THE HUMAN BIOLOGY RESEARCH CENTER (HBRC)

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INTRODUCTION

The HBRC is associated with the Department of Medical Biophysics and Nuclear Medicine and benefits from its active support. The HBRC serves as a biomedical research center unique to the Middle East and Middle and Eastern Europe in that it combines several basic research programs with clinical applications of the most advanced medical imaging equipment. It is composed of four main units:

1. An NMR (Nuclear Magnetic Resonance) Spectroscopy Unit equipped with: one high resolution 400 Mhz spectrometer dedicated to the analysis of small living organisms and organs; one 4.7 Tesla 40 cm wide spectroscopic imager, dedicated to animal research. This unit supports and complements the Clinical Magnetic Resonance Imaging Unit of the Hospital.

2. A Positron Emission Tomography (PET)-Cyclotron unit, allowing functional imaging of the human body under physiological and pathological conditions. PET imaging is one of the most advanced technologies in medical imaging. It makes use of short-lived radio-isotopes of natural chemicals of the body (produced by an onsite cyclotron) which permit the detection of subtle changes in the chemistry of various organs (such as the brain during mental activities, the heart during stress and drug-induced stimulation, cancers at different stages in any part of the body) without any injury to the patient.
This is the only PET-Cyclotron unit that exists in Israel. It is run by the Medical Biophysics and Nuclear Medicine Department at Hadassah Hospital and provides specific radio-isotopes to other centers in the country.

3. A unit of Image Computer Processing, Computer Modeling and Artificial Intelligence.

4. A basic research laboratory with emphasis on cell biophysics and in-vivo proteomics, immunology, and techniques for immunotherapy. The infrastructure includes a stage P3-lab, equipped and specialized in dealing with pathogenic microorganisms, e.g., HIV. Its major research is centered on Diabetes and Multiple sclerosis as autoimmune diseases, as well as research in AIDS, developing the concept of T cell vaccination into clinical trials. This research is the product of an active collaboration with Prof. Irun Cohen of the Weizmann Institute.

RESEARCH GROUPS

1. NMR (Nuclear Magnetic Resonance) Spectroscopy

PI: Goelman, G., PhD

Staff: Abramovitch, R., PhD

Introduction:

The following research projects are carried out:

- Functional MRI (Magnetic Resonance Imaging) studies of a rat model of Parkinson's disease.
- Functional characterization of motor cortical areas of a rat with fMRI.
- Development of MRI methods for evaluating the feasibility of VEGF (Vascular Endothelial Growth Factor)-mediated pro-angiogenic therapy.
- Transplantation of Glial Precursor cell spheres in chronic experimental autoimmune encephalomyelitis: Evaluation and follow-up by magnetization transfer MRI.
- Development of new approaches for Functional Neuroimaging (fMRI) by synchronization measurements in the functioning brain.
- Development of new MRI contrast-based on spatial correlation - application for tumor angiogenesis.

- Testing the effect of FTS (Farnesyl Thiosalicylic Acid) on recovery from head trauma.
- Perfusion, diffusion and blood volume measurement on a mouse model of head trauma of c57b CB1 (Central Cannabinoid) receptor transgenic mice and the effect of 2AG (Arachidonoyl Glycerol).
- High b values diffusion MRI to study tumor physiology.
- Cortical layer mapping using connectivity fMRI.
- Application of human brain magnetic resonance spectroscopy for characterization of lesions in Multiple Sclerosis patients.
- Neuronal plasticity and the reward system - fMRI study in animal model.

Keywords: Functional MRI. Parkinson's Disease. Head Trauma. Functional Collectivity. Tumor Vascularity.

Recent publications:

Zaroubi S., and Goelman G. (2000) Complex Denoising of MR Data Via Wavelet Analysis: Application for Functional MRI. Magn. Reson. Imaging, 18(1):59-68.

Goelman G. (2000) Fast 3D T2-Weighted MRI with Hadamard Encoding in the Slice Select Direction. Magn. Reson. Imag., 18:939-945.

Pelled G., Bergman H., and Goelman G. (2002) Bilateral overactivation of the sensorimotor cortex in the unilateral rodent model of Parkinson's disease - a functional magnetic resonance imaging study. European J. of Neuroscience, 15:389-394.

Dor Y., Djonov V., Abramovitch R., Itin A., Fishman G.I., Carmeliet P., Goelman G., Keshet E. (2002) Conditional switching of VEGF provides new insights into adult neovascularization and pro-angiogenic therapy. EMBO J, 21(8):1939-1947.

