CONJUGATION STRATEGY IN TARGETED ANTI-CANCER THERAPY

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Most targeted cancer therapies use small molecules that inhibit or block key signaling pathways necessary for tumor cell growth or survival. The development of such agents requires in-depth study of tumor cells, oncogenic driver mutations, and signaling pathways, which can vary widely even within the same tumor type. This requires a long time of research and study of prospective drug candidates. Anticancer drugs of a new class – peptide and protein conjugates – are deprived of such shortcomings. In the approach using these conjugates, an active cytotoxic substance is selectively delivered to cancer cells, the mechanism of action of which does not depend on specific oncogenic signaling pathways. The specificity of such drugs is provided by the targeting vector, and not by the pharmacological features of the substance associated with it. After binding to a receptor on the surface of the tumor cell and internalized by receptor-mediated endocytosis, a cytotoxic substance is released that destroys the cancer cell. The drug begins to work only after the destruction of the connection between the components: until this moment, the toxin is in a conjugated form and is not dangerous.

Most drugs used today in medicine can be divided into three main classes: low molecular weight compounds, oligopeptides and proteins. The last two classes include drugs consisting of a sequential chain of amino acids, and the difference between them is only in the size of the molecules: compounds containing up to 50 amino acid residues are classified as oligopeptides, more than fifty – to proteins. Each of these classes has its own advantages and disadvantages. Low molecular weight compounds are quite simple to synthesize, have high stability and biological permeability, however, they often have toxicity and lack selectivity. Oligopeptides have a high selectivity and safety, at the same time, they can rarely be used orally due to low stability and short half-life. The stability of proteins is usually higher than that of peptides, but there is a risk of immunogenicity, and in most cases, these compounds do not easily cross biological membranes.

THERAPEUTIC PROTEINS AND OLIGOPEPTIDES

The era of the use of proteins in medicine began over 100 years ago with the isolation of insulin, a small protein consisting of 51 amino acids. This compound was discovered by Frederick Banting in 1921 and within a year it became available for the treatment of patients with diabetes. The first batches of insulin were isolated from the pancreas of animals: dogs, cattle, and pigs [1]. However, its cost was high, and some patients had an immunological reaction to the drug. These problems were solved when recombinant insulin was developed and approved by the FDA in 1982 [2]. Today, only a small part of therapeutic proteins is still isolated from natural sources; most drugs are produced using recombinant DNA technology [3].

According to the field of application, therapeutic proteins can be classified into the following categories [4]:

- drugs that replace a deficient or abnormally functioning protein (all types of insulin, pramlintide acetate, etc.);
- drugs that enhance the effect of existing drugs;
- drugs that provide a new function or activity (L-asparaginase, streptokinase, etc.);
- drugs that interfere with the action of any molecule (antithymocyte globulin, palivizumab, etc.);
- targeted drugs that deliver other compounds or proteins (Gemtuzumab ozogamicin (Mylotarg)), Ibritumomab tiuxetan (Zevalin));
- vaccines;
- diagnostic preparations.

According to experts, by 2030 the global market for therapeutic proteins will reach approximately 719.94 billion US dollars compared to 366.50 billion in 2021, the average annual growth rate from 2022 to 2030 will be 7.15% [5]. Oligopeptides also hold a significant share of the pharmaceuticals market, with total global sales of over $70 billion in 2019, up more than two-thirds from 2013.

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In the 60s of the last century, chemists for the first time managed to synthesize natural oligopeptide hormones – oxytocin and vasopressin. However, liquid-phase synthesis was extremely laborious, and it took months, and sometimes years, to obtain a compound from 10-15 amino acids. The situation changed in 1963, when Robert Bruce Merrifield developed a method for the synthesis of peptides on a solid matrix – solid phase peptide synthesis [6]. From that moment on, the number of works devoted to the preparation and study of oligopeptides began to grow rapidly. Interest in oligopeptides was due not only to their unique biological properties, but also to the fact that rather simple synthesis on solid resin allowed chemical modifications that changed the activity profile of the compound, as well as improved its stability and bioavailability.

