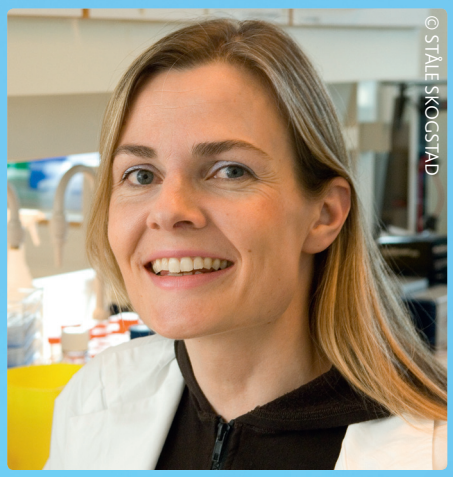
Time for T

Professor Johanna Olweus leads a research group currently using a radical approach to investigate the potential of donor-derived T cells to target and kill cancer cells, with groundbreaking results

PROFESSOR JOHANNA OLWEUS



Could you begin with a summary of your primary objectives within the Immunotherapy and Antigen Presentation Group?

The aim of our work is to develop new immunotherapy of cancer. Specifically, we identify and isolate T cells that kill tumour cells without harming healthy tissues. Studies have shown that T cells can be infused into patients to eradicate cancer. However, it is difficult to obtain effective T cells from the patients themselves. We have therefore taken a radically new approach. It has been known for decades that every individual has T cells that can kill cells from other individuals. This is why transplants are rejected. Our results show that some of these T cells are very selective in their killing. For example, we have obtained T cells that only kill B-lymphocytes. We will infuse such cells into patients with B cell lymphoma and determine whether they attack the tumour. In principle, the same approach can also be tailored to treat a number of other tumour types.

Who are the co-workers within the group, and how did you select them?

I am fortunate to lead a group of highly skilled and dedicated people. They come from India, China, Italy, Switzerland, Sri Lanka and Norway, and many have scientific experience from the U.S. Since many of our experiments are complex and high-tech, we depend strongly on our senior molecular biologists, T cell culture experts and protein chemists. Having said that, some of the most talented and inspiring people I have worked with had little or no scientific training when they came to the lab. We also have a mix of people with PhD and MD backgrounds to support the translational aspect.

Could you explain how T cells from a donor can recognise and kill patient cancer cells? Why are the T cells potent in this setting whereas they are inefficient in cancer vaccines?

The reason is that every person has a large number of T cells that can recognise the cells from another individual as foreign, due to individual differences in protein sequences and in tissue type molecules. In allogeneic hematopoietic stem cell transplantation, the patient receives bone marrow stem cells from a healthy donor. What is not so well known is that T cells transferred in the graft may be equally important as the stem cells for curing the patient. The problem is that allogeneic hematopoietic stem cell transplantation is dangerous, as not only leukaemia/lymphoma cells are recognised and killed, but frequently also various normal cells in the patient. This may cause so-called graft-versus-host disease, which, in the worst cases, may kill the patient. This is where our research is focused: to identify and isolate donor-derived T cells that attack and kill only cancer cells.

