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# IS SIWA318H OUR SALVATION FROM CANCER?
# (SIWA318H – НАШЕ СПАСІННЯ ВІД РАКУ?)

*У публікації порушено питання лікування раку та застосування експериментального антитіла SIWA318H в боротьбі з раком підшлункової залози.*

***Ключові слова:*** *рак, онкологічні захворювання, антитіло, клітини.*

*The publication raises the issue of cancer treatment and the use of the experimental antibody SIWA318H in the fight against pancreatic cancer.*

***Key words****: cancer, oncological diseases, antibody, cells.*

Oncological diseases, or cancer, still remain one of the biggest threats to human health around the world. Malignant tumors can occur in various organs and systems. Their detection and treatment is a serious challenge for modern medicine.

According to the WHO (World Health Organization), in 2022 the following were found in the world:

- almost 20 million new cases of oncological diseases;
- 9.7 million deaths due to this disease;
- 53.5 million people who were able to live 5 years after diagnosis;
- 2.5 million new cases of lung cancer;
- 2.3 million new breast cancer patients;
- 1.9 million new cases of colorectal cancer;
- 1.8 million deaths from lung cancer;
- 900,000 deaths from colorectal cancer [1].

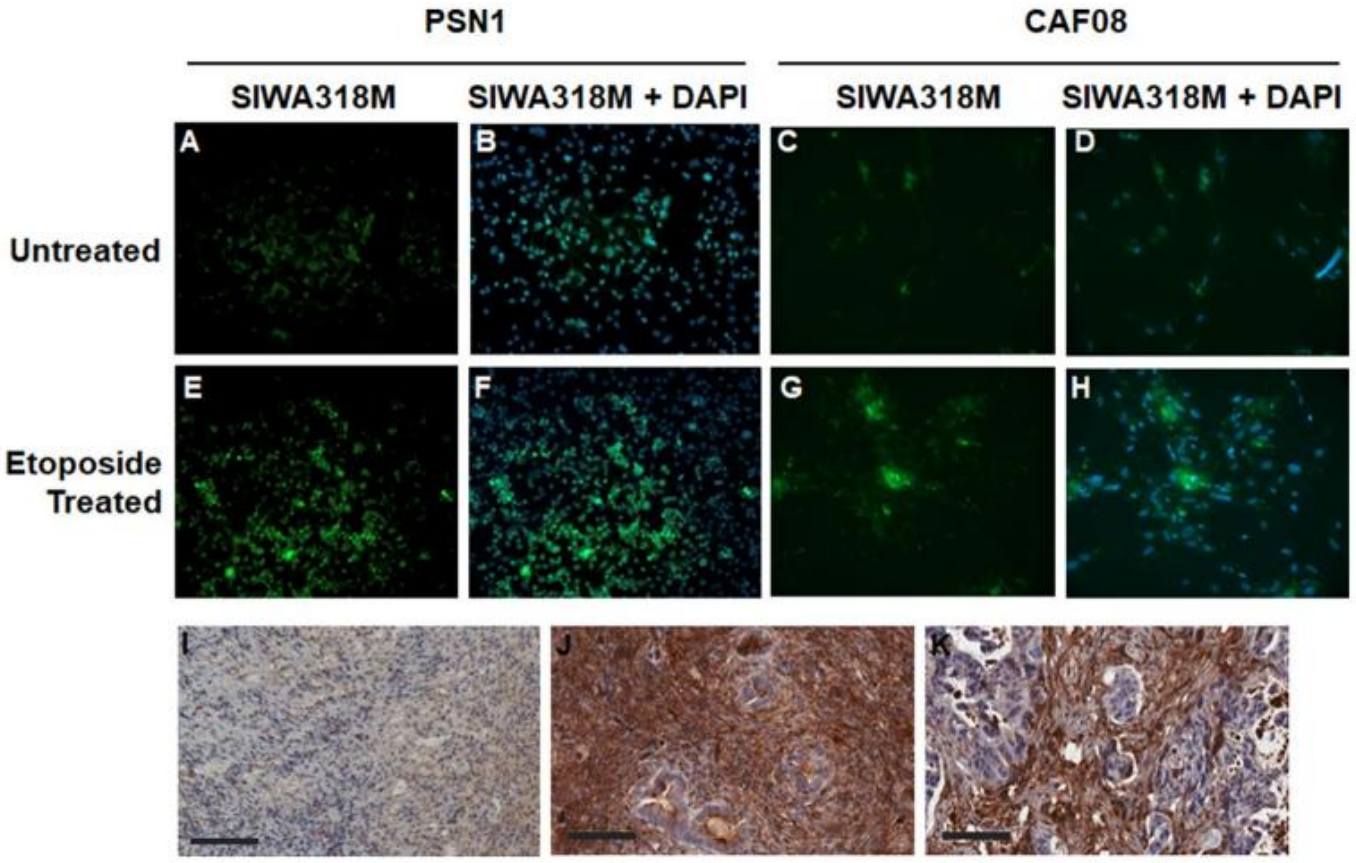
SIWA318H is a novel monoclonal antibody that selectively targets an advanced glycation end product biomarker found in damaged/dysfunctional cells exhibiting (a) aerobic glycolysis, and (b) oxidative stress. Cells with this biomarker are dysfunctional and are associated with stresses and/or damages relating to aging, cancer and other disease processes. SIWA318H binds to pancreatic cancer cells and cancer-associated fbroblasts, as well as tumor xenografts derived from pancreatic cancer patients. Furthermore, SIWA318H induced signifcant antibody-dependent cellmediated cytotoxicity (ADCC) against pancreatic cancer cells. In a humanized CD34+ NSG mouse xenograft model for pancreatic cancer, tumors in mice treated with SIWA318H grew signifcantly slower compared to those in control mice ($p< 0.001$). After 3 weeks of treatment with SIWA318H, the tumor growth was suppressed by 68.8% and 61.5% for the high and low dose regimens, respectively, when compared to the isotype antibody control (ANOVA $p< 0.002$). Moreover, a signifcant increase in complete remission (CR) rate was observed in mice receiving the high dose (60%, $p< 0.04$) or low dose (77.8%, $p< 0.02$) of SIWA318H treatment compared with control mice (6.7%). Immunohistochemical analyses of the tumor tissues showed a signifcant decrease in senescent cells in the tumor microenvironment of SIWA318H treated mice compared to that of control treated mice ($p< 0.05$). These results provide compelling evidence that SIWA318H is a promising novel therapeutic against pancreatic cancer [2].

