46. ANTIBODY BASED ONCOLOGY DRUGS, TARGETS, MOLECULAR FUNCTION. pdf

1: Molecular Pathways and Cancer Exploration | BioOncology

Conventional chemotherapy targets all dividing cells between healthy and cancerous cells by acting on specific molecular targets. antibody-based drugs are difficult to design and expensive.

Genentech is dedicated to defining the molecular basis of cancer Click on any section of the image below to explore the hallmarks of cancer. The process of tissue invasion and metastasis is not well understood, but, in general, it involves changes in the way cells attach to other cells and to the extracellular matrix. Distinct modes of invasion are seen in metastatic and nonmetastatic diseases. Activating invasion and metastasis3 Tumor cell migration is promoted in part through a paracrine loop involving CSF-1, EGF, and their corresponding receptors, which are differentially expressed on carcinoma cells and macrophages residing in the tumor microenvironment. An intrinsic cellular mechanism allows normal cells to divide a finite number of times and blocks cell division beyond a certain limit. This process is also aided in part by the loss of tumor-suppressor genes, such as p Enabling replicative immortality1,4 A shortening of telomere length activates replicative senescence in normal cells; however, tumor cells overcome the finite replicative ability by overexpressing telomerase, an enzyme that maintains telomere length. Particularly, the G1 phase of the cell cycle is a vital checkpoint wherein the antigrowth signals exert their influence to block cell proliferation. Induction of the G0 phase Induction of a postmitotic state, usually involving terminal differentiation of the cell However, most cancer cells circumvent normal growth suppressors in order to continue proliferating. In normal tissue, these proteins are part of a large network that controls the cell cycle. Evading growth suppressors7 Rb and p53 are 2 common tumor suppressors that are inactivated in tumor cells, leading to uncontrolled growth and proliferation. Preclinical studies have suggested that an active immune system continuously recognizes and eliminates the vast majority of cancer cells before they establish themselves and form a tumor mass. Evading immune destruction10,11 Cancer immuno-editing, an emerging hallmark, comprises 3 key phasesâ€”elimination, equilibrium, and escape. Cancer cells that successfully navigate these phases acquire the ability to evade immune destruction. Cancer cells take advantage of increased rates of mutations in order to accumulate several mutations needed to foster tumorigenesis. These genes are responsible for1 Detecting DNA damage and activating repair machinery Directly repairing damaged DNA Inactivating or intercepting mutagenic molecules By inactivating or suppressing caretaker genes, tumor cells can increase the rate of mutations and, subsequently, tumorigenesis. Genome instability and mutation12 Cancer cells take advantage of mutations in DNA repair pathways to promote genomic instability. Depicted above is one such mechanism, resulting from the defective BRCA signaling pathway. Tumor angiogenesis is a multistep process and involves signaling input from several pro-angiogenic growth factors. Pericytes are supporting cells that have long been associated with normal tissue vasculature; however, recent studies reveal that pericyte coverage is also important for tumor angiogenesis Molecular cancer research also indicates that bone marrowâ€”derived cells, such as macrophages and neutrophils, are recruited to lesions and may help initiate the angiogenic switch Figure 6. Inducing angiogenesis13,14 Tumor angiogenesis is a function of multiple signals from a number of cell types residing in the tumor microenvironment. Reprogramming energy metabolism17 Cancer cells convert available glucose to lactate irrespective of the availability of oxygen the Warburg effect , thereby diverting glucose metabolites to useful anabolic processes that accelerate cell proliferation. In contrast, cancer cells are generally less sensitive to similar stresses and tend to avoid apoptosis. These include DNA damage and growth factor deprivation, as well as treatment with chemo- and immunotherapeutics. The intrinsic pathway is tightly regulated by a group of related proteins called the BCL-2 family. Consistent with its role in the regulation of apoptosis, many cancers are able to resist the apoptotic pathway through dysregulation of BCL-2 family members. Cancer cells are thought to achieve this through 2 main mechanisms: For example, mutated p53, which normally can couple cellular stress to increased expression of pro-apoptotic proteins, results in cells less sensitive to DNA damage20; down-regulation of

caspase-3 has been linked to apoptotic resistance in some tumor types. Evading cell death Sustaining proliferative signaling Growth signaling in normal cells is a highly regulated process wherein proliferative signals are activated whenever necessary and deactivated when no longer necessary; this tight regulation ensures cell homeostasis. However, in cancer cells, this regulation is compromised. They achieve this in a number of ways1: Increasing growth factor production Stimulating normal cells in the microenvironment to provide cancer cells with growth factors Increasing the number of receptors on the cell surface Structurally altering receptors to facilitate cancer cell signaling Activating proteins in the downstream signaling pathway Recent studies also highlight the ability of cancer cells to disrupt negative feedback loops that constitute a safety mechanism to dampen a signaling pathway whenever a mitogenic signal is hyperactivated. One key example of this is the Ras oncoprotein. Sustaining proliferative signaling23 Tumor cells disrupt negative feedback loops in the oncogenic Ras signaling pathway, leading to sustained proliferative signaling in tumor cells. Current molecular cancer research indicates that this tumor-associated inflammation might aid in tumor growth.

