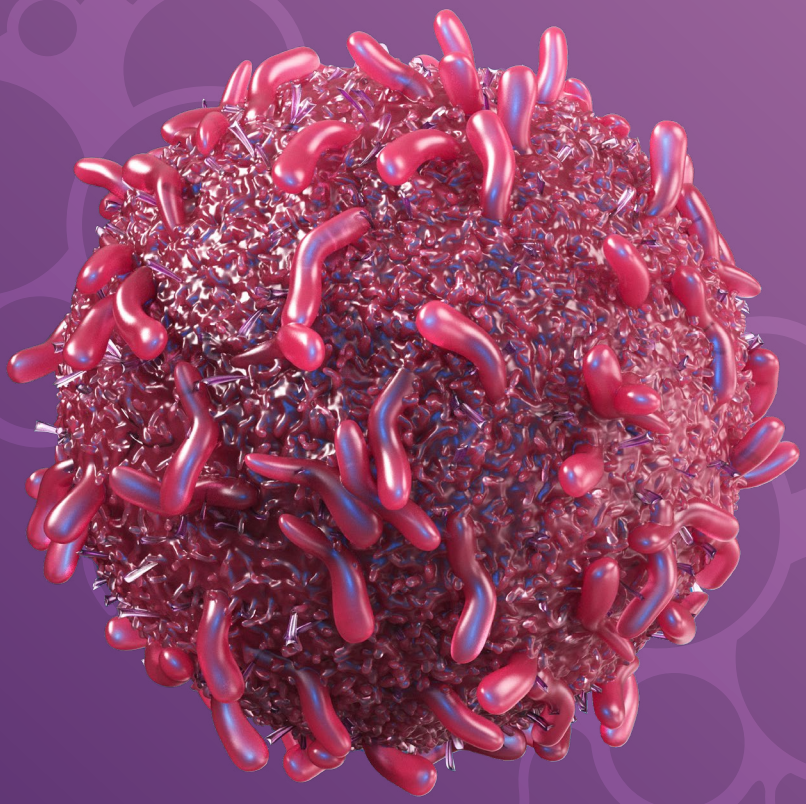
CASE STUDY REPORT

Unlocking the Future of Immune Cancer Therapy

A Concise Report Featuring Insights From The Prominent Thought Leaders Of Immuno 2024



Introduction

The future of cancer therapy will be highly influenced by the advancement of immunotherapies. Major growth is expected in the sector, with the immuno-oncology market expected to expand at a CAGR of 8.3% until 2030. Factors that are driving this growth include novel drug discovery techniques, a variety of new clinical trials, and an increasing movement toward precision and personalised approaches.

Specifically, we are seeing somewhat of a resurgence in cancer vaccines. Thanks to the accelerated validation of mRNA technology from the pandemic, clinical trials are rolling-out of some of the first ever personalised cancer vaccines to patients. Furthermore, cell therapies like CAR T are also making strides by tackling their major challenge of battling solid tumours, providing another boost to the field.

This report provides a comprehensive overview of some of these recent advancements with presentations in the field of immunotherapy and cancer treatment, highlighting key research and developments from prominent scientists and pharmaceutical companies. The primary focus is on innovative approaches to cancer immunotherapy, particularly the optimization and safety of T cell engagers, bispecific antibodies, and cancer vaccines.

Miguel Gaspar, Director at AstraZeneca, discusses the diverse strategies employed by AstraZeneca to combat cancer, including the development of synthetic immunity through T cell engagers. These therapies aim to bridge the gap between tumour cells and T cells, creating synthetic immune synapses to enhance anti-tumour activity while addressing significant toxicity challenges such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

Ida Uddbäck, Senior Scientist at Alligator Bioscience, presents the promising preclinical results of ATOR-4066, a bispecific antibody developed through the Neo-X-Prime™ platform. This antibody targets both CD40 and CEA, demonstrating robust anti-tumour efficacy and a favourable safety profile in various cancer types.

Benoit Van den Eynde from the Ludwig Institute for Cancer Research introduces the development of cancer vaccines using viral vectors targeting MAGE-type antigens in lung cancer. His team focuses on enhancing the immunogenicity of these vaccines and combining them with standard treatments like chemotherapy and immune checkpoint inhibitors to improve clinical outcomes.

John Maher, Chief Scientific Officer at Leucid Bio, explores the next generation of CAR T-cell therapies for solid tumors. Maher's research emphasizes the need for more effective CARs and introduces the concept of adaptor CAR T cells, which have shown superior anti-tumor activity and metabolic fitness in preclinical models.

This report encapsulates the cutting-edge research and therapeutic innovations presented at Immuno 2024, reflecting the ongoing efforts to improve cancer treatment through advanced immunotherapy strategies.

Tom Cohen,
Senior Digital Content Editor, Oxford Global

Contents

Key Speakers Include

Miguel Gaspar, Director, AstraZeneca

Ida Uddbäck, Senior Scientist, Alligator Bioscience

Benoit Van den Eynde, Professor, Ludwig Cancer Research

John Maher, Chief Scientific Officer, Leucid Bio

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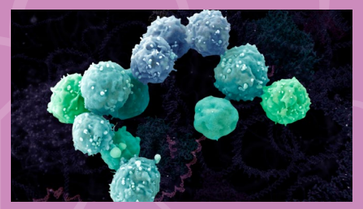
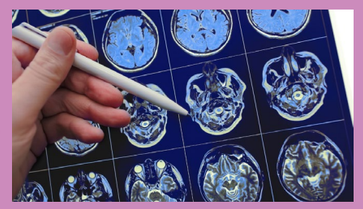
Finding New Immunotherapy Targets for Solid Brain Tumour CAR Ts with RNAseq in Cancer-Specific Exons

Zika Virus Tested as an Effective Oncolytic Agent for Glioblastoma in In Vitro Models

First Patient Dosed with NK Cell Therapy for the Treatment of an Autoimmune Disease, Lupus Nephritis



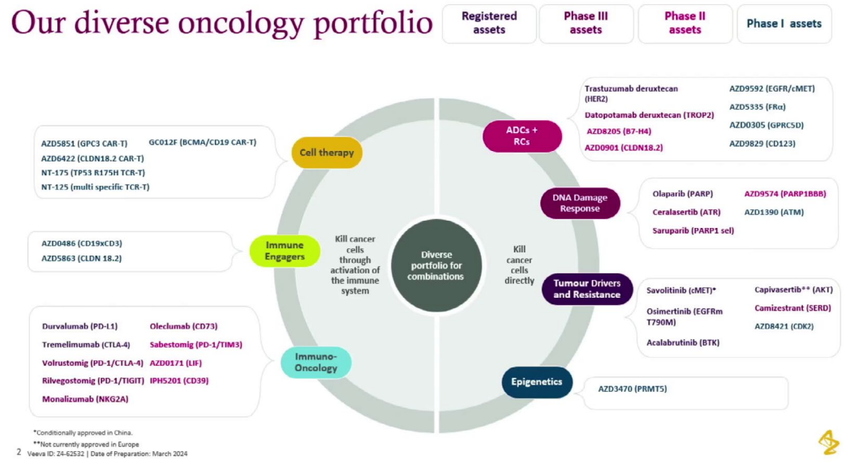


Novel Methods of Engaging the Immune System

Affinity Optimization of T Cell Engagers for Improved Safety

Cancer is a very diverse disease, as diverse as the cells and the tissues that it infects. Therefore, to treat cancer, AstraZeneca has been developing a diverse range of therapies, both as monotherapies, and as potential as combinations. Miguel Gaspar, a Director at AstraZeneca, presented at Immuno 2024.

Immunotherapy drugs can be divided into two categories: those that kill cancer cells directly (such as ADCs or radioimmunoconjugates), and those that aim to kill cancer cells through activation of the immune system (like ICIs or immune engagers).



Immuno-oncology has transformed cancer care in the last decade. Most IO drugs that aim to reignite existing immunity against cancer cells; however, in some cases there is no existing immunity. To bring immune activation to cases where immunity is not present, AstraZeneca leverage the potential for synthetic immunity. These drugs can take the form of cell therapies like CAR T or TCR T), or immune engagers that recognise a tumour's surface proteome to engage existing T cells.

The Problem with Immunotherapy and Cancer

Despite the 'immunotherapeutic turn' proving successful for cancer care, we know that some indications do not respond well to IO drugs. Digging into the biology of immunotherapy, research has shown that in certain indications like ovarian and colorectal cancer, only a small minority of T cell receptors (TCRs) recognise cancer cells.

