ASK THE EXPERTS

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Injecting hope into brain cancer treatment: is immunotherapy the way forward?

Pierre-Yves Dietrich*: Pierre-Yves Dietrich is a Full Professor of Medicine at the University of Geneva (Geneva, Switzerland) and Director of the Centre of Oncology in the Geneva University Hospital (Geneva, Switzerland). Since the early 1990s, his clinical and research activities have focused on the interplay between cancer and the immune system. He founded the Laboratory of Tumor Immunology in the Geneva University Hospital in 1994 and investigated mouse brain tumor models as well as human gliomas to firmly establish the existence of antiglioma immunity, a concept that was being debated at the time owing to

the special immune status of the brain. Dietrich then embarked upon translating these conceptual advances into glioma immunotherapy. This challenge involved identifying novel targets on the surface of glioma cells *in vivo*, an essential step in designing an efficacious vaccine. Thanks to a fruitful collaboration with Immatix (Tübingen, Germany), a spin-off from the University of Tübingen (Germany), this work led to the identification of ten novel glioma-associated antigens with high expression on tumor cells and faint or absent expression on normal tissues, an indispensable feature to avoid autoimmunity. This crucial advance allowed the initiation of clinical trials of peptide vaccination in patients with gliomas as well as the development of T-cell therapy.

What led you to work in the field of neuro-oncology & not other fields?

There are several reasons. Being a medical oncologist involved in the management of several cancer types, I am impressed by the fact that patients with brain tumors and their families face not only a frequently lethal cancer, but also a disease profoundly affecting the most essential human properties. How distressing it is to see your loved ones becoming disabled, with difficulties in walking, speaking and writing, or with major memory or behavior problems. An additional reason for focusing my research in the field of neuro-oncology was that 25 years ago there was

an absence of any efficient treatment, as well as the corresponding scientific and human challenges.

Congratulations on being awarded Cancer Researcher of the Year for 2013. What are you most proud of?

Cancer cells are derived from normal cells, and, thus, most tumor antigens are self-antigens. Therefore, there is a theoretical risk that tumor immunotherapy will unleash an uncontrolled and damaging immune reaction against normal tissues (i.e., autoimmunity). The clinical relevance of this danger is minimal for some tissue (e.g., prostate), moderate for others

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(e.g., skin) and critical for the brain. For 15 years, my research group has explored several ways to identify glioma antigens with exclusive or preferential expression by tumor cells, and we finally succeeded thanks to a fruitful collaboration with Immatics (Tübingen, Germany), a spin-off from the University of Tübingen (Tübingen, Germany). This now paves the way for the clinical development of vaccines and T-cell therapies targeting some of those newly discovered glioma antigens. I am very proud of my research team. I am very grateful to each of them for their scientific excellence and their solidarity, with a specific thanks to Paul R Walker and Valérie Dutoit.

You currently work on tumor immunology. What do you feel is the most promising immunotherapy treatment for brain tumors? Are we getting closer to delivering cytotoxic drugs efficiently using antibodies?

This is impossible to predict, however, the enemy is strong and subtle and we should probably attack glioma with different and complementary immune strategies, including multiepitopic vaccines, T-cell therapy, immune checkpoint blockade and by preparing the glioma microenvironment (e.g., depleting Tregs). The synergy of new treatments with current treatments (chemotherapy and irradiation) should also be further explored. With regards to cytotoxic drugs, I am impressed by the results recently obtained with such immunoconjugates for breast cancers or Hodgkin's lymphoma. In the case of tumors located in the brain, the main challenge that remains is how to allow the diffusion of big molecules through the brain parenchyma as well as designing small-sized antibody-like molecules.

What do you feel is the biggest hurdle in the world of tumor immunology/immunotherapy?

There are so many, however, the main obstacle remains the intrinsic nature of cancers with tumor heterogeneity and huge genetic instability. This means that we have several enemies with chameleon properties

to fight. A second major challenge is to get efficient immune-based treatments whilst minimizing side effects. Until now, therapeutic successes (e.g., T-cell therapies with engineered T-cell receptors or chimeric antigen receptors) are invariably accompanied by toxicity, with the possible recent exception of molecules controlling certain immune checkpoints.

A research team recently demonstrated glioblastoma development within a nervous tissue that was engineered *in vitro*. What exciting developments will this bring to the field?

This is the work of Olivier Preynat-Seauve. This *in vitro* model recapitulates several features of the relationships between glioma and its microenvironment. Since gliomas rarely metastasize outside the CNS, this model could be used to explore the mechanisms of tissue invasion by glioma, with the potential to identify druggable targets to counteract this phenomenon, which is the main origin of the therapeutic failures of surgery and radiotherapy. More generally, the model can be used to study the tumor–host tissue interaction. It may also serve as a preclinical tool for the screening of new compounds or innovative radiotherapy.

What is the biggest advancement you have observed while working in the field of CNS oncology? What are you most excited to work on in the future? How do you foresee the field progressing in the next 5 years? What major challenges need to be faced?

Temozolomide has changed daily practice. Before the era of temozolomide, there was no real hope for 'long-term' survival. This hope is still low, but does exist, and is making a major difference for patients and their families. In addition, the success of temozolomide gave the important message to the scientific community that gliomas are not always indestructible adversaries, leading to an unprecedented wave of research in this field. We are now at a stage where we can explore some hypotheses in clinical trials. This is exciting after 20 years of bench

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work. For the future, we need to persevere to break down the boundaries between science and medicine, between public and private research, in order to combine different immune-based strategies (the beginning of polyimmunotherapy), and to explore the synergy of immunotherapy with chemotherapy and/or radiotherapy. More importantly, we have to not rush to clinical trials without continuing thorough concomitant research. Our knowledge is still very superficial and any success will need several rounds of research between the bench and bedside.

Disclaimer

The opinions expressed in this article are those of the interviewee and do not necessarily reflect the views of Future Medicine Ltd.

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