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Effect of Monoclonal Antibodies Conjugation with Gallium-Containing Solamargine: Warburg Effect-Based Cancer Therapeutic Strategy. Article Review

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Abstract

Therapy by Monoclonal antibodies is considered extremely hoping method for cancer therapy. But cancer cells have variable methods for resistance by multiple genetic mutations. The aim of that article to illustrate tagging monoclonal antibodies by gallium containing solamargine glycoside within the antibody by glycosylation the asparagine of its Fc portion. Malignant cells need to a big extent high carbohydrate content for aerobic glycolysis for cancer progression. Solamargine as a specific glycoside can be diffused easily and effectively into malignant cells with a high degree of specificity. Complexion gallium to solamargine then conjugation into monoclonal antibodies will increase Monoclonal antibody potency and affinity by Warburg effect based mechanism and gallium particles. Gallium can be retained for a long time inside malignant cells. By that method, the monoclonal antibody will be targeted to cancer cells by solamargine, retained gallium particles besides its functioning specific Fab region.

Index terms— Fc region, solamargine, gallium, glycosylation, monoclonal antibody, rhamnose.

1 Introduction

onoclonal antibodies constitute hoping results for malignancy treatment. Cancer cells have the ability to invade the immune system to predispose invasion and metastasis. Monoclonal antibodies target specific antigens presenting on cancer cells, in a result more specificity for cancer treatment with less side effects. The main role of them is to suppress main checkpoints that are critical for malignancy dissemination such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and tyrosine kinase. Many examples of monoclonal antibodies are produced against specific cancer cell antigens such as antibodies that protects immune checkpoints from cancer cell aggression like lipilimumap, pembrolizumab and alemtuzumab. Also Bevacizumab (anti-VEGF) inhibits the angiogenic activity of VEGF expressing cancer cells. Bevacizumab showed satisfying results in the treatment of metastatic colon cancer, metastatic renal tumors besides nonsmall cell lung cancer and glioblastoma. Panitumumab (anti-EGFR) is responsible for treatment of metastatic colon cancer expressing epidermal growth factor receptor (EGFR) which has been shown resistance to chemotherapeutic agents. Cetuximab (anti-EGFR) inhibits EGFR related pathways and is used in the treatment of EGFR-positive colon malignant neoplasm and also for head and neck tumors. Ofatumumab showed high efficacy in the treatment chemo-resistant patients with chronic lymphocytic leukemia chemotherapy. Trastuzumab (anti-HER-2/neu) is used in patients with HER-2/neu-positive breast tumor, metastatic gastrointestinal (GI) malignant neoplasms [Pento, 2017]. Rituximab has been a cornerstone in treatment of non-Hodgkin's lymphoma, lymphocytic leukemia and other autoimmune diseases such as lupus erythematosus [Smolej, 2016]. Monoclonal antibodies have been recognized for radioisotopes delivery such as arcitumomab that is a murine antibody fragment that is technetium 99m-labeled. It is a therapeutic agent for patients with metastatic colorectal neoplasm [Hughes et al, 1997]. Ibritumomab tiuxetan (fig. 1) can be tagged with yttrium 90 or Indium 111 which showed high efficacy in treatment of patients with non-Hodgkin's lymphoma and regularity combined with Rituximab [Rizzieri, 2016]. Tositumomab (fig. 2) (a MAB labeled) is labeled with iodine 131 used for treatment patients with non-Hodgkin's lymphoma

who show bad outcome to other chemotherapeutic drugs **??**Shadman et al, 2016]. Also monoclonal antibodies can be labeled by chemotherapeutic agent [chemolabeled antibodiesbrentuximab vedotin (Adcetris)]. Another group of monoclonal antibodies are available which is called bispecific mAbs, that has double variable antigen binding fragments (Fabs) whose advantage is to attract cells together. For example, blinatumomab binds CD19 on lymphoma cells and CD3 on T cells, thus prompting T cell cytotoxicity against leukemic B cells [Goldenberg, 2007].

2 II. Structural Insights of Monoclonal Antibody

The general conformation of monoclonal antibody consists of three functional components, two Fragment antigen binding domains (Fabs) and the fragment crystallizable (Fc), with a hinge region between the two Fabs and the Fc that gives the advantage of wide range of flexible mobility to the Fabs. Each of the Fabs contain identical antigen-binding sites that bind with a specific antigen [Chiu et al, 2019]. The antigen binding sites of antibodies often results in structural variations in the contact surface zones of both the antibody and the antigen. That have been confirmed in the structure studies of both an antibody fragment **??**Fabs and Cohen, 1996]. The Fv region of the Fab consists of a pair of variable domains (VH and VL) together with the HC and LC. In contrast, the glycosylated Fc region binds to variable structures presented on malignant cells and components of the adaptive and humoral immunity. Fc region structure is nearly constant in many human IgG antibodies. It is formed of two constant domains, each one consists of CH2 and CH3. CH3 of both domains are joined tightly together, while CH2s have no protein-protein communication with each other (fig. **??**). The space in-between the CH2s is occupied partially by the carbohydrate attached at Asn297.In some antibodies, the two carbohydrate chains interact through hydrogen bonds or water bringing molecules

3 a) Genetic polymorphism and its effect on monoclonal antibodies efficacy

Cancer cells have multiple genetic variations that affect monoclonal antibodies efficacy. Genetic polymorphism targets recognition, presentation and metabolism of monoclonal antibodies. Monoclonal antibodies maximum absorption 1-8 days after SC or IM injection [Korth-Bradley et al, 2000] and it is determined by blood-tissue hydrostatic gradient besides diffusion through vascular endothelium [Baxter et al, 1994]. MABs uptake occurs after receptor-mediated endocytosis after binding of Fc domain with Fc?R expressed on different immune cells [Gessner et al, 1998]. However in a recent study, it has been shown that immune system has a necessary role in survival tumor cells that show loss of tumor suppressor genes or activated oncogenes Genetic mutations of cancer cells have inhibitory results on MAB efficacy. For example, BRAFV600E, PI3K/ m TOR and PI3K CA genetic mutations expressing colorectal cancer cell lines are associated with low cetuximab and panitumumab efficacy in colorectal cancer treatment potency [Xu et al, 2017]. Patients that show RAS gene KRAS G12 A/V stimulation of mediators secretion, and endocytosis of opsonized particles [Taylor and Lindorfer, 2015]. Now, The Fc region is the target of the developmental engineering for variable effector functions. Structural analysis showed a Fc ball-and-socket joint between CH2 and CH3 that permits the CH2 domain to circulate around its Leu251 side chain, which is buried in a pocket constituted of CH3 residues Met428, His429, Glu430, and His435. FcCH2 contains carbohydrate structures that conceal hydrophobic face of Fc region [Chiu et al, 2019]. Several Fc glycoform variants and aglycosylated forms have been confirmed such as sialic acids, N-acetylglucosamines, and galactoses, and in some cases, the absence of fucose [Jefferis, 2005]. Fc glycans improve the antibody biophysical stability [Lee et al, 2015]. Also they fills the separation distances between CH2. Besides all that they can redirect the effector functionality of the antibody besides changing its the pharmacokinetic profile [Kronimus et al, 2019].

mutation that upregulates VEGF show lower PFS and OS after treatment with bevacizumab (anti-VEGF) compared to wild type KRAS [Nakayama et al, 2017 The 2 rhamnose moiety of SM have a necessary function in initiation cell death by apoptosis and cytotoxic effects such as human hepatocytes (Hep3B) [Nakamura et al, 1996]. It was observed that the carbohydrate moieties of steroidal alkaloids augmented the binding specificity to steroid-associated receptors [Chang et al, 1998]. The trisaccharide of SM (two rhamnose units are bound to a glucose moiety), has more affinity to specific cell receptor sites than the corresponding trisaccharide of solasonine (SS) (one rhamnose and one glucose units are connected by a galactose monosaccharide) [Bill, 2013] 4). It is chosen from solasodine glycosides because it contains Dglucopyranose which can be conjugated with gallium particles (discussed later.) Solamargine uptake by endogenous endocytic lectins (EELs) expressed on malignant cells results in cellular shrinkage and lysis [Bill, 2013].(22R, 25R)-spiro-5-ene-3ß-yl-?-L- rhamnopyranosyl-(1-2glu)-0-?-L-rhamnopyranosyl-(1-4gl u)-ß-D-glucopyranose (fig.

