Research (What is it about?)	**Controlled consenescence of cancer cells by means of targeting toxins**
UNN authors	*Balalaeva I., Sokolova E., Deyev S., Vodeneev V., Guryev E.*
We find (The result)	The new recombinant proteins that comprise a targeting module and a toxic one (***targeting toxins***) have shown pronounced antitumor effect on cancer cells. The protein passes through retrograde trafficking route and forces cells to enter ***apoptosis***.
Abstract	The basis of targeted therapy is precise elimination of tumor cells in the body while minimizing systemic toxicity. This is achieved through the use of drugs of ***directed action*** that are able to recognize tumor-specific antigens, or targets. We have produced recombinant proteins ***4D5scFv-PE40*** and ***DARPin-PE40*** in which the targeting modules are 4D5scFv antibody or the protein of non-immunoglobulin nature DARPin9_29, while the toxic module is the same one (a highly effective fragment of Pseudomonas exotoxin A) (***PE***). We first clarified the action mechanism of new recombinant proteins that is of particular importance in the case of targeted therapeutic agent aimed at personalized treatment of disease in relation to molecular genetic characteristics of each patient. After specific binding of the protein to the HER2 receptor of the cancer cell, it internalizes via clathrin shell. The internalized protein undergoes both lysosomal degradation and productive trafficking into Golgi apparatus of the cell. In Golgi apparatus the protein binds to the specific receptor (KDEL-R) that mediates the protein retrograde transport into endoplasmic reticulum (ER). Along the transport pathway the separated functionally active PE fragment comes out of ER into the cytoplasm and inhibits protein synthesis there. Protein synthesis inhibition leads to ***apoptosis*** (a sort of "natural consenescence") of cancer cell.

Representative articles 2017-2018, quartiles	1. *Sokolova E., Guryev E., Yudintsev A., Vodeneev V., Deyev S., Balalaeva I.* HER2-specific recombinant immunotoxin 4D5scFv-PE40 passes through retrograde trafficking route and forces cells to enter apoptosis. Oncotarget. **8**(13), 22048-22058 (2017).	Q1, Q2
	2. *Sokolova E.A., Proshkina G.M., Kutova O.M., Balalaeva I.V., Deyev, S.M.* The effect of the targeted recombinant toxin DARPin-PE40 on the dynamics of HER2-positive tumor growth. Acta Naturae. **9**(3), 103-107 (2017).	Q4
	3. *Balalaeva I.V., Sokolova E.A., Puzhikhina A.D., Brilkina A.A., Deyev S.M.* Spheroids of HER2-positive breast adenocarcinoma for studying anticancer immunotoxins in vitro. Acta Naturae. **9**(1), 38-43 (2017).	Q4
	Q-index (Qi) for the result	**1.83**
	high yellow	

