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Meeting Report

Immuno-oncology: the next generation of breakthrough therapies. Highlights from The Society for Medicines Research Symposium

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Summary

The approval of immune checkpoint inhibitors has revolutionized cancer therapy. Even so, there remains an urgent need to find treatments for patients that do not respond to or are not eligible to receive this class of drugs. Given this, many more innovative approaches are now being developed to redirect the immune system toward tumor cells, ranging from small molecules and novel biologics to cell therapies and gene therapy approaches. The aim of the 1-day meeting was to bring together renowned experts from academia and industry to discuss the latest immunotherapy advances and highlight how these discoveries form the basis of novel drugs that are designed to target key immunology pathways and transform the lives of cancer patients. This meeting was aimed at students and practicing professionals from academia and industry looking to gain an understanding of the pathological mechanisms at play within immune oncology and their targeting in discovery and development of novel immunotherapies. The symposium was held at St. Hilda's College, Cowley Place, Oxford, UK, and sponsored by AstraZeneca.

Key words: Immuno-oncology – T-cell receptor – Cancer vaccines – Gene therapy

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Introduction to Novel Immunotherapies and T-cell Targets

Sifting the surfeit of novel immunotherapies: a phase I triallist's view

The first presentation of the day was given by Professor Mark Middleton, University of Oxford, who outlined the challenges of developing new immune-oncology agents. In particular, he highlighted that despite the revolutionary impact of immune checkpoint inhibitors in the treatment of melanoma, non-small cell lung cancer (NSCLC) and other tumors, the majority of cancer patients do not stand to benefit from immunotherapy. Professor Middleton noted that most common tumor types have largely proved refractory to this approach and even in sensitive cancers only a minority of those patients treated derive benefit. This has driven a wave of clinical trials evaluating novel agents designed to overcome what we understand to be the key obstacles to successful treatment or seeking to identify new indications for existing immunotherapies. In addition, the potential approaches to be tested far outstrip the available patient population for clinical studies and there is no agreed basis for identifying or prioritizing the most promising drugs or targets.

Professor Middleton went on to emphasize that mechanistic understanding, incorporating both biological and clinical endpoints, is required to better develop new treatments. He emphasized that results need to be interpreted within the context of the tumor immunology of the patient population, which if not specified in the protocol, might be skewed toward particular groups such as microsatellite stable colorectal cancer or checkpoint inhibitor-refractory patients. The tools available to researchers are improving all the time and although analyses are not cheap, they represent a tiny fraction of the cost of phase I clinical studies.

Professor Middleton proposed 5 key factors for improving the success of testing drugs in phase I studies, namely testing agents in potentially curable (earlier stage) patients, acquisition and detailed analysis of tumor and normal tissue, linking changes to potential surrogate tissue markers, understanding the biological effects of dosing and the ability to explain clinical results in other clinical studies.

While many patients have achieved clinical benefit with immuno-oncology therapies such as **ipilimumab**, **pembrolizumab** and **nivolumab**, Professor Middleton explained that many patients do not benefit from these treatments including 40-70% of patients with potentially sensitive diseases, people whose tumors are growing too fast, patients with breast, prostate and colorectal cancer, people with brain metastases and patients with autoimmune conditions or organ transplants.

Professor Middleton outlined 4 factors that determine sensitivity to immunotherapy, namely mutational burden, tumor sensitivity to immune effects (e.g., MHC expression and interferon [IFN]-γ sensitivity, exhaustion markers), checkpoint expression and immune cell infiltrate (e.g., intratumoral T cells).

In the last part of his presentation Professor Middleton gave an example of the ImmTAC (immune mobilizing monoclonal T-cell receptor against cancer) molecule **tebentafusp**, which binds a gp100 peptide presented by HLA-A2 on tumor cells. Mechanistic results from clinical studies suggest that patients with the greatest increase in CXCL10 have greater tumor shrinkage and longer survival.