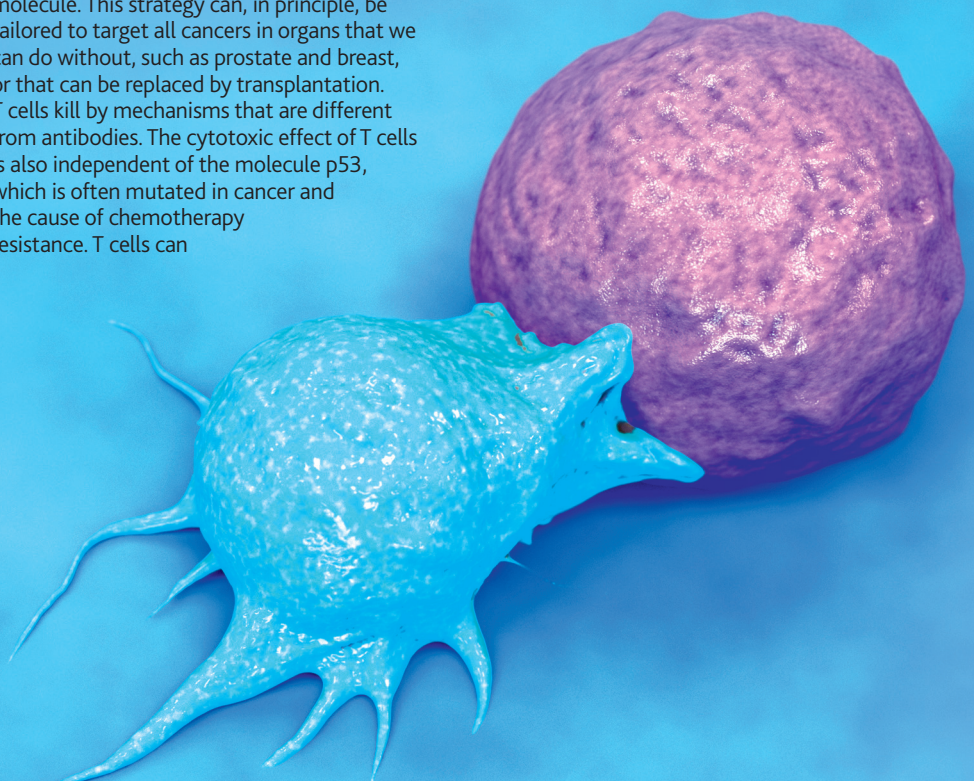
Our findings show that it is possible to identify and isolate T cells that kill cancer cells from patients with various types of leukaemia and lymphoma efficiently and specifically. We have demonstrated that T cells can be directed at various cell type specific proteins, in a similar way as therapeutic antibodies. The trick is to direct the T cells to a cell-type specific peptide in the context of a foreign tissue type molecule. This strategy can, in principle, be tailored to target all cancers in organs that we can do without, such as prostate and breast, or that can be replaced by transplantation. T cells kill by mechanisms that are different from antibodies. The cytotoxic effect of T cells is also independent of the molecule p53, which is often mutated in cancer and the cause of chemotherapy resistance. T cells can therefore complement, and act in synergy with, other cancer therapeutics.

How much work have you been able to conduct to forge partnerships with industry and complete the circle from bench to bedside?

We are working on a commercialisation strategy in collaboration with the technology transfer office of Oslo University Hospital and the University of Oslo, Inven2. We are patent-protecting our technology to allow for business development, which is a goal for the group in the future.

What is next for the group?

We have a large number of projects that we are excited about, ranging from basic molecular studies on T cell receptor biology, to planning our first clinical protocol. On the basic side, we have identified a number of novel T cell targets in leukaemia cells that are promising therapeutic targets, and we will next verify these results on cancer cells derived from patients. We are further developing our technology for production of soluble T cell receptors for cancer therapy. And we are planning our first clinical trial, infusing T cells that specifically kill B cells, for treatment of lymphoma patients.



Down to a T

The **Immunotherapy and Antigen Presentation Group** at Oslo University Hospital in Norway is conducting pioneering research into immune cells, generating recombinant T cell receptors that recognise cancer cells to create therapeutics that act as a fantastic weapon against cancer

ALTHOUGH STANDARD CANCER treatment such as irradiation and chemotherapy is effective for many cancer types, it is unselective. Thus, all cells that divide rapidly are damaged, and not just the cancer cells. Consequently, the corresponding side effects limit therapeutic intensity. In contrast, the human immune system is highly selective when it eradicates virus-infected cells. Long before the mechanisms were known, vaccines were made that could protect people and animals against serious infectious diseases – one of the greatest successes in medical history.

The aim of therapeutic vaccination, on the other hand, is different. Rather than preventing disease, the aim has been to stimulate the patient´s immune system to kill cancer cells that already have established a tumour. In spite of a large number of clinical trials over the last decades, therapeutic vaccination is still regarded as experimental therapy. The problem is that the majority of tumour-associated antigens are also present on normal cells. As T cells that react strongly with our own tissue are removed during development to protect us against autoimmunity, this is the likely explanation for why most cancer vaccination trials have failed thus far.

Yet another mechanism falls into place: altered proteins caused by mutations in the cancer cells may not be recognised as foreign and dangerous, because cancer – as opposed to infection – does not cause much inflammation. The immune system deletes the T cells that could do the job of removing the cancer cells if they are not activated by inflammation. Again, these are mechanisms that normally protect us from developing autoimmune disease, such as multiple sclerosis and rheumatoid arthritis.

TRICKING THE IMMUNE SYSTEM

In a different approach, the Immunotherapy and Antigen Presentation Group led by Professor Johanna Olweus at Oslo University Hospital in Norway is now utilising the unsurpassed specificity of T cells to create novel therapeutics for cancer. Their aim is to generate recombinant T cell receptors that recognise cancer cells: "If we could trick the immune system to kill cancer cells as efficiently and specifically as it kills for instance virally infected cells, this would represent a fantastic new weapon against cancer," Olweus postulates.

