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Towards the improvement of targeted cancer therapy: antitumor nanoparticles with dual functionality

Cancer treatment through targeted therapy continues to advance. The idea is to have drugs whose mechanism of action focuses directly on diseased cells and avoids damaging healthy cells. Protein engineering creates nanoparticles with toxic activity and others that carry the drug. The Nanobiotechnology group of the Institute of Biotechnology and Biomedicine, in collaboration with the Oncogenesis and Antitumoral Group of the Institut de recerca de l'Hospital de la Santa Creu i Sant Pau, has managed to develop stable nanoparticles that carry this double functionality in the same entity: toxin and drug. Although research is still required to achieve greater precision, the results open a window to a wide field of research for the design of tumor-targeted drugs.

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The major drawback of conventional anticancer treatments using pharmaceuticals (chemotherapy) is that they promote damage in cells and organs that are not affected by the disease. Because of this, the development of tumor-targeted therapies represents an opportunity to selectively destroy tumoral cells without causing off-side effects in the rest of the body.

To this end, our group of Nanobiotechnology (NBT) from the Institut de Biotecnologia i Biomedicina (IBB-UAB), in close collaboration with the group of Oncogènesi i Antitumorals (GOA) from the Institut de recerca de l'Hospital de la Santa Creu i Sant Pau (IIB-Sant Pau), is working to develop a new concept of pharmaceuticals based on protein nanoparticles. These drugs are selective for metastatic stem cells (those responsible of cancer propagation, recurrence and bad prognosis) that overexpress in their surface the CXCR4 receptor, present in 23 distinct types of cancer.

This research is conducted in the frame of the Director plan of CIBER-BBN, an excellence center from the *Instituto de Salud Carlos III*, to which both groups belong. Using a precise protein engineering, the group generates multi-functional protein nanoparticles that remain in the bloodstream for a long time and selectively enter and destroy metastatic stem cells, thus contributing to stop cancer progression. In the last years, two main strategies have been employed in the development of antitumoral protein nanoparticles. On one side, toxins, venoms or other death-inducer proteins have been introduced in the original targeted-protein design, conferring the product an antitumoral intrinsic activity. On the other side, current chemotherapeutics, already used in clinics in non-targeted approaches, have been chemically linked to inert targeted nanoparticles, directing their effect to the tumor. Both strategies are covered by intellectual property rights.

Recently, we have proposed the possibility of combining both strategies and have generated intrinsically toxic nanoparticles loaded with conventional chemotherapeutics in a single pharmacological entity. This way, we seek to potentiate their antitumoral effect and face the appearance of resistances in the tumor. In this initial step, the concept proposed has been demonstrated as fully feasible, as stable nanoparticles that contain both the toxin and the loaded chemotherapeutics were generated, though their toxic effect did not improve in CXCR4+ tumor cell lines. Nevertheless, thanks to this research, the main bottleneck of the technology has been identified. A precise control of drug binding site is needed to maintain the antitumoral capacity of targeted toxins, which act at the same time as active principle and anchoring site for chemical drugs.

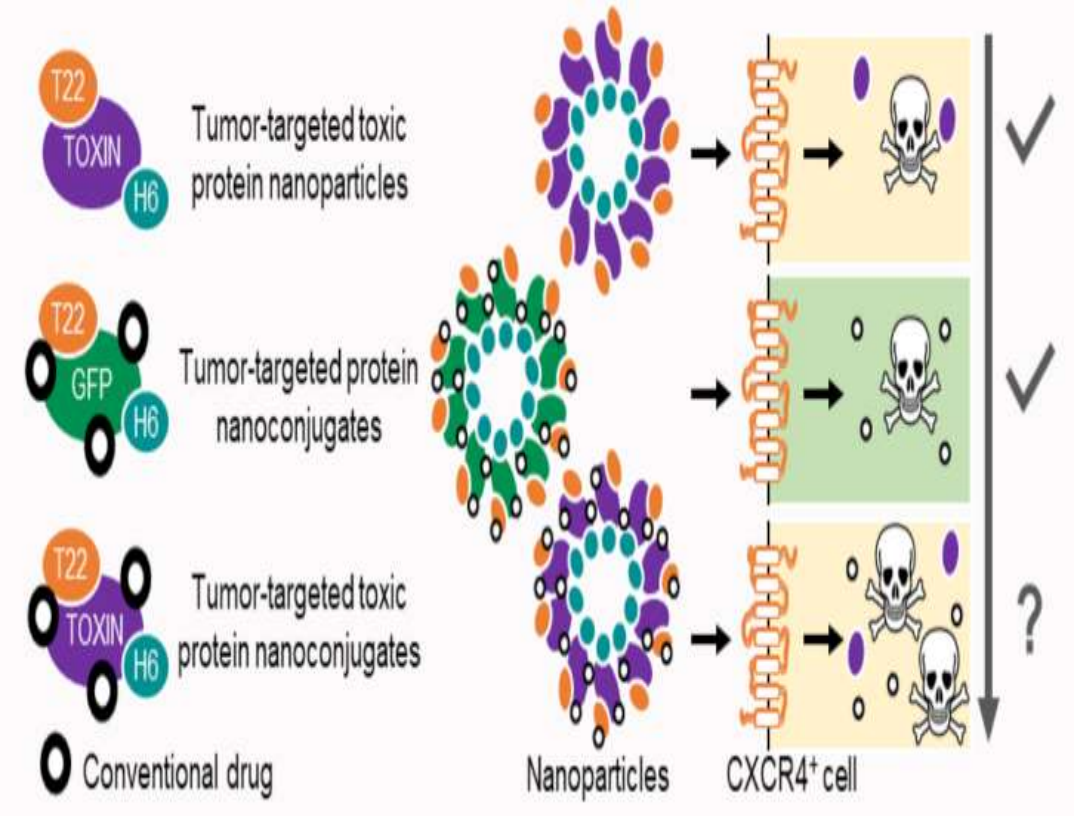

Figure 1 *Mechanism of action of antitumor nanoparticles.*

This novel platform, that recruits in a single pharmacological entity different therapeutic actions may open a broad investigation field in the design of antitumoral drugs.

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