TIGIT therapy for cancer treatment – TIGITtherapy – ERC

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Impact Objectives

- Test monoclonal antibodies (mAbs) for their ability to antagonise TIGIT activity
- Pave the way for the development of novel immune-related therapies for cancer

Treating tumours with immune-related therapies

__Professor Ofer Mandelboim__ and __Dr Pinchas (Pini) Tsukerman__ discuss how, along with their colleagues __Professor Stipan Jonjic__ and __Paola Kucan Brlic__, they are working on a project that aims to treat tumours with immune-related therapies

Professor Ofer Mandelboim

Dr Pinchas Tsukerman

Professor Stipan Jonjic

Paola Kucan Brlic

In lay terms, what is TIGIT and why is it important from a therapeutic standpoint?

OM: TIGIT is an important inhibitory receptor of immune cells. This means that cancer cells that express TIGIT ligands on their surface may suppress immune cells, which otherwise can lead to the cancer cell eradication. Our monoclonal antibody (mAb) blocks TIGIT and restores activity of immune cells that are vital for fighting cancer, such as NK and T cells. Moreover, combining anti-TIGIT mAbs with additional mAbs against other immune inhibitory molecules, such as PD-1 or CTLA4, results in an overall effect that is better than that achieved by each mAb on its own. This makes our mAb a good candidate to also improve existing anti-cancer treatments.

Could you describe the goal of the ongoing TIGIT therapy project?

PT: We hope that our mAb will become a marketed anti-cancer drug, with a significant impact on the treatment and curing of cancer patients, either as a single agent or in combination with other drugs.

How is the TIGIT therapy project progressing at present? Which milestones have been achieved and which remain to be accomplished?

OM: Our mAb went through a thorough *in vitro* characterisation. The main pre-clinical challenge that remains is to establish a suitable *in vivo* model for our mAb. As the antibody is highly specific for human TIGIT, humanised mice models are required. In these models, the specific interaction between the human tumour cells and the human immune cells may be assessed. However, others have studied anti-murine TIGIT mAbs *in vivo*, and provided evidence for the therapeutic potential of blocking this target.

What have been the main challenges faced by the research team over the course of this project?

PT: To efficiently assess the impact of the anti-TIGIT mAb, complex models are required. In particular, we had to resolve the issue of generating a polyclonal T cells response toward allogeneic tumour cell lines. We invested a lot of time and efforts in optimising the conditions for these co-culture assays, which eventually allowed us to efficiently test our mAb of interest.

Could you introduce Nectin Therapeutics Ltd and its background?