2. PET

PI: Chisin, R., MD

Staff: Bocher, M., MD
Freedman, N., PhD
Karger, H., MSc
Klein, M., MD
Krausz, Y., MD
Lester, H., PhD
Rubinstein, R., MD

Introduction:

The PET camera, the first to be installed in Israel in July '95, began to generate cardiac scintigraphies using Rubidium generators. In July '97, PET imaging was possible with cyclotron-produced radiotracers: first 18-FluoroDeoxyglucose and then 0-15-labelled water, C-11-Deprenyl, C-11-Choline and 18-F-FluoroDopa.
PET research projects are pursued in Cardiology, Oncology, Pulmonology, Neurology and Psychiatry through an active collaboration of the Department of Medical Biophysics and Nuclear Medicine, which runs the PET facility, with the physicians from these departments.

Keywords: PET. SUV. Patlak. Oncology. Melanoma. Lung cancer. Thyroid. Nasopharyngeal carcinoma. Neck. Rb-82. 150-H2O activation.

Recent publications:

Klein M., Freedman N., Mishani E., Gimon Z., Lotem M., Chisin R. (2000) PET and lymphoscintigraphic evaluation of malignant melanomas. Nuklear Medizin, 39:56-61.

Freedman N., Schechter D., Klein M., Marciano R., Rozenman Y., Chisin R. (2000) Retrospective Comparison between Rb-82 PET and Tl-201 SPECT Myocardial Perfusion Imaging: Insights into SPECT Attenuation Artifacts in Normal and Overweight Subjects. Clin. Nucl. Med., 25:1019-1023.

Nunez R., Yeung H., and Chisin R. (2000) Fluorine-18 FDG Positron Emission Tomography in Advanced Nasopharyngeal Carcinoma. Clin. Nucl. Med., 25:731-733.

Akhurst T., and Chisin R. (2000) Hybrid PET/CT machines: optimized PET machines for the new millennium? Letter to the Editor. J. Nucl. Med., 41:961-962.

Chisin R. and Macapinlac H.A. (2000) The Indications of FDG-PET in Neck Oncology. Radiological Clinics of North America, 38:999-1011.

Bocher M., Mishani E. (2000) The contribution of Positron Emission Tomography-PET to patient management in oncology. Harefuah, 139:64-67.

Rubinstein R., Broier R., Chisin R. (2001) The Contribution of FDG-PET to Diagnosis and Management of Lung Cancer - First Results. Harefuah, 140:100-103.

Ramos C.D., Erdi Y.E., Gonen M., Riedel E., Yeung H.W.D., Macapinlac H.A., Chisin R., Larson S.M. (2001) FDG-PET standardized uptake values in normal anatomical structures using iterative reconstruction segmented attenuation correction and filtered back projection. Eur. J. Nucl.Med., 28:155-164..

Ramos C.D., Chisin R., Yeung H.W.D., Larson S.M., Macapinlac H.A. (2001) Incidental focal thyroid uptake on FDG-PET scans should not be overlooked. Clin. Nucl. Med., 26:193-197.

Bocher M., Chisin R., Parag Y., Freedman N., Meir-Weil Y., Lester H., Mishani E., and Bonne O. (2001) Cerebral Activation Associated with Sexual Arousal in Response to a Pornographic Clip: A 15O-H2O PET Study in Heterosexual Men. Neuroimage, 14:105-117.

Freedman N.M.T., Sundaram S.K., Kurdziel K., Carrasquillo J.A., Whatley M., Carson J.M., Sellers D., Libutti S.K., Yang J.C., Bacharach S.L. (2002). Comparison of SUV and Patlak Slope to Monitor Cancer Therapy Using Serial PET Scans. Eur. J. Nucl. Med. (In Press).

3. Cyclotron

PI: Mishani, E., PhD

Staff: Froimovici, S., MSc
Rozen, Y., MSc

Introduction:

The aim of the research activities carried out in this unit is to non-invasively study human biology, using PET, and to promote the development and utilization of cyclotron-produced radiopharmaceuticals by 1) conducting basic research allowing for the development of new labeling agents, new labeling methods, design, synthesis, and biological evaluation of novel PET biomarkers with high "chemical resolution;" 2) improving existing methods in order to study physiological, biochemical and pharmacological functions at the molecular level, whether in healthy subjects or in patients; and 3) prompting technical developments supporting the above-mentioned activities, such as targeting development for the production of radioisotopes, automation of radiochemical processes, etc.

The following research projects are carried out:
- PET and EGFR (Epidermal Growth Factor Receptor);
- PET and MAO-B (Monoamineoxidase-B);
- Dopamine and PET;
- C-11Choline;
- Technical Developments;
- Monitoring gene expression using PET and
- 5FU; 124I and 76Br Production.

Keywords: PET. Carbon-11. Fluorine-18. EGFR-TK (Tyrosine Kinase). Isotopes.

Recent publications:

Mishani E., Bocher M., Ben David I., Rozen Y., Laki D., Marciano M., Chisin R. (2001) [C-11]Choline - automated preparation and clinical utilization. J. Labl. Comp. Radiopharm., 44S:379-381.