For example, an analog of the natural peptide hormone GLP-1, synthesized by adding an aliphatic fatty acid derivative to a truncated analog of the GLP-1 peptide, not only does not lose its activity, but also has increased stability. This important oligopeptide that regulates the production and secretion of insulin, due to its short life in vivo, has limited applications in medicine. Today, this drug is marketed under the name Victoza (liraglutide) for the treatment of type II diabetes mellitus [7] (Fig.1a).

Another example is the range of 6-8 membered somatostatin analogs, each with its own unique activity and selectivity profile (Fig.1b).

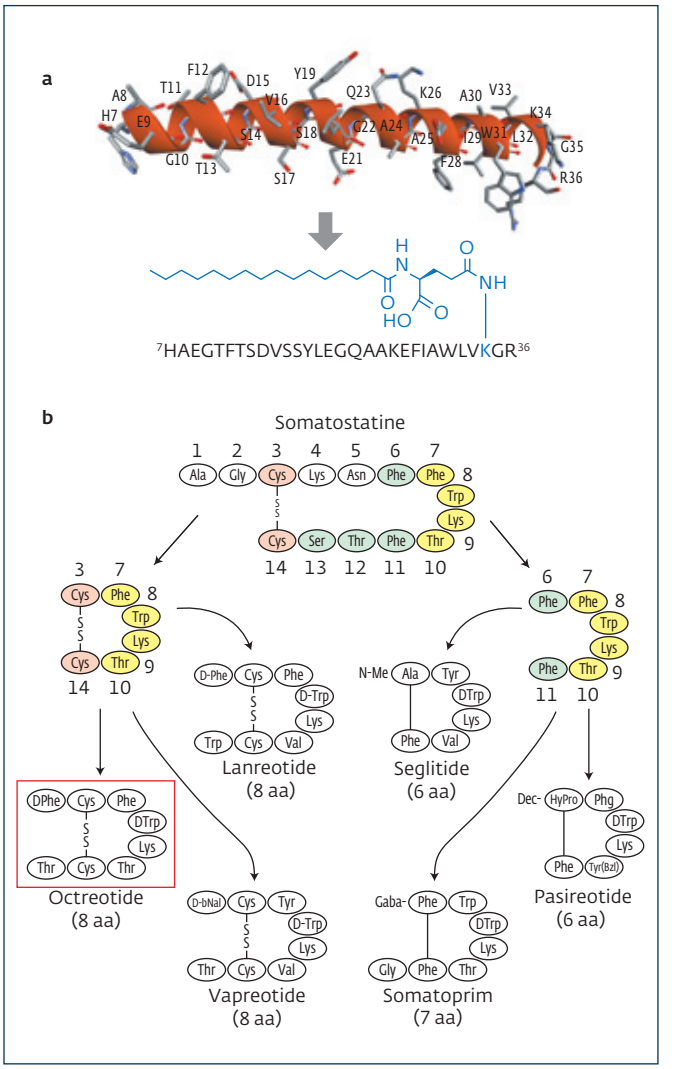

Fig.1. *Examples of modification of oligopeptides leading to a change in their properties: (a) GLP-1, (b) somatostatin*

PEPTIDE AND PROTEIN CONJUGATES FOR TARGETED DRUG DELIVERY

Important properties of proteins and oligopeptides are their high selectivity and low toxicity. At the same time, it is known that the level of some protein and peptide receptors on the surface of tumor cells is many times higher than that on the surface of healthy cells. This feature of cancer cells is used to create conjugates for targeted delivery of anticancer compounds.

Any conjugate consists of three parts: a vector or carrier that delivers the drug to a given target, a "cargo", which is a cytotoxic or other anticancer substance, a transcription factor, or a radionuclide, and a linker that connects these two components (Fig.2). The linker can be cleavable, releasing the "cargo" upon penetration into the cancer cell or tissue, and non-cleavable, releasing the "cargo" only after complete degradation of the vector. Selective cleavage of the linker when it enters the cancer tissue is based on the characteristic features that distinguish the tumor cell from the normal one: abnormally acidic pH, overexpression of certain proteases and other enzymes, as well as glutathione, the oxidative status of the cell, etc.