Furthermore, the few of those that do also recognise non-cancerous pathogens (viral antigens).

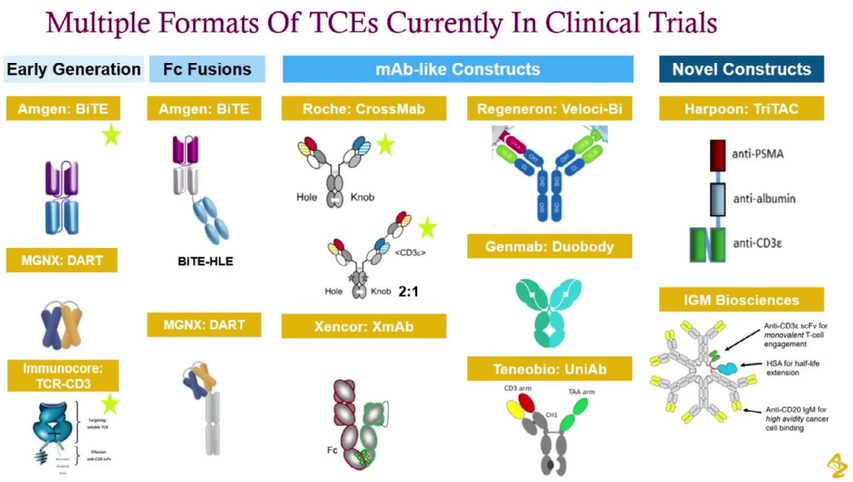
In essence, most tumour infiltrating T cells are not tumour specific. This begs the question: 'how do we bring the promise of long, durable responses from immunotherapy to those indications?'

Synthetic Immunity and T Cell Engagers

Synthetic immunity to cancer involves T cells recognising cancer cells, not through their own endogenous mutations, but via their surface proteome. Then, scientists can use cellular and molecular engineering to derive therapies which take advantage of these surface proteins.

T cell engagers mediate synthetic immunity using bi- or multispecific molecules that recognise both tumour cell surface receptors cells and T cell receptors. T cell engagers therefore bridge the gap between the tumour cell and T cells, creating a synthetic immune synapse which allows the tumour cells to be destroyed.

Another function of T cell engagers is that they lead to the release of inflammatory cytokines like IFN-gamma, which will have a direct effect on neighbouring tumour cells, whether they be TAA+ or TAA-. Drug designers have tested many different formats for T cell engagers; the emergent dominant format of which have been mAb-like constructs.



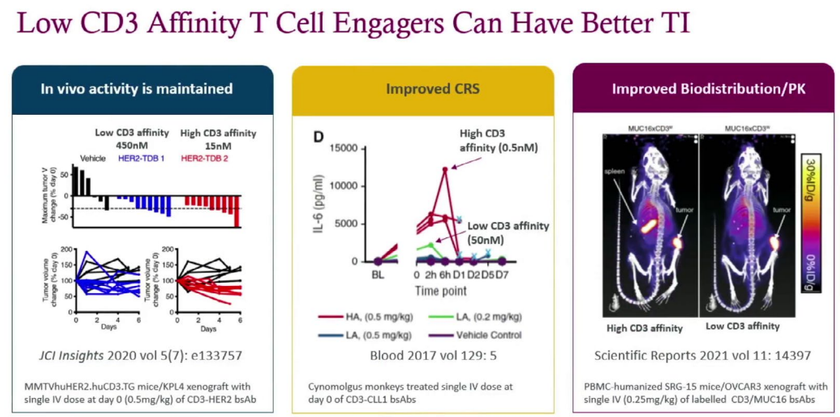
T cell engagers offer the opportunity to drive long, durable responses. In recent years, there has been a spate of approvals for the modality across a variety of indications.

However, T cell engagers also present toxicity challenges. Immune effector cell-associated neurotoxicity syndrome (ICANS) is a form of toxicity that leads to the degradation of the blood-brain barrier and is risked by the therapeutic use of T cell engagers. Further forms of toxicity mentioned by Gaspar's presentation, are cytokine release syndrome (CRS) and on target/off tumour toxicity.

Strategies to Overcome CRS

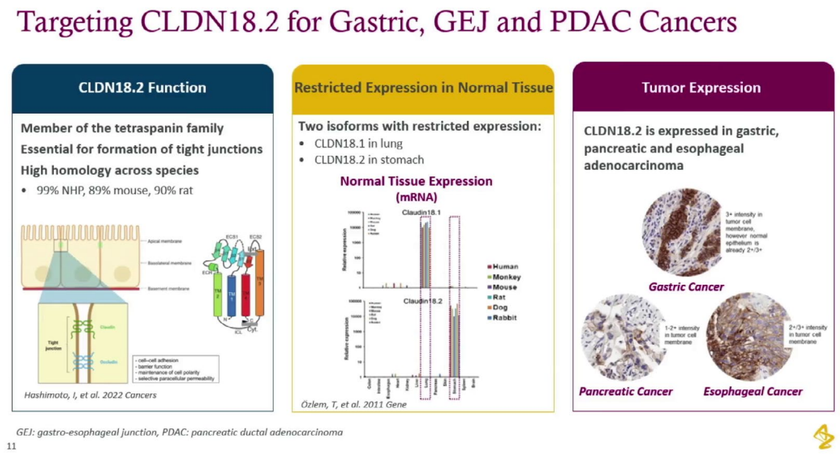
Gaspar then asked: 'How do you get t cells to efficiently kill T cells while not producing large amounts of cytokines?' It happens that the body has a natural technique to decouple cytotoxic activity from excessive cytokine release. Cytotoxic T cells have two activation thresholds: one for lytic synapse formation, and one for cytokine production.

To take advantage of this effect in T cell engager engineering, they reduced the CD3 affinity to differentiate cytotoxicity and cytokine release. They found that low CD3 affinity T cell engagers can maintain cytotoxic activity in vivo while having a reduced cytokine release.



Strategies For On Target/Off Tumour Toxicities

Another challenge to consider is the fact that targeting tumour-associated antigens puts healthy tissues that express those antigens at risk. However, not all tumour associated antigens are created equal - some are expressed in safer places than others; for example, healthy tissues that express DLL3 are protected behind the blood brain barrier. One of those targets is CLDN 18.2.



T Cell Engagers: AZD5863

CLDN 18.2 is a clinically validated target for which AstraZeneca's T cell engager, AZD5863, targets in gastric, pancreatic, and oesophageal cancer. In in vitro and humanised mouse models, they have seen that AZD5863 is well tolerated and able to drive anti-tumour

activity with reduced cytokine release. Dose escalation of AZD5863 is underway in a phase I study of gastric, gastroesophageal, and pancreatic cancer across multiple clinical centres.

ATOR-4066 – A Neo-X-Prime™ Bispecific Antibody Engaging Myeloid Cells For Immunotherapy Of CEACAM5-Expressing Cancers

Ida Uddbäck is a Senior Scientist at Alligator Bioscience. Her presentation highlighted Alligator's preclinical bispecific antibody, ATOR-4066. This therapy, a result of the company's Neo-X-Prime platform, targets both CD40 and CEA, the latter being expressed on multiple indications at high levels including colorectal, gastric, pancreatic, and lung cancer. The targeting of CEA also allows for ATOR-4066's secondary mode of action, due to the antigen being expressed on exosomes, extracellular vesicles, and tumour debris.

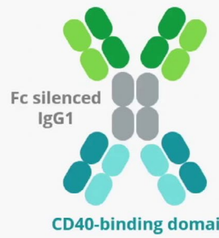
Uddbäck assured the audience that this drug candidate had outstanding functional properties and antitumour efficacy. ATOR-4066 promises a strong developability profile, favourable PK profile, low immunogenicity risk, as well as being well tolerated.

