Curriculum vitae

Dr. Hagai Ginsburg, Professor

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Born 1937, Ramat Hakovesh (Israel).
B.Sc. 1963; M.Sc. 1965; Ph.D. 1970, all degrees from The Hebrew University of Jerusalem
Married + 3 children

Academic appointment

1971-1975, Lecturer in physiology and biophysics, Hebrew University of Jerusalem
1976-1978, Senior Lecturer in physiology and biophysics, Hebrew University of Jerusalem
1979-1983, Assistant Professor in physiology and biochemistry, Hebrew University of Jerusalem
1983-2005 date, Professor in physiology and biochemistry, Hebrew University of Jerusalem.
2005 October – to date, Emeritus Professor, Hebrew University of Jerusalem.

Sabbaticals

Department of Biochemistry, University of Virginia School of Medicine, 1976-7
Department of Microbiology, Michigan State University, 1983-4
National Institute for Medical Research, London, UK, 1988-1989
Department of Genetics, Biology and Medicinal Chemistry, University of Torino, Italy, 1989
Walter and Eliza Hall Institute for Medical Research, Melbourne, Australia, 1996
Department of Biology and Genetics, University of Pennsylvania, Philadelphia 2002.
NCBI, NIH, Bethesda MD, 2004
Department of Theoretical Biophysics, Humboldt University, Berlin, Germany.

Societies

Israeli Societies for Parasitology, Molecular Biology and Physiology
European Red Cell Club, American Red Cell Club

Prizes and awards

E.D. Bergmann Prize, 1984
German Research Foundation (DFG) guest professorship 2004
Award for Life-time achievements in malaria research from BioMalPar, European Network of Excellence on malaria research. 2005

Academic activities

Member and Chairman of Admission Committee for Biology Students 1974-1977
Chairman of Physiology Teaching Committee 1974-1976

Chairman of Young Staff Promotion Committee in Biological and Medical Sciences, Hebrew University, 1982 - 1984
Member of Teaching Committee in Biology 1988-1992
Chairman of Promotion Committee in Biochemistry and Molecular Biology 1994-1996
Member of the Authority for Research Students, 1997- 2002, 2004 – 2005.

Editorial Activities

Editor of The Biosphere, monthly Journal on Environmental Protection, 1971-1982
Guest Editor Special issue of Blood Cells on The Malaria Parasite and the Red Blood Cell, 1990
Editorial Board Parasite, 1994- to date
Editorial Board Parasitology, 1995 - to date
Editorial Board International Journal for Parasitology, 1998- 2001
Advisory Editorial Board Trends in Parasitology 2002 – 2006
Guest Editor, Redox Report special issue on redox metabolism in malaria, 2004.
Editorial Board Malaria Journal, 2004 – to date
Editorial Board Eukaryotic Cell 2007 to date
Editorial Board The Open Parasitology Journal 2007 to date

Scientific Collaboration

Representative of Israel in COST –European Cooperation in the field of Science and Technology – Action 22: development of antiparasitic drugs. 2004 – to date.
Member of BioMalPar "Biology and Pathology of Malaria Parasite"- a Network of Excellence funded by the European Commission. 2005 – to date.
Member of External Scientific Advisory Committee of AntiMal – European Commission Research on Poverty-Related Diseases – Development of New Drugs for the Treatment of Malaria. 2006 -

Organization of Workshops

European Red Cell Club Meeting, Jerusalem, 1984
Development of New Antimalarial Drugs, ICOPA IX, Izmir, Turkey, 1994
Novartis Symposium: Trafficking of solutes drugs and Proteins in the Malaria-Infected Erythrocytes. London, 1999.
Redox metabolism in malaria – from genes to drugs. The Rockefeller Foundation Bellagio Conference Center, February 2003.
Mode of action and resistance to chloroquine – AAAS Conference, St. Louis. 2006
Severe Malaria – workshop held in Jerusalem December 2006.

RESEARCH PROFILE

Major research activities

- Reconstitution of membrane transporters in artificial membranes
- Kinetic analysis of carriers in the erythrocyte membrane
- Mode of action of antimalarial drugs and mechanisms of drug resistance
- Fate of heme in malaria-infected erythrocytes

- Metabolic interactions between parasite and host cell
- Redox metabolism in infected cells
- Characterization of transport systems in erythrocytes infected with *Plasmodium falciparum*
- Mathematical modeling of malaria chemotherapy
- Development and curation of a web site dedicated to the biology, physiology and biochemistry of the malaria parasite *Plasmodium falciparum*; http://sites.huji.ac.il/malaria/. The web site was selected by Science as "best on the web".

