Modular Nanopore Immunotoxins

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Immunotoxins are proteins containing a monoclonal antibodies paired with a cytotoxic element that used to target cancer cells. These agents, however, are chemically heterogeneous, difficult to prepare and, because of their large size, cannot efficiently be internalized into cells.[1] Here, we present a modular approach to prepare immunotoxins, in which a nanobody against tumour-associated antigens is coupled to an oligomeric pore-forming toxin. The targeting element can be easily exchanged allowing selecting multiple targets, while the pore-forming toxin does not require internalization. To prevent off-target activity, the transmembrane N-terminal domain of the toxin is linked to a protein domain to inhibit pore formation.
The pore-forming toxin was cytolysin A (ClyA) from *Salmonella typhi*, which was genetically fused to a nanobody against epidermal growth factor receptor (EGFR). EGFR is overexpressed in breast cancer [2]. The activity of the immunotoxin was tested on the model cancer cell line A431, overexpressing EGFR. Fusion to the nanobody increases toxicity of ClyA against the cancer cell line, while addition of the natural ligand EGF reverses the effect and reduces toxicity. The experiments show that it is a promising system for further investigation to increase selectivity even more to develop new anti-cancer drugs.

References

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