ATOR-4066 – First-in-class CD40xCEA Neo-X-Prime bsAb

Key benefits and opportunities of ATOR-4066

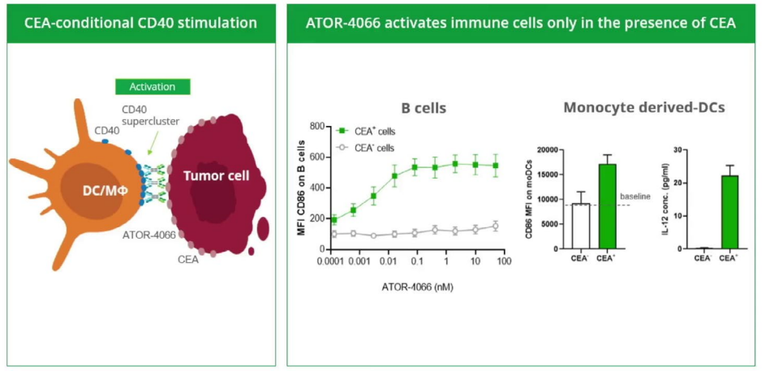
- Targets CEA (CEACAM5)
  - GPI linked glycoprotein involved in cell adhesion, migration and invasion
  - Highly expressed tumor-selective target
  - Expressed on tumor debris/ exosomes/ extracellular vesicles
- Drug candidate identified
  - Outstanding functional properties and anti-tumor efficacy
  - Strong developability profile
  - Favorable PK profile
  - Low immunogenicity risk
  - Surrogate CD40xCEA bsAb well tolerated ≤37.5mg/kg in NHP
- Opportunities in CEA-expressing indications including colorectal, gastric, pancreatic, and lung cancer

ATOR-4066 in the RUBY® format



ATOR-4066's first mechanism of action is the CEA-conditional activation of immune cells. Here the antibody binds to CEA on the tumour cells. At the same time in the CD40 supercluster, ATOR-4066 activates CD40 via cross-linking which means that CD40 signalling only occurs in the presence of CEA.

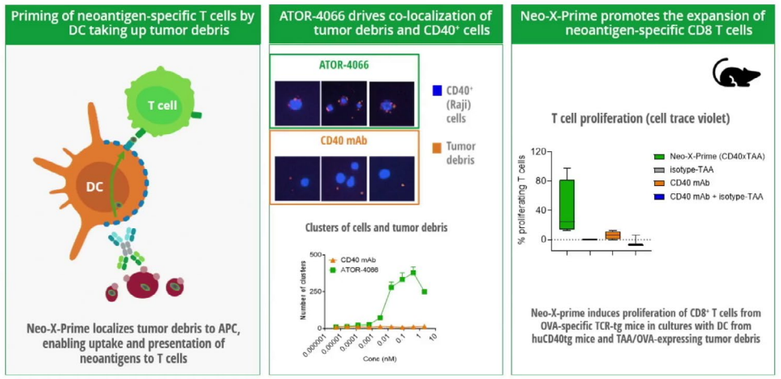
MoA A: CEA-conditional activation of primary immune cells



This mechanism has been shown in various different cell types. In B cells and monocyte-derived dendritic cells, Alligator have seen activation in the form of upregulation of CD86 in the presence of CEA.

The antibody's second mode of action is the activation of neoantigen-specific T cells. Apart from just binding to the tumour cells, the Neo-X-Prime antibody will also bind to tumour debris, extracellular vesicles, or exosomes that express the tumour associated antigen (in this case CEA). ATOR-4066 will then bind to both the extracellular tumour debris, and CD40 on the dendritic cells. This leads to internalisation and processing of the neoantigens from the tumour debris. Finally, through cross-presentation, the neoantigen is presented to the T cells.

MoA B: Activation of neoantigen-specific T cells by Neo-X-Prime



To show cross-localisation of these tumour debris and CD40 expressing cells, they cocultured them with ATOR-4066. Here, they observed nice clusters of CD40+ cells and the ATOR-4066 together. However, after swapping out ATOR-4066 with a CD40 mAb, they did not see any clusters occurring.

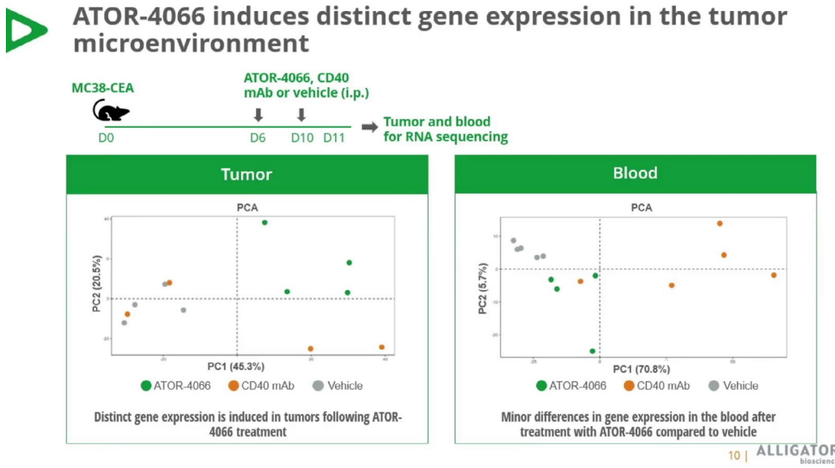
The priming and activation of the neoantigen specific T cells has more steps. The Alligator team used transgenic OT-I mice with human CD40, so all the T cells are specific for the

OVA protein. Here, tumour debris expressed a tumour associated antigen (TAA) (not CEA in this case but another TAA).

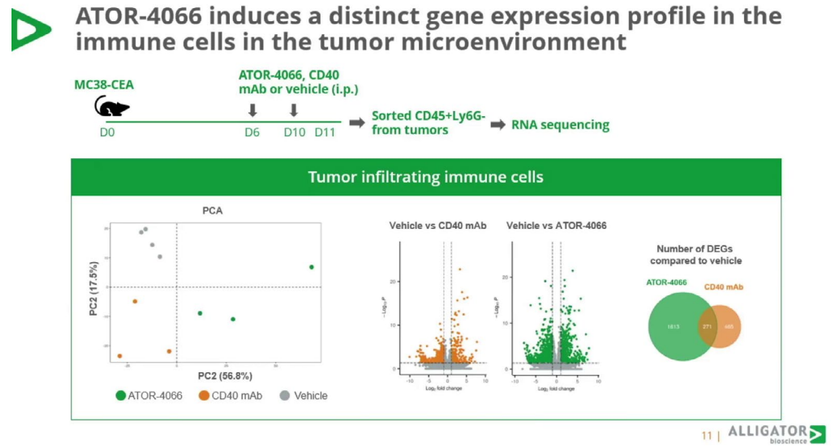
ATOR-4066 bonded to the TAA and the dendritic cells in the assay. Then, the dendritic cells internalised the tumour debris before presenting the neoantigens (in this case it's the OVA antigen). This was observed via proliferation of OVA-specific T cells when incubated with ATOR-4066 which was not seen when incubated with either an isotype-TAA antibody or a CD40 monoclonal antibody.

In humanised OT-1 mouse models, ATOR-4066 provided strong antitumour efficacy. When treated six days after inoculation, all mice saw a complete response to the treatment, this was also observed ten days after. From these studies, Alligator learned that their antibody was able to treat larger tumours and able to treat tumours with more heterogeneous expression of CEA (which was seen due to a fall off of CEA expression over time).

RNA sequencing experiments showed a distinct gene expression in the tumours of mice that were treated with ATOR-4066, compared to CD40 mAb and vehicle groups. However, when looking at the blood, the CD40 mAb stands out more than the 4066 group. This shows that the immune response in ATOR-4066 treated mice is very directed towards the tumour.

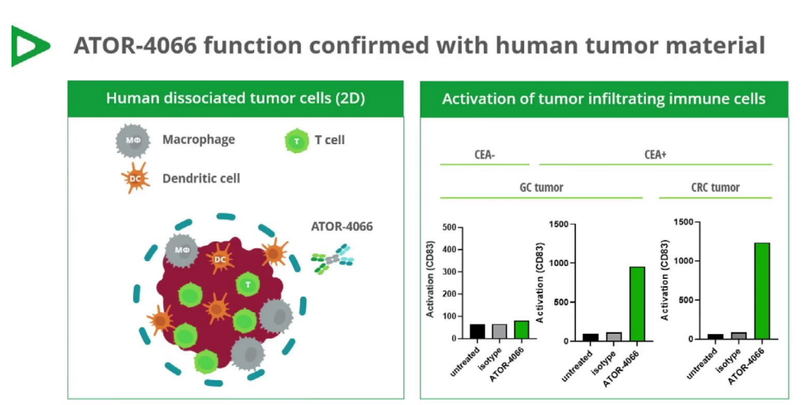


By, sequencing tumour infiltrating immune cells, the team found that the ATOR-4066 treated group again stands out from the other two (CD40 mAb and vehicle) in having more differentially expressed genes.