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2: Targeted Therapy Drugs for Non-Small Cell Lung Cancer

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") that are involved in the growth, progression, and spread of cancer. Targeted cancer therapies are sometimes called "molecularly targeted.

This approach could lead to a paradigm shift in the development of new methods for cancer treatment. The paper reporting the results of the study was published in Nano Letters. Conventional chemotherapy targets all dividing cells without exception, thus both healthy and cancer cells are affected. However, the advances in cancer research have led to a better understanding of the molecular mechanisms and the primary agents responsible for tumor development. New findings have enabled novel anti-neoplastic drugs that can distinguish between healthy and cancer cells by acting on specific molecular targets. Because the cells in tumors undergo rapid division, they rely on a constant supply of substances stimulating cellular growth and proliferation. These substances, known as growth factors, come from outside the cell and can be identified by corresponding receptor proteins on the cell surface. These external factors activate intracellular signaling, stimulating cancer cell proliferation. Over the past two decades, a series of therapeutic drugs acting on growth factors have been developed and clinically tested. The new medications suppress the binding of growth factors to the receptors, as well as directly affecting their enzyme activity. It is not surprising that the development of new synthetic drugs against this type of targets is a promising area of molecular pharmacology attracting close attention of researchers all over the world. The international research group led by Professor Nickolai Barlev, the head of the Laboratory of Cell Signaling Regulation at MIPT, has shown that it is possible to develop a new class of anti-neoplastic medicines based on a kind of particles called nanoMIPs, or nanosized molecularly imprinted polymers. NanoMIPs are a synthetic polymer alternative to antibodies with a 3D structure that enables them to bind only to a certain fragment of a target protein. This ensures their high specificity. Unlike antibodies, nanoMIPs can also carry additional anti-cancer agents. In their research, the authors proved for the first time that it is possible to synthesize nanoMIPs capable of selectively binding to the amino acid sequences of their target proteins. Through this process, nanoMIPs acquire the ability to selectively recognize the target molecule and bind to it. This protein is overexpressed in many types of tumors associated with colorectal, lung, brain, and breast cancer, including its most aggressive form, the triple-negative breast cancer. For this reason, EGFR served as one of the first targets for antibody-based anti-neoplastic medicines. The team worked with nanoparticles obtained using a double-imprinting approach against two target molecules: An epitope is the part of a target molecule that is recognized by the antibody which binds to it. Therefore, the final product both binds EGFR and delivers therapeutics to cancer cells. However, because the drug is unstable, new doses of antibodies have to be administered for the entire period of treatment. Synthetic antibody alternatives, such as nanoMIPs, do not have these limitations. Moreover, unlike biomolecules, their stability does not depend on temperature and acidity, which means they have a much wider range of potential applications. What is more, the synthesis of selective nanoMIPs does not necessarily require the imprinting of the whole cell. Rather, only a specific part needs to be imprinted. It should be noted that polyacrylamide, unlike its monomers, is biologically harmless and is used, for example, to produce soft contact lenses. When the temperature is increased, the monomers begin to polymerize, forming particles that are nanometers large, incorporate doxorubicin, and carry a molecular imprint of the target protein. This used to be impossible, because the available technology for nanoMIP synthesis did not allow us to standardize the conditions in which the particles were obtained, so the efficiency of the end product was unpredictable. We solved this problem by using solid-phase synthesis. The results of the study have also revealed moderate and specific toxicity of nanoparticles against tumor cells. Notably, the toxicity was entirely due to doxorubicin incorporation during the polymerization process, as the control nanoparticles, which did not contain the anti-cancer drug, did not have any effect on the cells. In addition, when therapeutic nanoMIPs were administered, the cells developed

multiple DNA breaks, which are a characteristic reaction to the effect of doxorubicin. Successful in vitro experiments suggest that nanoMIPs hold promise as vehicles for targeted drug delivery and call for further research. The laboratory, headed by Barlev, aims to further develop nanoMIP technology for cancer treatment.

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3: What Are the Functions of Antibodies & Antigens Binding? | Healthfully

Scientists have demonstrated the possibility of developing a new type of anti-neoplastic drugs based on nanoMIPs, or 'plastic antibodies'. NanoMIPs are synthetic polymers that can function as antibodies, selectively binding to target proteins on the surface of cancer cells.