It is believed that cleavable linkers have advantages in the treatment of solid tumors, while non-cleavable linkers – hematological [9]. Cleavable linkers are valued for their versatility, however they sometimes exhibit off-target toxicity. Non-cleavable linkers are safer and, given their high specificity and low toxicity, can therefore be used to treat hematological tumors. Since at least 99% of cancer cells must be destroyed to achieve cancer remission, the advantages of both types of linkers are used to achieve the optimal therapeutic effect.

The vector delivers the conjugate to and binds to a target on the cell surface, after which internalization usually occurs via receptor-mediated endocytosis, and the release of the "cargo" either by cleavage of the linker or complete degradation of the vector. The specificity of the conjugate is provided precisely by the targeting vector, and not by the mechanism of action of the cytotoxic "load" [10].

ANTIBODY-DRUG CONJUGATES (ADC)

The vast majority of protein-conjugated anticancer compounds contain a monoclonal antibody as a vector. Fig.3 shows a diagram of such a conjugate, in which the site responsible for bind-

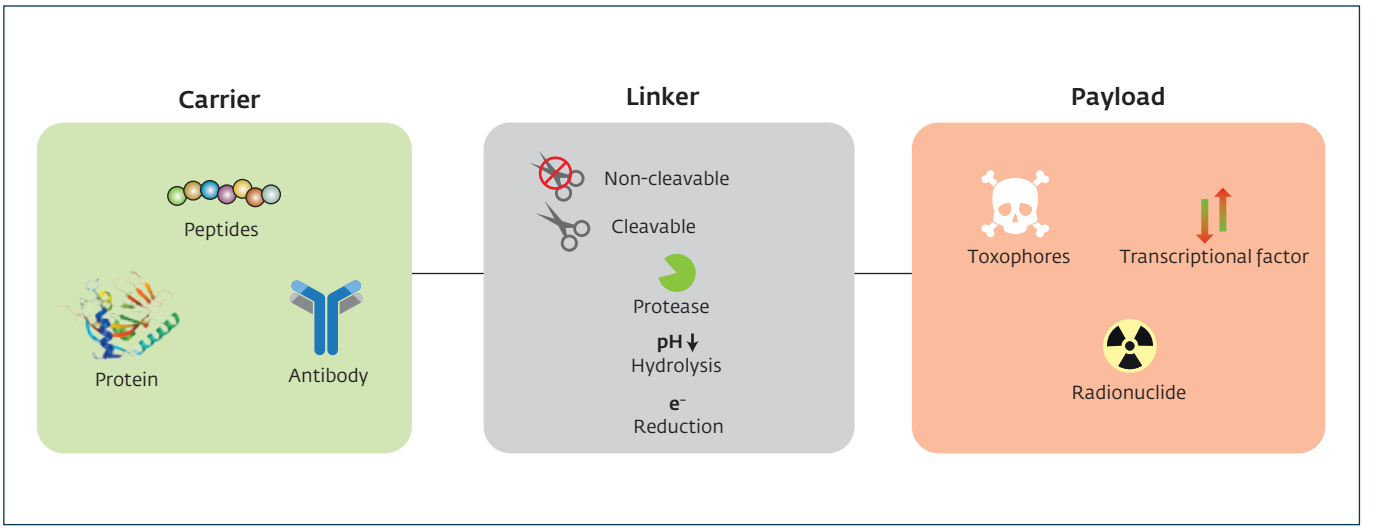

Fig.2. *Schematic representation of the conjugate molecule*

ing to the antigen is spatially removed from the site to which the drug is "sewn", so binding and internalization are not disturbed.