Digging into which genes were differentially expressed, they found that genes connected to T cell activation and cell cycle regulation are upregulated in ATOR-4066 treated mice. Furthermore, using flow cytometry to look at the immune cells in the tumour, they saw increased infiltration and activation markers (CD86 and PDL1) of myeloid cells in the tumour.

The team also confirmed these results using human tumour material. Using 2D human dissociated tumour cells, CEA negative cells had no response to ATOR-4066 while CEA positive cells saw immune activation - specifically, activation of macrophages and T cells.



Challenging the mice that completely responded to ATOR-4066 with the same tumour type again showed that they retained immunological memory and were able to keep the cancer under control. However, challenging them with a different type of tumour saw was no response. Using a T cell depletion experiment, they were able to show that this was due to T cell immunological memory.

Uddbäck rounded off the presentation by stating the clinical development opportunities that faced Alligator next. For example, further development may be sought for the antibody in combination with modalities like chemotherapy or immune checkpoint inhibitors. Furthermore, they could potentially clinically stratify patients by high levels of CEA, using liquid biopsies or exosomes.

Entering the Age of Cancer Vaccination?

Grand View Research's market report of the global cancer vaccine industry, predicted that the global cancer vaccine market size, estimated at USD 7.31 billion in 2022, would grow year-on-year at a CAGR of 11.04% from 2023 to 2030. This growth is predicted to be a result of various factors, including the recent resergence of cancer vaccine successes and rising investment in the sector.

Source: Grand View Research

Cancer Vaccination with Viral Vectors Targeting MAGE-Type Antigens in Lung Cancer

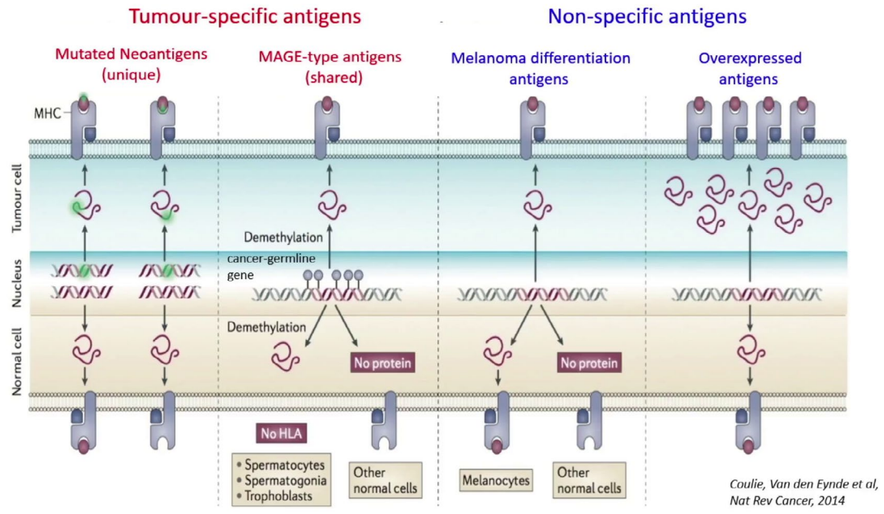
Benoit Van den Eynde, works at the Ludwig Institute for Cancer Research in Oxford and Brussels. His team is currently focused on the development of cancer vaccines.

Cancer Vaccines

Cancer vaccines aim to increase the number of T cells in the patient's tumour microenvironment - 'making a cold tumour hot'. The idea for cancer vaccines has been around for many years, since the 90s but have encountered a variety of challenges which have stunted their development.

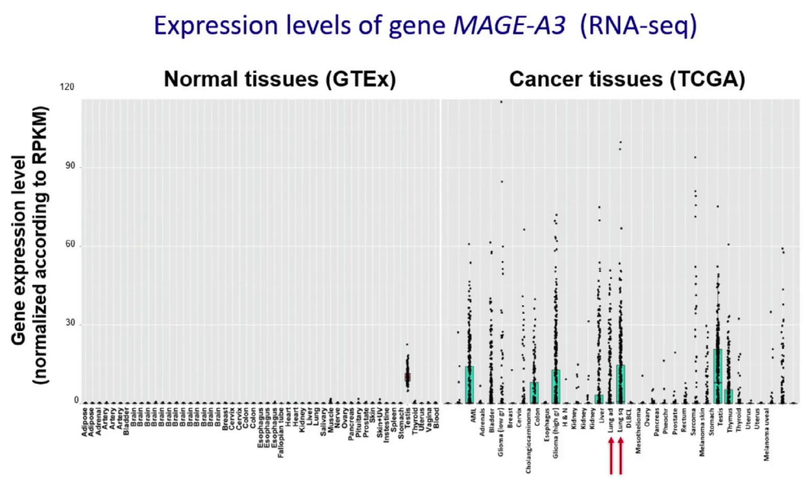
Choosing the right tumour antigen which has to be both tumour specific and immunogenic can be difficult. This makes neoantigens and personalised approaches popular solutions. Another choice that can create dilemmas for cancer vaccine developers is the choice of the tumour platform.

Choice of the Tumour Antigen



Tumour specific antigens are mutations that are absent in normal tissues whereas MAGE-type antigens are encoded by genes which are not mutated, but just silent in normal tissues.

MAGE-A3 and NY-ESO1 are both MAGE-type antigens that are frequently expressed. MAGE-A3 is the most frequently expressed MAGE-type antigen in human cancers. Both are recognized by anti-tumour CD8 T lymphocytes isolated from cancer patients. Furthermore, NY-ESOI (gene name CTAGI) induces strong CD8 responses in many cancer patients.



1 mRNA expression levels from RNA seq data in normal and cancerous tissues

This is why Van den Eynde's team selected MAGE-A3 and NY-ESO1 as candidates for their cancer vaccine antigens.

Choice of the Vaccine Platform

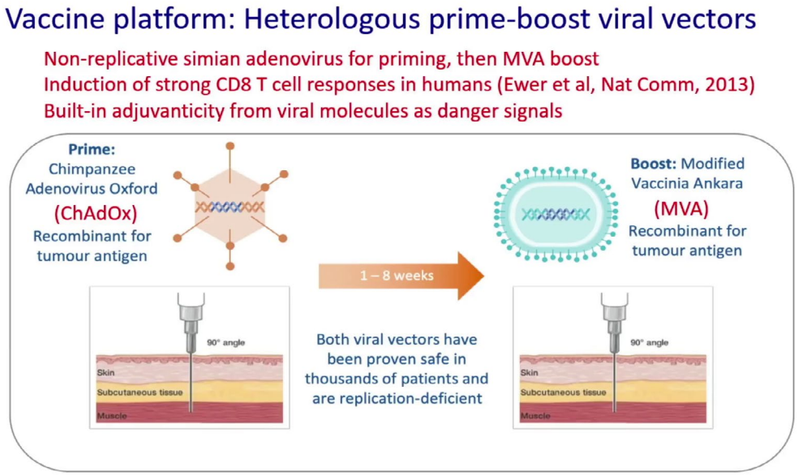
The choice of vaccine platform may have been one of the explanations for the numerous failures of cancer vaccines in the past. Large scale clinical trials of previous MAGE-A3

antigen targeting cancer vaccines have shown a lack of clinical efficacy.

Some of the largest vaccine clinical trials undertaken to date with NSCLC and melanoma have utilized a vaccine based on a recombinant MAGE-A3 protein injected with adjuvant. Here, they had suboptimal CD8 response but very good CD4 response.

To mitigate this, there is a need to deliver the antigen in the cytosol of antigen-presenting cells, to ensure proteasome processing and presentation on MHC-I. To do this, they used the viral vector platform ChAdOx from the Jenner Institute, Oxford. ChAdOx was used in the Oxford COVID vaccine commercialized by AstraZeneca.

ChAdOx: Viral Vector Platform



ChAdOx is a chimp adenovirus which can be made recombinant for the antigen of the researcher's choice. It is administered intramuscularly, is transcribed and translated in the cytosol, and presents on MHC I. After this, they also administer a different vaccine based on MVA as a booster to avoid neutralising antibodies. There is very good evidence that this will induce a strong CD8 response.

Choosing the Right Indication and Combination

Van den Eynde's team chose to focus on lung cancer. The standard of care in lung cancer is a combination of chemotherapy with pembrolizumab. With this in mind, the team wanted to combine the cancer vaccine with the standard of care treatment.

