T cell bispecific antibody for the immune-mediated killing of HER2+ breast cancer cells

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The engineered bispecific antibody targets p95HER2 (blue fragment), which is unique to malignant breast cancer cells (brown). The antibody can therefore guide T cells (blue cells) to cancer cells without attacking healthy breast epithelial cells (pink). Credit: Vall d'Hebron Institute of Oncology (VHIO)

Not so long ago, immunotherapy against cancer was positioned as an emerging or even promising treatment, but not one with a proven track record. Today however, novel immunotherapeutics across different tumor types, either as mono therapy or in combination, are increasingly

becoming one of the most innovative and powerful anti-cancer strategies.

One of the major challenges in ensuring that these novel treatments realize their true potential has been successfully equipping the immune system to launch its attack exclusively on tumour cells excluding all healthy tissues. Up until now.

Research led by Joaquín Arribas, Director of Preclinical Research at the Vall d'Hebron Institute of Oncology (VHIO), ICREA Professor, and Scientific Director of the Center for the Biomedical Research Network in Oncology (CIBERONC), has turned this obstacle into a therapeutic opportunity.

Published in *Science Translational Medicine*, the study, first co-authored by Irene Rius-Ruiz, Graduate Student of VHIO's Growth Factors Group, reveals that p95HER2-T cell bispecific antibody (TCB) can successfully guide immune cells, known as lymphocytes, directly to cancerous cells for their targeted killing.

This direct delivery is achieved thanks to the p95HER2 protein, which is only located in tumor cells. Representing a new therapeutic avenue and fresh hope for patients who have ceased to respond to current therapies, this novel immune-based approach can be used to tackle certain HER2+ breast cancers through its exclusive targeting of cancerous cells.

p95HER2-TCB: guiding the immune system for the targeted killing of HER2-positive breast cancer cells

T cell bispecific antibodies constitute a promising approach in harnessing the immune system to mount its anti-cancer response, and represent an increasingly valuable addition to the current arsenal against cancer. Not only are they highly specific but they can also hone in on

one protein among tens of thousands, in this particular case, p95HER2.

Furthermore, each antibody molecule has a bipartite structure containing two protein-binding sites. This means that they can simultaneously attach to immune cells and cancerous ones as well as take the lymphocytes hand-in-hand directly to the malignant cells for their subsequent destruction.

Acting as a magnet that lures the patient's immune system solely to tumor cells, p95HER2-TCB enables a targeted response by attacking these cells directly without affecting normal cells. "The immune system has the natural capacity to fight against disseminated disease. To do so more effectively, it must be better equipped to recognize and act against malignant cells. While bispecific antibodies are designed to do just that, they often signpost T cells to healthy ones," explains Joaquín Arribas, corresponding author of the study.

He continues, "Thanks to the distinct specificity of p95HER2-TCB and p95HER2's exclusive location in tumor cells, we have achieved a 'home delivery' of immune-based therapy. Our findings represent an important step towards ensuring that the immune system can successfully deliver its powerful anti-cancer blows."