One of the most important aspects of developing an ADC for cancer treatment is the identification of a unique antigenic target for a monoclonal antibody (mAb). The selected antigen must have a number of properties:

- have a high expression in the tumor and no or low expression in a healthy cell
- be located on the surface of the tumor cell to be accessible to circulating mAbs
- have the properties of internalization, ie. allow ADC to enter the cell.

The most commonly used antigens are ERBB2, CD19, CD33, CD22, and MSLN (mesothelin) [11,12].

The first ADC to receive clinical trial approval in 1983 in eight patients with advanced metastatic cancer was an anticarcinoembryonic antibody-vindesine alkaloid conjugate. The results of the study showed the promise of the new approach, the drug was successfully localized in the affected areas, however, whether the conjugate is stable in vivo has not yet been fully clarified [13].

In 2000, the first drug for the treatment of acute myeloid leukemia, Mylotarg (gemtuzumab ozogamicin), was approved, which includes a monoclonal antibody to CD33, expressed in most leukemic blast cells, and ozogamicin, a cytotoxic agent of the calicheamicin class. By November 2022, 14 more ADCs have been approved and several hundred conjugates are in clinical trials (Table 1)[14,15]

PEPTIDE-DRUG CONJUGATES (PDC)

While ADCs have already gained widespread acceptance in clinical practice, peptide-based conjugates are in their early stages of introduction, with only two Novartis patented products receiving FDA approval: Lutathera (2018) and Pluvicto (2022). Both preparations include not a cytotoxic substance, but a radionuclide fragment.

Due to the easier and cheaper method of synthesis, the possibility of varying the amino acid sequence to improve affinity, selectivity or physicochemical properties, and the absence of the risk of immunogenicity, the use of peptides as a vector is more promising than an antibody. Examples of such peptide receptors are the bombesin receptor (BnR) overexpressed in cancers of the lung, prostate, breast, pancreas, colon, etc., the somatostatin receptor (SSTR) in small cell lung cancer, neuroendocrine cancer, prostate cancer, and breast cancer. etc. (Table 2) [16].