New T-cell receptor targets by dissection of successful cancer immunotherapy

The next presentation was given by Professor Andrew Sewell from University of Cardiff. He outlined that over 20% of melanoma patients that have been refractory to other treatments undergo complete lasting remission after adoptive cell transfer of tumor-infiltrating lymphocytes (TILs). Dissection of these extraordinary successes by examining the dominant tumor-reactive T-cell clonotypes in the TIL infusion product and patient blood after 'cure' has revealed some surprising, exciting new HLA-restricted and non-HLA-restricted T-cell targets that are expressed by many other tumor types. Several of the new broadly expressed HLA-restricted cancer epitopes were unexpected as the proteins they derive from are thought to be expressed in some healthy cell types. In some cases, patients received billions of activated T cells with these specificities within their TIL infusion product that persist in the blood years after complete remission and large populations of such cells can be found in other remission patients. These data suggest that targeting these new epitopes is safe. The Sewell group has also used a whole genome CRISPR forward genetic screening to identify the cancer-specific ligands recognized by 'HLA-agnostic' T cells. Professor Sewell described how such ligands, and the T-cell receptors that recognize them, could be used to build therapies for most cancers in all individuals as they circumvent the hurdle of only a minority of patients having any given HLA type.

Professor Sewell also demonstrated how altered peptide ligands could be used to skew T-cell responses toward effective T-cell clonotypes identified in patients successfully treated with TIL therapy. This approach was used to induce T-cell lines from the blood of patients with several types of cancer. These altered peptide ligand-induced T-cell lines were shown to be far more effective at killing autologous tumor lines than lines induced by the natural peptide ligand. In Professor Sewell's opinion, new approaches to cancer vaccination that focus on the *quality* of the response induced at the clonotypic level rather than the *quantity* of the response could revolutionize future prospects for successful cancer vaccination.

TCR-based Therapies

Advancing the ImmTAC TCR-based bispecific biologic platform: preclinical data on the next clinical ImmTAC molecule

Dr. Joseph Dukes from Immunocore Ltd continued on the theme of T-cell receptors (TCRs) and gave an overview of Immunocore's **ImmTAC** technology. ImmTAC molecules are a novel class of biologics that consist of a soluble TCR-based targeting domain and an anti-CD3 effector domain. Utilizing TCRs as targeting domains provides access to potentially clean and cancer- or tissue-specific targets due to recognition of class I MHC molecules. The TCRs are highly selective against peptide–HLA complexes presented by cancer cells and affinity matured to picomolar affinity. The mode of action of these molecules consists of binding of the TCR domain to cancer cells and redirection of polyclonal T cells via the anti-CD3 fragment. Recruited T cells will then form an immunological synapse and destroy target tumor cells. Notably, ImmTACs can redirect T cells even if these are not specific for the target in question. To select tumor-specific targets, Immunocore has a large database of mass spectrometry (MS)-validated peptide epitopes from normal and cancer cells. As ImmTACs are human-specific, selectivity and safety screens are done using a fully human in vitro approach using cell and tissue models (1).

In the second part of his talk, Dr. Dukes outlined the key data and status of Immunocore's leading clinical molecules. He began with **tebentafusp** (IMCgp100), the most advanced drug that is currently in pivotal registrational clinical studies for metastatic uveal melanoma. Importantly, this molecule has provided clinical proof-of-concept for the ImmTAC platform with evidence for clinical activity and potential patient benefit in uveal and cutaneous melanoma. The activity in ocular melanoma is particularly

noteworthy as this hard-to-treat cancer type is insensitive to checkpoint inhibitors and has a low mutational burden. Two further ImmTAC molecules, directed against tumors positive for NY-ESO-1 (**IMCnyeso**, partnered with GlaxoSmithKline [GSK]) and MAGE-A4 (**IMC-C103C**, partnered with Genentech) are in phase I clinical development stage. Due to the much broader tumor expression profile of these targets, Immunocore expects applicability in a wide range of cancers. Dr. Dukes concluded that Immunocore has now built a strong emerging pipeline for internal and partnered programs to enter the clinic in oncology as well as in infectious and autoimmune diseases.

