevent graft versus host disease and to evade rejection by the patient's immune system. Many patients can be treated with each batch from a single donor.
- Stem cells – An induced pluripotent stem cell – a cell that can differentiate to become any cell in the body – is genetically modified to contain the constructs of interest and then expanded and frozen in cell banks. A single vial from the stem cell bank is differentiated to form a large batch of the desired product, which is then frozen down in multiple doses. Since genetic modification is completed prior to differentiation, every cell contains every single genetic edit, avoiding heterogeneity in the product.

Leveraging its autologous research expertise, Adaptimmune is looking at developing allogenic stem cell therapies as a future for cell therapy to make products that are more consistent in manufacturing quality and readily available to more patients. However, allogenic stem cell therapies have not yet been proven in clinical use and there is more work to be done to characterise stem cell derived products before they can be used in routine clinical practice.

"I think autologous and allogenic therapies are going to go hand in hand in the future, leading to a really bright future full of possibilities for cancer patients"

Dr Jo Brewer, Adaptimmune

3 Chimeric antigen receptor T cells: Genetically engineered T cells which attack and destroy cancer cells.

Cell therapy manufacturing and delivery challenges

Dr Stanley Frankel, Columbia University Vagelos College of Physicians and Surgeons, discussed the challenges associated with cell therapy design, manufacture and supply, highlighting the scale of investment required to provide patients with cell therapy products.

Autologous CAR-T cell products are now routinely used for the treatment of relapsed or refractory B cell malignancies including non-Hodgkin's lymphoma and acute lymphoblastic leukaemia, with further treatments for multiple myeloma also entering the market this year. However, reducing the costs of these products requires continuous innovation in design and manufacturing.

Cell therapy design and manufacturing

When designing a cell therapy product, factors such as cell type, cell source and the therapeutic target, all need to be known before starting production. Each design element requires a carefully curated and validated manufacturing process. Controls Manufacturing Chemistry (CMC) regulatory and quality requirements are critical ensuring the product is safe for patient use and are the rate limiting step in this process. Significant investment and advanced planning are both required for a smooth transition between clinical development and product approval.

Multiple steps are required in producing an autologous CAR-T cell therapy – including ensuring the viability, purity and potency of the product. Each step requires specific, reproducible manufacturing specifications. If these release criteria are not met at any stage, the product is not viable. Additionally, changes in manufacturing or site processes pose risks of delay or alterations in product characteristics that may require further clinical testing.

Supply chain complexity and scale of investment

Treating cancer patients with autologous cellular therapies is not an instant process, instead requiring a complex global supply chain. A patient's extracted cells are transported to two separate manufacturing facilities, modified, and then tested with a series of regulatory requirements. The modified cells are then shipped back to the healthcare provider who initiates lymphodepletion. The patient is treated with the product and a post infusion plan is set up. The process from cell extraction to treatment takes ~ three weeks.

Investment and skills requirements for the sector are significant. Following promising results of Bristol Myers Squibb's CART-T therapy development programs that have led to regulatory approval of two commercial cell therapy products, five cell therapy manufacturing facilities have been built globally to meet patient demand, requiring ~2,000 highly skilled staff. The immediate challenges will be to scale manufacturing effectively and tailor the process to allogenic therapies ensuring that the high prices driven by the current scale and complexity of manufacturing are reduced. If successful, far more patients will be able to benefit from cell therapies.

> "There is a bright future for alternative cell types, gene editing and allogenic approaches that are entering the clinic to provide better therapeutics, particularly for solid tumours"
>
> Dr Stanley Frankel, Columbia University Vagelos College of Physicians and Surgeons

CAR-T cell therapy in the clinic: lessons learned and road ahead

Dr Attilio Bondanza, AstraZeneca, outlined the science behind CAR-T cells, the determinants driving therapeutic efficacy and aspects related to manufacturing and supply. Gaps for translating CAR-T successes to solid tumours were also discussed.

Checkpoint inhibitors compared with CAR-T

Checkpoint inhibitors block proteins from preventing the immune system attacking cancerous cells and traditionally have been used as an off the shelf treatment. These treatments rely on a pre-existing immunity and are dependent on T cells identifying the cancer.