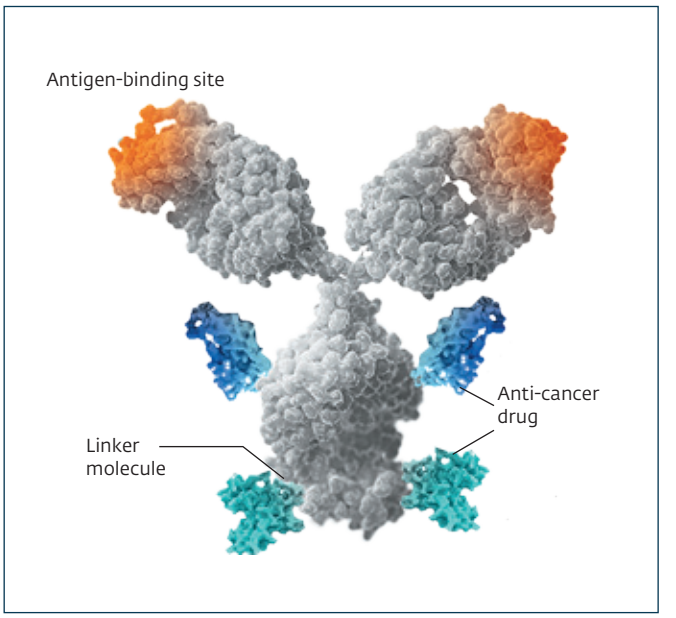

Fig.3. *Antibody-drug conjugate (ADC)*

Table 1. *ADC, approved for clinical use*

Drug	Company	Indication	Payload	Target	Linker	Year
Mirvetuximab soravtansine (ELAHERE)	ImmunoGen	Platinum-Resistant Ovarian Cancer	Maytansinoid DM4	FRα	none	2022
Tisotumab vedotin-tftv (Tivdak)	Seagen Inc	Recurrent or metastatic cervical cancer	MMAE/ auristatin	Tissue factor	enzyme cleavable	2021
Loncastuximab tesirine-lpyl (Zynlonta)	ADC Therapeutics	Large B-cell lymphoma	SG3199/PBD dimer	CD19	enzyme cleavable	2021
Belantamab mafodotin-blmf (Blenrep)	GlaxoSmithKline (GSK)	Relapsed or refractory multiple myeloma	MMAF/ auristatin	BCMA	Non-cleavable	2020, deleted 2022
Sacituzumab govitecan (Trodelvy)	Immunomedics	Metastatic triple-negative breast cancer (mTNBC)	SN-38/ camptothecin	TROP2	acid cleavable	2019
Trastuzumab deruxtecan (Enhertu)	AstraZeneca/ Daiichi Sankyo	Unresectable or metastatic HER2-positive breast cancer	DXd/ camptothecin	HER2	enzyme cleavable	2019
Enfortumab vedotin (Padcev)	Astellas/Seagen Genetics	Locally advanced or metastatic urothelial cancer	MMAE/ auristatin	Nectin4	enzyme cleavable	2019
Polatuzumab vedotin-piiq (Polivy)	Genentech, Roche	Relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL)	MMAE/ auristatin	CD79	enzyme cleavable	2018
Moxetumomab pasudotox (Lumoxiti)	AstraZeneca	Relapsed or refractory hairy cell leukemia (HCL)	PE38 (Pseudomonas exotoxin)	CD22	Cleavable	2018
Inotuzumab ozogamicin (Besponsa)	Pfizer/Wyeth	Relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia	ozogamicin/ calicheamicin	CD22	acid cleavable	2017
Trastuzumab emtansine (Kadcyla)	Genentech, Roche	HER2-positive metastatic breast cancer (mBC)	DM1/ maytansinoid	HER2	Non-cleavable	2013
Brentuximab vedotin (Adcetris)	Seagen Genetics, Millennium/ Takeda	Relapsed HL and relapsed sALCL	MMAE/ auristatin	CD30	enzyme cleavable	2011
Gemtuzumab ozogamicin (Mylotarg)	Pfizer/Wyeth	Relapsed acute myelogenous leukemia (AML)	ozogamicin/ calicheamicin	CD33	acid cleavable	2017, 2000

Table 2. *Peptide receptors overexpressed on the surface of tumor cells*

Peptide receptor	Overexpression in cancer cell type
Bombesin receptor (BnR)	Lung, prostate, breast, pancreatic, head/neck, colon, uterine, ovarian, renal cell, glioblastomas, neuroblastomas, gastrointestinal carcinoids, intestinal carcinoids, bronchial carcinoids
Somatostatin receptors (SSTR), SSTR2 is the most widely distributed	Small cell lung, neuroendocrine tumor, prostate, breast cancer, colorectal carcinoma, gastric cancer, hepatocellular carcinoma
Endothelin receptors (ETR)	Melanoma tissues
Integrins, αVβ3 is the most promising for drug targeting	Activated endothelial and tumor cells, glioblastoma, ovarian cancer
Folate receptors (FR), FRα is the most promising for drug targeting	Most tissues including breast cancer cells
Transferrin receptors (TfR)	Breast, ovarian and brain cancers, including glioma and glioblastomas
Epidermal growth factor receptor (EGFR)	Lung, breast, bladder and ovarian cancers
Fibroblast growth factors (FGFR)	Breast, prostate, bladder and gastric cancer
Sigma receptors (SR)	Non-small cell lung carcinoma, prostate cancer, melanoma and breast cancer
Follicle stimulating hormone receptor (FSHR)	Ovarian surface epithelium
Biotin receptor (BR)	Leukemia
C-type lectin receptor (CLR)	Hepatocytes, dendric cells, macrophages, vascular cells

The first attempts to use peptides to target cancer cells were made in the development of diagnostic rather than therapeutic drugs. In the 1990s, the possibility of radionuclide diagnostics of neuroendocrine tumors and metastases was studied using the radioactively labeled analog of somatostatin ^{111}In-DTPA-octreotide, and the sensitivity of the method exceeded magnetic resonance and computed tomography [17, 18]. The method is called octreotide scanning or somatostatin receptor scintigraphy (SRS). After intravenous injection of the drug into the circulatory system, octreotide selectively binds to somatostatin receptors overexpressed on the surface of tumor cells, and gamma radiation of radioactive indium or technetium-99 gives an image of the tumor and metastasis in the body.