SNPs (single nucleotide polymorphisms) within the PD-L1 gene CD274 have been demonstrated to affect patient improvement to the anti-PD-1 mAb nivolumab. Patients with non-small cell lung cancer that administrated nivolumab possessing the CD274 rs4143815 C/C and C/G genotypes had slightly more elevated median PFS in comparison to patients with the G/G genotype (P = 0.044). Also several studies suggested that PD-L1 rs4143815, that is situated in the 3' untranslated region (UTR) can affect the expression of PD-L1, in a result tumor cells can escape from immune system [Yeo et 2017]. Especially, it has been proven that the C allele of rs4143815 has an essential role in an increased production of PD-L1 by attenuating miR-570 [Wang et al, 2013]. Also it is clear that patients with the rs4143815 C/C genotype have lower clinical result to paclitaxel

and cisplatin chemotherapy [Lee et al, 2016]. In addition, during the haplotype analysis, that included seven SNPs (rs733618, rs4553808, rs11571317, rs5742909, rs231775, rs3087243 and rs7565213) within CTLA4 gene, it can be associated with no response to anti-CTLA-4 treatment [Breunis et al, 2008]. (HeLa 229), Ovarian Carcinoma (JAM), Mesothelioma (NO36),Glioblastoma, Astrocytoma (U87-MG), Prostate Carcinoma (DV-145, LNCap, PC-3), Melanoma (A2058), Breast Cancer (T47D, MDA-MB-231), Osteosarcoma (U20S) and Squamous Cell Carcinoma (A431, SCC4, SCC9, SCC25). Solamargine also showed selectivity as it did not induce apoptosis in normal cells such as bone marrow cells, fibroblasts, normal hepatocyte cells HL7702 and H9C2 [Bill, 2013].

The gene expression of TNFR1 was markedly increased by SM which contributes to the mechanism of the cytotoxicity of SM [Hsu et al, 1996]. Solamargine triggers the intrinsic and extrinsic pathway of apoptosis in lung and breast cancer cells. SM increased the expressions of external death receptors, such as tumor necrosis factor receptor 1 (TNFR-1), Fas receptor, TNFR-1-associated death domain (TRADD) and Fasassociated death domain (FADD). SM also upregulated (associated with myeloid cells) [Kumpel et al, 1994]. In the opposite, hypogalactosylation results in weak activity of IgG in ADCC. IVIG (intravenous immunoglobulins) attained their efficacy by binding of it Fc region with Fc?Rbearing host immune cells [Galeotti et al, 2009]. That effect can be because of initiation secondary cellular events, like Fc?R-induced apoptosis or anergy, including the phosphorylation of immunoreceptor tyrosinebased inhibition motif (ITIM) and immunoreceptor tyrosine-based activation motif (ITAM) [Hamerman and **??**anier, 2006, Siragam et al, 2006]. Therapeutic mAbs demand the presence of functioning Fc region to suppress tumor invasion and to raise survival rates in mouse models. Thus, because glycosylation is an essential factor for the functions of human IgG , now, new strategy is adopting conjugation MAB with certain efficient glycoforms for more positive results [Clynes et al, 1998].

In my study, solamargine will be conjugated to the glycosylated Fc portion from its steroidal backbone, so that its functioning rhamnose terminal end is free and will be bound to gallium particles (discussed later in the methodology). By that way monoclonal antibody will act directly on malignant cells facilitating the Cytotoxic T cell function. Cancer has the ability to resist monoclonal antibodies by genetic polymorphism (discussed before) and suppression of host immunity (cytotoxic T cells). Cancer immunosuppression is triggered by tumorderived soluble factors (TDSFs), like interleukin-10 (IL-10), transforming growth factor-b (TGF-b) and vascular endothelial growth factor (VEGF), and that spreads, starting from the primary tumour site reaching to secondary lymphoid organs and peripheral vascularity [Zou, 2005, Yang, 2004]. Tumor derived VEGF is considered a powerful chemoattractant that initiates migration of immature myeloid cells (iMCs) from the bone marrow into peripheral vessels, where they are attracted to the primary tumor site by the action of chemokines and chemokine receptors [Kusmartsev and Gabrilovich, 2002]. The iMCs, that entail immature dendritic cells (iDCs) and macrophages, have functional and biochemical remodelling within the tumor microenvironment into tumor-associated iDCs (TiDCs) and tumor-associated macrophages (TAMs) that are recruited to regional lymph nodes, spleen and peripheral circulation for immune evasion. The immunosuppressive iMCs and increased level of reactive oxygen species (ROS) suppress T-cell activation by specific tumor mechanism [Kusmartsev et al, 2004]. Also the deficient clearance of apoptotic cells triggers formation of anti-DNA-antibodies creating pseudo-autoimmune response against host antigens. In a result pro-inflammatory response appears that increases tumor progression [Kim et al, 2005]. High levels of auto-antibodies and iDCs stimulate production of CD4+ CD25+ regulatory T cells (Tregs) that suppress T-cell function. iMCs induce their immunosuppressive effect by stimulation of indoleamine 2,3-dioxygenase (IDO) (an enzyme responsible for tryptophan metabolism, tryptophan is needed for T-cell proliferation [Munn et al 1999] and ArgI (an enzyme responsible for L-arginine metabolism to ornithine and urea, and the polyamine oxidation from ornithine inhibits IL-2 production, that in a result suppresses T-cell proliferation [Flescher et al, 1989] by the help of IL-10 and TGF-b. The final result is production (ROS) that reduce the proliferation of T-cells [Zea et al, 2005]. c) Role of gallium compound (within the solamarginegallium compound) Gallium was chosen due to its role in tumor inhibition besides increased bioavailability and efficacy. Also prolonged presence of gallium intracellular raises its cytotoxicity level [Rasey et al, 1982]. Selectivity for malignant cells is one of gallium advantages. Ga atoms have the ability to combine to DNA phosphate, constituting a stable complex. Ga compete with magnesium for DNA binding especially affinity of Ga for DNA is 100 times more than of magnesium [Manfait and Collery 1984] Ga forms transferrin-Ga complex after favorable binding with transferrin that results in DNA synthesis inhibition by its action on ribonucleotide reductase [Chitambar et al, 1988]. Ga suppresses biosynthesis pathways within the cell and suppress protein synthesis [Aoki et al, 1990]. The impact of Ga in affection of cell membrane permeability could be explained by changing the cell membrane potential, modulationof electric charges at the protein synthesis [Collery et al, 1994]. Ga triggers efflux of calcium from mitochondria which is a necessary starting step for apoptosis [Gogvadze et al, 1996]. Ga triggers the collagen and fibronectin synthesis [Bockman et al, 1993] which might illuminate the cause of the tumor fibrosis after long term administration [Collery et al, 1986]. Ga is involved in intracellular oxidative stress, with a reduction in the ratio of cellular glutathione reduced form (GSH) on glutathione oxidized form (GSSG), an elevation in metallothionein (MT) and in hemeoxygenase-1 (HO-1) gene expression [Yang and Chitambar, 2008]. Gallium salicylate (fig. **??**) (tetrakis(1octanol) tris(5-aminosalicylate) gallium(III)) [Ismail et al, 2006] has anti-inflammatory, antitumor [Perugini et al, 2000] and antiangiogenic characteristics [Borthwick et al, 2006] besides the ability to suppress cancer cell progression [Murono et al, 2000]. Salicylates can reduce platinum-based drugs toxicity [Li et al, 2002]