Chimeric antigen receptors are proteins on the surface of T cells (CAR-T) that have been engineered to detect cancer. Three generations of chimeric antigen receptors have been developed and continually refined. Third generation chimeric antigen receptors have seen incremental improvements in T cell survival, cancer killing and proliferation.

CAR-T immunotherapies provide an individualised, directed response to cancer. However, CAR-T is still dependent on the patient's immune response and in some cases, cancers can evade treatment.

Toxicity of treatment

CAR-T treatments often develop toxicities including cytokine release syndrome (CRS) and neurotoxicity. CRS symptoms vary from mild flu-like symptoms to a severe life-threatening reaction, which requires effective management from the monoclonal antibody, tocilizumab (anti IL-6 receptor monoclonal antibody). However, tocilizumab is associated with some neurotoxicity, and additional treatment with high-dose corticosteroids is required. Anakinra, a recombinant interleukin-1 receptor antagonist, is currently being investigated in preclinical models as a potential neurotoxicity treatment.

Therapeutic efficacy and the road ahead

A study examining the pharmacology of CAR-T cells in patients with leukaemia found that the strongest determinant of anti-tumour effect and response to therapy was T cell proliferation, and not CAR-T dosage. Additionally, greater efficacy is associated with T cells extracted early in the maturation phase (stem cell-like) versus T cells primarily associated with cancer killing in chronic lymphocytic leukaemia.

For future efficacy in the treatment of blood cancers, specific drug combinations are being considered to allow for effective targeting of cancer cells without killing the surrounding healthy cells which would lead to patient intolerability. Solid tumours require identification of good target antigens. This problem could be solved by considering glycoproteins as targets or using target combinations facilitated by using new selection technologies.

> "We should always remember T cell gene therapy is very complex, but there is an amazing ability for these therapies to defeat the final remaining tumour cells"
>
> Dr Attilio Bondanza, AstraZeneca

Session 2:
Recent Immuno-oncology breakthroughs

The role of the gut and tumour microbiome

Dr Jennifer Wargo, The University of Texas MD Anderson Cancer Center, highlighted the growing awareness of the impact the cancer microbiome, gut microbiome and diet are having on carcinogenesis and cancer therapy response.

There have been major advances in cancer treatment with the use of immunotherapy, resulting in an overall decline in cancer mortality. However, there is a still a critical need to improve responses to cancer therapy, limit toxicity and prevent cancer altogether.

Responses and toxicity to immunotherapy are dependent on several factors that shape tumour growth and immunity. Recently, the microbiome and diet have been shown to also play a role.

The cancer microbiome

Dr Wargo's laboratory used models that discovered certain stromal cells capable of mediating resistance to cancer therapies in melanomas. This model was used to study resistance to chemotherapy in colorectal and pancreatic cancers, where bacteria were found to break down gemcitabine – a chemotherapy drug – into its inactive form. Findings were then validated in human samples and mouse models, suggesting that intra-tumoural bacteria may mediate resistance to chemotherapy.

Intra-tumoural microbes may also affect anti-tumour immunity, with some intra-tumoural microbes having a negative, and others a positive impact. Intra-tumoural microbes may serve as important biomarkers and may even serve as therapeutic targets. Microbial signatures are now being identified across all tumour types, suggesting target opportunities that could improve outcomes and even prevent cancer.

The gut microbiome

Gut microbes could also influence response to cancer immunotherapy. Studies have showed that the diversity of the gut microbiome has positive outcomes for cancer patients undergoing immunotherapy. Additionally, murine models have highlighted differential responses to immunotherapy based on the composition of the gut microbiome.

Studies of oral and gut microbiomes for patients with metastatic melanoma have also shown a link between diversity in the microbiome and better responses to anti-PD-1 cancer immunotherapies. These studies also highlighted microbiome 'signatures' that could be associated with response to anti-PD-1, which could be used as potential biomarkers to identify disease.

The role of diet and other factors in response to cancer treatment

Antibiotics have been shown to negatively impact responses to checkpoint inhibitors. Patients taking antibiotics prior to treatment show dramatic reductions in survival. In contrast, positive responses were seen in patients with a high fibre diet including increased microbiome diversity, higher abundance of response-associated bacteria, and a greater response to immunotherapies.