Bonasera T.A., Ortu G., Rozen Y., Krais R., Freedman N.M.T., Chisin R., Gazit A., Levitzki A., and Mishani E. (2001) Potential 18F-Labeled Biomarkers for Epidermal Growth Factor Receptor Tyrosine Kinase. J. of Nucl. Med. and Biol., 28(4):359-374.

Mishani E., Ben David I., Rozen Y., Ortu G., Levitzki A. (2001) Carbon-11 Labeled Irreversible Inhibitors for Mapping Epidermal Growth Factor Receptor Tyrosine Kinase (EGFR-TK). J. Labl. Comp. Radiopharm., 44S:94-96.

Mishani E., Ben David I. (2001) [C-11] Acryloyl Chloride- A Fully Automated Preparation and Reaction with Model Amine. J. Labl. Comp. Radiopharm., 44S:475-476.

Ortu G., Ben-David I., Rozen Y., Levitzki A., Mishani E. (2001) Biological Evaluation of A Novel C-11 Labelled Irreversible EGFRTK Inhibitor. The Quar. J. of Nucl. Med., 45S:7.

Ortu G., Ben-David I., Rozen Y., Freedman N.M.T., Chisin R., Levitzki, A., Mishani E. (2002) In-vitro and In-vivo investigation of an irreversible labeled EGFr inhibitor (ML03) and its potential as PET biomarker in cancer and feasibility as an anticancer drug. Int. J. of Cancer, 101:360-370.

Mishani E., Ben-David I., Rozen Y. (2002) Improved method for the quality assurance of [C-11]choline. J. of Nucl. Med. and Biol., 29:359-362.

Ben-David I., Rozen Y., Ortu G., and Mishani E. (2002) Radiosynthesis of a Novel Positron Emission Tomography Biomarker, Targeting Epidermal Growth Factor Receptor Tyrosine Kinase Via [C-11]Acryloyl Chloride Labeling Synthon. Appl. Rad. And Isotp. (In Press).

4. Immunology and T-Cell Vaccination

PI: Abulafia-Lapid, R., Ph.D.

Staff: Amiel, M., M.Sc.
Baruch, K., B.Sc.
Keren-Zur, Y., B.Sc.
Schor, H., Ph.D.
Yachnin, J.,B.Sc.

Introduction:

T-cell Vaccination for HIV-infected Patients
Project 1. A protocol was developed for treating HIV-infected patients using attenuated autologous anti-CD4 auto-reactive T-cells as vaccines.
Project 2. T-Cell and peptide vaccination - a novel therapy for HIV-seropositive patients.
T-Cell Responses and auto-antibodies to human hsp70, but not to hsp90 in children with Type 1 diabetes
A new protein involved in Type 1 diabetes autoimmmunity was found. Peptides from this new protein (hsp70) can be used for vaccination therapy.
T-Cell Vaccination for patients with Multiple Sclerosis (MS)
We shall perform a phase I/II double-blind, controlled clinical trial designed to evaluate the safety and response to autologous T-cell vaccination in MS patients which showed severe progression/deterioration in the functional status. This protocol has been approved by the Helsinki Committee of the Hadassah Medical Center and by the Israeli Health Ministry, 2002 (Abulafia-Lapid R., Schor H., and Karusis D. T-cell Vaccination for Multiple Sclerosis Patients: A Phase I/II Clinical Trial Protocol).

Keywords: Autoimmunity. Diabetes Type 1. MS-Multiple Sclerosis. T-Cell Vaccination. MBP-Myelin Basic Protein. MOG-Myelin Oligodendrocyte Glycoprotein.

Recent Publications:

Abulafia-Lapid, R., Bentwich, Z., Keren-Zur, Y., Cohen, I.R., and Atlan, H. (2002) Anti-CD4 Autoimmunity in HIV-infected Patients: An Open Trial of T-cell Vaccination. AIDS (In Press).

Abulafia-Lapid R., Gillis D., Yosef O., Atlan H., and Cohen I. (2002) T-Cell and Auto-antibodies to Human hsp70 in Type 1I Diabetes (IDDM) Children. Journal of Autoimmunity (In Press).

5. In-vivo functional proteomics and Epigenetic Memory

PI: Atlan, H., MD, PhD

Staff: Panet, R., PhD
Stav. I., BA
Taraboulos, A., PhD (Hebrew University)

Introduction:

1. The role of ion-protein interactions in signal transduction has been documented: the bumetanide and furosemide sensitive $Na^+K^+Cl^-$ cotransporter controls cell growth in 3T3 mouse fibroblasts and in primary cultures of human lymphocytes. This finding was supported by studying the effects of overexpression of the transporter gene on cell proliferation and the effects of the cotransporter activity on the signaling pathway in normal and transfected cells under arrest and after stimulation by growth factors.

