Hadassa Degani

Sveta Adamsky
Liora Bogin
Maya Chetrit
Galit Eliyahu
Edna Haran
Raanan Margalit
Nimrod Maril
Yael Paran
Dalia Segal
Edna Rushkin
Dalia Seger

Breast and prostate cancer research; From molecular to *in vivo* imaging studies

Department of Biological Regulation

Tel. 972 8 934 3920 **Fax.** 972 8 934 4186
E-mail: hadassa.degani@weizmann.ac.il

The goals of our research are based on investigating tumor growth, progression, treatment and eradication, using molecular, cellular and non invasive imaging methodologies.

In recent years our work focused on

1. Regulation of tumor angiogenesis and metastasis.
2. Regulation of glucose transport and metabolism in breast cancer.
3. The role of phospholipid metabolism in malignant transformation.
4. Developing sodium MRI as a tool to monitor regional and cellular changes in sodium gradients

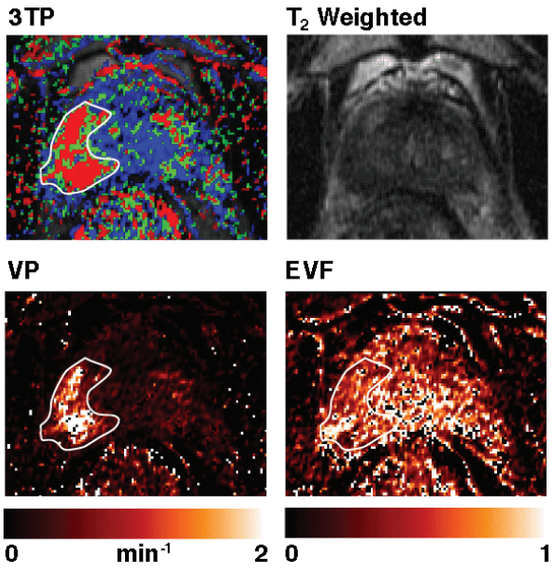

Fig. 1 *Parametric MRI of the prostate. The tumor is characterized by high vascular permeability (VP) and hetrogeneous extracellular volume Fraction (EVF). The 3TP image delineates better tumor margins.*

Part of our efforts focused on developing and improving magnetic resonance imaging (MRI) and spectroscopic (MRS) methods that are non-invasive and can be applied *in vivo*. These methods can monitor dynamic processes at steady state and during changing conditions. It has the capability to provide image contrast based on several independent nuclear magnetic properties as well as on metabolic and physiologic characteristics. It can also image molecules tagged with magnetically sensitive probes and thereby enhance molecular targeted imaging.

The imaging technology developed in our laboratory in recent years reached the state of clinical testing. New parametric MRI methods, including the 3TP (Three Time Point) method for the diagnosis of prostate cancer and of breast cancer are being evaluated in Israel (Tel Aviv Sourasky Medical Center) and USA (University of Wisconsin, Illinois Masonic Medical Center, Hospital of Boca Raton). An example of parametric MRI of the prostate is shown in Fig. 1.

Our current research activities include

1. Investigations of hormonal and drug induced modulations in tumor vasculature. Along with molecular studies of VEGF expression, *in vitro*, methods to monitor tumor perfusion and vascular function *in vivo* are applied. For example, a method based on deuterium MRI with deuterated water as a tracer was developed and utilized to map at high resolution the perfusion rate and the percentage of vascular fraction in orthotopic human breast cancer tumors in nude mice (Fig. 2).

2. Establishing animal models for breast and prostate cancer metastasis and developing MRI and molecular imaging methods to monitor *in vivo* invasion into lymph nodes, bone and lung.

3. Characterization of estrogen and retinoic acid regulation of the glucose transporter - GLUT1, glucose transport, and glycolysis in human breast cancer cells and in tumors in animal models using molecular, cellular and *in vivo* methodologies.

4. Investigating the cause and involvement of increased phosphocholine in the initiation and progression of malignant transfortmaion in human mammary epithelial cells.

5. Imaging tissue sodium at high resolution. As sodium gradients play a major role in the function of the kidney we developed Na- renal imaging and monitored dynamic changes in the spatial distribution of sodium *in vivo*. This approach is being extended to study tumors and to monitor changes in cellular sodium gradients.