Clinical Trial

Concept: use the vaccine to heat the "cold" tumours to make them sensitive to anti-PD-1

Non-small cell lung carcinoma (Stage III or IV)

- 47% of NSCLC express MAGE-A3
- 27% of NSCLC express both MAGE-A3 and NY-ESO1
- Anti-PD-1 (pembro) combined with chemo is standard of care in advanced NSCLC

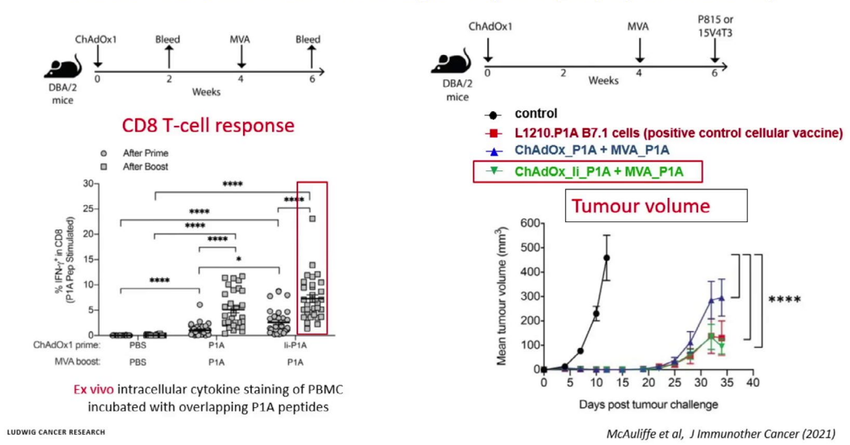
-> combine the ChAdOx1/MVA/MAGE-A3/NY-ESO1 vaccine with the current standard of care, namely chemotherapy + anti-PD-1 (pembrolizumab) in MAGE-A3/NY-ESO1 tumours

Welters et al Sci Transl Med, 2016, 8, 334ra52
"Vaccination during myeloid cell depletion by cancer chemotherapy fosters robust T cell responses"
Carboplatin + paclitaxel reduces immunosuppressive Myeloid-Derived Suppressor Cells (MDSC)

Combining the vaccine with anti-PD1 is sensible, but combining the therapy with chemo was thought to be more difficult. However, with the right type of chemo administered at the right time in relation to the cancer vaccine, beneficial effects can be seen.

Preclinical Work

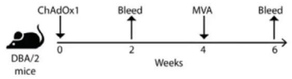
For their mouse model, the team chose a surrogate MAGE-type antigen called P1A, which has similar features to the human antigen. They created a cancer vaccine using ChAdOx against P1A and found that it was very immunogenic. Encouragingly, they observed a strong CD8 response.



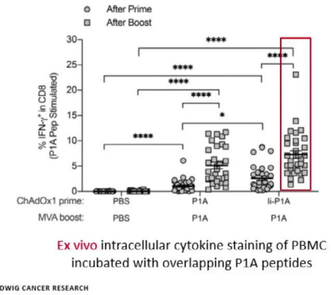
McAuliffe et al, J Immunother Cancer (2021)

However, developing the therapeutic setting is much more difficult to get efficacy than the preventative setting - when the tumour pre-exists the vaccination, the efficacy falls off. That's why it was important to combine the vaccine with other therapeutic options like anti-PD1. Doing so, combining anti-PD1 with the vaccine, saw some tumour growth inhibition.

ChadOx-P1A/MVA-P1A immunogenicity and prophylactic activity



CD8 T-cell response



Ex vivo intracellular cytokine staining of PBMC incubated with overlapping P1A peptides

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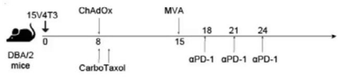
McAuliffe et al, J Immunother Cancer (2021)

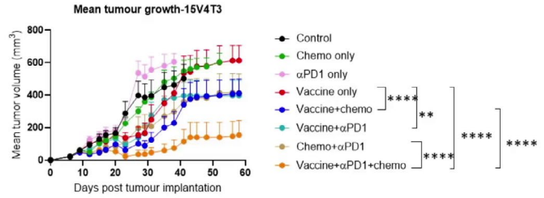
Furthermore, combining the vaccine with chemo also saw similar tumour growth inhibition. But vaccine, plus anti-PD1, plus chemo increased tumour growth inhibition even further and translated into survival of the mice.

Therapeutic setting: triple combo with anti-PD-1 and chemo



CarboTaxol:
Carboplatin (intercalating agent)
and
paclitaxel (antimitotic)

Laurine Noblecourt



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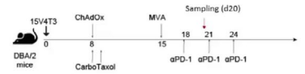
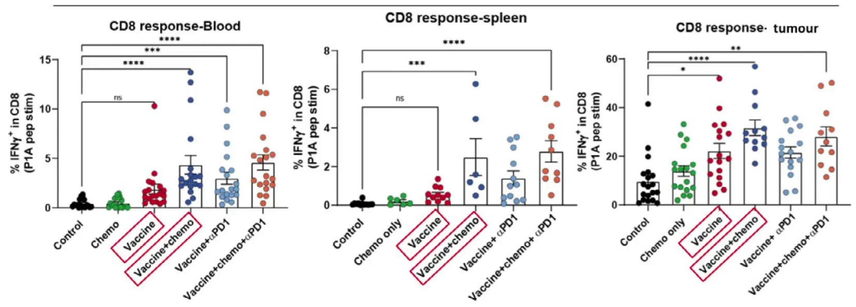
Chemotherapy improves immunogenicity of ChAdOx-P1A/MVA-P1A vaccination



% P1A-specific CD8 T cells ex vivo

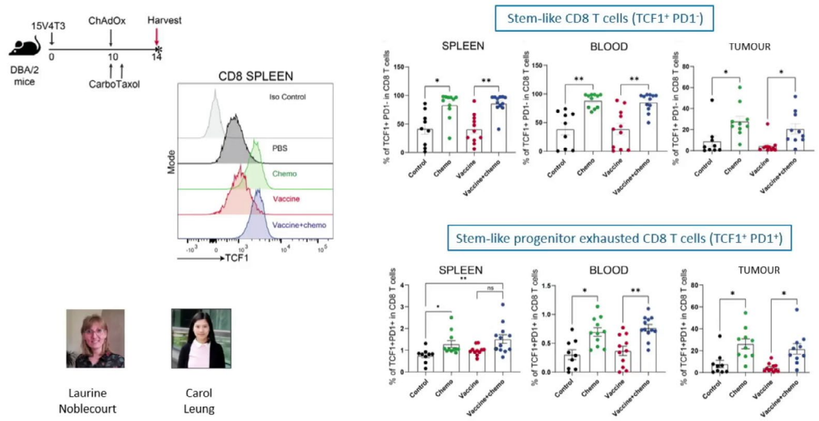


The Immunogenicity Mystery

When adding chemo to the vaccine, the immune response is even stronger, which was unexpected. They investigated why this was and saw a depletion of myeloid cells. But through further testing, they saw that depletion of granulocytic-MDSCs with mAb did not recapitulate the chemo effect on vaccine efficacy. So myeloid cell depletion was not the answer.

Further research uncovered a difference in the phenotype of the T cells induced by their vaccine in combination with chemotherapy, particularly in the TCF1 expression. These T cells have stem like properties which lead to their long term persistence.

Chemotherapy increases TCF1 expression in CD8 T cells



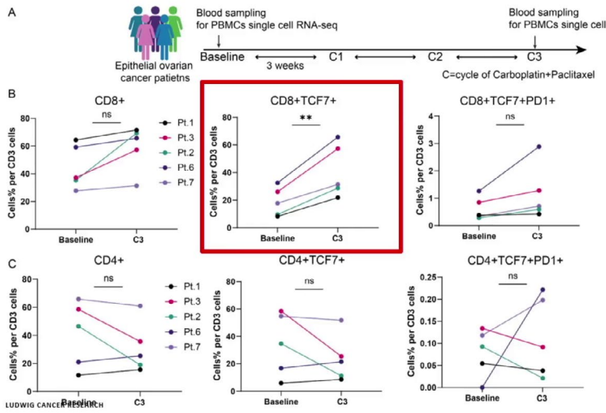
Laurine Noblecourt

Carol Leung

Both the level of TCF1 and the proportion of cells expressing TCF1 increase with the addition of chemo to treatment.

In lieu of clinical trial data, to see if this is also the case in humans, they looked at a database of a clinical trial that investigated ovarian cancer. They found that cells that expressed CD8 and TCF7 (the gene name for TCF1 in humans) increase after chemotherapy. Therefore, this suggests that the hypothesis is also true in humans.

