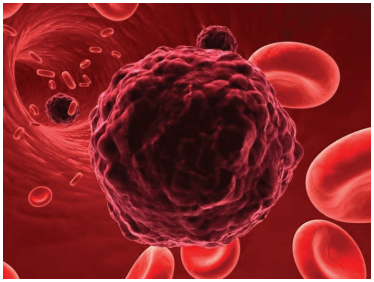
| | |
|---|---|
| Research (What is it about?) | **Targeted toxins** |
| UNN authors | *Deyev S.M., Sokolova, E.A., Balalaeva I.V.* |
| We find (The result) | We produce a new ***recombinant*** tumor-targeting toxin based on the non-immunoglobulin scaffold which possesses a strong selective cytotoxic effect in vitro and a potent antitumor activity in vivo |
| Abstract | Contemporary chemotherapeutic agents used to treat cancer are powerful, but toxic for normal tissues. To overcome this obstacle, a new approach for drug delivery, called targeted therapy, has been developed. This therapy is based on the idea of a "target", the molecule that is present on a cancer cell surface but is absent on the surface of a normal cell thus allowing selective recognition and elimination of cancer cells by a target specific agent. It is more common to use quantitative differences in the expression level of target molecules in cancer and normal cells to achieve selectivity. The use of antibodies as tumor-targeting moieties is associated with a number of difficulties, such as a low level of tissue penetration. Non-immunoglobulin scaffold proteins such as DARPins are expected to have much better tissue penetration and higher clearance than antibodies recognizing the same protein targets when administered in vivo.<br>Human epidermal growth factor receptor HER2 belongs to a family receptors that are involved in the regulation of cell growth. When overexpressed, HER2 promotes a constitutive signaling of downstream pathways leading to tumorigenesis.<br>We describe for the first time the use of a high affinity HER2-specific DARPin for generation of a fusion toxin with a truncated variant of *Pseudomonas exotoxin A* (referred as PE40). We show that ***recombinant toxin DARPin-PE40*** exerts specific cytotoxicity against HER2-positive cells *in vitro* and causes their apoptosis.<br>Cytotoxic effect of DARPin-PE40 strongly correlates with the level of the HER2 expression. Treatment of athymic mice with DARPin-PE40 caused a strong and prolonged inhibition of xenograft tumor growth. DARPin-PE40 posesses a potent antitumor activity *in vivo*. |

| | | |
|---|---|---|
| Representative articles 2016-2017, quartiles | 1. *Sokolova E., Proshkina G., Kutova O., Shilova O., Ryabova A., Schulga A., Stremovskiy O., Zdobnova T., Balalaeva I., Deyev S.* Recombinant targeted toxin based on HER2-specific DARPin possesses a strong selective cytotoxic effect in vitro and a potent antitumor activity in vivo. J. Controled Release. **233**, 48-56 (2016). | Q1 |
| | 2. *Sokolova, E.A., Schulga A.A., Stremovskiy O.A., Balalaeva I.V., Proshkina G.M., Deyev S.M.* Production and Functional Characteristics of the Recombinant Targeted Toxin Based on the HER2-Specific Non-Immunoglobulin Scaffold. Biologicheskie membrany. **33**(6), 429-434 (2016). | Q4 |
| | Q-index (Qi) of the result | **2.5** |

| | |
|---|---|
| In collaboration | Russian Acad Sci, Shemyakin Ovchinnikov Inst Bioorgan Chem, Ul Miklukho Maklaya 16-10, Moscow 117997, Russia<br>Natl Res Tomsk Polytech Univ, Pr Lenina 30, Tomsk 634050, Russia |

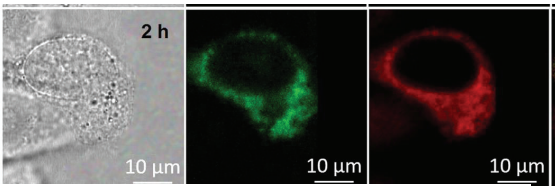


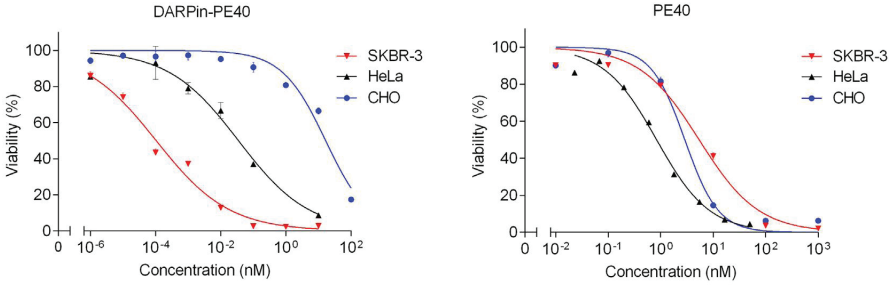
Cancer cell


Design of recombinant targeted toxin DARPin-PE40: DARPin (dark green), HER2-specific DARPin; H (gray), hinge-like linker PE40 (purple), *Pseudomonas exotoxin A*; His6 (light green), C-terminal hexahistidine tag; K (orange).

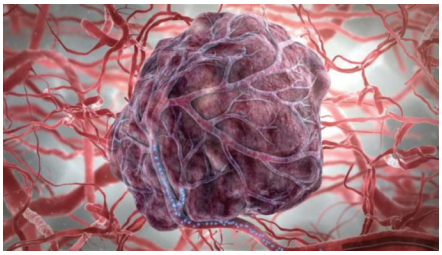
Intracellular localization of DARPin-PE40.

SKBR-3 (human breast adenocarcinoma) cells were stained with organelle dyes (red)

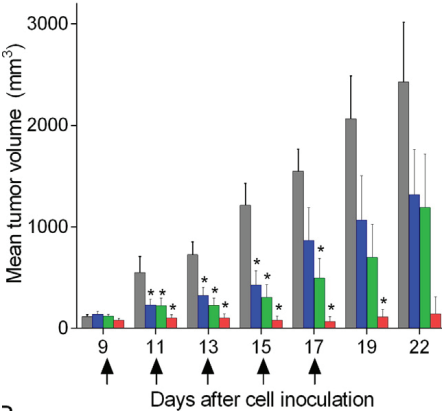



*In vitro* analysis of the DARPin-PE40 cytotoxicity. Relative viability of the ***HER2-positive cells***, SKBR-3 (red line), HeLa (black line) and ***HER2-negative cells***, CHO (blue line) after a 72 h treatment with different concentrations of DARPin-PE40 and PE40 only.



Cancer tumor




Tumor size dynamics for groups of animals with different schemes of treatment by DARPin-PE40 (colors). The day of inoculation of SKBR-3 cells to animals was set as day 0. Treatment started when tumors reached ~100 $mm^3$, the days of injections are indicated with arrows.