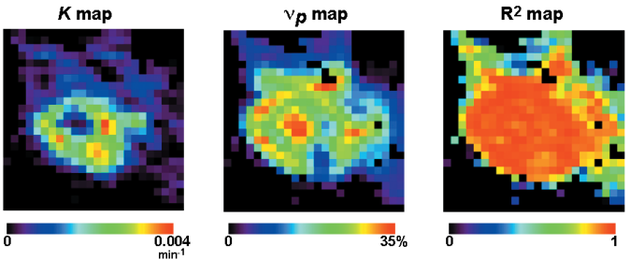

Fig. 2 *Parametric MR imaging of HDO perfusion in MCF7 human breast tumors. K - Pertusion rate, υ_p - percentage of intravascular volume, R^2 - quality of fitting.*

Selected Publications

Bogin L. , M. Z. Papa, S. Polak-Charcon, and H. Degani. (1998) TNF modulations of membrane associated enzymes in human breast cancer cells: NMR studies Biochem. Biophys. Acta , 1392, 217-232.

Dahan-Grobgeld E., Z. Livneh, A. F. Maretzek, S. Polak-Charcon, Z. Eichenbaum, and H.Degani. (1998), Reversible Induction of ATP synthesis by DNA Damage and Repair in *E. coli*; *In vivo* NMR Studies. J. Biol. Chem. 273, 30232-30238.

Furman-Haran E., D. Grobgeld and H. Degani, (1998) Decreased cellular volume fraction and increased microvascular permeability indicate response of MCF7 xenografts to tamoxifen; application of the 3 time point contrast enhanced MRI method. Clin. Cancer Res. 4, 2299-2304.

Weinstein D., S, Strano, P. Cohen, S. Fields, J. M. Gomori, and H. Degani, (1999) Mapping pathophysiologic features of breast fibroadenoma by the three time point (3tp) contrast enhanced MRI method: pilot study. Radiology 210, 233-40.

Maril N., H. Degani, E. Rushkin, A. D. Sherry and M. Cohn, (1999), The mechanism of cyclocreatine activity in human breast cancer cells: kinetics of cyclocreatine and sodium co-transport. J. Am. Physiol., 277, C708-C716.

Rivenzon-Segal D., E. Rushkin, S. Polak-Charcon and H. Degani, (2000) Glucose transporters and transport kinetics in retinoic acid-differentiated T47D human breast cancer cells". Am. J. Physiol 279, E508-E519.

Furman-Haran E., D. Grobgeld, F. Kelez and H. Degani, , (2001) The critical role of spatial resolution in dynamic contrast enhanced breast MRI. J. Magn. Res. Imag. 13, 862-867.

Katz-Brull R., R. Margalit and H. Degani, (2001) Differential routing of choline in implanted breast cancer and normal organs. Magn. Reson. Med. 46, 31-38.

Ikeda D.M. , N.M. Hilton, K. Kinkel, M.G. Hochman, C.K. Kuhl, W.A.Kaiser, J.C. Weinreb, S.F. Smazal, H. Degani, P. Viehweg, J. Barclay, M.D. Schnall. (2001) Development, standardization, and testing of a lexicon for reporting contrast enhanced breast magnetic resonance imaging studies. J. Magn. Reson. Imag. 13, 889-895.

Acknowledgements

H.D is the incumbent of the Andrea Fallek Professorial Chair for Breast Cancer Research and heads the Willner Family Center for Vascular Biology.

We are very grateful for the continuous support and encouragement of Mrs. Andrea Fallek, USA and of Sir David Alliance, CBE UK.

The work is supported by the NIH, Komen Foundation, Capcure Foundation, BSF Foundation, Washington Square Health Foundation, Keren Izvonot Israel Ministry of Health, Pasteur-Weizmann-Negri Cooperation and Israel Science Foundation.

We would like to acknowledge the productive cooperation with Prof. Kelcz, University of Wisconsin; Dr. Kirshenbaum, Illinois Masonic Medical Center; Drs. Wiener and Schilling, Hospital of Boca Raton; Profs. Matzkin and Greif, Drs. Ben Bashat, Levine, Bar Yosef, Schreiber, Tel Aviv, Sourasky Medical Center.