CarboTaxol induces an expansion of systemic TCF1+ CD8 T cells in ovarian cancer patients



Analysis using the dataset of : Improved T-cell immunity following Neoadjuvant Chemotherapy in Ovarian cancer, **Clinical cancer research, Min Liu *et al*, 2022**

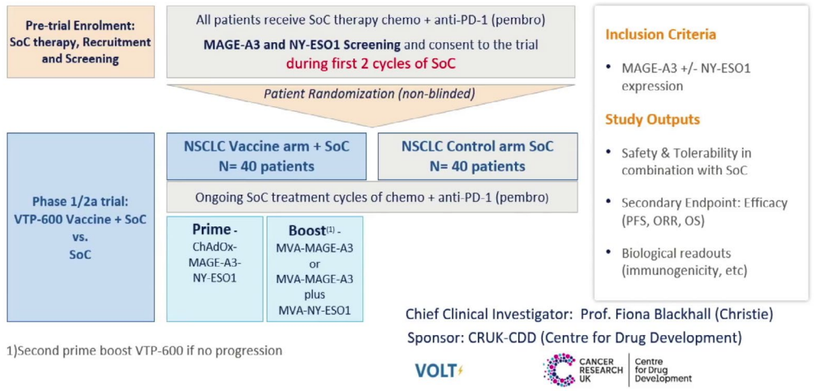
Carboplatin and paclitaxel induce CD8+TCF1+ T cells in the blood of ovarian cancer patients

TCF7= gene name for TCF1 protein

Phase I/II Clinical Trial for Advanced NSCLC

Based on their preclinical work, they were ready to translate their findings into the clinic. They are currently running a phase I/II clinical trial with the support of Cancer Research UK for advanced non-small cell lung cancer (NSCLC) with the expression of MAGE-A3. One arm will receive the standard of care, the other will receive the standard of care plus the vaccine.

Phase 1/2a clinical trial
NSCLC Stage III-IV, PD-L1<50%, no EGFR/ALK mutation, MAGE-A3-positive



1)Second prime boost VTP-600 if no progression

Chief Clinical Investigator: Prof. Fiona Blackhall (Christie)
Sponsor: CRUK-CDD (Centre for Drug Development)

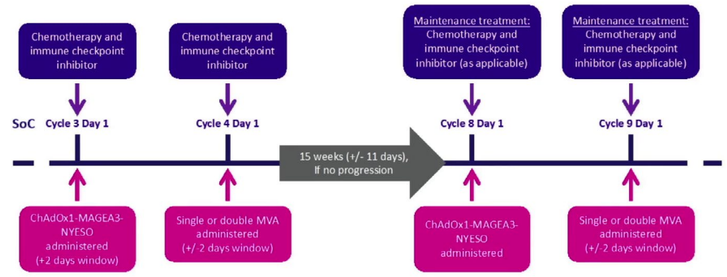


Figure 1: Treatment Schedule

One drawback is the difficulty in getting biopsies from lung cancer patients, therefore, they are launching a second oesophageal cancer cohort of this trial. The trial is still in the early stages, but the group are hoping to achieve positive results.

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Cancer Vaccines: Analysing the Resurgence

The emerging development of cancer vaccines is an exciting branch of immuno-oncology. Vaccination against tumours is achieved by having the immune system recognise cancer-associated antigens to help fight cancer. Immuno 2023 featured a panel of experts discussing analysing the resurgence of this territory, its past attempts, and up-and-coming strategies.

Colleen Winstead is Director of Immunology at biotech startup Epitopea which develops mRNA LNP-based immunotherapies. Joining her was Livija Deban, Chief Scientific Officer at Prokarium, a company [re]engineering evolution into a synthetic biology platform for novel immunotherapies. The final member of the panel was Francesca Barone, Chief Scientific Officer at Candel Therapeutics. Candel uses viral immunotherapies in order to vaccinate against tumours.

What is the Definition of Cancer Vaccines?

The panel kicked off with a fundamental question of the discussion: what is the definition of a cancer vaccine? Barone said that this was a very challenging question without a simple answer. She added that this discussion centres around therapeutic vaccination rather than prophylaxis.

“Vaccination is also not simply about delivering a tumour specific antigen – it can be broader than this and includes different modalities,” she said. Candel’s approach is to use viruses to induce cell death and the release of a multitude of antigens to activate immune cells. “It’s an important concept that you can deliver these modalities directly to the tumour, particularly to produce a systemic response.”

Another approach uses mRNA LNP vaccines: this is the technique that Winstead is interested in. “The origin of our startup is in identifying those targets that provide the most therapeutic efficacy for vaccination,” she explained. These targets are generally cancer-specific and are able to generate a very productive immune response. Winstead too said that systemic vaccination was important in order to provoke an immune response that targets the tumour.

Prokarium’s modality encompasses the direct targeting of specific antigens and broader immune stimulation. Deban said that their salmonella-based therapy can induce immunogenic cell death and the release of antigens from tumour cells. They can also engineer the salmonella to deliver antigens, neo antigens, and other molecules that drive the desired immune response. In the context of cancer vaccines, it is important to guide the immune response in the right direction and to make sure that it is not overwhelmed by the suppressive tumour microenvironment.

Reasons For Past Failings

In analysing the resurgence of any modality, it is also critical to take a look back at past attempts that were perhaps not so successful. The panel next considered what the reasons for past failings were and how researchers can learn from these digressions toward a more efficacious model. This is a topic with many different interpretations, and each of our panellists gave their viewpoint:

With regard to the tumour microenvironment, the absence of the right cells in the area of vaccination, or the inability of the right cells to migrate to the tumour is a worry for Deban.

Barone is focused on the ability of the immune system to recognise the right clones of tumours. One of the main problems here is that tumours can be very smart. Creating an immune response against a specific clone may end up with it downregulating a specific antigen through clonal escape – this is often how metastases form.

Tumours can mutate to elude the immune system, and so for Winstead, finding the right targets to vaccinate against can be a huge challenge. She said that the field of neoantigen vaccination is still very broad with some major issues. “If you design a vaccine and you don’t have any means to address immune escape, that’s an issue that will result in failure.” Here, Winstead is focussed on finding the right ways to solve this issue.

Will the Next Generation of Cancer Vaccines Lead to Better Clinical Outcomes?

From the viewpoint of an mRNA LNP focused company, Winstead commented that the recent success of that field had ignited some interest in using the technology to drive cancer vaccines. Furthermore, advancements in overcoming the issue of immune escape have bolstered interest in immuno-oncology more generally. This has all coincided with the technology for the development of cancer vaccines becoming cheaper, faster, and safer in the last few years.

The influence of the COVID-19 pandemic has brought to the fore public awareness around vaccination and driven its science and technology. Barone said that the science of sequencing tumours is much easier and cheaper than it ever was before. She said: “All the knowledge that we have developed through the use of checkpoint inhibitors and immunotherapy in general has enabled us to better understand how the immune system works.”

Moreover, immuno-oncologists have had to grapple with understanding the immune systems of patients that have had or are simultaneously undergoing treatments like chemotherapy and radiotherapy. Obtaining this better grasp on the tumour microenvironment has been vital for clinicians. Barone said: “We can engineer some of our vectors – our HSVs – to deliver to the liver chemokines or cytokines that can reignite the tumour microenvironment where it is needed.”

Deban agreed that since immunotherapy had become a hot topic, the field had enjoyed a reinvigoration and had seen new advances. “There are still a lot of hurdles to overcome,” she added. She offered that leveraging combinatorial approaches was a way in which to address the diversity of cancer patient populations.

Vaccines: Oncological versus Traditional Approaches

The oncological approach to developing vaccines will no doubt be very different to the way in which traditional vaccines are developed. The first contrasting feature is the timings for each, “how you induce the dynamics of an immune response in a cancer patient will be very different from a healthy individual,” said Deban. Furthermore, the COVID pandemic has accelerated the number of studies that look at regular vaccination in cancer patients.

