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Immunotherapy: the rocky road to clinical application

Hans-Georg Rammensee has one major goal: he wants to contribute to the successful application of immunotherapy in clinical settings and is convinced that this will only be possible once individualised immunotherapies are used. Individualised immunotherapy refers to the induction of a specific immune response against specific tumour-associated antigens. Rammensee has made major progress in this area and is now focused on overcoming the obstacles on the rocky road to obtaining the authorisation for producing the substances required and for carrying out clinical trials.

Therapeutic vaccination: Prof. Dr. Hans-Georg Rammensee hopes to bring cancer immunotherapy to clinical application
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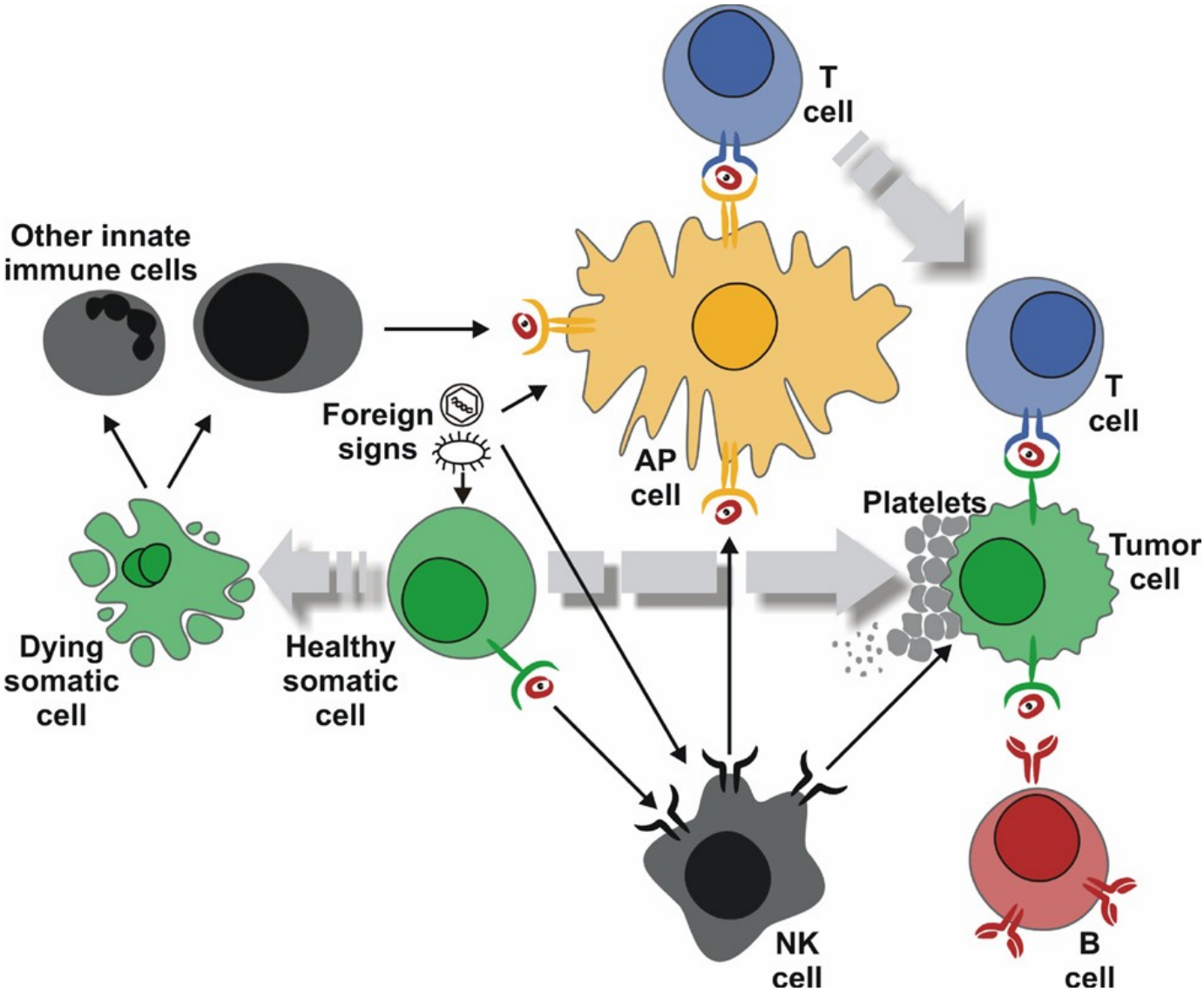
In July 2010, Tübingen University Hospital and the medical faculty of the University of Tübingen

officially opened their new GMP research building. Approximately 430 square metres would then have become available for the production of peptides and antibodies for patient- and tumour-specific therapeutics, with emphasis on the word "would" – the rooms and the staff for GMP compliant peptide and antibody production are available, and only a few minor additions to the interior of the building are still required. "We are working in the new laboratories, but we cannot start production as we have not yet been granted the authorisation to do so," said Prof. Dr. Hans-Georg Rammensee from the Interfaculty Institute for Cell Biology in Tübingen.