Subsequently, instead of indium-111 and technetium-99, gallium-68 and copper-64 isotopes emitting positrons began to be used, which made it possible to use positron emission tomography for scanning, which provides higher resolution and faster visualization [19].

In the 2000s, clinical studies of radionuclide-conjugated octreotide analogues for the treatment of patients suffering from somatostatin-positive cancers began, using Y-90 and LU-177 as radionuclides, and in 2018 the FDA approved lutetium dotatate Lu 177 (Lutathera®) , for the treatment of adult patients with progressive gastroenteropancreatic neuroendocrine tumors (Fig.4) [20, 21].

A similar approach was used to create a second peptide-based conjugate drug: in March 2022, Pluvicto (^{177}Lu-

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СИМПОЗИУМ ПО ХРОМАТОГРАФИИ, ПОСВЯЩЕННЫЙ 120-ЛЕТИЮ СО ДНЯ ОТКРЫТИЯ ХРОМАТОГРАФИИ М.С.ЦВЕТОМ

ПОДВЕДЕНИЕ ИТОГОВ КОНКУРСА РАБОТ МОЛОДЫХ УЧЕНЫХ ИМ. М.С.ЦВЕТА В ЧЕСТЬ 120-ЛЕТИЯ ОТКРЫТИЯ ХРОМАТОГРАФИИ

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Цель конференции – обмен современными знаниями о физико-химических основах сорбционных процессов и методах разделения на их основе в широком круге исследований, а также расширение профессиональных контактов между учеными научных центров и институтов, студентами и аспирантами профильных вузов, специалистами коммерческих компаний, представителями общественных организаций и государственных структур.

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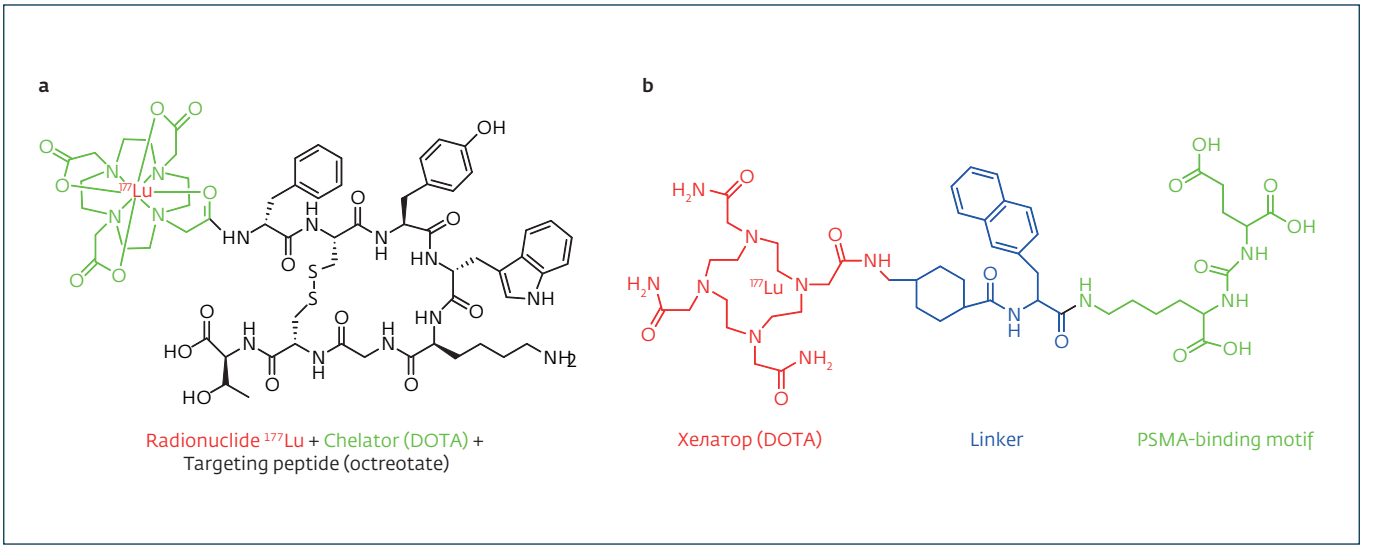