> "We have made significant progress in terms of melanoma and other cancers with the use of immunotherapy, but not all patients respond so more therapeutic options are needed"
>
> Dr Jennifer Wargo, The University of Texas MD Anderson Cancer Center

Using genomics for the design and response monitoring of personalized cancer vaccines

Dr Elaine Mardis, Nationwide Children's Hospital, introduced the prediction of neoantigens in next generation sequencing by looking at early efforts to identify neoantigens in cancer vaccines, as well as covering more recent advances in the field.

Neoantigens are new sequences in proteins that form in cancer cells when specific tumour mutations occur. Peptides from these mutated proteins can be presented through the surface HLA molecules on tumour cells and can be used to spotlight cancerous cells to the cellular immune system. By predicting neoantigen formation, scientists can produce vaccines that present tumour-specific neoantigens and activate T cells to attack.

Early efforts to identify neoantigens

Dr Mardis' group first used exome sequencing to identify neoantigens, comparing sequences from murine models exhibiting high mutational load tumours with standard models. Sequence comparisons highlighted mutations in the tumours, then the RNA sequence data was used to identify mutations expressed by the tumour. Standard algorithms such as NetMHCpan were used to predict binding affinities for the mutated peptide neoantigens for the major histocompatibility complex (MHC) class I molecules. Peptides were synthesised with alterations that predictions suggested had the strongest differential binding. In vivo analysis demonstrated that mice vaccinated with these peptide neoantigens could stimulate T cells and be cured of their tumours.

With the confirmed prediction, a personalised vaccine trial began for patients with high mutational load melanoma tumours. Dendritic cells were isolated and loaded with synthetically produced neoantigen-derived peptides before being administered into patients. This process identified challenges associated with finding certain tumour-specific neoantigens.

One challenge with metastatic melanoma is that neoantigens may or may not be present at multiple tumour sites. Testing tumours from melanoma patients identified a set of mutations which were subsequently filtered to seven shared or unique neoantigen peptides and combined to form a personalised cancer vaccine. Three of these unique peptides were found to elicit a T cell response to the cancer vaccine, showing relatively good neoantigen prediction but identifying some gaps in the process.

Improvements

Improvements are made continuously to the tumour neoantigen identification pipeline, including a consideration of unique variants in each patient's germline genome, increasing the scope of mutations to frameshift insertion/deletion variants, and to fusion protein junction sequences. Improvements in neoantigen prediction are anticipated as an expansion to the number of neoantigens that can be offered to personalised vaccine-based approaches. Continuing to identify peptides for personalised cancer vaccines with the greatest potential effectiveness will also be essential.

Current studies

A new study in glioblastoma multiforme (GBM) is focusing on the detection of shared neoantigens in different portions of the tumour mass. Unique mutations were first identified from 3-4 individual biopsied regions and compared to identify shared mutations. In one patient, 35 shared mutations were identified between four different regions for the GBM. Applying neoantigen prediction then reduced the number of shared neoantigens to six. Further filtering to restrict to strong binders left only one common neoantigen across all regions, highlighting the challenges for personalised cancer vaccine development in GBM.

> "There has been rapid progress in neoantigen prediction from next generation sequencing data and this has really been accelerated by the interest in personalised cellular therapies"
>
> Dr Elaine Mardis, Nationwide Children's Hospital

Oncolytic immune-virotherapy: promises, barriers and recent progresses

Dr Eric Quéméneur, Transgene, outlined how oncolytic viruses are viable therapeutic options for cancer patients, detailing current products under consideration and future research directions.

Oncolytic immune-virotherapy involves engineering viruses to attack and kill cancer cells. Viruses are designed with the aim of ensuring the following 3 outcomes:

1. The successful replication of the virus in tumour cells which induce selective tumour cell death.
2. Optimising a change in signalling mechanisms in the tumour to help identify the tumour to the immune system (ie turning a cold tumour hot).
3. Successful delivery of recombinant payloads into the tumour microenvironment (such as antibodies, cytokines, or enzymes) to help destroy the cancer.