4 Monoclonal antibodies production and glycosylation using CHO-S cells culture

By the help of PiggyBac (PB) as transposon to carry out the integration of transgenes into the mammalian cells genome [Wilson et al, 2007]. The PB transposon system can be of one or more transposon donor vectors, that express the transgene(s) and a helper vector encoding the PBase enzyme [Balasubramanian et al, 2015]. The pB513B1 donor vector and pB200A helper vector will be brought. For construction a dual promoter vector, LC and BGH polyA sequences will be PCR amplified from the pUC-LC and pTracer-CMV2 vectors respectively. After cloning -into an intermediate vector, they will be cloned into pB513B1 by the help of EcoRI/ BamHI enzymes, and pBLP vector The aim of that reaction to yield solamargine with rhamnose free group, also bound to glucose on its steroidal backbone.

will be obtained. CMV-HC sequence will be sub-cloned from the pTracer-HC vector, into the pBPL vector by BglII/NotI to yield pBLPCH final construct. LC-IRES-HC and LC-F2A-HC (F2A; furin-containing 2A peptide sequence) fragments. LC-IRES-HC containing vector will be digested with NheI/NotI and the resulted fragment attached to the pB513B1 to produce pBLIH donor vector. LC-F2A-HC-cloned into pB513B1 by XbaI/NotI enzymes and pBL2AH will be resulted [Ahmadi et al 2017]. Also another vector containing amplified sequence of glucosyltransferase enzyme will be prepared and injected into culture media cells. Then using suspension adopted CHO-S cells culture and (by the regular conditions and steps for purification) Reaction (**??**): Synthesis of gallium octyl ?-glucoside (glucoside: solamargine glucosyl monoclonal antibody).

Then the efficacy of the modified monoclonal antibody can be compared with the original form of the same monoclonal antibody type, for example comparing cetuximab solamargine -gallium MAB with the efficacy of Cetuximab on epidermal growth factor expressing cancer cell lines such as colorectal cancer cell lines Cac0-2, DLD-1, HCT116 and HT-29.

5 III.

6 Conclusion

Modification of monoclonal antibody with gallium containing solamargine can be a general modification to different types of monoclonal antibodies because it is conjugated on Asn 297 which is a fixed structure to all monoclonal antibodies. That modified form can be easily targeted to cancer cells then endocytosis occurs after binding to malignant cell Fc?R. Also inhibition the signaling pathway by the action of MAB Fab region will facilitate the suppressive effect of both gallium and solamargine. Besides that, Fab region of MAB can be a targeting structure to direct solamargine and gallium towards tumor cells. On the other side, cancer cells will be suppressed by the modified form of MAB by three components in the same time, MAB itself, gallium and solamargine. By that way, tumor resistance even by genetic polymorphism or immunosuppression of T cells will be markedly affected by the modified MAB if compared to the unmodified one.

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Figure 1: Figure (1):

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Figure 2: Figure (2):

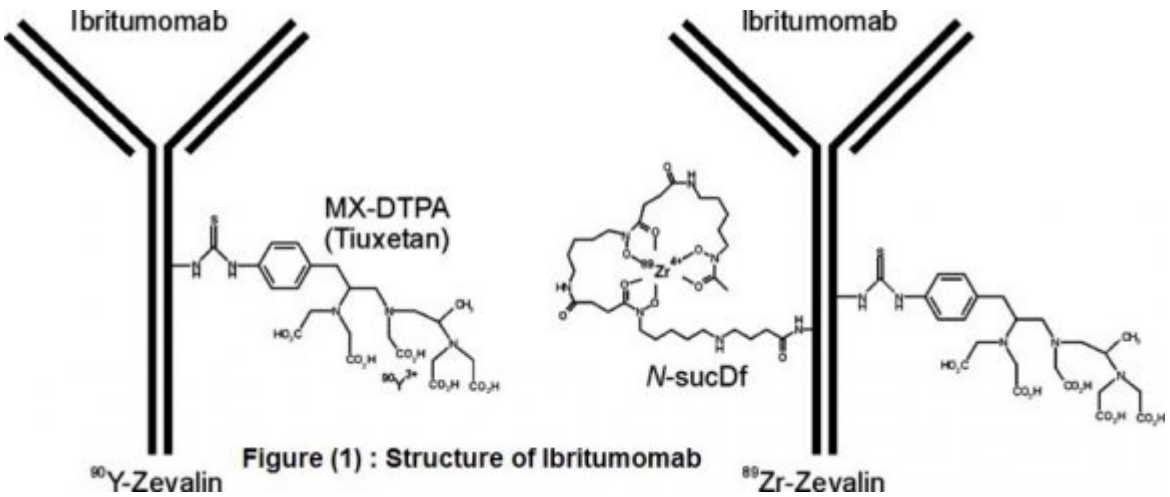

Figure 3:

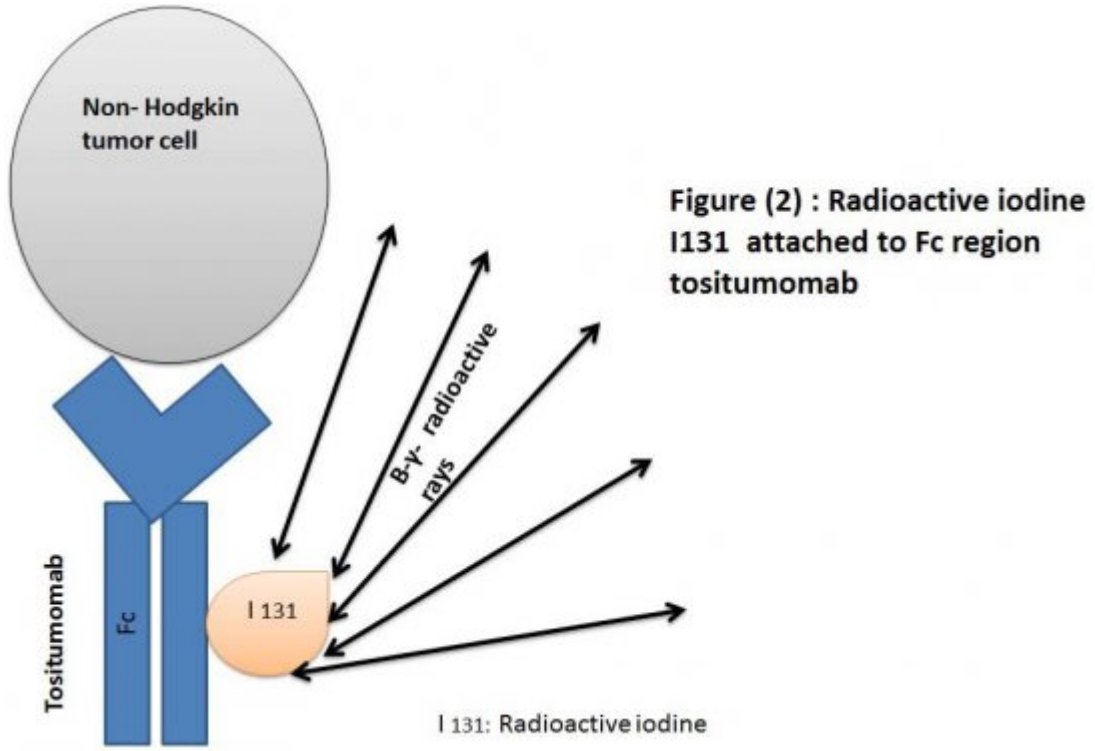

Figure 4: [

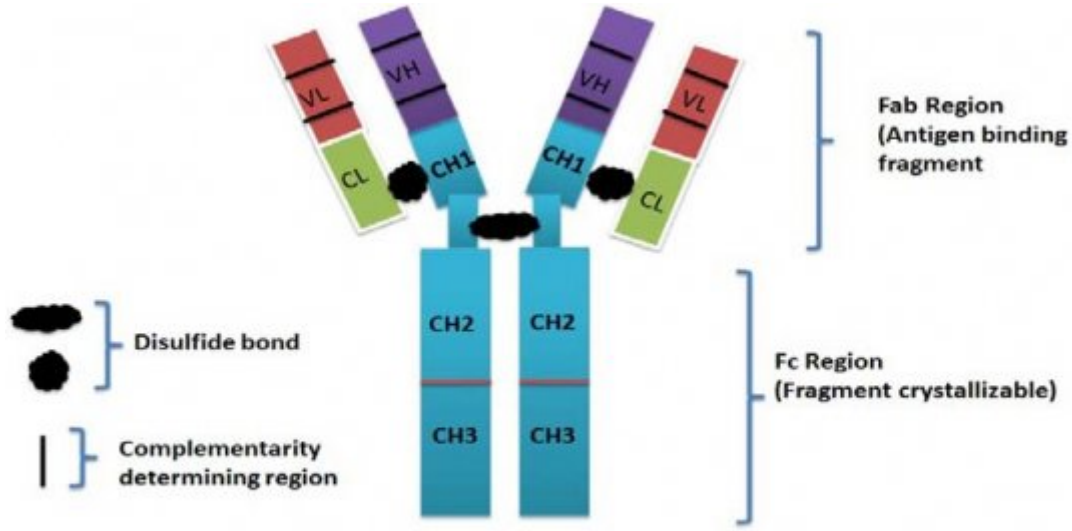

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Figure 5: Figure (4):

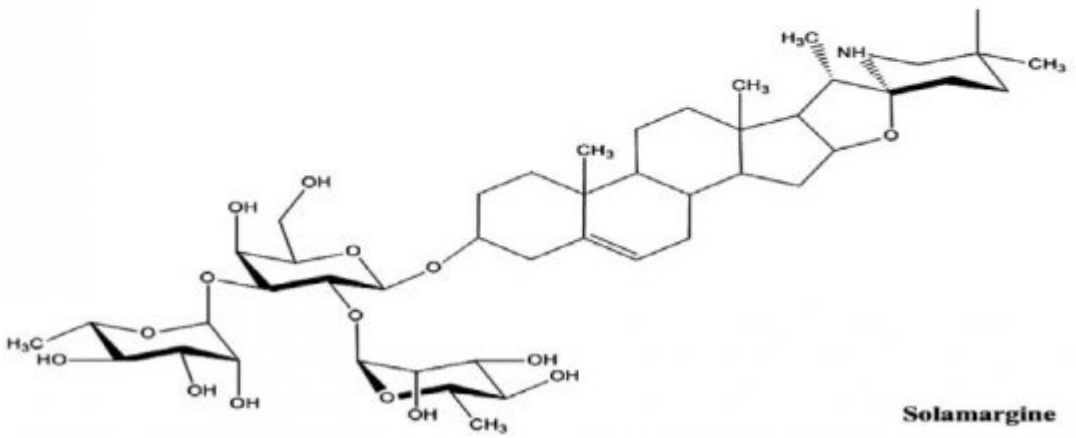


Figure 6:

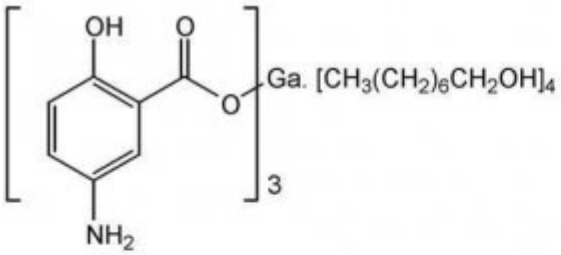
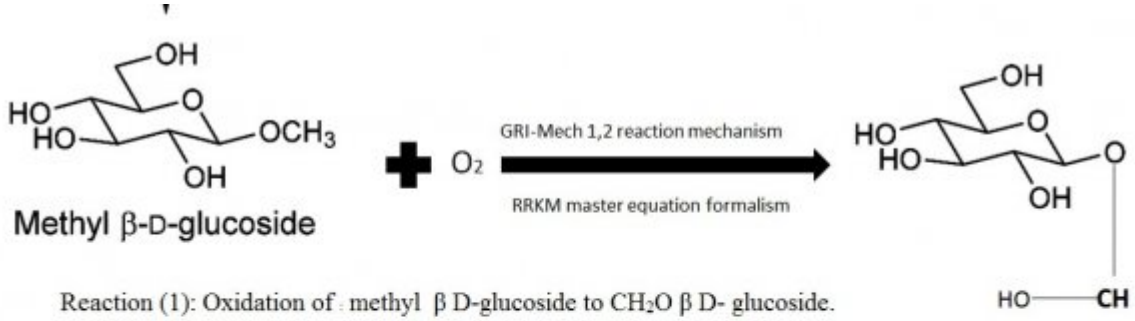


Figure 7:



Reaction (1): Oxidation of methyl β D-glucoside to CH_2O β D- glucoside.

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Figure 8: Figure (5): 2 - 1 .

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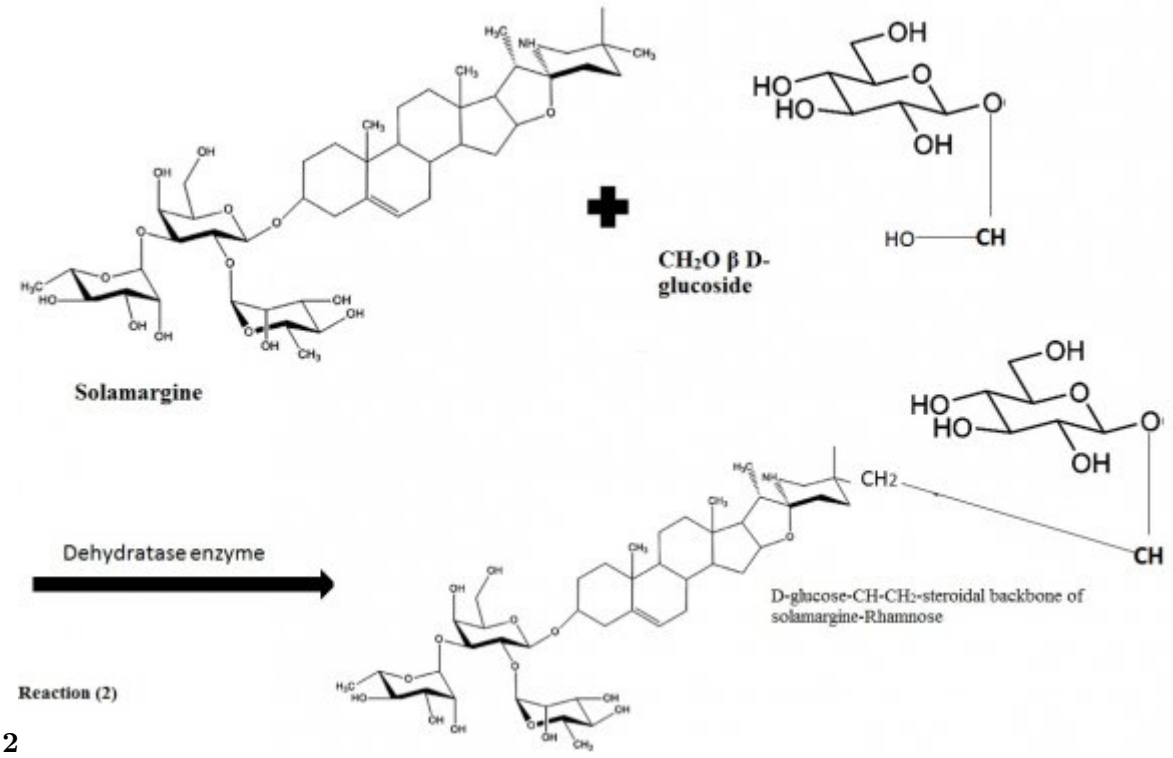