The immunologist has focused for many decades on the development of immunotherapies for the treatment of cancer. Tumour cells present structures on the surface of cells that are different from those of healthy, non-mutated cells. These structures can be identified and synthetic copies, i.e. peptides, for injecting into patients can be produced relatively easily. The synthetic peptides are a kind of vaccination that prompts the patient's immune system to recognise structures that only occur on the cells of specific tumours. Recognition of the tumour cell structures then triggers a signalling chain that causes the patient's immune system cells to destroy the tumour cells.

Therapeutic vaccination helps the body to correct itself



The molecular and cellular interactions of an antigen-presenting cell (AP cell) are highly complex.
© Prof. H.-G. Rammensee, SFB685

Numerous studies have shown that this concept actually works. The first, although not yet entirely successful, active immunotherapy has been authorised for patient application in the USA. The companies immatics biotechnologies GmbH and CureVac GmbH, University of Tübingen start-ups, have initiated the clinical testing of improved therapies. In the meantime, Rammensee and his team of scientists are focusing on the broad application of immunotherapies for cancer treatment. Studies that are normally required before the marketing authorisation for new therapies can be obtained are very expensive. However, this is not Rammensee's major concern. "Industrial or other profit-oriented investors are not interested in financing the development of individual therapies that have no potential to become the major revenue driver of conventional pharmaceutical companies. Public funding or funds from foundations can be used to cover the cost of our studies if we are then able to produce our peptide drugs at a relatively low cost in own GMP laboratories."

Rammensee's team is hoping to identify between 10 and 15 of a total of around 80 to 100 tumour-specific surface peptides that have the potential to be the best targets for immunotherapies. "In order to do this, we are using bioinformatic methods that we have developed ourselves," said Rammensee. Peptides purchased from a specialist manufacturer cost around 150,000 euros per peptide and patient. And this is difficult to finance. "However, we will be able to produce peptides for around 5,000 euros in the new GMP laboratories that have been financed by the Baden-Württemberg government and the University Hospital of Tübingen (UKT). And we will be able to do

this more quickly," said Rammensee pointing out that such advantages tend to convince investors. "We have also received financial support from the German Ministry of Education and Research as they have realised that carrying out science-driven clinical studies at the University Hospital is a worthwhile endeavour. A few years ago, German Cancer Aid established a professorship for experimental immunotherapy in Rammensee's department to pursue another strategy, namely passive immunotherapy with optimised antibodies.

The hospital as one-stop shop: the production and application of drugs

So the question arises as to why the green light has not yet been given for the production of immunotherapeutics. "Up until 2004, universities and university hospitals were able to carry out studies with compounds that fulfilled certain prerequisites and that were rated as appropriate by the treating physicians following evaluation of the immunotherapeutic drugs. This is no longer possible. The legislative framework has changed and much stricter regulations have been put in place," said Rammensee who does not in any way wish to criticise the regulations. The only thing he would wish to see is that therapeutics and therapies are not all lumped together in the same regulations. "The German Drug Law (AMG) has the same requirements for pain killers for virtually healthy people as it does for therapeutics for severely ill brain tumour patients. I don't think this is justified. The law should be amended by adding a paragraph that facilitates the production of substances for use in early clinical trials in at least some cases."

The German Drug Law should be amended and adapted to new therapies

From laboratory bench to clinical settings: the newly constructed GMP building at the University of Tübingen is suitable for the production of antibodies for clinical pilot studies according to GMP standards. The GMP unit can produce antibodies of industrial quality and quantity: "Disposable technology" refers to upstream fermentation (photo at the top) and downstream purification (photo at the bottom) using disposable materials.

Rammensee is well acquainted with the odyssey of applying for manufacturing authorisation. In 2008, Rammensee's team submitted an application for the production of immune vaccines, and the application was refused due to a number of formalities. After a lot of hard work they were eventually able to solve the major problems and a new application was submitted in March 2010. The team then received another list of flaws and worked on the resolution of the problems. The team has since moved on to the extent that Rammensee is confident that they will soon be granted the authorisation to produce medicinal drugs and this will be quickly followed by the authorisation to produce peptides and antibodies according to AMG.

Rammensee nevertheless criticises the system. "Take our cleanrooms for example. Much stricter regulations apply to cleanrooms than to operating theatres," said Rammensee who believes that the reason for this is historical. "The experts who created the German Drug Law were not able to foresee new therapies and the associated requirements. Of course, we are well aware that the regulations are right for the processes for which they were put in place." Rammensee and his team are determined to bring immunotherapies to clinical application despite all the difficulties they are facing. And they also hope that the dialogue with legislative authorities will make it possible to adapt existing laws more quickly to fundamental innovations.

Further information:
University of Tübingen
Interfaculty Institute for Cell Biology
Dept. of Immunology
Prof. Dr. Hans-Georg Rammensee
Auf der Morgenstelle 15
D-72076 Tübingen
Tel.: +49 (0)7071 2980991
E-mail: rammensee(at)uni-tuebingen.de

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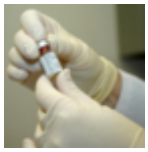

Boosting the immune system can improve cancer prevention and treatment