Speaker Insight

THERAPEUTICS FOR TUMOURS EXPRESSING MEMBRANE HSP70

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Graham Pockley is the CEO of multimmune GmbH. multimmune's unique and proprietary technology platform is based on the discovery (by Gabriele Multhoff and Claus Botzler) that a cell surface bound form of Hp70 is selectively, and widely expressed on on the plasma membranes of many tumour entities and is developing innovative theranostics on the basis of this cell surface-expressed form of Hsp70.

Graham Pockley is also Professor of Immunobiology and Associate Director of the John van Geest Cancer Research Centre (JvGCRC) at Nottingham Trent University. The JvGCRC uses integrated genomic, proteomic, immunological and bioinformatics platforms to identify biomarkers of disease and disease progression, predict therapeutic responses and develop diagnostic and immunotherapeutics. Programmes study the orchestration of innate and adaptive immunity in cancer, discover immunological and protein biomarkers of disease and therapeutic responsiveness, and its findings inform the development and delivery of new diagnostic and immunotherapeutic strategies.

For over 100 years, scientists and clinicians have been trying to eradicate cancer using highly toxic chemicals (chemotherapies), radiation and/or surgery. Although these approaches can control and eradicate disease in many patients, severe side-effects are common. Although progress in the diagnosis of cancer and in the development of new cancer therapeutics for the majority of tumour entities progresses at a pace, key challenges in the identification, management and treatment of aggressive disease remain, with 90% of cancer-related deaths being attributed to metastatic disease. Despite significant progress, the considerable amount of time and money which has been invested in cancer research has only resulted in incremental improvements in the treatment of many cancers, with limited success in some.

Significant improvements in the treatment, quality of life and survival of patients with cancer are therefore critically dependent on addressing the challenges posed by these aggressive forms of the disease. Traditional reductionist study methods which, at best, identify and target single or small numbers of molecules have a limited capacity to address the complexity or heterogeneity of disease in a single patient. Another big challenge relates to the time and cost of drug development, and thereby the ability of the healthcare providers to afford the therapeutics that are developed.

The identification of more "universal" targeting structures that are present across different cancer entities has the potential to consolidate the costs of developing therapies during the pre-clinical and early clinical phases. One such biomarker is a membrane form of the 70 kDa heat shock (stress) protein which has been shown to be selectively expressed on cancer cells by Professor Gabriele Multhoff using a unique monoclonal antibody (cmHsp70.1).

Subsequent and ongoing studies interrogating the expression of membrane Hsp70 by cancer cell lines and viable cells isolated from different tumours have revealed that membrane Hsp70 is most frequently expressed on a variety of different tumor types, including lung, colon, breast, head and neck, stomach, pancreas carcinomas, malignant melanoma and haematological diseases, but never on the corresponding normal tissues. Membrane Hsp70 is particularly highly expressed in glioblastoma multiforme and metastases.

Based on its discovery of membrane Hsp70, multimmune has succeeded in developing a powerful product, termed ENKASTIM, which allows, for the first time, a unique and specific activation of human natural killer (NK) cells which are programmed to recognize and kill cancers expressing membrane Hsp70 via the release of a cytotoxic molecule called granzyme B. These cells destroy tumors and metastases that are invisible to the cell killing (cytolytic) consequences of more conventional T cell-based immunotherapies. The concept of using *ex vivo* activated natural killer (NK) cells as a therapeutic approach for the treatment of non small cell lung carcinoma is currently being assessed in a multicenter, randomized trial in Germany. The data arising from this clinical trial will support the acquisition of financing to support the next phase of its clinical development.

Hsp70-expressing tumors can also be targeted using a unique monoclonal antibody which can detect the membrane form of Hsp70 (mi-TUMEXtx, pre-clinical stage) and a human recombinant form of a serine protease (granzyme B, mi-APO, pre-clinical stage) which can selectively kill cancer cells expressing the membrane form of Hsp70 (see www.multimmune.com for more details).

The identification of a single molecule which is widely expressed by cancers, and the expression of which is enhanced by conventional therapy (membrane Hsp70), has provided an exciting platform on which to develop an innovative toolbox of cancer theranostics and drug delivery platforms. Although the term has already been used in several settings, one could consider membrane Hsp70 as being the 'Swiss Army Knife' of cancer therapeutics - one therapy, multiple indications