There are currently ~30 different viruses that can be used to target cancers with several large pharmaceutical firms investing in oncolytic immune-virotherapy, demonstrating both the range of viruses available and also the interest in the use of viruses against cancer. This interest has been heightened with the approval of T-Vec by the Food and Drug Administration (FDA) and European Medicines Agency in 2015.

Oncolytic viral therapy is currently used mainly in combination with other immunotherapies due to the enhanced benefits combining oncolytic viruses with other treatments on patient survival. Combination therapy can be avoided by encoding an antibody directly in the virus which targets tumour antigen directly such as Transgene's product BT-001. BT-001 has undergone testing in mouse models showing good survival outcomes and systemic engagement of the immune system. BT-001 has met safety requirements and Phase 1 trials have started, with Phase 2a clinical trials projected to start in 2022, therefore demonstrating promising advancements in the field of antibody-armed oncolytic viruses.

The next stage of developing oncolytic viruses would be to adapt also intravenous (IV) administration. Pre-clinical studies have been undertaken where single IV administration has been shown to be sufficient in inducing partial cure in orthotopic models, and also demonstrating the ability to cross membrane barriers. There are also promising results in humans where, for example, Transgene's Pexa-Vec or TG6002 oncolytic viruses have successfully reached tumour sites in certain settings, showing promise for the future of IV treatment.

Research directions

From altering the properties of the vector used to deliver the virus, to undertaking different routes of administration of the virus, there are many ways to optimise oncolytic viruses in cancer treatment. Action could also be taken to combine virus genomes, each with different optimal immune properties, to produce an oncolytic virus with less problematic functions. Finally, optimising the transfer of the oncolytic virus from the blood to the site of the tumour could be beneficial for the treatment of cancers which are not easily accessible to the virus.

> "We are in a period where oncolytic viruses will confirm their potential as therapeutics for patients with cancer and we have all the tools to succeed in that challenge"
>
> Dr Eric Quéméneur, Transgene

Session 3:
Barriers and pitfalls

Artificial intelligence for digital tissue biomarker discovery in immuno-oncology

Dr Günter Schmidt, AstraZeneca discussed how computational pathology is focussing on identifying biomarkers for disease progression, therefore identifying patients who are suitable for immuno-oncology treatment and suggesting alternative treatments for those who will not respond.

The deep learning revolution using convolutional neural networks started with Alex Krizhevsky (Univ Toronto, 2012) outperforming all other computational approaches in classifying 1.2 million natural images of the ImageNet database. As the next major deep learning milestone, the AlphaGo system (DeepMind, 2017), managed to outperform humans in a Go tournament. And recently, AlphaFold2 (DeepMind) accurately predicted 3D protein structures from 1D amino acid sequences, demonstrating the use of artificial intelligence (AI) for drug discovery.

Deep learning for biomarker discovery and diagnostics

In a digital pathology application (PathAI, 2019) to predict response to anti-PD-L1 therapy in lung cancer, multiple pathologists provided ground truth for a fully supervised deep learning system comprising more than 250,000 annotations. The system can predict tumour regions and cells in PD-L1 stained sections, showing a 93% correlation with pathologists scoring. This means a pathologist may not be needed for routine diagnostic work, which addresses the common shortage of pathologists. However, the system solely reproduces known knowledge and therefore it is unable to discover novel cancer biology.

Deep learning has also been utilised for novel digital biomarker discovery for Antibody Drug Conjugates (ADC). An ADC delivers toxic warheads into cancer cells post ADC cell surface binding, therefore inducing cell death. A deep learning system (AstraZeneca Computational Pathology, 2020) has been trained to precisely delineate cells in immunohistochemically stained tissue sections, and to estimate the amount of target protein on the cell surface. This assessment is beyond the visual capabilities of pathologists, and thus enabled the discovery of novel biomarkers to identify patients which benefit from ADC treatment.

In end-to-end deep survival learning, images from cancer patient samples are directly fed into the computational system and classified according to the patients' survival risk. Studies are ongoing; however, data suggest that training of such a system by expensive and biased pathologists is not required, and that such a "digital biomarker" system is able to discover novel cancer biology. The drawback of this approach is the lack of interpretability since all knowledge is implicitly encoded in the neural network.