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Figure 9: 2 .

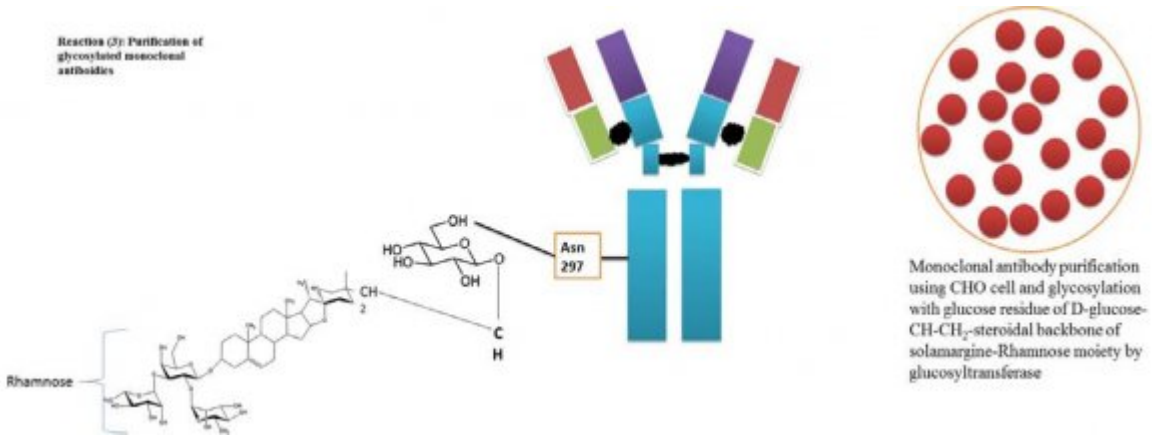

Figure 10:

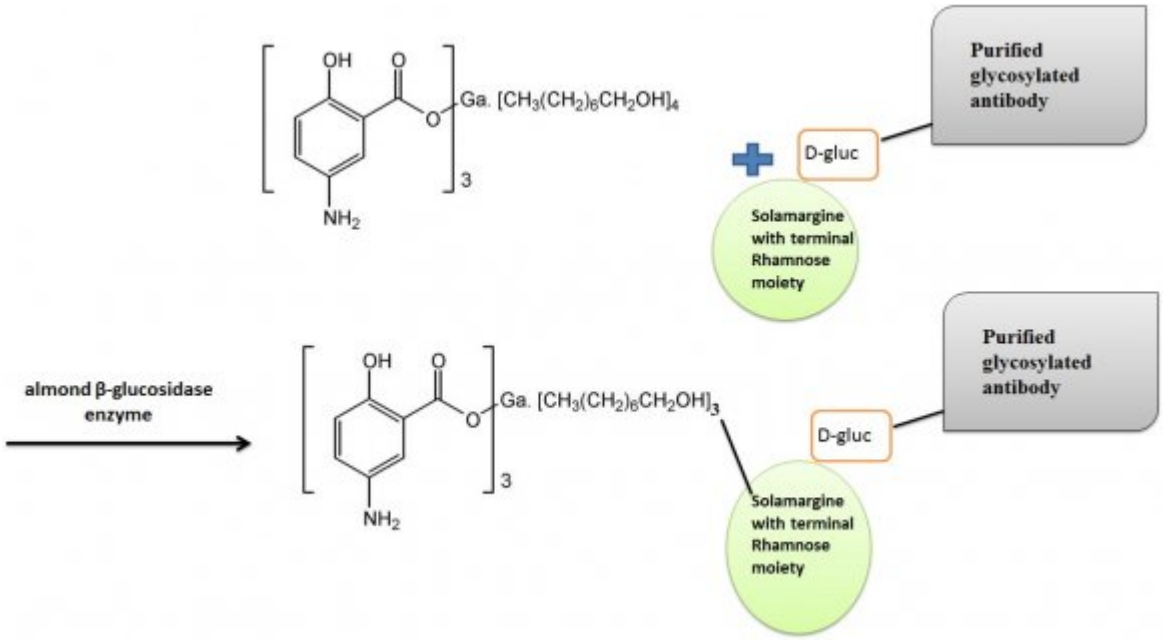

Figure 11:

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From all
previous advantages of raid aerobic glycolysis and Warburg effect, we can say that tagging monoclonal antibodies glycosides Fc region with solamargine (glycoside which has high affinity for cancer cells) can be attracting factor for malignant as it can be a glucose supply for their Warburg effect, especially within the low glucose nutrient in the tumor microenvironment (author).
2. Solamargine anti-cancer properties: solamargine is considered one of the glycoalkaloid class (solasodine rhamnosyl glycosides) which shows positive immune response to cancer cells.
Solasodine rhamnosyl glycosides are secondary metabolites of plants. They consist of a mono or oligosaccharide chain attached at the C3 position of the nitrogenous steroid alkaloid backbone [Bill, 2013].

[Note:]. b) Value of monoclonal antibodies conjugation with solamargine-gallium containing saccharide i. Value of solamargine 1. Glycoside nature of solamargine: tumor cells have increased needs of glucose for their high rate of replication and invasion. Malignant cells prefer aerobic glycolysis other than mitochondrial oxidation. Rate of glucose metabolism by aerobic glycosylation is roughly 10 -100 more rapid than that of mitochondrial oxidation [Locasale and Cantley, 2011]. Also aerobic glycolysis results in production considerable amount of lactic acid after glucose fermentation in the presence of oxygen and functioning mitochondria which is called "Warburg effect". Lactic acid is important for tumor survival and progression [Maria et al, 2015]. Besides that, aerobic glycolysis satisfy cancer cell needs of the high requirement of ATP which is necessary for tumor cells division [Epstein, et al. 2014]. Also, aerobic glycolysis is considered major factor for carbon production that is crucial for formation of nucleotides, lipid and protein for cancer anabolism and carcinogenic-associated pathways [Boroughs and DeBerardinis, 2015]. Warburg effect is essential for NAD+ regeneration that is important for keeping glycolysis active [Lunt and Vander Heiden, 2011]. In tumor microenvironment, glucose supply is limited. So tumor cells, stromal cells and immune cells compete for glucose consumption [Chang C-H, et al, 2015]. Also within the tumor, glucose as a nutrient is needed for tumor-infiltrating lymphocytes (TILs) for their effect or functions, also it is needed for cancer cell itself. Warburg effect through high aerobic glycolysis within tumor cells compensate TILs for glucose needs [Chang C-H, et al, 2015].]