Small Molecule Approaches

Going beyond combinations, bispecific and bifunctional approaches in IO

Dr. Tilo Senger (Development Program Lead in Oncology/Immuno-oncology) eloquently described aspects of Merck KGaA's research in an excellent talk. He began by presenting the options for addressing the challenges that face the immuno-oncology development community. Dr. Senger then outlined Merck KGaA's twin paradigm of developing bifunctionals/bispecifics with strong rationale of superiority versus combinations of two compounds for the same targets and advancing effective partnerships with academia/biotech/pharma to maximize resources and permit the integration of emerging technologies. His talk centered on three development programs that featured different aspects of these paradigms.

Firstly, studies around the investigational tumor-targeting immunocytokine **M9241** (NHS-IL12) (2) were described. This work was conducted in partnership with the National Cancer Institute in Bethesda, USA. Preclinical data were presented demonstrating that the activity of **avelumab** (anti-programmed cell death 1 ligand 1 [PD-L1]) is increased in combination with NHS-IL12 (3). Treatment with NHS-IL12 also led to increased PD-L1 expression in mouse tumors and induction of TIL infiltration in EMT6 and MC38 murine models. Increased proliferation and activation of tumor-associated macrophages, T cells and NK cells was also observed. Indeed, this program has reached an exciting stage; a phase Ib, open-label, dose-escalation trial (JAVELIN study design) of NHS-IL12 and avelumab treatment of advanced solid tumors, with sequential assignment of expansion cohorts, is underway and primary data are expected in January 2020.

Dr. Senger then discussed approaches to targeting indoleamine 2,3-dioxygenase 1 (IDO1) and tryptophan 2,3-dioxygenase 2 (TDO2), key players in establishing immune resistance in tumors and catalyzing the commitment step of the kynurenine pathway (4). The profile of **M4112**, a dual IDO1/TDO2 inhibitor, was highlighted which offers an opportunity for differentiation; IDO1 and TDO2 have distinct natural expression sites and are upregulated on different tumor cells. Interesting results from a recent American Association for Cancer Research (AACR) meeting disclosure (5) on clinical responses in an M4112 dose-finding trial and unexpected pharmacodynamic effects in plasma (limited decrease of kynurenine on day 1 then returning to baseline levels by day 15) were presented. Further investigation is currently underway.

Dr. Senger's third case study described the discovery of an innovative first-in-class bifunctional molecule (**bintrafusp alfa**, M7824) in partnership with GSK. It is hoped that this transforming growth factor-β (TGF-β) plus PD-L1-targeting bifunctional fusion protein will overcome poorly addressable tumor biology; M7824 exhibits stronger antitumor activity to coadministration of TGF-β trap and anti-PD-L1 in preclinical models (6). He showed promising data that indicated durable responses across all PD-L1 expression levels in a phase I/II NSCLC trial and marked responses in a phase I human papillomavirus-associated cancer trial. The Merck–GSK Alliance is currently evaluating the potential of M7824 to treat difficult-to-treat cancers such as unresectable NSCLC, biliary tract cancer and others, with results keenly anticipated.

Small molecule approaches to immune oncology

To set the scene for his engaging talk, Dr. Simon Barry (Senior Principal Scientist and Small Molecule Immune-oncology lead at AstraZeneca, Cambridge) stated that the immune-oncology community is aiming to build on the foundation of PD-1/L1 and cytotoxic T-lymphocyte protein 4 (CTLA-4) (7). Also, driving effective antitumor T-cell immune responses may be accomplished by targeting the tumor microenvironment (to reverse immunosuppression) or tumor cells (to enhance immune engagement) or by enhancing immune priming and sustaining T-cell activation.