New linker technology associated with novel highly potent cytotoxic payloads has permitted the development of more effective and safe ADCs. In recent years, two ADCs have been licensed, T-DM1 and brentuximab vedotin, and are already establishing their place in cancer treatment. As we deepen our understanding of what makes a successful ADC, an increasing number of ADCs will likely become viable treatment options as single agents or in combination with chemotherapy. This review will present the philosophy underlying ADCs, their main characteristics and current research developments with a focus on ADCs in solid tumours. Monoclonal antibodies have proved to have an important role in cancer treatment with drugs such as trastuzumab, pertuzumab, cetuximab and rituximab becoming the standard of care in selected solid tumours and lymphomas. Classic chemotherapy, the mainstay of anticancer treatment, demonstrates limited selectivity against cancer cells leading to a small therapeutic window, thus limiting its efficacy. Antibody-drug conjugates could bring these two classes of drugs with their complementing properties together, in creating a highly selective and highly cytotoxic cancer treatment with an increased therapeutic window, as envisaged by Paul Ehrlich Hughes, Looking back into the reasons for previous failures gives us an opportunity to identify the crucial characteristics that will make ADC an effective anticancer treatment. The low chemotherapy drug potency, unstable linkers and low antigen selectivity are the most commonly identified weaknesses limiting the efficacy of an ADC Perez et al, In addition, in some of the first clinical trials murine antibodies were used leading to high rates of immunogenicity and, therefore, to low efficacy Hughes, Antibody-drug conjugates have a complex structure with many moving parts, each of which has different properties and desirable characteristics. An ADC can be divided into three main structural units: Antibody-drug conjugates Target antigen The ideal target antigen should be: The target antigen should not be downregulated after treatment with the ADC Mack et al, The minimum threshold of the different variables that are required to a make a tumour antigen an effective target is still undetermined and interdependent. Studies in lymphoma and prostate cancer have shown that a minimum value of tumour-antigen density is a prerequisite for ADC efficacy. The biomarker analysis study for TDM1 showed that although it was active across different HER-2 expression subgroups, patients with tumours who expressed HER-2 more highly derived the greatest benefit Baselga et al, The desirable cutoff value of antigen expression varies greatly and depends on other target antigen properties such as the internalisation rate and binding affinity, as well as other ADC characteristics, such as cytotoxic payload and linker stability. There is evidence that ADCs can be effective even when they target antigens with low expression given minimal normal tissue expression Perez et al, The problem of non-homogeneous expression of the target antigen in solid tumours could potentially be addressed by the bystander effect, that is, the process by which membrane-permeable free cytotoxic payload is able to induce cell death to the neighbouring cells after being internalised and cleaved from the linker. Conversely, the bystander effect can increase the ADCs off-target systemic toxicity. Various factors can affect the rate of internalisation of the ADC in the cancer cell, which is a poorly understood process. One such factor is the epitope on the target antigen. For example, different epitopes of the HER-2 receptor have resulted in significantly different rates of internalisation and degradation of the mAb-Ag molecule. In addition, there are other difficulties while targeting cancer cell surface antigens, such as the high interstitial tumour pressure, downregulation of the antigen and the presence of other physical and kinetic barriers that diminish the cytotoxic payload uptake Mack et al, ; Perez et al, Although most licensed or at an advanced research stage ADCs target tumour antigens, alternative approaches are actively being investigated to overcome some of the above mentioned limitations Casi and Neri, Another approach is to target antigens in stroma and vasculature. There is evidence

in the preclinical and clinical setting that components of the neovasculature subendothelial extracellular matrix and of the tumour stroma could be valuable target antigens. A characteristic example is the extra-domain B ED-B of fibronectin which is a marker of angiogenesis, specifically highly expressed in vasculature of aggressive solid tumours Palumbo et al, Figure 1. This target was successfully exploited by conjugating it with tubulin inhibitors showing that non-internalising vascular targeting ADCs could offer other treatment approaches Perrino et al, , Table 1.

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4: Nanoscale polymer antibodies efficiently target and eliminate cancer cells

Although many surface targets are a focus of immune-oncology therapies, a unique target is the TNFR2 receptor which is not only concentrated on the Treg cells of the tumor infiltrate but also now a newly identified and prevalent oncogene for diverse human tumors.

History[edit] The idea of " magic bullets " was first proposed by Paul Ehrlich , who, at the beginning of the 20th century, postulated that, if a compound could be made that selectively targeted a disease-causing organism, then a toxin for that organism could be delivered along with the agent of selectivity. In the s, the B-cell cancer multiple myeloma was known. It was understood that these cancerous B-cells all produce a single type of antibody a paraprotein. This was used to study the structure of antibodies, but it was not yet possible to produce identical antibodies specific to a given antigen. Production[edit] Researchers looking at slides of cultures of cells that make monoclonal antibodies. These are grown in a lab and the researchers are analyzing the products to select the most promising of them. Monoclonal antibodies can be grown in unlimited quantities in the bottles shown in this picture. Technician hand-filling wells with a liquid for a research test. This test involves preparation of cultures in which hybrids are grown in large quantities to produce desired antibody. This is effected by fusing myeloma cell and mouse lymphocyte to form a hybrid cell hybridoma. Lab technician bathing prepared slides in a solution. This technician prepares slides of monoclonal antibodies for researchers. The cells shown are labeling human breast cancer. Polyethylene glycol is used to fuse adjacent plasma membranes, [6] but the success rate is low, so a selective medium in which only fused cells can grow is used. This is possible because myeloma cells have lost the ability to synthesize hypoxanthine-guanine-phosphoribosyl transferase HGPRT , an enzyme necessary for the salvage synthesis of nucleic acids. The absence of HGPRT is not a problem for these cells unless the de novo purine synthesis pathway is also disrupted. Exposing cells to aminopterin a folic acid analogue, which inhibits dihydrofolate reductase , DHFR , makes them unable to use the de novo pathway and become fully auxotrophic for nucleic acids , thus requiring supplementation to survive. The selective culture medium is called HAT medium because it contains hypoxanthine , aminopterin and thymidine. This medium is selective for fused hybridoma cells. Unfused spleen cells cannot grow indefinitely because of their limited life span. Only fused hybrid cells, referred to as hybridomas, are able to grow indefinitely in the media because the spleen cell partner supplies HGPRT and the myeloma partner has traits that make it immortal similar to a cancer cell. This mixture of cells is then diluted and clones are grown from single parent cells on microtitre wells. The antibodies secreted by the different clones are then assayed for their ability to bind to the antigen with a test such as ELISA or Antigen Microarray Assay or immuno- dot blot. The most productive and stable clone is then selected for future use. The hybridomas can be grown indefinitely in a suitable cell culture medium. They can also be injected into mice in the peritoneal cavity , surrounding the gut. There, they produce tumors secreting an antibody-rich fluid called ascites fluid. The medium must be enriched during in vitro selection to further favour hybridoma growth. This can be achieved by the use of a layer of feeder fibrocyte cells or supplement medium such as briclone. Culture-media conditioned by macrophages can be used. Production in cell culture is usually preferred as the ascites technique is painful to the animal. Where alternate techniques exist, ascites is considered unethical. Different from traditional hybridoma technology, the newer technologies use molecular biology techniques to amplify the heavy and light chains of the antibody genes by PCR and produce in either bacterial or mammalian systems with recombinant technology. One of the advantages of the new technologies is applicable to multiple animals, such as rabbit, llama, chicken and other common experimental animals in the laboratory. Purification[edit] After obtaining either a media sample of cultured hybridomas or a sample of ascites fluid, the desired antibodies must be extracted. Cell culture sample contaminants consist primarily of media components such as growth factors, hormones and transferrins. In contrast, the in vivo sample is likely to have host antibodies, proteases , nucleases , nucleic acids and viruses. In both cases, other secretions by the