Fig.4. *Peptide-radionuclide conjugates approved for clinical use (a) Lutathers, (b)*

PSMA-617) was approved for the treatment of castration-resistant metastatic prostate cancer. Prostate-specific membrane antigen (PSMA), a type II transmembrane glycoprotein, was chosen as a vector, the expression of which in prostate cancer cells is significantly increased, and the level is closely related to the degree of tumor malignancy and correlates with patient survival [22,23].

Both diagnostic and therapeutic peptide conjugates containing radionuclides do not impose any requirements on the linker, since to achieve the result, only the binding of the drug to the receptor and subsequent internalization into the cell, but not the release of the "cargo", is necessary. In contrast, a cytotoxic drug attached to a vector begins to work only after the connection between the components is broken: until this moment, the drug is in conjugated form and is absolutely safe.

The idea of creating targeted conjugates connecting oligopeptides with a cytotoxic compound belongs to Nobel laureate Andrew V. Schally, in whose laboratory the first such compound, Zoprex-Zoptarelin doxorubicin, containing doxorubicin, was created. The vector was a peptide agonist of the luteinizing hormone releasing hormone (LHRH) receptor, which is overexpressed on the surface in 80% of endothelial and ovarian cancers, 86% of prostate cancers, and 50% of breast cancers. After binding to the receptor and entering the cell, the ester linker connecting doxorubicin to the peptide was cleaved with the participation of esterases, with the formation of a cytotoxic substance that destroys the cancer cell. Phase I studies in patients with prostate cancer demonstrated stabilization of the disease in 90% of subjects. Also promising results were obtained in a phase II study in patients with ovarian cancer. However, Zoprex did not demonstrate convincing efficacy in the next phase of the study and was withdrawn in 2017 [24,25].

Another example of a peptide-drug conjugate is paclitaxel trevatide (NG1005, GRN1005), an experimental chemotherapy drug under development by Angiochem Inc that has shown good results in phase II trials and is being prepared for phase III trials. This drug is intended for the treatment of CNS malignancies, including glioma, and uses as a vector angiopept-2, which targets low-density lipoprotein receptor-1 (LRP1)-associated protein on the surface of brain capillary endothelial cells. The "cargo" is the microtubule polymerization stabilizer paclitaxel, which is linked to the vector by an ester bond. The authors showed that the transport of the conjugate through the blood-brain barrier exceeds the transport of free paclitaxel by more than 100 times [26,27].

In the examples above, the linker connecting the vector and the cytotoxic agent included an ester bond. And although tumor cells contain an excessive amount of specific esterases, there remains the possibility of linker cleavage during its circulation in the circulatory system, both biochemically and chemically. Therefore, work continues to find more stable and specific linkers that will make the use of conjugates safer. For example, an activated carbamate linker has been developed that releases a hydroxyl-containing anticancer drug through intramolecular cyclization. The rate of linker degradation depends on the acidity of the hydroxy group of the toxin and the basicity of the amino group of the side chain of the linker, and can be selected taking into account the rate of internalization and accumulation of the conjugate in the cancer cell [Fig. 5c, 28].