Regulatory and clinical use

As of 2020, 29 AI-based medical technologies have been approved by the FDA, mainly in the field of non-invasive imaging. This year, the FDA submitted an action plan highlighting their commitment to encourage the implementation of Good Machine Learning Practice (GMLP) so that the future hopes to see an increase in the number of approved AI-based tissue diagnostic systems in immuno-oncology.

> "Our work on Computational Pathology in Munich is focussing on how we can discover and validate predictive tissue-based biomarkers which are able to select those cancer patients which more likely respond to an immuno-oncology drug"
>
> Dr Günter Schmidt, AstraZeneca

Employing novel technologies to improve immunotherapy

Professor Emile Voest, Netherlands Cancer Institute, introduced neo-adjuvant checkpoint inhibition as a novel immunotherapy and how individualised immunotherapy will be a future challenge with organoid technology supporting research in this area. Personalised cellular therapy by individualised neoantigen discovery was also covered.

The development of new forms of cancer immunotherapy, such as neo-adjuvant checkpoint inhibition, have shown promising results. This new therapy is administered before curative surgery to target the primary tumour. Depending on the tumour type, the vast majority of cancers show complete regression, whereas this is seen in far fewer cases in metastatic tumours. In addition to neo-adjuvant immunotherapy, cellular therapies are now demonstrating their strong potential with tumour regression. However, for metastatic cancers, only ~30% of patients are responding to immunotherapies, so research continues into identifying how immuno-oncology can benefit a wider patient population.

Tumour Organoids

Tumour organoids are obtained from a single biopsy from a metastatic lesion or resection material which can be grown under specific culture conditions for individual patients. The tumour organoids act as a representation of the tumour and allow for better understanding of the interaction between cancer cells and the immune system. By co-culturing tumour organoids and autologous T cells immune response can be studied.

As a reflection of the in vivo situation, the presentation of T cells to tumour organoids shows an increase in T cell activation compared to T cells alone. Although individualised immunotherapy will be a future challenge, tumour organoid technology is a useful tool to demonstrate T cell activation and tumour killing which could potentially facilitate a personalised approach.

Professor Voest's team at the Netherlands Cancer Institute, in collaboration with Dr Garnett's team at the Sanger Institute, are looking to build on the tumour organoid platform by combining it with techniques such as genome wide CRISPR screening that may encourage T cells to recognise tumour cells. Drug screening is also being implemented to assess the response of tumour organoids during combination therapy.

Identifying neo-antigens using organoids

The novel HANSolo method aims to use organoids to identify neo-antigens for potential applications in personalised cellular therapy. Mutated tumour organoids are grown and combined with a reactive T cell population. The mutations from the tumour organoids are then transduced into immortalised B cells and combined with the reactive T cell population. Analysis of which cells that are killed can then be used to identify the neoantigen. This approach was applied to a patient with a microsatellite instable (MSI) colorectal cancer, displaying a clear dropout of specific tumour cells and therefore identifying the required neoantigen.

> "Only six weeks of neoadjuvant therapy already has a great opportunity for cure as the primary tumour responds far better than a treated metastasis"
>
> Professor Emile Voest, Netherlands Cancer Institute.

Tumour re-engineering: developing novel immuno-gene therapies for cancer

Dr Brian Champion, PsiOxus Therapeutics, outlined the current challenges brought about when using combination therapies, as well as giving clinical and pre-clinical stage examples of 'tumour re-engineering' to combat issues with systemic delivery.

Combining different anti-cancer immunotherapeutics is currently a major focus of clinical oncology studies. Combination therapies have the benefit of increasing efficacy of treatment but are often limited by serious side effects preventing a further increase in dose. Combination therapies are typically dosed systemically, and therefore cause unwanted immune inflammation in a variety of organ systems as well as in the targeted tumours.

'Tumour re-engineering' enables selective delivery of therapeutic agents or combination therapies to tumour sites, with the ability for the therapeutic agent to be produced within tumour tissues. This minimises systemic exposure, therefore preventing intolerable side effects. PsiOxus are developing a tumour-specific immune-gene (T-SIGn) vector approach that aims to promote anti-tumour immunity by targeting elements of the tumour and its microenvironment

The T-SIGn vector can be modified to include a whole range of payloads, including four or five transgenes, with their expression tightly linked to the replication of the virus. The virus is highly specific which results in tumour specific expression of the transgene payloads. Good tolerability and effective intravenous (IV) delivery have been demonstrated clinically as well as in preclinical models. Additionally, efficient delivery has been seen in primary and metastatic tumours with potential for long term modification of the tumour microenvironment.