Olweus' group's work involves generating efficient immune responses outside the patient that are transferred to the patient. They are using an innovative strategy to select T cells that kill specific cell types. Cell type-specific T cells are generated by exposing normal T cells to a foreign HLA molecule complexed with a peptide from a cell type-restricted protein. The T cells will effectively be tricked to 'believe' that the cell-type specific peptide is actually foreign in this new context, like a viral peptide.

The Olweus group has successfully demonstrated that such T cells from healthy individuals efficiently and selectively kill patient-derived cancer cells. Rather than searching for rare cancer-specific proteins, research can now target cell-type specific proteins. Since normal cells of the same origin as the cancer cells will also be killed, this approach could be used to treat cancers in tissues that are dispensable to the host, such as ovary and prostate, or replaceable by transplantation, such as bone marrow, liver and kidney.

TREATING CANCER PATIENTS

Essentially, the scientific approach of the Olweus group is to use mechanisms of transplant rejection in a therapeutic manner.

SOLUBLE TCR IS INTERNALISED UPON BINDING TO CELLS

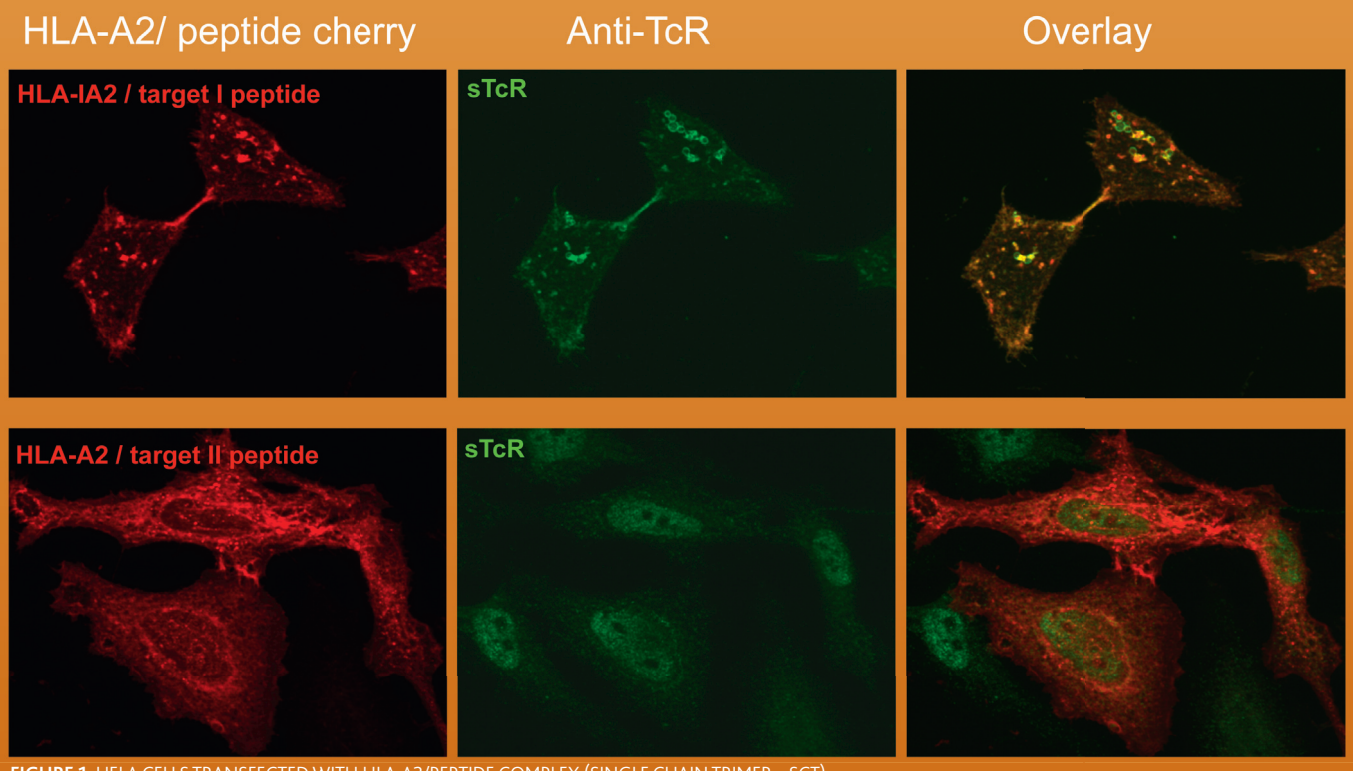


FIGURE 1. HELA CELLS TRANSFECTED WITH HLA-A2/PEPTIDE COMPLEX (SINGLE CHAIN TRIMER – SCT) INCUBATED WITH STCR SUP FOR 2H @ 37°, FIXED AND STAINED WITH ANTI-TCR

IMMUNOTHERAPY AND ANTIGEN PRESENTATION GROUP

OBJECTIVES

The aim of the group is to develop new immunotherapy of cancer. The team has developed technology that allows them to identify and isolate T cells that efficiently kill specific tumour cells without harming healthy tissues. T cells can specifically recognise cancer cells via their T cell receptor. The goal is to use the T cells, or their T cell receptors, to design new immunotherapeutic strategies.