hybridomas such as cytokines may be present. There may also be bacterial contamination and, as a result, endotoxins that are secreted by the bacteria. Depending on the complexity of the media required in cell culture and thus the contaminants, one or the other method in vivo or in vitro may be preferable. The sample is first conditioned, or prepared for purification. Cells, cell debris, lipids and clotted material are first removed, typically by centrifugation followed by filtration with a 0. These large particles can cause a phenomenon called membrane fouling in later purification steps. In addition, the concentration of product in the sample may not be sufficient, especially in cases where the desired antibody is produced by a low-secreting cell line. The sample is therefore concentrated by ultrafiltration or dialysis. Most of the charged impurities are usually anions such as nucleic acids and endotoxins. These can be separated by ion exchange chromatography. Various proteins can also be separated along with the anions based on their isoelectric point pI. In proteins, the isoelectric point pI is defined as the pH at which a protein has no net charge. For example, albumin has a pI of 4. Thus, at a pH between 4. Transferrin, on the other hand, has a pI of 5. A difference in pI of at least 1 is necessary for a good separation. Transferrin can instead be removed by size exclusion chromatography. This method is one of the more reliable chromatography techniques. Since we are dealing with proteins, properties such as charge and affinity are not consistent and vary with pH as molecules are protonated and deprotonated, while size stays relatively constant. Nonetheless, it has drawbacks such as low resolution, low capacity and low elution times. However, this method may be problematic for antibodies that are easily damaged, as harsh conditions are generally used. A low pH can break the bonds to remove the antibody from the column. Gentle elution buffer systems that employ high salt concentrations are available to avoid exposing sensitive antibodies to low pH. To achieve maximum purity in a single step, affinity purification can be performed, using the antigen to provide specificity for the antibody. In this method, the antigen used to generate the antibody is covalently attached to an agarose support. If the antigen is a peptide , it is commonly synthesized with a terminal cysteine , which allows selective attachment to a carrier protein, such as KLH during development and to support purification. The antibody-containing media is then incubated with the immobilized antigen, either in batch or as the antibody is passed through a column, where it selectively binds and can be retained while impurities are washed away. An elution with a low pH buffer or a more gentle, high salt elution buffer is then used to recover purified antibody from the support. Antibody heterogeneity[edit] Product heterogeneity is common in monoclonal antibodies and other recombinant biological products and is typically introduced either upstream during expression or downstream during manufacturing. The generally accepted purification method of process streams for monoclonal antibodies includes capture of the product target with protein A , elution, acidification to inactivate potential mammalian viruses, followed by ion chromatography , first with anion beads and then with cation beads. Recombinant antibody engineering involves antibody production by the use of viruses or yeast , rather than mice. These techniques rely on rapid cloning of immunoglobulin gene segments to create libraries of antibodies with slightly different amino acid sequences from which antibodies with desired specificities can be selected. Chimeric antibodies While mouse and human antibodies are structurally similar, the differences between them were sufficient to invoke an immune response when murine monoclonal antibodies were injected into humans, resulting in their rapid removal from the blood, as well as systemic inflammatory effects and the production of human anti-mouse antibodies HAMA. In one approach, mouse DNA encoding the binding portion of a monoclonal antibody was merged with human antibody-producing DNA in living cells. The expression of this " chimeric " or "humanised" DNA through cell culture yielded part-mouse, part-human antibodies. Two successful approaches have been identified: As of November , thirteen of the nineteen fully human monoclonal antibody therapeutics on the market were derived from transgenic mice technology. Adopting organizations who market transgenic technology include: Medarex â€” which marketed the UltiMab platform. Abgenix was acquired in April by Amgen.