T-SIGn candidate examples

Resistance to immunotherapies is often driven by cancer associated fibroblasts in the stroma, and so PsiOxus are currently developing NG-641, a T-SIGn vector tackling the stroma instead of tumour cells. An anti-FAP bispecific T-cell activator has been encoded within NG-641, allowing T cells to be activated and kill tumour associated fibroblasts. Two chemokines are also encoded to help attract more T cells to aid with immune activation, as well as interferon alpha to help activate the overall immune response.

The leading pre-clinical stage candidate – NG-796A – has the primary aim of driving T cell and Natural Killer (NK) cell recruitment and activation. Within the virus, IL-12 and IL-15 are encoded to drive T cell and NK cell responses. The chemokine CCL-21 is also encoded to help recruit other immune cells, in particular dendritic cells, which have been shown to migrate towards CCL21 produced by NG-796A treated primary tumour cultures.

In addition to NG-641 and NG-796A, there are a host of other candidate optionalities – differentiated by mechanism and target patient populations – with a number currently in preclinical and clinical development, leading to a hopeful future for local re-engineering of the tumour microenvironment to treat cancer patients.

> "Immunotherapy has progressed into an amazing new realm in the last decade or so, putting biologics at the forefront of treatment for patients, which opens up new opportunities for targeting tumours and their microenvironment"
>
> Dr Brian Champion, PsiOxus Therapeutics

Session 4:
Panel discussion

Panel discussion on solving the issues of cost and regulations for new therapeutics

This panel discussion, chaired by Professor Luke O'Neill FRS, featured Dr Jaqueline Barry, Cell and Gene Therapy Catapult; Professor Fiona Thistlethwaite, The Christie NHS Foundation Trust; and Dr Stuart Farrow, Cancer Research UK Therapeutic Discovery Laboratory. The participants commenced by considering the high costs associated with therapeutics, leading onto the regulations involved in bringing cancer immunotherapies to market. Accessibility of treatments to patients was also touched upon.

Costs for new therapeutics

- Cancer immunotherapy is an expensive and complicated process with charities such as Cancer Research UK considering how effective and affordable treatments can be made accessible to all.
- The cost of reagents and supply chain fragility are also increasing prices.
- Despite the cost, the treatments are potentially curative and therefore there is a long-term benefit associated with therapy.
- In general, large pharmaceutical companies do not have extensive experience in procuring tissues and cells to be used as starting materials in medicinal product manufacture. It was suggested that developing infrastructure around therapies and increasing education on the topic will also help bring down the cost of cancer immunotherapy.
- Adoption by the NHS is a lengthy process. Not-for-profit organisations are working with industry to find ways to introduce therapeutics smoothly and in a cost-effective manner.
- Clinically, cost is not solely a financial issue, but also needs to consider the wider costs to the patient, such as toxicities.
- Expensive treatments require prioritising patients who have a high chance of responding. It is hard to justify treating patients who will experience severe long-term toxicities and experience a greatly reduced quality of life because of treatments.
- The biotechnology industry needs to be promoted and supported, but it must also ensure the groundwork is undertaken to make immunotherapies accessible and affordable.
- One of the main strengths of UK is the ability to work within a network, and the ability to use this network to identify drugs which have the potential to be repurposed so that full trials do not have to be undertaken and costs can start to be lowered.
- There is substantial investment in the immuno-oncology field, and as technologies improve, the cost of cancer immunotherapies should reduce, in turn allowing the NHS to adopt a broader range of treatments.