KEY COLLABORATORS

Arne Kolstad, MD, PhD, Specialist in Oncology, Senior Consultant, Deptpartment of Oncology, Oslo University Hospital (OUS) Radiumhospitalet • **Fridtjof Lund-Johansen, MD, PhD**, Senior scientist/group leader, Institute of Immunology, OUS Rikshospitalet • **Kjetil Taskén, MD, PhD, Professor**, Director Biotechnology Centre of Oslo and Centre for Molecular Medicine Norway, Nordic EMBL Partnership • **Ton Schumacher, PhD, Professor**, Head Division of Immunology, The Netherlands Cancer Institute (NKI) • **Harlan Robins, PhD**, Fred Hutchinson Cancer Research Center, Seattle, USA, and founder of Adaptive TCR technologies

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JOHANNA OLWEUS got her MD degree in 1992, and PhD degree in 1998, at the University of Bergen, Norway. Between these events she worked as a scientist at Becton Dickinson, California, for almost five years. In parallel with a residency as an MD in immunology and transfusion medicine (specialist in 2006), she built up a research group at Oslo University Hospital. In 2008, she was appointed Head of Department of Immunology, Institute for Cancer Research at Oslo University Hospital Radiumhospitalet, and Professor at the University of Oslo.

Oslo universitetssykehus

THE IMMUNOTHERAPY AND ANTIGEN PRESENTATION GROUP

"The idea came as I worked as a resident in the immunology department of a transplantation hospital," recalls Olweus. "In the hospital setting you are directly exposed to clinical problems, and I think this is an important inspiration to explore new options. However, I doubt that I would have thought about the therapeutic potential in transplant rejection without my background from basic research."

Currently, the therapeutic use of T cells requires individual preparation for each patient; isolation of donor-derived T cells for infusion into patients requires expertise and facilities that are only available in the large university hospitals. Olweus believes that the treatment could be made more generic: "A T cell attaches specifically to the cancer cell via the T cell receptor. The genetic code for the T cell receptor can be isolated. Thus, a more generic therapeutic approach that still requires high technological competence, is the genetic transfer of cancer-targeted T cell receptors to patient T cells," she explains.

Professor Steven Rosenberg's group at the U.S. National Cancer Institute in Maryland has already tested this approach successfully in melanoma patients. As Olweus' group has now identified a number of T cell receptors targeted to other cancer types, this strategy provides an attractive option. Yet another promising alternative, for which they won the Innovation award 2011 for the University of Oslo and Oslo University Hospital and the South-Eastern Norway Regional Health Authority, is to use soluble T cell receptors. When coupled to toxic or radioactive substances, they can potentially be administered as soluble and generic therapeutic agents. In principle, they can be applied to all patients with the tissue type molecule HLA-A2, which is expressed in 50 per cent of Caucasians.

Olweus is hopeful about the future for a more personalised, tailored approach to cancer treatment: Olweus believes that personalised medicine will be increasingly used in the near future owing to rapidly developing technologies such as deep sequencing, which allows the genetic profile of tumours to be characterised. This approach can be utilised to identify known genetic aberrations for which there is already a treatment today. "Importantly, it can also be used to discover novel targets for therapy, such as immunotherapy," she adds.

INSPIRING GROUNDBREAKING RESEARCH

The Olweus Group's identification and isolation of T cells that efficiently kill cancer cells from patients by recognition of cell-type specific peptides has been a major breakthrough. Another key result for Olweus was the demonstration of, down to the molecular level, that T cells recognising cells from another individual can be as specific as T cells recognising for instance viral peptides: "These results bear great promise that such T cells can be equally successful at eradicating cancer as virus-specific T cells are at eradicating chicken pox or the flu".

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In collaboration with oncologists at Oslo University Hospital, Olweus and her group are now designing clinical trials. They will benefit from the hospital facilities, which are amongst the best for GMP cell production for therapy in Northern Europe, and from excellent clinicians with longstanding experience in conducting investigator initiated phase I/II trials, combined with basic research training. Olweus is passionate about her work at the hospital: "I cannot think of a better and more inspiring environment for someone involved in biomedical research," she smiles. "I have also been fortunate to get to know the families of some exceptional young men and women who died from leukaemia. To see how these families are working to improve the lives of others in the same situation has been a great inspiration for my work."