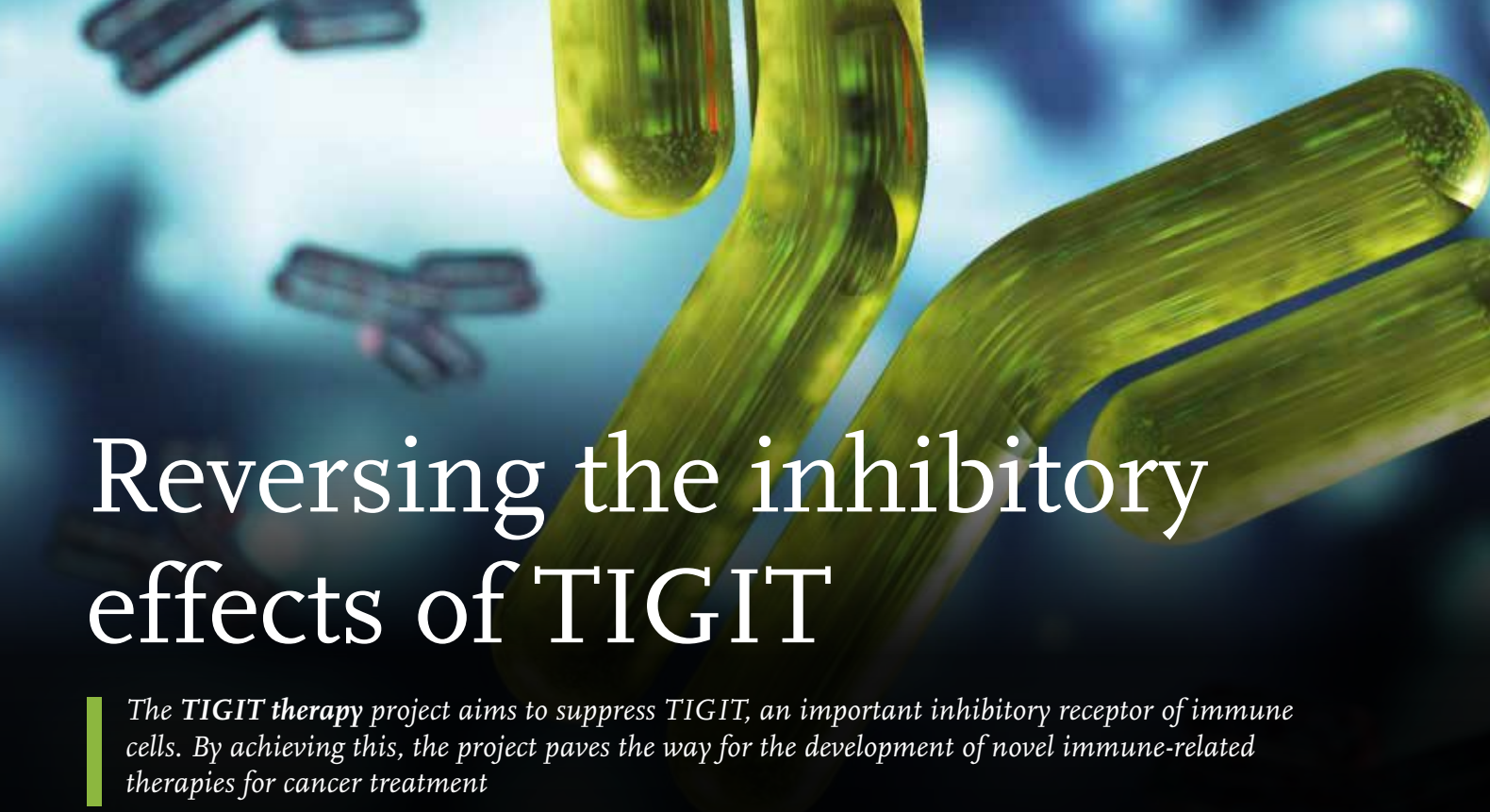
PT: Nectin Therapeutics is a start-up company that is dedicated to the development of next-generation immuno-oncology antibodies. It was established by Integra Holdings in 2017. Nectin therapeutics' antibodies are based on the discoveries and inventions made by Professor Ofer Mandelboim from the Immunology & Cancer Research Center at the Hebrew University and Professor Stipan Jonjic from the Department of Histology and Embryology/Center for Proteomics, Faculty of Medicine, University of Rijeka. Integra Holdings and Yissum (the Technology Transfer Unit of the Hebrew University of Jerusalem) are the key shareholders.

Do you have any advice you would like to give to other academics who might be considering starting a spin-off company?

OM: I would say one of the most important considerations is ensuring that you recruit people with experience in the pharmaceutical world. A strong and experienced industrial partner is always a good thing to have.

Ultimately, what challenges remain to be overcome if this research is to be translated into real-world therapeutic applications?

PT: Like any other drug found at pre-clinical stages of development, our mAb will have to go through all formal clinical phases and demonstrate good efficacy combined with acceptable toxicity in patients. ▶



Reversing the inhibitory effects of TIGIT

*The **TIGIT therapy** project aims to suppress TIGIT, an important inhibitory receptor of immune cells. By achieving this, the project paves the way for the development of novel immune-related therapies for cancer treatment*

Cancer is a broad term that denotes a wide range of related diseases that can begin almost anywhere in the human body. In lay terms, the word 'cancer' refers to a breakdown in the process by which new cells take the place of dead cells. When there is a problem in this process, old and damaged cells can survive when they should die, and new cells can form when they are not needed. When these additional cells begin to divide without stopping, they can form growths known as tumours.

Cancer is the cause of significant societal and economic burden. According to the World Health Organization, it is the second leading cause of death globally, with almost one in every six deaths attributed to the disease. For this reason, scientists from around the world continue to perform research that looks at new methods of treating and curing cancer.

THE PROMISE OF IMMUNE ONCOLOGY

One avenue of investigation in recent years has been immune oncology, which encourages the human body to make use of its natural defences to combat cancer. The activation of immune cells against tumours is seen to be an extremely promising approach, as it allows the efficient eradication of existing tumour cells through the generation of long-term protective immune memory. Moreover, unlike common oncologic treatments, immune activation is associated with targeted effects and lower toxicity, and may lead to extremely long recurrence-free events due to the generation of this protective memory.

As such, it is hardly surprising that the immune oncology market is expanding rapidly. In 2015, sales figures for just three commercially available monoclonal antibodies (mAbs) – Yervoy, Keytruda and Opdivo – exceeded US $2.5 billion. What is more, this figure is projected to rise to more than $15 billion by 2020. In total, the global immune oncology market is expected to grow to $34 billion over the next decade.

