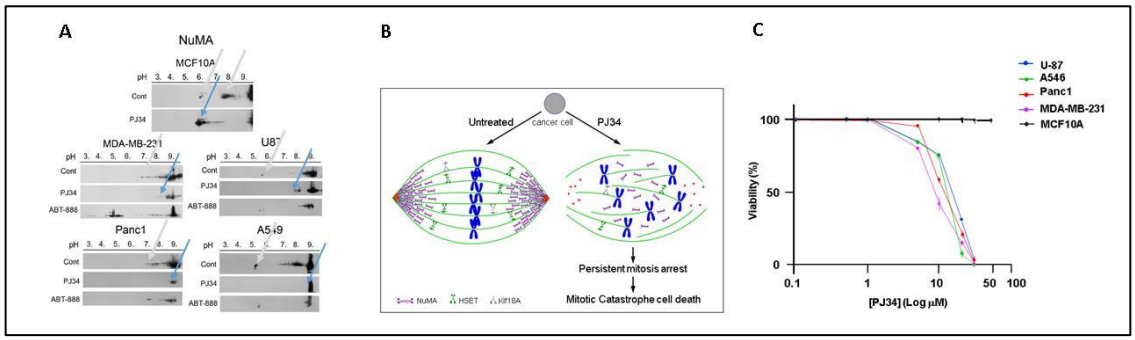
COMPANY OVERVIEW

- Phenancure is a preclinical stage drug discovery company based in Tel Aviv (Israel) with very successful preclinical data and a robust IP portfolio. The company is focused on developing precision medicines that exclusively eradicate human cancer cells during mitosis while sparing healthy cells. Currently focused on eradication of pancreatic cancers, a huge market, as a first entry indication, even though the preclinical experiments indicate a similar application in other epithelial cancer types including gastric, colon, liver, lung, ovary, glioblastoma. The therapeutic approach is based on faults exclusively inserted in the structure of the mitotic spindles of human cancer cells. The treatment causes a persistent mitosis arrest that ends by Mitotic Catastrophe cell death. Cancer cells in dish are eradicated within 72-96 hours. Cancer cells are eradicated in human tumors developed in immunocompromised mice (xenografts) after 14-days treatment. In order to reach clinical trials, the company is raising Round A investment, which will be based on achieved milestones.

- Scientific overview: Our goal is to develop the modified phenanthridine PJ34 for cancer therapy, including currently incurable cancer types. This therapy is based on a recently discovered cell-death mechanism induced in human malignant cells during mitosis. While PJ34 -treated healthy proliferating cells are not affected and continue to proliferate as untreated cells, PJ34 arrests mitosis in the anaphase in a variety of human malignant epithelial cells, including cancer cells resistant to current therapies, by introducing structural anomalies in their mitotic spindles. This prevents compliance with the Spindle Assembly Control mechanisms that arrest mitosis (G2/M arrest), and cell death follows. We identified by screening three proteins (the kinesins KifC1/HSET and kif18A and the protein NuMA). Their post-translational modification is prevented by PJ34 in human cancer cells, but not in healthy cells. Their post translational modification guarantees proper division of the chromosomes in the two "daughter" cells which is crucial for mitosis progress. Thus, by the exclusive block of specific kinases and tankyrase by PJ34, the required modification of these proteins in human malignant cells is prevented, faults are inserted in the mitotic spindle, mitosis is arrested and cell death follows. This linkage between the proteins' modifications, spindle structure and the cells' viability was documented by confocal imaging. In this cell death mechanism, malignant cells are self-eradicated during mitosis by violation of the spindle assembly control (SAC) mechanism. Thus, the more frequently PJ34 treated cancer cells start mitosis (or the more rapidly cancer tumors grow) the more efficiently they are eradicated.

Cohen-Armon, Drug Discovery Today, 2022
https://authors.elsevier.com/a/1ebx-4r9Rkjn4d



Exclusive cytotoxicity of PJ34 in malignant cells by blocking the post translational modification of NuMA. **A.** PJ34 blocks the post translational modification of NuMA only in malignant cells. Immunoblots of NuMA on 2-D gels indicating the post translational modification of NuMA , as measured by the shift in its isoelectric point in benign and malignant human cells treated with PJ34 versus untreated cells. **B.** A schematic presentation of faults inserted in the spindle structure by PJ34 in human cancer cells as identified by confocal microscopy. In the PJ34 treated cancer cell, aberrant microtubules (**green**),

aberrant spindle poles, un-clustered NuMA (**purple**), dispersed chromosomes (**blue**) and un-clustered centrosome (**red**) ***C.*** PJ34 is cytotoxic only in the four human malignant epithelial cells. Healthy human epithelial cells are not affected.