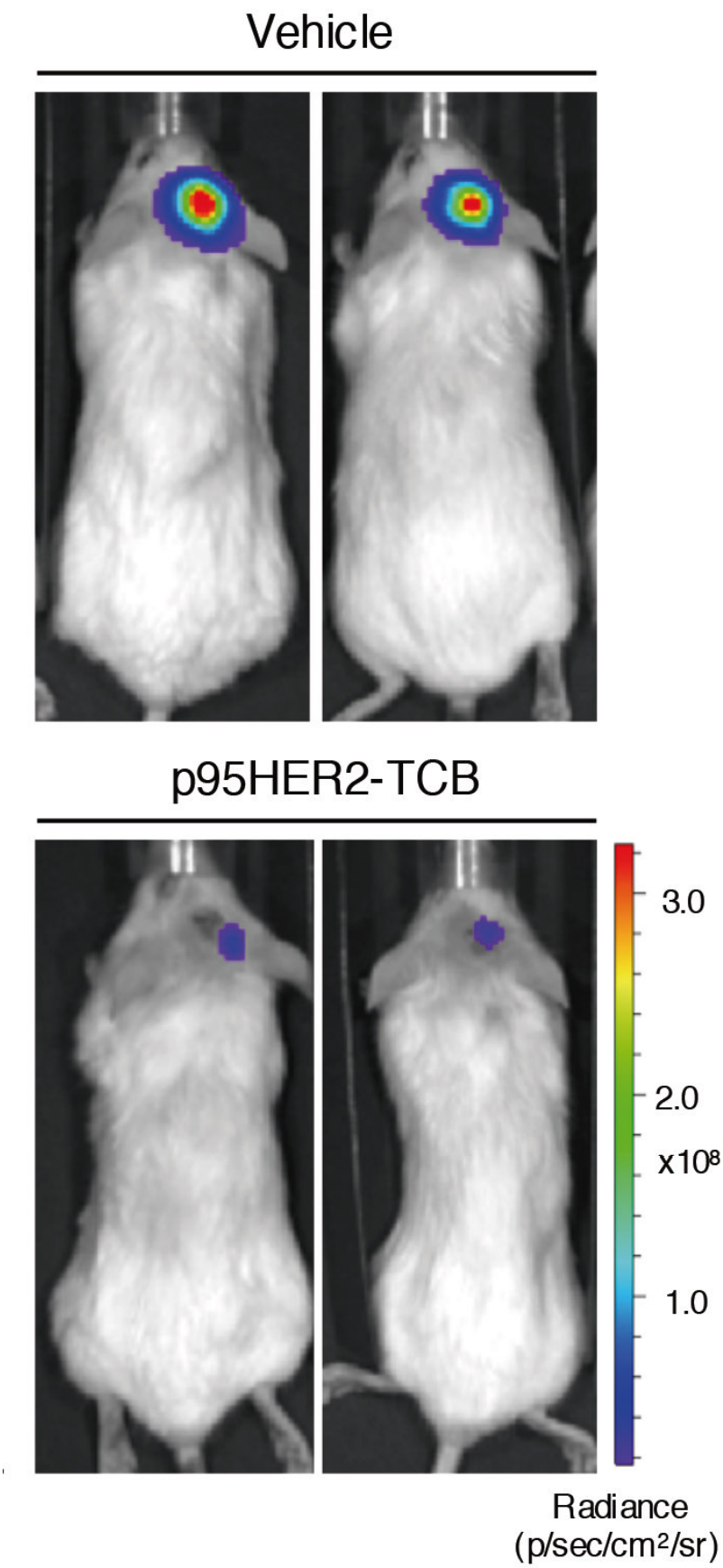
Immunotherapies for cancer are proving increasingly more effective in the treatment of metastatic disease. Generally, advanced and metastatic cancers eventually develop resistance to different lines of therapies. When patients eventually cease to respond to current therapies, leading to cancer cell spread, they have few therapeutic options available.

While the immune system represents powerful weaponry in thwarting the spread of disease, it can only effectively do so by recognizing and launching its attack on malignant cells. "The real added value of our findings is that the bispecific antibody, p95HER2-TCB, directs

lymphocytes exclusively to tumour cells harboring p95HER2," observes Irene Rius Ruiz, first author of the study.

Approximately 10% of patients with HER2-positive breast cancers expressing p95HER2 could stand to benefit from this novel strategy.

"While our approach can only be extended to a relatively small subset of patients with HER2-positive disease, for those who stand to gain, the benefits could be significant. By more precisely matching novel therapy to a particular patient population, we are getting closer to delivering on the true promise of precision medicine in oncology," says Irene Rius Ruiz.


Vehicle
p95HER2-TCB
3.0
2.0
x10⁸
1.0
Radiance
(p/sec/cm²/sr)

Treatment with the T cell bispecific antibody (TCB) for the p95HER2 fragment reduced tumor growth (colored sections) in mouse models of HER2-positive breast cancer. Credit: I. Rius Ruiz et al., Science Translational Medicine (2018)

These findings are the fruit of a decade of research at VHIO, beginning with Joaquín Arribas' group's identification of the p95HER2 protein, which was initially used as a biomarker to identify a subgroup of patients with HER2-positive breast cancer who no longer responded to standard therapies.

Their later discovery that this protein only resides on the surface of tumour cells as opposed to healthy cells led to the development of a specific targeted therapy.

As a leading reference in advancing modelling systems, VHIO is dedicated to delivering the predictive data required to reliably inform the clinical development of innovative agents and evidence reproducibility before moving to the clinic.

VHIO's Growth Factors Group focuses on more accurately modeling anti-tumor immunotherapy strategies and has generated humanized patient-derived xenograft models (Hu PDXs), in which the human immune system is established in immunodeficient mice. These experimental models have been invaluable in validating the efficacy of the p95HER2-T cell bispecific antibody.

Having now completed the pre-clinical phase of development, Arribas' team will seek to advance the therapy so that it can be administered in humans for investigation in clinical trials. Next steps will also include

developing additional therapies against p95HER2 such as antibody-drug conjugates or chimeric antigen receptors (CARs).

"These future treatments will likely be as effective and safe as p95HER2-TCB. We are confident that our findings will enable the exclusive targeting of malignant cells by different means through p95HER2," concludes Joaquín Arribas.

Reflective of VHIO's purely multidisciplinary and translational research model, several of its preclinical, translational and clinical groups, along with colleagues belonging to CIBERONC, have collaborated in this research.

The project has also relied on the participation of other physician-scientists and oncology professionals of the Vall d´Hebron University Hospital and within the Vall d´Hebron Barcelona Hospital Campus.

More information: I. Rius Ruiz el al., "p95HER2–T cell bispecific antibody for breast cancer treatment," *Science Translational Medicine* (2018). stm.sciencemag.org/lookup/doi/ … scitranslmed.aat1445

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