Dr. Barry described the fact that targeting phosphoinositide 3-kinase α/δ (PI3Kα/δ) (using **AZD8835**) appeared to be superior in his team's hands than targeting PI3Kδ alone (using **PI-3065**) for driving immune-dependent antitumor activity in a CT-26 syngeneic model (8). The question of whether inhibitors of the PI3K pathway have positive or negative effects on the antitumor immune response was also addressed with the demonstration that PI3Kδ inhibitors dosed intermittently are more active in mouse syngeneic models than when dosed continuously (8). He also emphasized that transient suppression of PI3Kδ regulatory T cells was associated with the antitumor response following intermittent dosing but sustained elevation of $CD8^+$ T cells was achieved (8). Moving on to the evaluation of mammalian target of rapamycin complex 1 (mTORC1/2), results were shown that **vistusertib** and α-CTLA-4 checkpoint blockade promotes immune antitumor responses in the CT26 model (9). In addition, vistusertib/α-CTLA-4 combination promotes a nonexhausted Th1 effector response

plus the activity of checkpoint inhibitors α-CTLA-4, α-PD-1 and α-PD-L1 is all enhanced with vistusertib (mTORC1/2) treatment in MC38 tumors (9).

Another interesting feature of this presentation involved the hypothesis of using unformulated next-generation (Gen 2.5) antisense oligonucleotides (ASOs) to degrade mRNA of the transcription factor FOXP3 (forkhead box protein P3) in order to provide anticancer benefit. Dr. Barry shared results of a collaboration between AstraZeneca and Ionis demonstrating that mouse FOXP3 ASOs promote potent FOXP3 downregulation in primary regulatory T cells and deliver monotherapy efficacy in ID8-VEGF and A20 syngeneic models (dosing 50 mg/kg b.i.w. from day 1 post-implantation). Gratifyingly, the immune changes induced by mouse FOXP3 ASOs are localized to the tumor (A20 mouse model), rather than the spleen, and FOXP3 ASO/PDx combination augments the depth of antitumor response. Modulation of STAT3 (signal transducer and activator of transcription 3) is known to be a global regulator of the tumor microenvironment (10) and Dr. Barry proceeded to show that downregulation of STAT3 by the ASO **AZD9150** (danvatirsen) enhances PD-L1 inhibitor efficacy in the CT26 model. Collaborative efforts indicate that AZD9150 provides early evidence of clinical activity (11) in diffuse large B-cell lymphoma and lung cancer and in combination with durvalumab (PD-L1 inhibitor) for the treatment of head and neck squamous cell carcinoma.

Specific tumor metabolites are thought to play a pivotal role in regulating T-cell function. Adenosine signaling also offers a therapeutic opportunity by tackling the immune suppressive tumor microenvironment. Dr. Barry shared data for the adenosine A_{2A} receptor inhibitor **AZD4635**'s (licensed from Heptares) ability to potently reverse adenosine-mediated suppression of $CD8^+$ T-cell activity and reduce tumor volume in combination with anti-PD-L1 monoclonal antibody in MC38 and MCA205 models. Targeting lactate transport offers yet another potential therapeutic approach (12). For example, the monocarboxylate transporter 4 (MCT4) inhibitor **AZD0095** exhibits efficacy at 30 mg/kg oral dosing b.i.d. in an MC38 MCT1 knockout model in combination with checkpoint inhibitors using various mass spectrometry (MS) techniques including MS imaging tumor cell lactate sequestration caused by AZD0095 has been analyzed and the associated increased infiltration of immune cells to be imaged by mass cytometry.

Tumor genetics are likely to be important regulators of the response to immunotherapy. Loss of the phosphatase and tensin homolog PTEN promotes resistance to T cell-mediated immunotherapy (13). Dr. Barry informed the meeting that PTEN-mediated immune resistance may be reversed by administration of the PI3Kβ inhibitor **GSK2636771**. Similarly, in the context of BRCA mutation, positive antitumor activity of the poly (ADP-ribose) polymerase (PARP) inhibitor **olaparib** (AZD2281) is achieved in combination with anti-PD-L1 in a BRCA-mutant syngeneic model.