- Pancreatic Cancer: This is an unmet clinical need and a major therapy market. Global incidence of the condition is, with a market value of 1,904.20 million in 2019 and expected to reach $4,728.19 Million by 2026 (CAGR of 10.6%) (https://www.marketwatch.com/press-release/pancreatic-cancer-market-size-valued-at-472819-million-by-2026-and-expected-to-grow-with-cagr-of-106-2019-08-23)

  Despite a substantial advance in cancer treatment, pancreatic ductal adenocarcinomas (PDAC) have a limited response to current treatments, and the lowest 5-years survival rate of about 6%. With an incidence of around 55,000 cases a year, pancreatic cancer is designated as an orphan indication. However, due to the very poor survival rate of patients, pancreatic cancer, is the third leading cause of cancer related deaths in the US (~45, 000 deaths annually) and will be second only to lung cancer by 2030. The advances in therapies for other solid tumors, using a molecular targeted approach, are not replicated for treating PDAC pancreatic cancer, with median overall survival remaining less than one year. Thus, there is an urgent need to explore improved therapies with better efficacy and less toxicity. While genomic analyses of pancreatic cancers may result in therapeutic modalities that exploit differences in growth, proliferation and metastasis by trying to target specific aberrant pathways, a therapy with broader application would make a larger impact on overall outcomes for pancreatic cancers as a whole. Therapies that are currently widely used have significant toxicities. Thus, specific cancer targeted drugs are required. A stand-alone drug therapy that is not toxic to healthy cells, but is highly lethal to cancer cells would be a major advancement for the treatment of pancreatic cancers. Recent reports of the selective interference of the modified phenanthridine PJ34 in the replication of carcinoma cells, may present such an opportunity.

- Phenancure's differentiated approach:

  Depending on the type and stage of the cancer and the patient health condition, treatment options for people with resistant cancer types can include: surgery, ablation, radiation therapy, chemotherapy, immunotherapy, and targeting mutant gene either by silencing using a local application of siRNA or by systemic application of small molecules destroying all types of cells, for example by causing a persistent DNA damage. Except for surgery for patients that can benefit from this treatment, none of the other treatments significantly increased the life span and quality of life of incurable cancer patients. Unlike various chemotherapy or invasive interference, in the approach of Phenancure, only malignant cells are efficiently eradicated by an exclusive cell death mechanism that does not harm healthy cells. All the tested cancer cells that were eradicated by PJ34, are resistant to currently used cancer therapy. Furthermore, unlike chemotherapy and radiations, PJ34 does not impair the weight gain of treated mice that developed the human cancer tumors (xenografts), neither during treatment nor up to 4 months following the treatment. The toxicity of PJ34 was tested in PDAC xenografts and in triple negative breast cancer xenografts. In addition, a slowly released PJ34 for 14 days (from implanted osmotic Alzet pump) prevented the formation of tumors in immunocompromised mice injected with triple negative breast cancer cells MDA-MB-231. This stand-alone drug therapy that is not toxic to healthy cells, but is selectively lethal to cancer cells would be a major advancement for cancer treatment invented by Phenancure. Recent reports of the selective interference of the modified phenanthridine PJ34 with the replication of carcinoma cells suggest a new mechanism of cancer therapy, which is efficient in various cancers types https://doi.org/10.3390/cancers12061628.

  Experiments with human cancer cell cultures and xenografts show exclusive cell eradication in a variety of highly resistant cancer types. In-vivo experiments are performed at the CRO company, Pharmaseed (Israel). In human PANC1 derived xenografts in murine models, 14 days of PJ34 daily IV treatment eradicated 90-95% of the PANC1 cells in the tumors without impairing weight gain and development of the treated mice. PJ34 is well tolerated without any signs of stress in the IV injected mice. PJ34 is injected in saline. The measured parameters of PK, PK of repetitive dosing, MTD, per-os bioavailability, efficacy and permeability in the cell membranes justify testing PJ34 for drug design. According to the PK pharmacokinetics of PJ34, the molecule is rapidly

distributed from the plasma into tissues with a high volume of distribution (Vd), yet it does not accumulate in the tissues after repetitive IV applications. In view of the oral bioavailability of 33.3% formulation of PJ34 for oral application is required. The experimental reports are confidential and will be shared under NDA.
In collaboration with the college of Pharmacy, University of Florida, analog molecules with similar features will be tested.

- Team: Prof. Cohen-Armon, Founder of Phenancure and CTO, earned her degrees in the Technion, Haifa (B.Sc.in Chemistry, *Cum Laude*, D.Sc. in Biophysics & Electrophysiology, Supervisor: prof Yoram Palti), was a visiting researcher in Columbia University NY, a leader of research group in the Tel-Aviv University Sackler School of Medicine Dept. of Physiology and Pharmacology. Her collaborators are consultants in Phenancure: the oncologists Prof. Tamar Peretz (head of Sharet oncol. In Hadassah medical center), Prof. Shai Izraeli (director of the Hematology-oncology Dept. in Schneider Children's medical center). Other team members are Dr. Asher Castiel (COO), Dr. Dana Inbar-Rozensal (QA) and Dr. Leonid Visochek (director of Lab).

- IP: US:"Cancer therapy":US 8,729,080 B2, granted,2014; CIP US 9,486,449 B2, granted, 2016.European (UK, Germany, France):"Breast cancer therapy": WO2009/047752, granted, 2013, EP2207548B1. The patents cover our therapeutic approach.