***SIWA318 binds to senescent pancreatic cancer cells and cancer associated fbroblasts.***

To investigate the reactivity of SIWA318M (the murine equivalent of SIWA318H) towards pancreatic cancer cells and stromal fbroblasts, we performed immunofuorescence staining of the antibody in PSN1 (pancreatic cancer cells) and CAF08 (pancreatic cancer-associated fbroblasts) cells with or without the treatment of etoposide, a topoisomerase inhibitor known to induce cellular senescence. As shown in Fig. 1, without etoposide treatment, SIWA318M showed moderate reactivity to a small number of the cells (Fig. 1A–D). With etoposide treatment, the

immunofuorescence intensity and percent of cells stained positive were increased considerably (Fig. 1 E–H), which is consistent with the induction of senescence by etoposide [3].

**Figure 1**. SIWA318M and SIWA318H react with pancreatic cancer cells and cancer associated fbroblasts. Immunofuorescence staining was used to detect the binding of SIWA318M to pancreatic cancer cells (PSN1) and pancreatic cancer-associated fbroblasts (CAF08) untreated (A–D) or treated (E–H) with etoposide. IHC staining was used to detect the binding of SIWA318H to




the PSN1 xenograf tumor (I) and two pancreatic cancer patient derived xenograf tumors (J,K). Scale bar in (I–K)=100 μm. DAPI: 4′,6-diamidino-2- phenylindole.

To further verify the reactivity of SIWA318H towards pancreatic tumors, we performed immunochemical staining with SIWA318H in a PSN1 xenograf tumor and two pancreatic cancer PDX tumors. As can be seen in ***Fig. 1 I***, the PSN1 tumor cells showed moderate reactivity to SIWA318H, similar to PSN1 cells grown in vitro. In both PDX tumors, the stromal cells showed intense reactivity whereas the tumor cells showed relatively weak and patchy staining (Fig. 1J,K), indicating that in patient tumors the majority of the senescent cells are in the stroma compartment. SIWA318H mainly showed membranous and cytoplasmic staining with occasional nuclear staining in the PDX tumors whereas in the PSN1 tumors the staining intensity in cytoplasm/nuclei was much stronger than that on cell surface, which is again consistent with the cultured PSN1 cells in vitro. Te diference in the staining pattern between PDX tumors and the PSN1 tumor is probably due to the diference in stromal content between the two tumor types (PDX tumors have a much higher stroma content than the PSN1 tumor).

Terapeutic antibodies have been shown to interact with the immune activating Fcγ receptor, FcγRIIIa, and induce antibody-dependent cell-mediated cytotoxicity (ADCC) in solid tumors. To determine the binding afnity of SIWA318H towards FcγRIIIa we performed an FcγRIIIa binding immunoassay. SIWA318H binds to human FcγRIIIa at an afnity similar to that of the positive control antibody (antiCML monoclonal antibody, R&D Systems) (EC50: 59 vs. 13 μg/mL). Consistent with its binding activity towards FcγRIIIa, SIWA318H demonstrated a concentration dependent cytotoxicity against PSN1 cells in an ADCC.

Treatment of PSN1 cells with etoposide further increased the ADCC activity, consistent with the fnding that SIWA318H binds to senescent cells at a greater afnity [4].

Therefore, biotechnology experiments help us to obtain new possible cures for cancer. However, this problem remains relevant to this day, because universal drugs do not yet exist. So, it is necessary for everyone to undergo a full examination of the body once a year, in order to prevent the formation and spread of oncological diseases.

**References:**


1. Онкологічні захворювання: сухі цифри статистики - новини про медицину Запоріжжя та області Онкологічні захворювання: сухі цифри статистики. новини про медицину Запоріжжя та області. URL: https://medinfo.zp.ua/ua/novosti_mediciny_zaporozhya/onkologicheskie-zabolevanija-suhie-cifry-statistiki/ (дата звернення: 20.03.2024).
2. Advanced glycation end product (AGE) targeting antibody SIWA318H is efficacious in preclinical models for pancreatic cancer - Scientific Reports. Nature. URL: https://www.nature.com/articles/s41598-023-44211-6 (date of access: 20.03.2024).
3. Bousset, L. & Gil, J. Targeting senescence as an anticancer therapy. Mol. Oncol. 16, 3855–3880. (2022).
4. NK-mediated antibody-dependent cell-mediated cytotoxicity in solid tumors: biological evidence and clinical perspectives. Home Page. URL: https://doi.org/10.21037/atm.2019.01.42 (date of access: 20.03.2024).