Figure 12:

Effect of Monoclonal Antibodies Conjugation with Gallium-Containing Solamargine: Warburg Effect-Based Cancer Therapeutic Strategy. Article Review
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Solamargine (SM) molecular formula is C45H73NO15 with the mass of 868.04 Da. It

Solamargine has potent multiple anti-tumor properties. It showed efficient results in MDR (multiple drug resistance) tumor cells. Solamargine has shown high potency by apoptosis induction in Ehrlich Carcinoma, Leukemia (K562), Colon Cancer (HT-29, HCT-15), Liver Cancer (HepG2, PLC/PRF/5, SMMC-7721), Lung Cancer (A549), Gastric Carcinoma (AGS), Pancreatic Carcinoma (MIA PaCa-2), Renal Adenocarcinoma (786-0) Uterine Adenocarcinoma

Figure 13:

[Ahmadi et al 2017] and solamargine-glucose (formed in step 2), glycosylated monoclonal antibodies will be produced (rhamnose moiety is still not bound)

(reaction 3).

[Note: Reaction (3): Purification of glycosylated monoclonal antibodies 4. Formation the final form (Monoclonal antibodysolamargine gallium salicylate) tetrakis (1-octanol) tris (5-aminosalicylate) gallium(III) is the target gallium compound. Its octanol component will be reacted with D-glucopyranose of solamargine rhamnose moiety within the purified glycosylated monoclonal antibody by almond ?-glucosidaseenzyme (reaction 4).(Mladenoska, 2016)]

Figure 14:

.1 Conflict of Interest

Author declares no conflict of interest about the article review.

[Wang et al. ()] 'A miR-570 binding site polymorphism in the B7-H1 gene is associated with the risk of gastric adenocarcinoma'. W Wang , F Li , Y Mao , H Zhou , J Sun . *Hum Genet* 2013. 132 p. .

[Lunt and Vander Heiden ()] 'Aerobic glycolysis: meeting the metabolic requirements of cell proliferation'. S Y Lunt , M G Vander Heiden . *Annual review of cell and developmental biology* 2011. 27 p. .

[Aoki et al. ()] 'Alteration in protein synthesis in primary cultures of rat kidney proximal tubule epithelial cells by exposure to gallium, indium, and arsenite'. Y Aoki , M M Lipsky , B A Fowler . *Toxicol Appl Pharmacol* 1990. 106 p. .

[MaryJohnson ()] 'Antibody Storage and Antibody Shelf Life'. MaryJohnson . *Mater Mthods* 2012. 2012. 2 p. 120.

[Mark et al. ()] 'Antibody Structure and Function: The Basis for Engineering Therapeutics'. L Mark , Dennis R Chiu , Alexey Goulet , Gary L Teplyakov , Gilliland . 10.3390/antib8040055. *Antibodies (Basel)* 2019. 3 (4) p. 55.

[Kusmartsev et al. ()] 'Antigenspecific inhibition of CD8+ T cell response by immature myeloid cells in cancer is mediated by reactive oxygen species'. S Kusmartsev , Y Nefedova , D Yoder , D I Gabrilovich . *J Immunol* 2004. 172 p. .

[Ismail et al. ()] 'Antitumor effects of gallium(III) tris (salicylate)-ethanol on malignant cell lines and tumor bearing swiss albino-mice'. D A Ismail , A M Badawi , P Collery , Zakhary Ni , A R Raouf , M C Alpoim , M A Santos , A J Cristovao , J A Centeno . *Metal Ions in Biology and Medicine*, P Collery, P V Morais (ed.) (Paris) 2006. 9 p. .

[Zea et al. ()] 'Arginaseproducing myeloid suppressor cells in renal cell carcinoma patients: amechanism of tumor evasion'. A H Zea , P C Rodriguez , M B Atkins . *Cancer Res* 2005. 65 p. .

[Murono et al. ()] 'Aspirin inhibits tumor cell invasiveness induced by Epstein-Barr virus latent membrane protein 1 through suppression of matrix metalloproteinase-9 expression'. S Murono , T Yoshizaki , H Sato , H Takeshita , Furukawa M Pagano , JS . *Cancer Res* 2000. 60 p. .

[Yeo et al. ()] 'Association of PD-L1 expression and PD-L1 gene polymorphism with poor prognosis in lung adenocarcinoma and squamous cell carcinoma'. M K Yeo , S Y Choi , I O Seong , K S Suh , J M Kim . *Hum Pathol* 2017. 68 p. .

[Rather et al. ()] 'Biotransformation of methyl ?-dglucopyranoside to higher chain alkyl glucosides by cell bound ?-glucosidase of Pichiaetchellsii'. M Y Rather , S Mishra , V Verma , S Chand . *Bioresour Technol* 2012. 107 p. .

[Kim et al. ()] 'Cancer cell immune escape and tumor progression by exploitation of anti-inflammatory and pro-inflammatory responses'. R Kim , M Emi , K Tanabe . *Cancer Biol Ther* 2005. 4 p. .

[Yu et al. ()] 'Chemical kinetics of Methyl oxidation by molecular oxygen'. C , -L Yu , M Wang , Frenklach . *J. Phys. Chem* 1995. 99 p. .

[Nakamura et al. ()] 'Cytotoxic activities of Solanum steroidal glycosides'. T Nakamura , C Komori , Y Lee , F Hashinoto , S Yahara , T Nohara , A Ejina . 10.1248/bpb.19.564. *Biological Biopharmaceu-tical Bulletin* 1996. 19 p. .

[Cham ()] 'Drug therapy: Solamargine and other solasodine rhamnosyl glycosides as anticancer agents'. Bill E Cham . 10.4236/mc.2013.22005. doi.org/10.4236/mc.2013.22005 *Modern Chemotherapy* 2013. 2 (2) p. .

[Collery et al. ()] 'Effects of gallium chloride oral administration on transplanted C3HBA mammary adenocarcinoma: Ga, Mg, Ca and Fe concentration and anatomopathological characteristics'. P Collery , H Millart , Pluot M Anghileri , LJ . 10.1371/journal. *Anticancer Res* 1986. 6 p. .

[Lee et al. ()] 'Effects of N-glycosylation on protein conformation and dynamics: Protein Data Bank analysis and molecular dynamics simulation study'. H S Lee , Y Qi , W Im . *Sci. Rep* 2015. 5 p. 8926.

[Manfait and Collery ()] 'Etude in vitro par spectroscopie Raman de la conformation d'un ADN sous l'influence des ions magne´-sium et gallium'. M Manfait , P Collery . *Magnesium Bull* 1984. 4 p. .

[Clynes et al. ()] 'Fc receptors are required in passive and active immunity to melanoma'. R Clynes , Y Takechi , Y Moroi , A Houghton , J V Ravetch . *Proc. Natl. Acad. Sci*, (Natl. Acad. SciUSA) 1998. 95 p. .

[Taylor and Lindorfer ()] 'Fcgamma-receptormediated trogocytosis impacts mAb-based therapies: Historical precedence and recent developments'. R P Taylor , M A Lindorfer . *Blood* 2015. 125 p. .

[Kumpel et al. ()] 'Galactosylation of human IgG monoclonal anti-D produced by EBVtransformed B-lymphoblastoid cell lines is dependent on culture method and affects Fc receptor-mediated functional activity'. B M Kumpel , T W Rademacher , G A W Rook , P Williams , I B H Wilson . *Human Antib.Hybridomas* 1994. 5 p. .