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5: Antibody-drug conjugate - Wikipedia

Oncology Reports, 36 Cekanova, M., & Rathore, K. (). Animal models and therapeutic molecular targets of cancer: Utility Therapeutic Targeting of Cancers with Loss of PTEN Function.

Antibodies track these proteins down in the body and attach themselves to the surface of cancer cells. The biochemical reaction between the antibody and the target protein antigen triggers a signal in the tumor cell, which then absorbs or internalizes the antibody together with the cytotoxin. After the ADC is internalized, the cytotoxic drug is released and kills the cancer. These advantages have led to ADC technologies being featured in many publications, notably The New York Times , [5] [6] as well as numerous scientific journals. However, after a request from the U. Mylotarg , withdrew the drug from the market in June [7] although still marketed in Japan [8]. It was re-introduced into the US market in Kadcyla, marketed by Genentech and Roche. Brentuximab vedotin [10] was granted accelerated approval by the U. Trastuzumab emtansine ado-trastuzumab emtansine or T-DM1 was approved in February for the treatment of people with HER2-positive metastatic breast cancer mBC who have received prior treatment with trastuzumab Herceptin, Genentech and Roche and a taxane chemotherapy. Linkers are based on chemical motifs including disulfides, hydrazones or peptides cleavable , or thioethers noncleavable and control the distribution and delivery of the cytotoxic agent to the target cell. Cleavable and noncleavable types of linkers have been proven to be safe in preclinical and clinical trials. Brentuximab vedotin includes an enzyme-sensitive cleavable linker that delivers the potent and highly toxic antimicrotubule agent monomethyl auristatin E or MMAE, a synthetic antineoplastic agent, to human specific CDpositive malignant cells. Because of its high toxicity MMAE, which inhibits cell division by blocking the polymerization of tubulin, cannot be used as a single-agent chemotherapeutic drug. However, the combination of MMAE linked to an anti-CD30 monoclonal antibody cAC10, a cell membrane protein of the tumor necrosis factor or TNF receptor proved to be stable in extracellular fluid, cleavable by cathepsin and safe for therapy. The availability of better and more stable linkers has changed the function of the chemical bond. The type of linker, cleavable or noncleavable, lends specific properties to the cytotoxic anti-cancer drug. For example, a non-cleavable linker keeps the drug within the cell. As a result, the entire antibody, linker and cytotoxic anti-cancer agent enter the targeted cancer cell where the antibody is degraded to the level of an amino acid. The resulting complex â€” amino acid, linker and cytotoxic agent â€” now becomes the active drug. In contrast, cleavable linkers are catalyzed by enzymes in the cancer cell where it releases the cytotoxic agent. The difference is that the cytotoxic payload delivered via a cleavable linker can escape from the targeted cell and, in a process called "bystander killing", attack neighboring cancer cells. This linker technology allows researchers to create ADCs with more flexibility without worrying about changing cleavage kinetics. Researchers are also developing a new method of peptide cleavage based on Edman degradation , a method of sequencing amino acids in a peptide. This approach leads to suboptimal safety and efficacy properties and makes optimization of the biological, physical and pharmacological properties of an ADC challenging. This enables the production of homogeneous ADCs with the antibody precisely linked to the drug and controlled ratios of antibody to drug, allowing the selection of a best-in-class ADC. Swartz, allows the synthesis of proteins containing site-specifically incorporated non-natural amino acids and has been optimized for predictable high-yield protein synthesis and folding at any scale with straightforward downstream purification processes. The absence of a cell wall allows the addition of non-natural factors to the open system in order to manipulate transcription, translation and folding to provide precise modulation of the protein expression process. However, some drug developers are also looking to expanding the application of ADCs beyond oncology and hematology to other important disease areas. A CDtargeted immunoconjugate of calicheamicin for the treatment of B-lymphoid malignancies". Nature Reviews Drug Discovery. In print on June 1, , on page B1 of the New York edition with the headline: Pharmaceuticals and Medical Devices Agency of Japan, Proceedings of the National Academy of Sciences.

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6: Monoclonal antibody drugs for cancer: How they work - Mayo Clinic

A joint research team from Russia and the U.K. has demonstrated the possibility of developing a new type of anti-neoplastic drugs based on nanoMIPs, or "plastic antibodies." NanoMIPs are synthetic polymers that can function as antibodies, selectively binding to target proteins on the surface of cancer cells.