"The therapies are costly, but potentially curative, so there is a lifelong benefit associated"

Dr Jaqueline Barry, Cell and Gene Therapy Catapult

"Durable remissions will ultimately justify very high-cost therapies"

Professor Fiona Thistlethwaite,
The Christie NHS Foundation Trust

"Drugs are sitting on the shelves of big pharma companies and could be usefully repurposed in a combination or even a standalone setting"

Dr Stuart Farrow, Cancer Research UK
Therapeutic Discovery Laboratory

The Regulatory Environment

- Building networks between regulators and industry, charity and academics will allow for conversations about what is really needed to progress therapies so they are more beneficial to patients.
- COVID has changed the research landscape through the rapid development of new vaccines. There are opportunities through this momentum that can be applied to the field of oncology.
- In the UK in the past decade, MRHA, NICE and the other regulators are really looking towards innovation and how they can support it.
- Regulatory approval can be quick – the recent CAR-T therapies gained approval from the European Medicines Agency (EMA) had received approval from NICE and was commissioned by the NHS in approximately 3 weeks from the EMA approval.
- A new scheme, the Innovative Licensing and Access Pathway, has launched with the support of MHRA, NICE, NHS England, Scottish Medicines Consortia and other parties, which aims to reduce time to market, facilitating patient access to medicines.
- Additional regulatory complexities have been brought about by the UK leaving the European Union, but there have been some advantages such as the ability to streamline regulation surrounding certain cancer immunotherapies.
- Regulators require a huge level of competence to deal with the complexities of advanced therapies, aided by an open, collaborative approach between stakeholders
- Regulators have been quick to approve therapies and bring them to market so that patients can experience potentially curative outcomes.

Access to Treatment

- As progress is made with cancer immunotherapies, the cost and accessibility of treatments needs to be considered. Cancer therapies must be accessible to everyone.
- There are slight biases in referrals towards certain demographic and socio-economic factors, which really needs to be addressed.
- Certain groups have less knowledge or interest on the topic of advanced therapies and therefore the public need to be given more opportunities to learn about the clinical trials available to them, and not just rely on waiting for referrals from oncologists.

"What we have seen in the UK for the last decade is the MHRA, NICE and the other regulators really looking towards innovation and how they can support it"

Dr Jaqueline Barry, Cell and Gene Therapy Catapult

"Cell therapies are so expensive that you have to see durable remissions in patients, not just a year or two, effectively having to cure patients to justify both the complexity of the cost, and also the cost to the patient"

Professor Fiona Thistlethwaite,
The Christie NHS Foundation Trust

"The challenge of doing everything in a publicly funded way is enormously expensive, and charities cannot afford to take the risk of taking a therapy forward"

Dr Stuart Farrow, Cancer Research UK
Therapeutic Discovery Laboratory

CLOSING KEYNOTE

Cancer immunotherapy: today's triumphs and tomorrow's treatments

Dr Laurie Glimcher, Dana-Farber Cancer Institute, outlined the endoplasmic reticulum stress response as an adaptive cancer response to inadequate nutrient supply, as well as introducing the highly immunosuppressive tumour microenvironment. The current ability to treat cancers was also considered, with thoughts on areas of concentration for future success in cancer treatment.

The IRE-1α-XBP1 transduction pathway from the endoplasmic reticulum (ER) to the nucleus protects cells from stress caused by unfolded or misfolded proteins. An abnormal accumulation of these proteins leads to the ER stress response which is a hallmark feature of secretory cells in many diseases including cancer. The ER stress response is also activated in the tumour microenvironment due to stress caused by the hostile environment, chemo and radiotherapy, genetic alterations, and the high metabolic demand of the tumour. The ER stress response has also been found to be essential for the growth of several cancer types including myeloma and breast cancer.

The tumour microenvironment

The tumour is surrounded by a highly immunosuppressive microenvironment, preventing activated immune cells getting into the tumour and destroying it. By targeting the ER stress response in certain immune cells, the tumour microenvironment can be reprogrammed to stop its immunosuppressive nature and allow for tumour cell killing to take place.

Dendritic cells are an example of immune cells present in the microenvironment of ovarian cancer. These cells tend to be hostile as they can both promote tumour growth and secrete immunosuppressive molecules, preventing T cell activation. Removing XBP1 – a transcription factor responsible for mediating the ER stress response – in murine models showed a return of immune function of the dendritic cells, and a greater activation of T cells to combat the tumour.