This type of linker has been implemented in the JF-10-81 somatostatin analogue-camptothecin conjugate. It has been

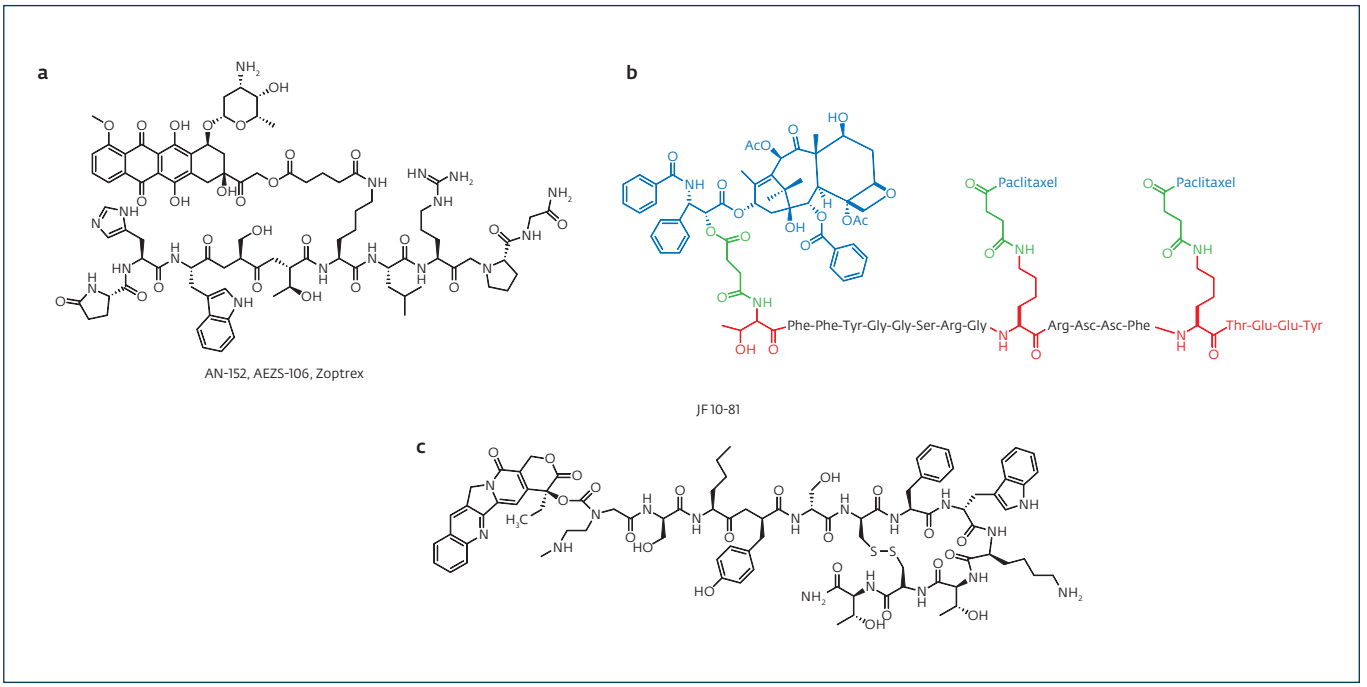

Fig.5. *Peptide–cytotoxic substance conjugates: (a) Zoptarelin doxorubicin, (b) Paclitaxel trevatide, (c) JF-10-81*

demonstrated that cytotoxin attachment does not impair binding and internalization through the somatostatin receptor subtype 2 (SSTR2). JF-10-81 inhibited the growth of human tumors in vitro, including neuroblastoma (IMR32), pancreatic cancer (CFPAC-1), leukemia (MOLT-4), pancreatic carcinoid (BON), and prostate cancer (PC-3). In in vivo experiments, treatment with JF-10-81 resulted in a reduction in tumor size by 87% in animals with IMR32 neuroblastoma and by 97% in animals with MOLT-4 leukemia [29].

* * * *

Chimeric conjugates containing an anticancer drug and a peptide or protein vector are a promising strategy used in the development of targeted therapeutic drugs. Currently, about 14 such conjugates containing specific antibodies and 2 conjugates containing oligopeptides are used in clinical practice. As a result of the targeted delivery of a substance to a cancer cell or tissue, it is possible to reduce the toxicity of the chemotherapy drug and increase its selectivity, which is achieved not through the use of specific signaling pathways used by the cancer cell for survival, but due to the binding of the vector to receptors.

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