Disorders of the Peripheral Nervous System Antibodies are a type of specialized protein generated by the immune system. Antibodies each contain two heavy chain proteins, which link to two smaller light chain proteins. The light chain contains a variable region that allows for an antibody to bind to one specific antigen. Upon exposure to a foreign material, or antigen, specialized immune system cells generate antibodies that bind to the antigen. Antibody binding to an antigen has many functions, both within the body and in laboratory testing. Defense Against Infection The major function of antibody-antigen binding within the body is to fight off infections. There are a number of different types of antibodies synthesized within the body, with the majority of the antibodies classified as immunoglobin G, or IgG. IgG antibodies produced by B-cell lymphocytes, a type of white blood cell, circulate throughout the body within the blood and bind to any available antigen. The antibody-antigen binding then stimulates the activation of other immune system cells, which engulf the foreign particle. Defects in antibody-antigen binding prevent the immune system from recognizing and attacking foreign particles within the body. Without proper antibody function, a person is left vulnerable to infection and disease. Cancer Therapy Antibody-antigen binding also has a role in cancer therapy, and the use of antibody-based therapeutics allows for the selective targeting of cancer cells. Traditional chemotherapy drugs target proliferating cells thoughout the entire body, whether those cells are cancerous or not. This results in damage to a number of normal tissues throughout the body as a side effect of treatment, which may cause discomfort and pain over the course of chemotherapy treatment. Antibody-based therapies consist of antibodies designed to selectively bind proteins found on cancer cells. Since the antibody binds selectively to cancer cells, healthy proliferative cell populations are largely unharmed by the therapy, decreasing the side effects experienced during treatment. The National Cancer Institute indicates that Herceptin, a breast cancer therapeutic, uses antibody-antigen binding to target and kill breast cancer cells. Laboratory Testing Antibody-antigen binding also has a function in laboratory and medical testing. Since antibodies bind specifically to one antigen, the use of antibodies during laboratory testing can indicate the presence of a specific factor within a tissue sample. Antibody-antigen binding can be used to detect the presence of a specific protein within specific cells, a piece of biopsy tissue or the blood. NYU Langone Medical Center indicates that antibody-based tests are routinely used to characterize cancers and help distinguish between types of lymphoma. Antibody-antigen binding tests in the laboratory detect the presence of a specific protein by testing for the binding of an antibody. If a sample is positive for an antigen, the corresponding antibody will bind strongly to the sample, so the presence of the antibody acts as a marker for the presence of the antigen. If a sample is negative for an antigen, the antibody will not bind. Trastuzamab About the Author Sylvie Tremblay holds a Master of Science in molecular and cellular biology and has years of experience as a cancer researcher and neuroscientist. Cite this Article A tool to create a citation to reference this article Cite this Article.

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7: Polymer antibodies efficiently target and eliminate cancer cells â€” News MIPT

Targeted therapies, which include monoclonal antibodies and small molecule inhibitors, have significantly changed the treatment of cancer over the past 10 years. These drugs are now a component of.

The red dots represent the cytotoxic agent doxorubicin, which is delivered by nanoMIPs and penetrates the cell membrane. This approach could lead to a paradigm shift in the development of new methods for cancer treatment. The results of the study were published in Nano Letters. The main drawbacks of most anti-cancer medications are their low specificity and the associated side effects. Conventional chemotherapy targets all dividing cells without exception, so both healthy cells and cancer cells are affected. However, the advances in cancer research have led to a better understanding of the molecular mechanisms and the primary agents responsible for tumor development. New findings have enabled novel anti-neoplastic drugs that can distinguish between healthy and cancerous cells by acting on specific molecular targets. Because the cells in tumors undergo rapid division, they rely on a constant supply of substances stimulating cellular growth and proliferation. These substances, known as growth factors, come from outside the cell, and can be identified by corresponding receptor proteins on the cell surface. These external factors activate intracellular signaling, stimulating cancer cell proliferation. It turned out that the receptor proteins on the cell surface are often overexpressedâ€”that is, synthesized in excessâ€”in various solid tumors. Over the past two decades, therapeutic drugs acting on growth factors have been developed and clinically tested. The new medications suppress the binding of growth factors to the receptors, and directly affect their enzyme activity. It is not surprising that the development of new synthetic drugs against this type of target is a promising area of molecular pharmacology attracting close attention of researchers all over the world. The international research group led by Professor Nickolai Barlev, the head of the Laboratory of Cell Signaling Regulation at MIPT, has shown that it is possible to develop a new class of anti-neoplastic medicines based on a kind of particles called nanosized molecularly imprinted polymers nanoMIPs. NanoMIPs are a synthetic polymer alternative to antibodies with a 3-D structure that enables them to bind only to a certain fragment of a target protein. This ensures their high specificity. Unlike antibodies, nanoMIPs can also carry additional anti-cancer agents. In their research, the authors proved for the first time that it is possible to synthesize nanoMIPs capable of selectively binding to the amino acid sequences of their target proteins. The study has also demonstrated the potential for nanoMIP application in targeted drug delivery figure 2. NanoMIPs are synthesized in the presence of a target protein, which leaves a "mark" on the nanoparticle. This process is called imprinting, and it can be compared to mold castingâ€”the end product takes on the shape of the original template. Through this process, nanoMIPs acquire the ability to selectively recognize the target molecule and bind to it. This protein is overexpressed in many types of tumors associated with colorectal, lung, brain and breast cancer, including its most aggressive form, triple-negative breast cancer. For this reason, EGFR served as one of the first targets for antibody-based anti-neoplastic medicines. The team worked with nanoparticles obtained using a double-imprinting approach against two target molecules: An epitope is the part of a target molecule that is recognized by the antibody which binds to it. Therefore, the final product both binds EGFR and delivers therapeutics to cancer cells. Tumors with EGFR overexpression are successfully treated with specific monoclonal antibodies targeting this receptor cetuximab, or Erbitux. However, because the drug is unstable, new doses of antibodies have to be administered for the entire period of treatment. Synthetic antibody alternatives, such as nanoMIPs, do not have these limitations. Moreover, unlike biomolecules, their stability does not depend on temperature and acidity, which means they have a much wider range of potential applications. Looking forward, they could expand the range of options available for diagnostics and treatment of many diseases," says Barlev, who is the senior author of the study. Rather, only a specific part needs to be imprinted. This small partâ€”a short oligopeptideâ€”is attached to glass beads via covalent chemical bonds. The beads are then mixed with acrylamide monomers and doxorubicin. Polyacrylamide, unlike its monomers,