In addition to dendritic cells, T cell metabolism in a hostile tumour microenvironment has been shown to lead to T cell exhaustion, caused by a lack of glucose uptake into the tricarboxylic acid (TCA) cycle – the process by which body cells break down organic molecules to harvest energy – preventing the production of DNA and RNA. Usually, the TCA cycle can be rescued by glutamate, however glutamate receptor expression is reduced under the control of XBP1, therefore preventing its uptake.

Murine models of ovarian cancer in mice lacking IRE1α or XBP1 show an enhanced T cell response, resulting in reduced tumour growth and increased survival. In the human ovarian tumour microenvironment, activation of IRE1α-XBP1 can be seen in T cells, preventing their anti-tumour activity. In turn, the TCA cycle cannot be rescued by glutamate. Silencing IRE1α-XBP1 signalling restores T cell metabolic fitness and anti-tumour capacity in cancer. Research now looks to develop small molecule IRE1a inhibitors to mutually reinforce the direct inhibition of tumour growth and activation of anti-tumour immunity.

Cancer: today and tomorrow

There has been a lot of progress in treating tumours, namely breast and prostate cancer and Hodgkin lymphoma, but little progress in other tumours such as glioblastoma and pancreatic cancer (Figure 3). Future investment will need to concentrate on cancer genomics in addition to using rational drug combinations and understanding how cancer resistance occurs following mutation of the tumour. The field of chemical biology also needs to be expanded to increase the number of targeted proteins.

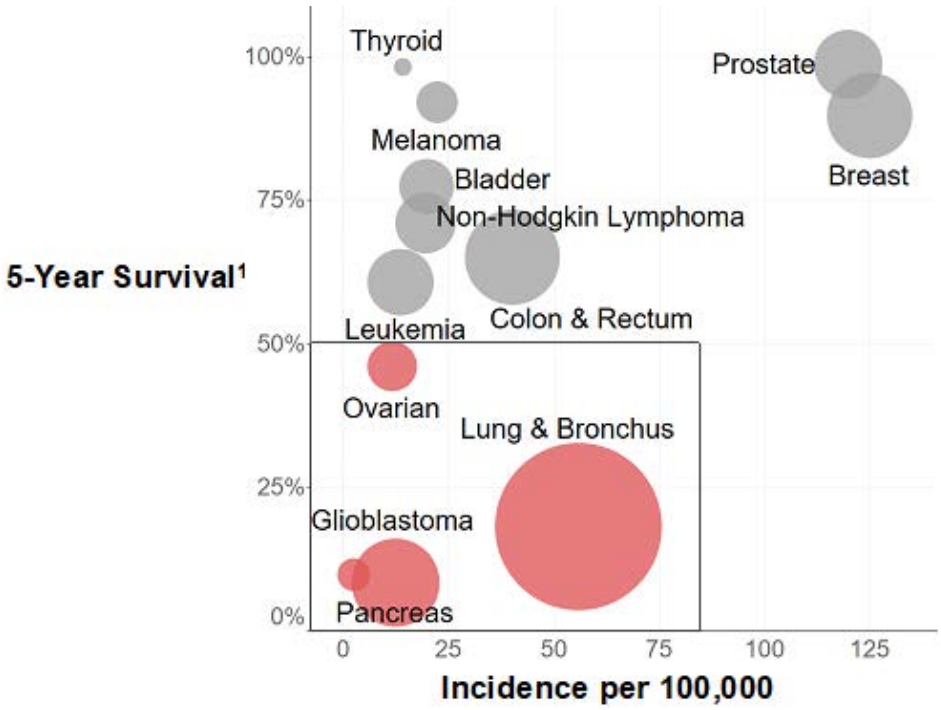
Further research regarding cancer immunotherapy in both academia and industry could be extended to identify new drug targets and possible combination therapies. Lastly, the treatment of stage one cancers results in a much greater likelihood of curing the cancer with immunotherapy, and so focusing on early detection of cancers is of paramount importance.

> "Why do so many cancer drugs fail? They fail because there are not very good cancer models of cancer in mice and so I would urge everyone to focus whenever you can on primary human cells"
>
> Dr Laurie Glimcher, Dana Farber Cancer Institute

FIGURE 3

Cancer types by incidence and survival

Cancer types by incidence per 100,000 and 5-year survival. The size of each circle represents the percentage of cancer deaths.



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