Novelties

- The malaria parasite *Plasmodium falciparum* displays a pentose phosphate pathway activity independent of that of the host cell.
- Phagocytosis of *Plasmodium falciparum* infected erythrocytes is very similar to that observed in oxidatively damaged The isosomotic water transport in plant roots can be described by a biophysical model that considers the morphological anatomical complexity of roots.
- The transport of hexoses and nucleosides across the membrane of the human erythrocytes can be described as a simple asymmetric carrier.
- The parasite induces new permeability pathways in the host cell membrane.
- The new permeability pathways are responsible for altered cation levels in the cytosol of the infected erythrocyte.
- A novel method was developed for the isolation of free parasites from infected cells using Sendai virus-induced lysis of the host cell. This method allows compartment analysis of solutes and enzymes in host cell and parasite cytosol and investigation of the transport properties of the parasite membrane.
- The ultrastructural details of endocytosis of hemoglobin in the malaria-infected erythrocyte are revealed, implicating intraparasitic digestion as the target of chloroquine.
- The parasite regulates its pH and sodium content by means of a Na^+/H^+ antiporter
- Most of the oxidative stress that the parasite impinges on the host cell results from reactive oxidative species produced during the digestion of host cell cytosol. This stress activates the antioxidant defense of the host cell.
- The parasired blood cells: parasite activity induces changes in the host cell membrane, including the clustering of band 3; this causes extensive binding of auto-anti-band 3 antibodies that activates the alternative complement pathway with the consequent deposition of the complement components C3. Both the antibodies and the C3, as well as phosphatidylserine molecules that appear on the outer face of RBC are recognized by their specific receptors on the macrophage and phagocytosis ensues. Some antimalarial drugs inhibit phagocytosis.
- Hemozoin incapacitates the phagocytic activity of human monocytes.
- *Plasmodium falciparum*-infected erythrocytes induce nitric oxide synthetase activity in mammalian endothelial cells
- The action of antimalarial drugs in murine malaria is stage-dependent, and drug effect can be enhanced by timing the dose to the appearance of the sensitive stage

- The resistance to chloroquine in murine malaria species is directly related to the degree of asynchronicity of infection due to stage-dependence of drug action and rapid pharmacokinetics of the drug, but not to innate resistance.
- The parasite supplies ATP and glutathione to the host cell.
- Drugs that specifically interact with AT-rich DNA preferentially inhibit the growth of malaria parasites.
- Methylene blue inhibits the growth of malaria parasites by inhibiting the polymerization of ferriprotoporphyrin IX.
- Mefloquine exerts its antimalarial activity by inhibiting the endocytosis of host cell cytosol.
- Glutathione degrades ferriprotoporphyrin IX, either in solution, when bound to proteins or dissolved in membranes, and in intact erythrocytes. The released iron contributes through redox-cycling to oxidative stress in cells containing unstable form of hemoglobin.
- The degradation of ferriprotoporphyrin IX by glutathione is inhibited by chloroquine and amodiaquine, thus explaining their antimalarial mode of action
- Resistance of parasites to chloroquine is due to impeded acidification of parasites food vacuole and to increased glutathione concentration.
- Drugs that reduce glutathione levels in cells potentiate the antimalarial activity of chloroquine in mouse malaria models in vivo.
- Mathematical modeling of chloroquine chemotherapy suggests novel treatment protocols that may cure infection caused by drug resistant parasites
- Mathematical modeling of artesunate or artemisinin chemotherapy, suggests that the drugs render a small fraction of the parasites dormant and refractory to the drug. This effect bears on the choice of therapeutic protocols.
- A mathematical model describes the within-host development of malaria infection and acquisition of immunity.
- The parasite utilizes only a small fraction of the amino acids it gets from the digestion of host cell globin. It digests so much globin in order to preserve the osmotic integrity of its host erythrocyte.
- The volume of the erythrocyte affect the invasion of malaria parasites: shrunken cells are refractory to invasion.
- Several antimicrobial peptides derived from dermaseptin and subsequently chemically modified, are strong inhibitor of parasite growth in culture.
- Analysis of the transcriptome of the malaria parasite *Plasmodium falciparum* reveal that transcription of genes coding for enzymes involved in the same metabolic pathway is not always coordinated.
- Simulation of metabolic pathways indicate that kinetic parameters of enzymes can serve as selection factors in evolution.