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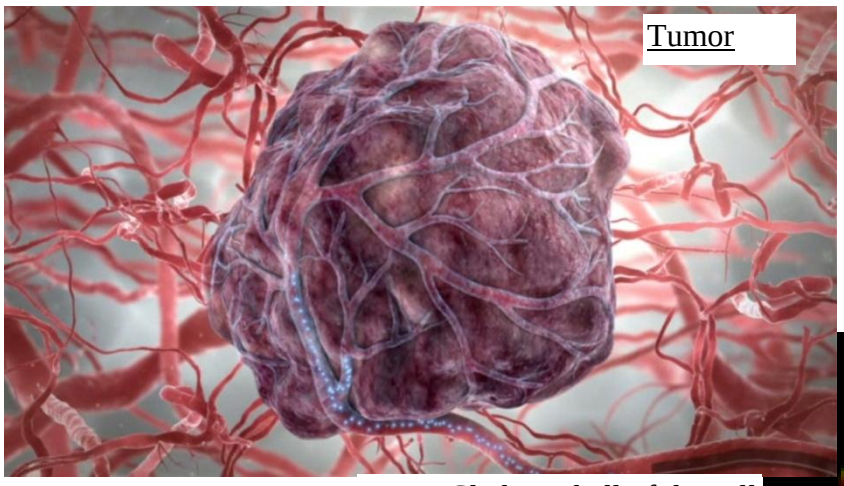
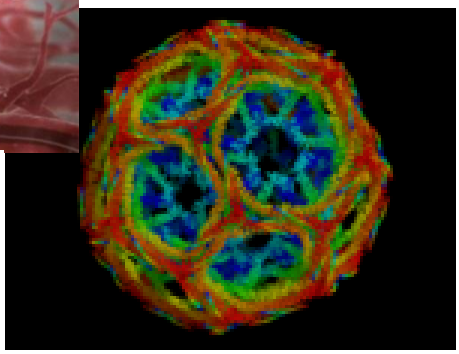
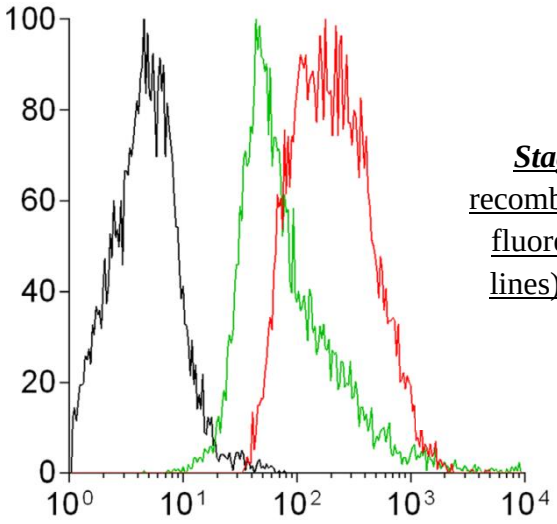
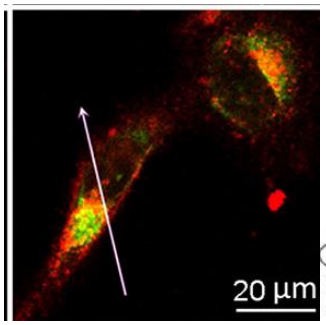




Clathrin shell of the cell

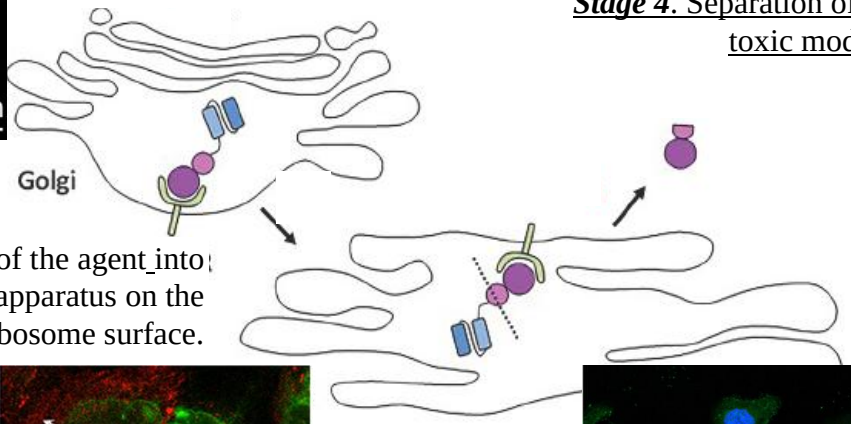


Stage 1. Operation of targeting module to transfer the recombinant protein through clathrin shell (growth of the fluorescent marker concentration) in two options (color lines). Black line corresponds to control cells (targeting module is absent).

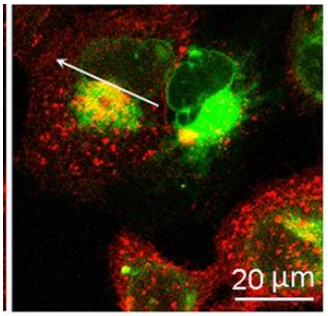


Stage 2. Trafficking of the agent into Golgi apparatus of the cell and binding to the specific receptor (KDEL-R).

Stage 4. Separation of the toxic module.



Stage 3. Embedding of the agent into the protein synthesis apparatus on the ribosome surface.



Stage 5. Inhibiting of protein synthesis. ***Apoptosis*** of cells.