2. In vivo changes in protein structures correlating with different cellular states are studied by looking for changes in the hydrophobicity of proteins by means of hydrophobic interaction chromatography (HIC) and for changes in their attachment to cellular membranes by means of a novel CHAPS flotation technique. Such modifications were observed on Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in human lymphocytes two hours after PHA activation.

Keywords: $Na^+K^+Cl^-$ cotransport. Signal transduction. MAPkinase. GAPDH. HIC. CHAPS flotation.

Recent Publications:

Panet R., Marcus M., and Atlan H. (2000) Over-expression of the $Na^+K^+Cl^-$ cotransporter gene induces cell proliferation and phenotypic transformation in mouse fibroblasts. Journal of Cellular Physiology, 182:109-118.

Atlan H. (2001). Epigenesis and Self-Organization: New Perspectives in Biology and Medicine, in Conformational Diseases - A compendium, B. Solomon, A. Taraboulos, E. Katchalski-Katsir eds., The Center for the Study of Emerging Diseases, Bialik Institute Jerusalem and Karger, Basel, 291-297.

Panet R., Eliash M., Pick M., and Atlan H. (2002) $Na^+/K^+/Cl^-$ Cotransporter Activates Mitogen-Activated Protein Kinase in Fibroblasts and Lymphocytes. J. Cellul. Physiol.,190:227-237.

6. Theoretical Biology and Philosophy of Biology

PI: Atlan, H., M.D., Ph.D.

Staff: Becker, T., Ph.D. Student
Cohen, I.R., Ph.D. (Weizmann Institute)
Louzoun, Y., Ph.D. Student
Solomon, S., Ph.D. (Hebrew University)
Stroweis, I., MA

Introduction:

Structural and functional self-organization properties are studied by computer simulations. Different classes of self-organization can be defined according to the degree to which the meaning of their emerging properties is pre-defined. The biological relevance of these top-down, generic models is compared with that of bottom-up modeling of specific data on biological complex systems. The power and limitations of different modeling techniques are exemplified by applications to sets of data on the onset, prevention and treatment of experimental autoimmune diseases.
In addition to technical problems of modeling complexity, the present genomic and post-genomic state of biology creates ethical problems which must be approached at different levels, from viewpoints. both internal and external. to biological data proper.

Keywords: Self-organization. Artificial Intelligence. Bio-complexity. Immune Systems. Ethics of Biology.

Recent Publications:

Atlan H. (2000) Self-organizing networks: weak, strong and intentional, the role of their underdetermination, in Self-Organizing Dynamics and Semantic Structures in Cognitive Systems, ed. A. Carsetti, Kluwer Academic Publ. Dordrecht, pp.127-142.

Koppel M., and Atlan H. (2000) Self-Organization and Computability, in Self-Organizing Dynamics and Semantic Structures in Cognitive Systems, ed. A. Carsetti, Kluwer Academic Publ. Dordrecht, pp.201-209.

Atlan H. (2000) Vivere e conscere, Pluriverso, (Milano), 5(2):24-31.

Shnerb N., Louzoun Y., Bettelheim E., Solomon S. (2000) The importance of being discrete - life always wins on the surface. Proc. Natl. Acad. Sci. USA, 97:10322-10324.

Shnerb N., Bettelheim E., Louzoun Y., Agam O., Solomon S. (2000) Adaptation of autocatalytic fluctuations to diffusive noise. Physical Review E 63.

Atlan H. (2001) Genealogy and Levels of Ethics, in Frontiers of Life, Academic Press, N.Y., pp.707-727.

Hershberg U., Louzoun Y., Atlan H., Solomon S. (2001) HIV time hierarchy: winning the war while loosing all the battles. Physica A, 289:178-190.

Louzoun Y., Atlan H., Cohen I.R. (2001) Modeling the influence of TH1 and TH2 type cells in autoimmune diseases. Journal of Autoimmunity, 17(4).

Louzoun Y, Solomon S., Atlan H., Cohen I.R. (2001) The Emergence of Spatial Complexity in the Immune System. Physica A, 297 (1-2):242-252.

Louzoun Y., Solomon S. (2001) Volatility driven markets in a generalized Lotka Voltera formalism. Physica A, 302:220-233.

Beker T., Aharonov-Barki R., and Ruppin R. (2001) Emerging Command Neuron Circuitry in Evolved Autonomous Agents. Neurocomputing, 38-40.

Aharonov-Barki R., Beker T., and Ruppin E. (2001) Emergence of Memory-Driven Command Neurons in Evolved Artificial Agents. Neural Computation, 13(3).

Louzoun Y., Atlan H., Solomon S., Cohen I.R. (2002) Proliferation and competition in discrete biological systems. Bulletin of Mathematical Biology (In Press).