[Miku? et al. ()] 'Gallium compounds in nuclear medicine and oncology Main Group Met'. Peter Miku? , Milan Melník , Andrea Forgácsová , Dominika Kraj?iová , Emil Havránek . *Chem* 2014. 37 (3-4) p. .

[Bockman et al. ()] 'Gallium nitrate increases type I collagen and fibronectin mRNA and collagen protein levels in bone and fibroblast cells'. R S Bockman , P T Guidon , L C Pan , R Salvatori , A Kawaguchi . *J Cell Biochem* 1993. 52 p. .

[Jefferis ()] 'Glycosylation of natural and recombinant antibody molecules'. R Jefferis . *Adv. Exp. Med. Biol* 2005. 564 p. .

[Akazawa-Ogawa and Nagai ()] 'Heat denaturation of the antibody, a multi-domain protein'. Yoko Akazawa-Ogawa , Hidenori Nagai . *Yoshihisa Hagihara* 2018. 10 (2) p. . (Biophys Rev)

[Akazawa-Ogawa et al. ()] 'Heat induced irreversible denaturation of the camelid single domain VHH antibody is governed by chemical modification'. Yoko Akazawa-Ogawa , Mizuki Takashima , Young-Ho Lee , Takahisa Ikegami , Yuji Goto , Koichi Uegaki , Yoshihisa Hagihara . *Journal of biological chemistry* 2014. 289 p. .

[Kronimus et al. ()] 'IgG Fc N-glycosylation: Alterations in neurologic diseases and potential therapeutic target?'. Y Kronimus , R Dodel , S P Galuska , S Neumann . *J. Autoimmun* 2019. 96 p. .

[Kusmartsev and Gabrilovich ()] 'Immature myeloid cells and cancer-associated immune suppression'. S Kusmartsev , D I Gabrilovich . *Cancer Immunol Immunother* 2002. 51 p. .

[Zou ()] 'Immunosuppressive networks in the tumor environment and their therapeutic relevance'. W Zou . *Nat Rev Cancer* 2005. 5 p. .

[Breunis et al. ()] 'Influence of cytotoxic T lymphocyte-associated antigen 4 (CTLA4) common polymorphisms on outcome in treatment of melanoma patients with CTLA-4 blockade'. W B Breunis , E Tarazona-Santos , Chen R Kiley , M Rosenberg , SA . *J Immunother* 2008. 31 p. .

[Hamerman and Lanier ()] 'Inhibition of immune responses by ITAM-bearing receptors'. J A Hamerman , L L Lanier . *Sci. STKE* 2006. 320 p. 1.

[Chitambar et al. ()] 'Inhibition of leukemic HL60 cell growth by transferrin-gallium: effects on ribonucleotide reductase and demonstration of drugsynergy with hydroxyurea'. C R Chitambar , W G Matthaeus , W E Antholine . *Blood* 1988. 72 p. .

[Munn et al. ()] 'Inhibition of T cell proliferation by macrophage tryptophan catabolism'. D H Munn , E Shafizadeh , J T Attwood , I Bondarev , A Pashine , A L Mellor . *J Exp Med* 1999. 189 p. .

[Davies and Cohen ()] 'Interactions of protein antigens with antibodies'. D R Davies , G H Cohen . 10.21873/anticanres.12040. *Proc. Natl. Acad. Sci. USA*, (Natl. Acad. Sci. USA) 1996. 93 p. .

[Siragam et al. ()] 'Intravenous immunoglobulin ameliorates ITP via activating Fc gamma receptors on dendritic cells'. V Siragam , A R Crow , D Brinc , S Song . *Nat. Med* 2006. 12 p. .

[Galeotti et al. ()] 'Intravenous immunoglobulins in autoimmune and inflammatory disorders: Beyond a simple substitution'. C Galeotti , M S Maddur , M D Kazatchkine , L Mouthon , S V Kaveri . *Transfus. Clin. Biol* 2009. 16 p. .

[Chang ()] 'Metabolic Competition in the Tumor Microenvironment Is a Driver of Cancer Progression'. C-H Chang . *Cell* 2015.

[Locasale and Cantley ()] 'Metabolic flux and the regulation of mammalian cell growth'. J W Locasale , L C Cantley . *Cell metabolism* 2011. 14 (4) p. . (PubMed: 21982705)

[Boroughs and Deberardinis ()] 'Metabolic pathways promoting cancer cell survival and growth'. L K Boroughs , R J Deberardinis . *Nature cell biology* 2015. 17 (4) p. . (PubMed: 25774832)

[Ahmadi et al. ()] 'Monoclonal antibodies expression improvement in CHO cells by PiggyBac transposition regarding vectors ratios and design'. Samira Ahmadi , Fatemeh Davami , Noushin Davoudi , Fatemeh Nematpour , Maryam Ahmadi , Saeedeh Ebadat , Kayhan Azadmanesh , Farzaneh Barkhordari , Fereidoun Mahboudi . 10.1371/journal.pone. https://doi.org/10.1371/journal.pone *PLoS ONE* 2017. 12 (6) p. e0179902.

[Thomas ()] 'Monoclonal Antibodies for the Treatment of Cancer'. Joseph Thomas , Pento . *ANTICANCER RESEARCH* 2017. 2017. 37 p. .

[Lee et al. ()] 'PD-L1 polymorphism can predict clinical outcomes of non-small cell lung cancer patients treated with first-line paclitaxel-cisplatin chemotherapy'. S Y Lee , D K Jung , J E Choi , C C Jin , M J Hong . *Sci Rep* 2016. 6 p. 25952.

[Ryman and Meibohm ()] 'Pharmacokinetics of Monoclonal Antibodies'. J T Ryman , B Meibohm . *CPT Pharmacometrics Syst Pharmacol* 2017. 6 p. .

[Baxter et al. ()] 'Physiologically based pharmacokinetic model for specific and nonspecific monoclonal antibodies and fragments in normal tissues and human tumor xenografts in nude mice'. L T Baxter , H Zhu , D G Mackensen , R K Jain . *Cancer Res* 1994. 54 p. .

[Wilson et al. (2006)] *PiggyBac transposon-mediated gene transfer in human cells. Molecular therapy: the journal of the American Society of Gene Therapy*, M H Wilson , C J Coates , A L George . 10.1038/sj.mt.6300028. 17164785. https://doi.org/10.1038/sj.mt.6300028 2007. 2006/12/14. 15.

[Xu et al. ()] 'PIK3CA mutations contribute to acquired cetuximab resistance in patients with metastatic colorectal cancer'. J M Xu , Y Wang , Y L Wang , Y Wang , T Liu . *Clin Cancer Res* 2017. 23 p. .

[Flescher et al. ()] 'Polyamine oxidation down-regulates IL-2 production by human peripheral blood mononuclear cells'. E Flescher , T L Bowlin , N Talal . *J Immunol* 1989. 142 p. .

[Mccarty and Block ()] 'Preadministration of high-dose salicylates, suppressors of NF-kappaB activation, may increase the chemosensitivity of many cancers: an example of proapoptotic signal modulation therapy'. M F Mccarty , K I Block . *Integr Cancer Ther* 2006. 5 p. .

[Shadman et al. ()] 'Radioimmunotherapy consolidation using 131I-tositumomab for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma in first remission'. M Shadman , A K Gopal , B Kammerer , P S Becker , D G Maloney , B Pender , A R Shustov , Press Ow , J M Pagel . *Leuk Lymphoma* 2106. 57 p. .

[Goldenberg ()] 'Radiolabelled monoclonal antibodies in the treatment of metastatic cancer'. D M Goldenberg . *Curr Oncol* 2007. 14 p. .