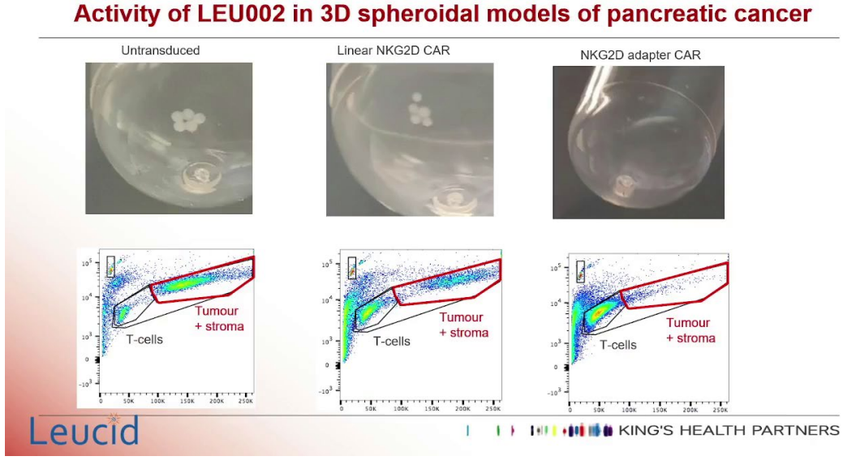
“We also need to understand immune fitness in patients and how to boost it,” added Deban. One of Prokarium’s hypotheses is that controlled infection with an attenuated pathogen can boost the immune fitness of patients’ myeloid cells which can drive a better T cell response and systemic anti-tumour immunity.

Investigating CAR T Cell Therapies

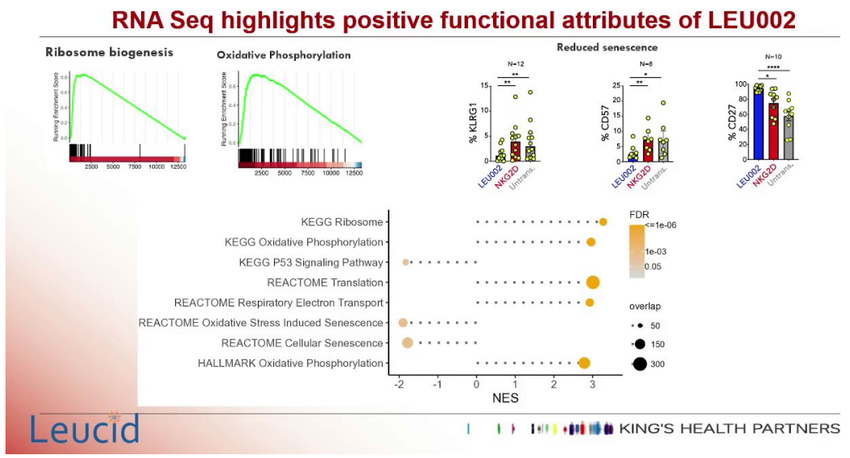
CAR T-Cell Immunotherapy Of Solid Tumours: Moving Through The Generations

John Maher, Chief Scientific Officer, Leucid Bio, explained that the CAR T field causes a lot of excitement due to second generation CAR T therapies the success of the modality in blood cancers. However, that 25 year old technology has not seen the same success in solid tumours. So our thesis is we need better CARs.

Leucid's CAR T programme has been keen on targeting NKG2D ligands because there are eight available which mitigates the risk of antigen loss and heterogeneity of targets causing therapeutic failure. These targets are also expressed on both malignant and non-malignant cells within the tumour microenvironment, and they are relatively lacking in healthy tissues.

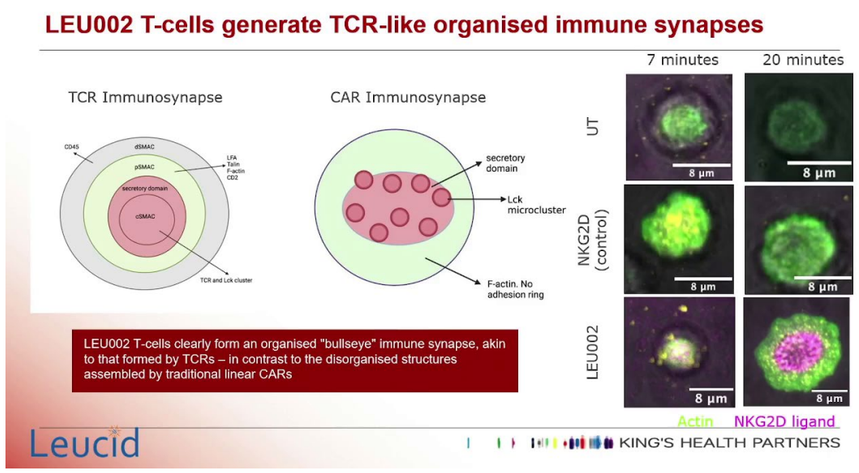


The CAR T team at Leucid demonstrated in vitro anti-tumour activity of adaptor CAR T cells in a tumour spheroid model: a mixture of tumour and stroma growing together in a tight ball. After adding non-transduced T cells to the spheroids, no activity was observed, and the spheroids remained intact and visible to the naked eye. Adding linear NKG2D CAR T cells had a similar lack of response; there was some anti-tumour activity, but it was incomplete. However, using an adapter CAR saw a complete clearance of the tumour spheroids.

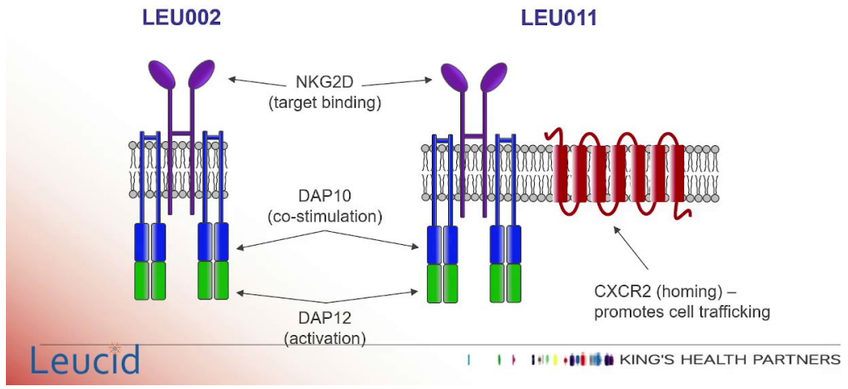


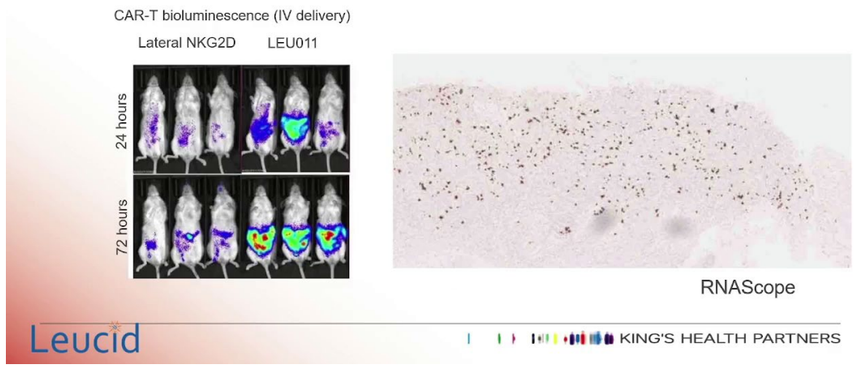
Why did these adapter CARs work better than matched linear CARs? The Leucid team used RNA sequencing to investigate this. Using RNA sequencing, they saw increased ribosome biogenesis and oxidative phosphorylation gene sets. This was confirmed by seahorse analysis. In summary, they were metabolically fitter T cells.

Another interesting attribute of these CAR T's is that when the team expanded them, older T cells which up-regulate NKG2D ligands were selectively eliminated. In other words, expansion caused a reduction in senescence expression. This was also reflected in the gene set enrichment analysis.



The adapter CAR is very close to a natural structure, and so Leucid added a DAP12 onto the endo domain of DAP10, which naturally pairs with NKG2D. As a result, these CAR T cells form typical TCR-like 'bullseye' immune synapses. This contrasts with the behaviour of traditional linear CARs which form highly disorganised immune synapses.