The talk concluded with an impressive overview of the challenges facing the immune-oncology field. While there remains a sizeable opportunity around tumor-targeted combinations, Dr. Barry pointed out that nonclinical disease models remain suboptimal for effective decision-making, signals beyond the backbone therapy are currently limited and that increasing response rate in each disease segment is problematic. We are entering an exciting season in immune-oncology treatment with features associated with response emerging in some settings.

Vaccines and Gene Therapy

Targeted immunotherapy for preinvasive human papillomavirus disease

Professor Lucy Dorrell (Head of Translational Medicine - Infectious Diseases at Immunocore and Professor of Immunology at the Nuffield Department of Medicine within the University of Oxford) gave an insightful presentation into the progress that her team and collaborators have made in developing therapeutic vaccines for high-risk (oncogenic) human papillomaviruses (hrHPV). hrHPV are responsible for a substantial disease burden globally, comprising virtually all cervical cancers and a high proportion of anogenital and head and neck cancers (14). Importantly, cervical cancer is the second leading cause of cancer death in women living in low/middle income countries, where access to cervical screening and prophylactic vaccines is limited (15). Globally, it is predicted that 600,000 women will be diagnosed in 2020, rising to 1.3 million a year in 2069, mainly due to the increasing size and average age of the population (15).

Therapeutic vaccination is a highly attractive, feasible and noninvasive approach to eliminating persistent hrHPV infection and cervical intraepithelial neoplasia (CIN) (16). Professor Dorrell and her team at Oxford have led the development of a potent heterologous viral vector "prime-boost" platform (a replication-defective chimpanzee adenovirus, ChAdOx1 [17], and modified vaccinia Ankara, MVA [18]) to deliver a unique, bioinformatically designed HPV immunogen. '5GHPV3' comprises sequences from the 6 early proteins that are conserved across 5 high-risk genotypes including HPV16 and HPV18. In mouse models, they detected high frequencies of polyfunctional $CD8^+$ and $CD4^+$ T cells specific for 5GHPV3 in both the circulation and the cervix following systemic administration of viral vectored 5GHPV3 vaccines. HPV-specific T cells persisted for at least 6 weeks and were targeted to all early proteins in outbred mice.

In parallel, Professor Dorrell's team is also conducting a prospective observational longitudinal study to explore the immunological correlates of viral clearance and

persistence in women with current or prior hrHPV infection. One hundred and forty-five women aged 16-55 years have been recruited to date, with nearly half completing 1-year of follow-up to date. Up to 20% women had detectable T-cell responses to reference early protein sequences from HPV16 and HPV52, the majority of whom also made responses to 5GHPV3-derived peptides. This data confirmed the relevance of their immunogen sequence to natural hrHPV control.

Professor Dorrell concluded by stating that, based on their encouraging preclinical data, GMP manufacture and preclinical toxicology of their vaccines are underway in preparation for a proof-of-concept clinical trial in women with low-grade cervical HPV lesions. In addition, this vaccine technology has potential application to other populations including HIV+ patients and other HPV-driven diseases.

Systemic delivery of localized combination immunogene therapy within the tumor microenvironment

Dr. David Krige (Director of Translational Medicine, PsiOxus Therapeutics) gave an excellent overview of the novel and versatile oncolytic adenoviral vector platform for the selective systemic delivery of tumor-specific immuno-gene therapy (T-SIGn) that has been established by PsiOxus Therapeutics.