[Balasubramanian et al. (2015)] 'Rapid recombinant protein production from piggyBac transposonmediated stable CHO cell pools'. S Balasubramanian , M Matasci , Z Kadlecova , L Baldi , D L Hacker , F M Wurm . 10.1016/j.jbiotec.2015.03.001. 25758242. https://doi.org/10.1016/j.jbiotec.2015.03.001 *Journal of biotechnology* 2015. 2015/03/12. 200 p. .

[Nakayama et al. ()] 'Retrospective study of RAS/PIK3CA/BRAF tumor mutations as predictors of response to first-line chemotherapy with bevacizumab in metastatic colorectal cancer patients'. I Nakayama , E Shinozaki , T Matsushima , T Wakatsuki , M Ogura . *BMC Cancer* 2017. 17 p. 38.

[Chitambar ()] 'Role of oxidative stress in the induction of metallothionein-2A and heme oxygenase-1 gene expression by the antineoplastic agent gallium nitrate in human lymphoma cells'. Yang M Chitambar , CR . *Free Radic Biol Med* 2008. 45 p. .

[Li et al. ()] 'Salicylate protects hearing and kidney function from cisplatin toxicity without compromising its oncolytic action'. G Li , S H Sha , E Zotova , J Arezzo , T Van De Water , J Schacht . *Lab Invest* 2002. 82 p. .

[Epstein ()] 'Separation of metabolic supply and demand: aerobic glycolysis as a normal physiological response to fluctuating energetic demands in the membrane'. T Epstein . *Cancer Metab* 2014. 2 (7) .

[Perugini et al. ()] 'Sodium salicylate inhibits proliferation and induces G1 cell cycle arrest in human pancreatic cancer cell lines'. R A Perugini , T P Mcdade , F J VittimbergaJr , Duffy , M P Callery . *J Gastrointest Surg* 2000. 4 p. .

[Shiu et al. ()] 'Solamargine induces apop-tosis and enhances susceptibility to trastazumab and epirubicin in breast cancer cells with low or high expression levels of HER2/neu'. L Y Shiu , C H Liang , L C Chang , H M Sheu , E M Tsai , K W Kuo . doi: 10.1042/ BSR20080028. *Bioscience Reports* 2009. 29 p. .

[Hsu et al. ()] 'Solamargine purified from Solanum incanum Chinese herb triggers gene expression of human TNFR1 which may lead to apoptosis'. S H Hsu , T R Tsai , C N Lin , M H Yen , K W Kuo . 10.1006/bbrc.1996.1748. *Biochemical and Biophysical Research Communication* 1996. 229 p. .

[Sun et al. ()] 'Solamargine, a steroidal alkaloid glycoside, in-duces oncosis in human K562 leukemia and squamous cell carcinoma KB cells'. L Sun , Y Zhao , H Yuan , X Li , A Cheng , H Lou . *Cancer Chemotherapy Pharmacology* 2010. 65 p. .

[Mladenoska ()] 'Synthesis of Octyl-?-Glucoside Catalyzed by Almond ?-Glucosidase in Unconventional Reaction Media Food Technol'. Irina Mladenoska . *Biotechnol* 2016. 54 (2) p. .

[Timothy D Martin et al. (2021)] 'The adaptive immune system is a major driver of selection for tumor suppressor gene inactivation'. Timothy D Martin , S Rupesh , Danielle R Patel , Mei Yuk Cook , Ajinkya Choi , Patil , C Anthony , Mamie Z Liang , Kevin M Li , Haigis , J Stephen , Elledge . *Science* 2021 Sep. 373 p. .

[Collery et al. ()] 'The cell membrane, target of antitumour gallium compounds'. P Collery , L Khassanova , Z Kuramshina , A Ivanov . *Annals Oncol* 1994. 7 p. . (suppl.1)

[Gogvadze et al. ()] 'The effect of gallium on the calcium retention capacity of rat liver mitochondria'. V Gogvadze , A Zhukova , A Ivanov , L Khassanova , Z Khassanova , P Collery , P Collery , J Corbella , J L Domingo , J C Etienne , J M Llobet . *Metal ions in biology and medicine*, (Paris) 1996. John Libbey Eurotext. 4 p. .

[Shain ()] 'The Genetic Evolution of Melanoma from Precursor Lesions'. A H Shain . *New England Journal of Medicine* 2015. 373 (20) p. . (PubMed: 26559571)

[Gessner et al. ()] 'The IgG Fc receptor family'. J E Gessner , H Heiken , A Tamm , R E Schmidt . *Ann Hematol* 1998. 76 p. .

[Pyzik et al. ()] 'The Neonatal Fc Receptor (FcRn): A Misnomer?'. Michal Pyzik , M K Kine , Jonathan J Sand , Jan Hubbard , Terje , Inger Andersen , Richard S Sandlie , Blumberg . 10.3389/fimmu.2019.01540.eCollection. *Front. Immunol* 2019. 2019. 10 p. 1540.

[Korth-Bradley et al. ()] 'The pharmacokinetics of etanercept in healthy volunteers'. J M Korth-Bradley , A S Rubin , R K Hanna , D K Simcoe , M E Lebsack . *Ann Pharmacother* 2000. 34 p. .

[Chang et al. ()] 'The rhamnose moiety of solamargine plays a crucial role in triggering cell death by apoptosis'. L C Chang , T R Tsai , J J Wang , C N Lin , K W Kuo . 10.1006/bbrc.1997.7903. *Bio-chemical and Biophysical Research Communication* 1998. 242 p. .

[Liberti and Locasale (2016)] 'The Warburg Effect: How Does it Benefit Cancer Cells?'. Maria V Liberti , Jason W Locasale . 10.1016/j.tibs.2015.12.001. *Trends Biochem Sci* 2016 March. 41 (3) p. .

[Smolej ()] 'Therapeutic approach to patients with chronic lymphocytic leukemia and significant comorbid conditions'. L Smolej . *Curr Cancer Drug Targets* 2016. 16 p. .

[Borthwick et al. ()] 'Therapeutic levels of aspirin and salicylate directly inhibit a model of angiogenesis through a Cox-independent mechanism'. G M Borthwick , A S Johnson , M Partington , J Burn , Wilson R Arthur , HM . *FASEB J* 2006. 20 p. .

[Rasey et al. ()] 'Tumor cell toxicity of stable gallium nitrate: enhancement by transferrin and protection by iron'. J S Rasey , Nelson Nj , S M Larson . *Eur J Cancer Clin Oncol* 1982. 18 p. .

[Bud et al. ()] 'Tumor cells express Fc?R which contributes to tumor cell growth and a metastatic phenotype'. M Bud , Julie K Nelson , Katherine I Nyhus , Emilio Barbera Oravecz -Wilson , Guillem . *Neoplasia* 2001. 3 (2) p. .

[Yang and Carbone ()] 'Tumor-host immune interactions and dendritic cell dysfunction'. L Yang , D P Carbone . *Adv Cancer Res* 2004. 92 p. .

[Hughes et al. ()] 'Use of carcinoembryonic antigen radioimmuno detection and computed tomography for predicting the resectability of recurrent colorectal cancer'. K Hughes , C M Pinsky , N J Petrelli , F L Moffat , Y Z Patt , Hammershaimb L Goldenberg , DM . *Ann Surg* 1997. 226 p. .

[Rizzieri ()] 'Zevalin ((R)) (ibritumomab tiuxetan): After more than a decade of treatment experience, what have we learned?'. D Rizzieri . *Crit Rev Oncol Hematol* 2016. 105 p. .