However, if immune oncology is to achieve its full potential, certain challenges must still be overcome. Specifically, the tumour microenvironment is highly immunosuppressive, containing inhibition mechanisms that can be used by cancer cells against the body's immune cells. Immune-related therapies aim to remove these obstacles and allow our natural defence mechanisms to fight cancer.

OVERCOMING IMMUNOSUPPRESSION

One project aiming to activate the immune system against cancer is TIGIT therapy. It originated at the labs of Professor Ofer Mandelboim from the Immunology and Cancer Research Center at the Hebrew University of Jerusalem, and Professor Stipan Jonjic from the Department of Histology and Embryology/Center for Proteomics, Faculty of Medicine, University of Rijeka.

In 2009, Mandelboim and his colleagues became the first research group to identify the direct inhibitory function of TIGIT and its major role in the inhibition of NK cells. Identifying this contributed to providing the rationale for the development of anti-TIGIT mAbs to block this inhibitory function. 'Novel immune oncology antibodies aim to reverse immunosuppression to allow the immune cells to fight cancer,' explains Mandelboim. 'The existing immunotherapy includes mAbs targeting PD-1, PD-L1 and CTLA4, with a vast number of additional targets being developed.'

ANTI-TIGIT mAbs

The team has ascertained that TIGIT is constitutively expressed by a variety of immune cells and is increased further on tumour infiltrating lymphocytes (TILs). In addition, TIGIT recognises two main ligands, PVR and Nectin-2, that are highly expressed on various tumours. The team's project so far has discovered that the blocking of TIGIT on TILs, either alone or in combination with another checkpoint inhibitory receptor, PD-1, leads to an increase in T and NK cell activity *in vitro*.

Already, the team has succeeded in developing an anti-TIGIT mAb. 'We have a highly potent anti-TIGIT mAb which is reversing all inhibitory effects of TIGIT,' explains Mandelboim. 'Biochemical data set its affinity at the pM range, and more importantly, our mAb is effectively activating T and NK cells from a wide range of donors and against a variety of target cells from different tumours.'

While this mAb is still in the pre-clinical stages of development, it shows remarkable promise. Ultimately, the researchers hope to market it as an anti-cancer drug, either as a single agent or in combination with

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other drugs. Of course, much more research and clinical testing are required if this novel therapy is to be approved. However, based on the results obtained so far, the researchers are confident that their drug has the potential to contribute to a world where humans can make use of their own immune systems to attack cancerous cells.

NECTIN THERAPEUTICS

Nectin Therapeutics is a start-up company dedicated to the development of next-generation immuno-oncology antibodies. One of its key focal points is centred around the fact that the human immune system is capable of eradicating tumours, and that novel antibodies may release its cancer-induced inhibition and maximise this potential

Nectin Therapeutics was established by Integra Holdings in 2017. The antibodies that the company develop are based on work performed by Professors Ofer Mandelboim and Stipan Jonjic. With investment from the Hebrew University of Jerusalem and Integra Holdings, Nectin Therapeutics develops antibodies that block the inhibition mechanisms that are used by cancer cells against the body's natural immune cells.

The team's goal in developing these mAbs is to boost the activity of immune cells against tumours and ultimately eliminate cancer. Excitingly, the first generation of antibodies that block immune checkpoint targets was recently introduced to clinical usage and changed the field of cancer therapy. However, many patients are unable to benefit from these developments and it is therefore essential that additional antibodies are developed to block other immune checkpoint molecules.

With that in mind, Nectin Therapeutics is developing novel mAbs directed towards members of the Nectin family of receptors and ligands. These receptors and ligands play major roles in the mechanisms of immune checkpoints, which makes them valid targets in the development of anti-cancer antibodies. Ultimately, the team hopes to develop novel antibodies to treat both solid and haematological malignancies.

To find out more about the work that Nectin Therapeutics do, visit: http://www.nectintx.com/

Project Insights

FUNDING
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Hebrew University of Jerusalem (Israel) • University of Rijeka, Faculty of Medicine (Croatia) • Nectin Therapeutics (Israel)

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BIOS

Professor Ofer Mandelboim is a Principal Investigator and a Professor at the Hebrew University of Jerusalem. There, he leads a research laboratory and serves as the head of both the Lautenberg Center for General and Tumor Immunology and the Department of Immunology and Cancer Research.

Professor Stipan Jonjic is a Principal Investigator and a Professor in the Faculty of Medicine at the University of Rijeka in Croatia, where he also serves as the Chairman of the Department for Histology and Embryology and the Chair of the Center for Proteomics.

Dr Pinchas (Pini) Tsukerman is Chief Scientific Officer at Nectin Therapeutics. He received his PhD from the Hebrew University of Jerusalem in the Mandelboim Laboratory.