is biologically harmless, and is used to produce soft contact lenses, among other things. When the temperature is increased, the monomers begin to polymerize, forming particles that are â€” nanometers large, incorporate doxorubicin, and carry a molecular imprint of the target protein. Unreacted monomers and nonspecific nanoparticles are eluted, while the synthesized "plastic antibodies" remain bound to the glass beads figure 3. This used to be impossible, because the available technology for nanoMIP synthesis did not allow us to standardize the conditions in which the particles were obtained, so the efficiency of the end product was unpredictable. We solved this problem by using solid-phase synthesis. The results of the study have also revealed moderate and specific toxicity of nanoparticles against tumor cells. Notably, the toxicity was entirely due to doxorubicin incorporation during the polymerization process, as the control nanoparticles, which did not contain the anti-cancer drug, did not have any effect on the cells. In addition, when therapeutic nanoMIPs were administered, the cells developed multiple DNA breaks, which are a characteristic reaction to the effect of doxorubicin. Finally, the binding of the "plastic antibodies" to EGFR led to a decrease in the density of receptors on the cell surface. Successful in vitro experiments suggest that nanoMIPs hold promise as vehicles for targeted drug delivery and call for further research.

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8: Targeted Therapies: A New Generation of Cancer Treatments - - American Family Physician

Monoclonal antibody drugs are cancer treatments that enlist natural immune system functions to fight cancer. These drugs may be used in combination with other cancer treatments. If you and your doctor are considering using a monoclonal antibody drug as part of your cancer treatment, find out what to expect from this therapy.

Aug 23, Nanoscale polymer antibodies efficiently target and eliminate cancer cells Nanowerk News A joint research team from Russia and the U. This approach could lead to a paradigm shift in the development of new methods for cancer treatment. The red dots represent the cytotoxic agent doxorubicin, which is delivered by nanoMIPs and penetrates the cell membrane. Conventional chemotherapy targets all dividing cells without exception, thus both healthy and cancer cells are affected. However, the advances in cancer research have led to a better understanding of the molecular mechanisms and the primary agents responsible for tumor development. New findings have enabled novel anti-neoplastic drugs that can distinguish between healthy and cancer cells by acting on specific molecular targets. Because the cells in tumors undergo rapid division, they rely on a constant supply of substances stimulating cellular growth and proliferation. These substances, known as growth factors, come from outside the cell and can be identified by corresponding receptor proteins on the cell surface. These external factors activate intracellular signaling, stimulating cancer cell proliferation. It turned out that the receptor proteins on the cell surface are often overexpressed -- that is, synthesized in excess -- in various solid tumors. Over the past two decades, a series of therapeutic drugs acting on growth factors have been developed and clinically tested. The new medications suppress the binding of growth factors to the receptors, as well as directly affecting their enzyme activity. It is not surprising that the development of new synthetic drugs against this type of targets is a promising area of molecular pharmacology attracting close attention of researchers all over the world. The international research group led by Professor Nickolai Barlev, the head of the Laboratory of Cell Signaling Regulation at MIPT, has shown that it is possible to develop a new class of anti-neoplastic medicines based on a kind of particles called nanoMIPs, or nanosized molecularly imprinted polymers. NanoMIPs are a synthetic polymer alternative to antibodies with a 3D structure that enables them to bind only to a certain fragment of a target protein. This ensures their high specificity. Unlike antibodies, nanoMIPs can also carry additional anti-cancer agents. In their research, the authors proved for the first time that it is possible to synthesize nanoMIPs capable of selectively binding to the amino acid sequences of their target proteins. The study has also demonstrated the potential for nanoMIP application in targeted drug delivery. NanoMIPs are synthesized in the presence of a target protein, which leaves a "mark" on the nanoparticle. This process is called imprinting and it can be compared to mold casting -- the end product takes on the shape of the original template. Through this process, nanoMIPs acquire the ability to selectively recognize the target molecule and bind to it. This protein is overexpressed in many types of tumors associated with colorectal, lung, brain, and breast cancer, including its most aggressive form, the triple-negative breast cancer. For this reason, EGFR served as one of the first targets for antibody-based anti-neoplastic medicines. The team worked with nanoparticles obtained using a double-imprinting approach against two target molecules: An epitope is the part of a target molecule that is recognized by the antibody which binds to it. Therefore, the final product both binds EGFR and delivers therapeutics to cancer cells. Tumors with EGFR overexpression are successfully treated with specific monoclonal antibodies targeting this receptor cetuximab, or Erbitux? However, because the drug is unstable, new doses of antibodies have to be administered for the entire period of treatment. Synthetic antibody alternatives, such as nanoMIPs, do not have these limitations. Moreover, unlike biomolecules, their stability does not depend on temperature and acidity, which means they have a much wider range of potential applications. Looking forward, they could expand the range of options available for diagnostics and treatment of many diseases," says Barlev, who is the senior author of the study. What is more, the synthesis of selective nanoMIPs does not necessarily require the imprinting of the whole cell. Rather, only a specific part needs to be imprinted. This small part -- a short oligopeptide -- is attached to

