The long-term goal of our laboratory is to understand the mechanism that drives cancer cells to resist therapy, invade and metastasize, and eventually to develop the means to inhibit it. Our group focuses on solid tumors such as glioblastoma, melanoma, thyroid and pancreatic cancer. We have found evidence that the normal cells in the vicinity of tumors secret factors that change its microenvironment and contribute to cancer resistance to treatment, progression and dissemination. The rationale for the research is that once it is known which proteins trigger invasion and metastases, their activity could be targeted pharmacologically in an innovative approach to prevent cancer spread. Our approach is based on newly developed in vitro assays that allow us to image cancer cell locomotion and invasion using video microscopy and live fluorescent imaging. Furthermore, novel in vivo genetic models that were developed in the laboratory allow us monitoring of cancer cell invasion and proliferation using high resolution imaging modalities. The staff of the laboratory consists of a multidisciplinary research team from different fields including: molecular biology, neurobiology, oncology, surgery, imaging, protein analysis and pathology. The scientific environment at the lab allows the students and researchers to master technologies directed at investigating cancer cells in their natural environment and to obtain training in applied cancer research. The program involves collaboration with the Department of Surgery, Memorial Sloan-Kettering Cancer Center, including exchange of students, knowledge and scientific tools.

Ongoing research projects

Mechanisms of neural invasion by pancreatic cancer

Tumor invasion onto peripheral nerves is a notorious clinical feature of various cancers, including head and neck, prostate and pancreatic carcinomas. In order to investigate the patterns of neural invasion we developed a novel in vitro model in which we neural cells within their microenvironment are simultaneously grown with cancer cells in a plate. The ability of various neurotrophic carcinomas to migrate along nerves was investigated. Confocal microscopy and time-lapse analysis showed that immune cells called macrophages support cancer cell unidirectional migration along nerves. Our current research concentrate on exploring the mechanisms involved in neural invasion; and to evaluate the ability of small molecules to inhibit
this process using a novel transgenic in vivo animal model that reliably recapitulate human pancreatic cancer.

**Mechanisms of drug resistance of pancreatic cancer**

Resistance to pharmacologic agents used in chemotherapy is common in most human carcinomas, including pancreatic cancer, which is resistant to almost all drugs, including gemcitabine, a nucleoside analog used as a first-line treatment. Poor survival rates of PDA patients have, therefore, not changed much over 4 decades. Our data shows that macrophages, which are abundant in the microenvironment pancreatic cancer, secrete pro-tumorigenic factors that contribute to cancer progression. Our team discovered the mechanism responsible for chemoresistance of pancreatic cancer by reducing gemcitabine-induced cancer cell "suicide". Our current efforts focus on the communication between macrophage and cancer cells via nanovesicles called exosomes. These vesicles carries genetic data that modulate cancer cells sensitivity to chemotherapy by inducing cytidine deaminase (CDA), the enzyme that metabolizes the drug following its transport into the cell; hence make them resistant to therapy. Inhibiting this mode of communication may offer a new strategy for augmenting the response of PDA to chemotherapy.

**Oncogenesis mechanisms of thyroid cancer**

Thyroid cancer is a common endocrine malignancy, which in recent years has steadily increased world-wide. In the last two decades, many studies have focused on the genetic factors behind the origin and the development of thyroid cancer, in order to investigate and shed more light on the molecular pathways implicated in different differentiated or undifferentiated types of thyroid tumors. The aim of our research is to further explore the role protein post-translational modification and intracellular trafficking and thyroid oncogenesis. This is a new field of study in thyroid tumorigenesis but we believe that this might play a major role in the initiation and progression of thyroid cancer and will lead to novel detection methods, biomarkers and therapeutic targets for thyroid cancer.

**Endoscopic delivery of cold plasma for treatment of cancer**

Minimally invasive surgery (MIS) technology has revolutionized the practice of surgery. In MIS surgeons use a variety of techniques to operate with less injury to the body than with open surgery. In general, it is safer than open surgery and allows faster recovery with less pain and scarring. MIS is usually done on an outpatient basis or requires only a short hospital stay.

Inspired by use of plasma in industrial processes such as sterilization and material fabrication, plasma medicine is emerging as a new independent medical field. Plasma medicine is envisioned to transform the landscape of many medical procedures such as the treatment of chronic wounds, tissue regeneration, skin disease and dental applications. One exceptionally appealing form of plasma, Non-Thermal Plasma (NTP), has been proposed in recent years as new modality for cancer treatment. NTP is a stream of a low-ionized gas at room-temperature generated by dielectric barrier discharge (DBD). It is accompanied by visible, infra-red (IR) and UV radiations, as well as with free-radicals and ozone. The type and intensity of the radicals and radiation emitted with NTP depends on the gas used for its formation.

NTP is suggested as a promising new modality for cancer treatment owing to its ability to selectively kill cancer cells without causing harm to the adjacent normal cells. Moreover, at different doses of exposure, NTP has divergent effects on mammalian cells: at a low delivery
power for short exposure periods, NTP will encourage cell proliferation and promote wound healing; at median power and exposures, NTP causes cells to undergo programmed cell death (Apoptosis); at high power and exposure, NTP causes necrosis, an unregulated digestion of cellular components. NTP probably poses its activity on biological material by exposure to reactive chemical species, and especially reactive oxygen and nitrogen species. NTP exposure leads to oxidative stress in the treated tissue, triggering the death of the more stress-sensitive tissue component - the cancer cells \(^6\).\(^1\).

In 2014 we have established collaboration with the Physics Department at the Technion, aiming to develop an NTP source suitable for endoscopic use. Our team has designed, developed and patented a prototype of an NTP source enabling safe and efficient delivery of NTP to desired locations inside the human body, on top of conventionally used endoscopes. The properties of our NTP generator and the NTP itself are compatible with the guidelines of the International Commission on Non-Ionizing Radiation Protection (ICNIRP), and the EU directives (2002/3/EG) for long-term expositions to toxic gas.

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