The platform was developed using a directed evolution process that involved passaging a very large randomly created library of chimeric adenoviruses repeatedly on human carcinoma cells, selecting for the most potent tumor killing viruses and then back-selecting these for lack of activity against normal human cells. The most potent of these were then screened against human carcinoma cells in the presence of fresh human blood to ensure stability and therefore suitability for intravenous systemic delivery. This resulted in the final selection of a viral vector known as **enadenotucirev** (EnAd), which forms the basis of the platform (19). EnAd consists of an Ad11 capsid, to which there is low pre-existing immunity, a chimeric Ad11/Ad3 E2B region and deletions in E3 and E4orf4. In preclinical models, EnAd has demonstrated broad-spectrum, potent antitumor activity and tumor-selective replication. In cancer patients, EnAd has displayed a predictable and manageable safety profile following systemic (i.v.) dosing (20) as well as virus delivery and selective replication in tumor cell (21).

The deletions in the genome provide space for the insertion of multiple custom transgenes under the control of the virus major late promoter, allowing the EnAd vector to be armed while maintaining its tumor-selective properties—"T-SIGn" viruses. Given that the encoded therapeutics are expressed from the virus major late promoter, products are only made in cells supporting virus replication, i.e., tumor cells. T-SIGn genome modification produces no changes to the structural properties of the virus particles, and several different therapeutic transgene payloads can be encoded within a single virus without impacting virus or payload production levels (up to 5, with a cloning capacity of approximately 3 kb). This approach has several advantages, including:

- intravenous systemic delivery of the viral vector but local production of biologics within tumor tissues, thereby enhancing local effects in the tumor microenvironment while minimizing systemic toxicities;
- the use of novel therapeutic approaches for molecules with poor pharmacokinetics or which are poorly tolerated when dosed systemically.

A pipeline of T-SIGn candidates, differentiated by mechanism and targeted patient populations, are in both preclinical and clinical development. Dr. Krige gave an overview of two such products: **NG-641** (expressing fibroblast activating protein [FAP]-targeting bispecific T-cell activator [FAP-Tac], CXCL9, CXCL10 and IFN-α transgenes) and **NG-350A** (anti-CD40 agonist antibody).

Extensive preclinical data were presented demonstrating that NG-641 has the desired antitumor properties including the ability to induce rapid activation of T cells and killing of stromal fibroblasts, and to promote the selective T-cell-mediated killing of FAP^+ fibroblasts by infected tumor cells in primary malignant cell cultures leading to decreased TGF-β levels. Because in cold tumors the activity of FAP-TAc alone may be limited by insufficient T cells, NG-641 includes CXCL9 and -10 to induce the migration of T cells and IFN-α to drive innate immune cell (e.g., dendritic cell) activation and T-cell priming. A wide-ranging translational strategy for clinical trials has been developed which will use multiple different experimental methods, designed to investigate virus delivery to, and transgene expression within, tumors (proof of mechanism), the immune effects of virus/transgene (proof-of-principle and pharmacodynamic readouts) and potential predictive biomarkers.

The second T-SIGn candidate presented by Dr. Krige (NG-350A) has already reached the clinic and is currently in a multicenter, open-label, first-in-human phase I trial (ClinicalTrials.gov Identifier NCT03852511). The study was initiated in February 2019 and will examine safety, tolerability and preliminary efficacy of NG-350A together with virus kinetics, immunogenicity and other pharmacodynamic effects in patients with advanced or metastatic epithelial tumors. The phase Ia dose-escalation phase will investigate NG-350A given to patients by i.v. infusion on day 1, 3 and 5. A parallel cohort will be given a single dose of NG-350A by intratumoral injection on day 1 to provide an opportunity to perform translational research. Phase Ib of the study, using the recommended dose from phase Ia, will investigate efficacy in up to three separate i.v. dosed cohorts of patients with epithelial tumor types.

In summary, PsiOxus has developed a platform that allows selective systemic delivery of tumor-specific immuno-gene therapy (T-SIGn) combinations locally within tumor tissues, thereby providing a route for "gene therapy" of cancer. They have a pipeline of candidates, differentiated by mechanism and targeted patient populations, which are in preclinical and clinical development.

Disclosures

J. Ritchie, A. Sykes, P. Weber and S.P. Wren are in paid employment of their respective organizations. The authors are SMR Committee members, for which no remuneration is paid.

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