glass beads via covalent chemical bonds. The beads are then mixed with acrylamide monomers and doxorubicin. It should be noted that polyacrylamide, unlike its monomers, is biologically harmless and is used, for example, to produce soft contact lenses. When the temperature is increased, the monomers begin to polymerize, forming particles that are nanometers large, incorporate doxorubicin, and carry a molecular imprint of the target protein. Unreacted monomers and nonspecific nanoparticles are eluted, while the synthesized "plastic antibodies" remain bound to the glass beads. This used to be impossible, because the available technology for nanoMIP synthesis did not allow us to standardize the conditions in which the particles were obtained, so the efficiency of the end product was unpredictable. We solved this problem by using solid-phase synthesis. The results of the study have also revealed moderate and specific toxicity of nanoparticles against tumor cells. Notably, the toxicity was entirely due to doxorubicin incorporation during the polymerization process, as the control nanoparticles, which did not contain the anti-cancer drug, did not have any effect on the cells. In addition, when therapeutic nanoMIPs were administered, the cells developed multiple DNA breaks, which are a characteristic reaction to the effect of doxorubicin. Finally, the binding of the "plastic antibodies" to EGFR led to a decrease in the density of receptors on the cell surface. Successful in vitro experiments suggest that nanoMIPs hold promise as vehicles for targeted drug delivery and call for further research. These articles might interest you as well:

46. ANTIBODY BASED ONCOLOGY DRUGS, TARGETS, MOLECULAR FUNCTION. pdf

9: Antibody-drug conjugatesâ€”an emerging class of cancer treatment

Glypican-3 (GPC3) is an emerging therapeutic target in hepatocellular carcinoma (HCC), even though the biological function of GPC3 remains elusive. Currently human (MDX and HN3) and humanized mouse (GC33 and YP7) antibodies that target GPC3 for HCC treatment are under different stages of.

References Traditional cytotoxic chemotherapy works primarily through the inhibition of cell division Figure 1. In addition to cancer cells, other rapidly dividing cells e. In contrast, targeted therapy blocks the proliferation of cancer cells by interfering with specific molecules required for tumor development and growth Figure 2. Some of these molecules may be present in normal tissues, but they are often mutated or overexpressed in tumors. Among the earliest targeted therapies were antibodies directed against the cell surface markers cluster of differentiation 20 CD20 , CD33, and CD52, which are present on lymphoma and leukemia cells. Because CD20 is also present on normal lymphoid cells, targeting of this molecule affects overall immune function. Mechanisms of traditional chemotherapy. These drugs act on rapidly dividing cells, which include normal tissues e. Topoisomerase inhibitors prevent DNA uncoiling. Taxanes and vinca alkaloids interfere with micro-tubule function required for cell mitosis. Antimetabolites block the formation and use of nucleic acids essential for DNA replication. The molecular pathways most often targeted in the treatment of solid tumors e. Such pathways can be inhibited at multiple levels: Monoclonal antibodies, which are usually water soluble and large typical molecular weight of approximately , Da , target extracellular components of these pathways, such as ligands and receptor-binding domains. In contrast, small molecule inhibitors typical molecular weight of approximately Da can enter cells, thereby blocking receptor signaling and interfering with downstream intracellular molecules. Mechanisms of targeted therapies. The molecular targets in this figure are not overexpressed in a single cell type, but rather on various malignant and normal tissues. Downstream intracellular signaling molecules, some of which are targeted by small molecule inhibitors, are not depicted. EGFR, which is present in multiple tumor types, contributes to cancer cell proliferation, invasion, and migration. Of note, in many cases the development of a rash seems to indicate that the treatment may be working. For most patients, this toxicity is self-limited and responds to symptomatic treatment, such as loperamide Imodium. Acneiform rash on A the face and B back of patients treated with cetuximab Erbitux , a monoclonal antibody targeting epidermal growth factor receptor. Targeting of VEGF limits cancer growth by preventing angiogenesis i. For example, the anti-VEGF monoclonal antibody bevacizumab Avastin is approved for treatment of non-small cell lung cancer in patients with adenocarcinoma histology, but not in those with squamous cell tumors. In clinical trials, patients with squamous cell histology had unacceptably high rates of life-threatening hemoptysis. For decades, the use of the hormone receptor modulator tamoxifen Nolvadex, brand no longer available in the United States has been limited to the two thirds of patients with breast cancer whose tumors express estrogen or progesterone receptors. The effect of cetuximab Erbitux , an anti-EGFR monoclonal antibody used in the treatment of colorectal cancer, is independent of the degree of EGFR expression in the tumor.

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