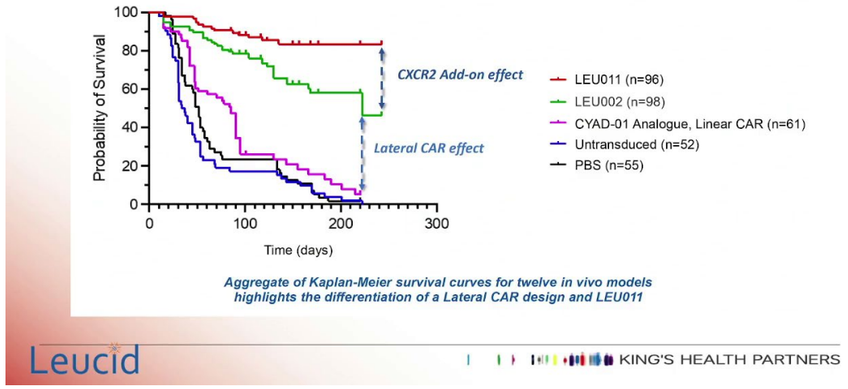




One final preclinical addition was to armour the adapter CAR with a chemokine receptor to facilitate the delivery of T cells to the tumour microenvironment, specifically CXCR2. Drug delivery to the site of disease is one of the many hurdles faced by CAR T cells treating solid tumours. Many solid tumours produce chemokines like IL-8 and CXCL5, which are cognate for CXCR2.

Imaging from mouse models provided some evidence that the CXCR2 armouring was successful. They injected mice with an intraperitoneal tumour and injected the CAR T cells intravenously, they then imaged the T cells in the mice (see slide). By 72 hours, more T cells were at the site of disease when the cells were armoured with CXCR2.

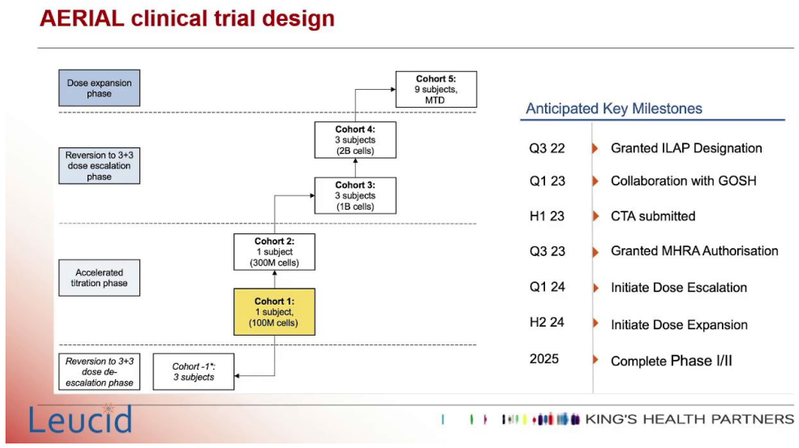
Unexpectedly however, this armouring did more than just facilitate trafficking. Armouring with CXCR2 also enhanced the ability of the T cells to infiltrate within the core of the solid tumour: imaging showed CAR T cells evenly distributed across a subcutaneous pancreatic tumour xenograft.



Maher then showed Kaplan-Meier survival curves which outlined the in vivo efficacy of their CAR T therapy. The curves were based on mice with an established tumour burden, representative of common adult onset solid tumours, including ovarian cancer, pancreatic cancer, colorectal cancer, and malignant pleural mesothelioma.

The mice were treated with a variety of different CAR T approaches as listed in the key (see slide). As expected, the control group all died rapidly of their disease. Mice which were treated with a linear CAR directed against the same target, using the NKG2D receptor to confer specificity, had a significantly better probability of survival than the controls. However, after around day 60 to 70, the responses were not durable.

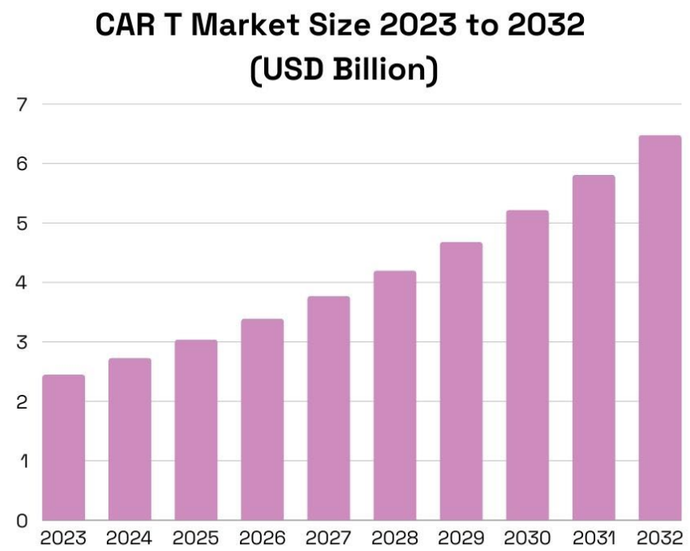
The adapter CAR did much better, at around 50% long term survival. Furthermore, by armouring with CXCR2 they were able to achieve 85% long term survival in the tumour bearing mice with a plateau on the curve.



Leucid have now designed a clinical trial called AERIAL for their CAR T cell therapy which they hope to start very soon. They will enrol patients with NKG2D ligand-expressing adult-onset solid tumours. Two single patient cohorts will be dosed at 100 and 300 million CAR T, followed by a 3+3 design with 1 billion and 2 billion CAR T. Finally, there will be an expansion cohort of at least nine subjects.

Global Market Summary: CAR T Cell Therapy

The global CAR T-cell therapy market is experiencing significant growth across various regions, driven by advancements in cancer treatment technologies and increasing investment in healthcare. This report provides a detailed analysis of the CAR T-cell therapy market across North America, Europe, Asia-Pacific (APAC), and Latin America, Middle East, and Africa (LAMEA).



Source: www.biospace.com

North America

2023 Market Size: USD 3.36 billion
2032 Market Projection: USD 35.50 billion
CAGR (2023-2032): 29.9%

North America leads the CAR T-cell therapy market, benefiting from a robust healthcare infrastructure, significant R&D investments, and early adoption of innovative therapies. The region's market is set to expand more than tenfold by 2032.

Europe

2023 Market Size: USD 2.37 billion
2032 Market Projection: USD 25.82 billion
CAGR (2023-2032): 30.3%

Europe's CAR T-cell therapy market is experiencing rapid growth, driven by favorable government policies, increasing prevalence of cancer, and strong support for advanced medical research. The market is expected to grow over ten times its current size by 2032.

Asia-Pacific (APAC)

2023 Market Size: USD 1.69 billion
2032 Market Projection: USD 18.65 billion
CAGR (2023-2032): 30.5%

APAC is emerging as a significant player in the CAR T-cell therapy market, supported by a large patient pool, growing healthcare expenditure, and increasing adoption of innovative therapies. The region is projected to see a more than tenfold increase in market size by 2032.

Latin America, Middle East, and Africa (LAMEA)

2023 Market Size: USD 1.01 billion
2032 Market Projection: USD 8.54 billion
CAGR (2023-2032): 26.8%

The LAMEA region is experiencing steady growth in the CAR T-cell therapy market, facilitated by improving healthcare infrastructure and increasing awareness of advanced cancer treatments. The market is expected to grow significantly, reaching over eight times its current size by 2032.

Conclusion

The CAR T-cell therapy market is poised for substantial growth across all regions, with North America and Europe leading the way in terms of market size and innovation. The APAC region shows the highest growth potential, while LAMEA also presents significant opportunities as healthcare infrastructure and awareness improve. Overall, the global CAR T-cell therapy market is on track for a transformative decade, driven by technological advancements and increasing demand for effective cancer treatments.

Source: biospace.com

Report Summary

The future of cancer therapy is poised for significant growth and transformation. The immuno-oncology market is expected to expand at a compound annual growth rate (CAGR) of 8.3% until 2030. Key drivers include advancements in drug discovery, the initiation of novel clinical trials, and a shift toward precision and personalized medicine. The accelerated validation of mRNA technology during the COVID-19 pandemic has reinvigorated the development of personalized cancer vaccines, promising to bring new therapies to patients more swiftly.

Looking ahead, the ongoing efforts to optimize the safety and efficacy of immunotherapies will likely result in more effective and safer cancer treatments. The combination of innovative therapies such as T cell engagers, bispecific antibodies, and cancer vaccines with existing treatments like chemotherapy and immune checkpoint inhibitors is expected to yield improved clinical outcomes. The continued research and development in this field, supported by clinical trials and collaborations, will be crucial in overcoming current challenges and achieving long-term success in cancer immunotherapy.

As these promising therapies advance through clinical trials, there is a strong potential for new approvals and the introduction of breakthrough treatments that can offer patients more effective and personalized options. The commitment of researchers and pharmaceutical companies to innovate and refine these therapies will be instrumental in the ongoing battle against cancer, ultimately improving survival rates and quality of life for patients worldwide.