BIOGRAPHICAL SKETCH

NAME: **Kaempfer, Raymond**

POSITION TITLE: Dr. Philip M. Marcus Professor of Molecular Biology and Cancer Research

Biochemistry and Molecular Biology, Faculty of Medicine, The Hebrew University, Jerusalem

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Leiden, The Netherlands	B.Sc.	08/1961	Chemistry
MIT, Cambridge, MA	Ph.D.	03/1965	Microbiology
Weizmann Institute of Science, Rehovot, Israel	postdoc	1965-1966	Biochemistry
Harvard University, Cambridge, MA	postdoc	1966-1969	Molecular Biology

A. Positions and Honors

1978-now Professor of Molecular Biology, Hebrew University-Hadassah Medical School
1974-78 Associate Professor of Molecular Biology, Hebrew University-Hadassah Medical School
1969-74 Assistant Professor of Biology, Harvard University
1968-69 NIH Special Fellow, Harvard University
1967-69 Tutor of Biology, Harvard College
1966-68 Fellow of the Jane Coffin Childs Memorial Fund for Medical Research, Harvard University
1965-66 Van Leer Fellow, Weizmann Institute of Science
1965 Instructor of Microbial Genetics, MIT

Other Experience

1976 Visiting Professor, Laboratoire de Biochimie Virale, Fondation Curie, Paris (one month)
1977 Visiting Professor, Laboratoire de Biochimie Virale, Fondation Curie, Paris (one month)
1979-80 Visiting Scientist, Laboratory of Molecular Biology, State University of Gent, Belgium
1980 Staff Member, NATO Advanced Study Institute on Protein Biosynthesis in Eukaryotes
1981 Visiting Exchange Professor, Institute of Virology, University of Rome and Laboratory of Cell Biology, National Research Council of Italy (one month)
1982 Elected a member of EMBO
1984-91 Chairman, Graduate Program Committee on Biotechnology, The Hebrew University
1984-91 Member, Steering Committee on Biotechnology, The Hebrew University
1984-88 Member, National Subcommittee on Manpower and Infrastructure in Biotechnology, Ministry of Science and Development, Israel
1985 Visiting Exchange Scientist in Biotechnology, Japan (one month)
1990 Visiting Professor of Molecular Biology, GBF-Braunschweig, Germany (one month)
1998 Chief Organizer, Joint Meeting of International Interferon and Cytokine Societies, Jerusalem
2000-06 Chairman, Awards and Honors Committee, International Cytokine Society
2009-10 Visiting Professor, Institute of Molecular Biology, Univ of Strasbourg, FR (3 months/year)
2010-19 Visiting Professor, Laboratory of Experimental Virology, Univ of Amsterdam, NL (2 months/year)
2023 Visiting Professor, Dept. Biol. and Biotech. "Charles Darwin", Sapienza University of Rome

Professional Memberships

1987- International Society for Interferon and Cytokine Research
1993- International Cytokine Society

Distinctions

1964-65 Woodrow Wilson Fellow, MIT
1982- Elected member, European Molecular Biology Organization (EMBO)
1983-now Appointed to the Dr. Philip M. Marcus Chair in Molecular Biology and Cancer Research of Hebrew University
2013 Kaye Innovation Award at Hebrew University for development of the project: Reduction of Inflammatory Disease Symptoms with Short Peptides that Inhibit Signaling through CD28

B. Contributions to Science

1. ***Discovery of the ribosome cycle.*** Ribosomes are composed of two subunits, but into the late 1960s, the reason for their universal bipartite construction remained elusive. Were subunits necessary simply to assemble these mega complexes or did they have a function in protein synthesis? In heavy isotope transfer experiments, I demonstrated that ribosomes come apart into two subunits every time they complete a polypeptide chain and are formed anew at the initiation of the next round, a seminal finding underlying the mechanism and control of translation initiation. This laid the foundation for much of the later work on control of protein synthesis in gene expression.
    a. **Kaempfer R**, Meselson M, Raskas HJ (1968) Cyclic dissociation into stable subunits and reformation of ribosomes during bacterial growth. ***J Mol Biol*** 31, 277-289
    b. **Kaempfer R** (1968) Ribosomal subunit exchange during protein synthesis. ***Proc Natl Acad Sci USA*** 61, 106-113
    c. **Kaempfer R** (1969) Ribosomal subunit exchange in the cytoplasm of a eukaryote. ***Nature*** 222, 950-953
    d. **Kaempfer R** (1970) Dissociation of ribosomes on polypeptide chain termination and origin of single ribosomes. ***Nature*** 228, 534-537
    e. **Kaempfer R** (2017) Ribosome cycle emerges from DNA replication. ***Nature Reviews Mol Cell Biol*** 18, 470
2. ***Stress and the control of gene expression.*** I discovered a novel class of intragenic elements that by evoking a cellular stress response, regulate expression of the gene carrying such an element at either mRNA splicing or mRNA translation. I had discovered that dsRNA-mediated activation of cellular stress kinase PKR inhibits translation by causing the inactivation of an initiation factor, eIF2. This was a seminal finding also relevant to IFN mode of action in the host antiviral response. We then discovered *cis*-acting intragenic RNA activators of PKR within inflammatory cytokine (*IFN-γ, TNF-α*) and the human *globin* genes, even within HIV RNA, that control their splicing and translation through eIF2α phosphorylation, linking the cellular stress response to gene regulation. This work is unique and we lead the world on this front.
    a. **Kaempfer R**, Kaufman J (1973) Inhibition of cellular protein synthesis by double-stranded RNA: Inactivation of an initiation factor. ***Proc Natl Acad Sci USA*** 70, 1222-1226
    b. **Kaempfer R** (1974) Identification and RNA-binding properties of an initiation factor capable of relieving translational inhibition induced by heme deprivation or double-stranded RNA. ***Biochem Biophys Res Commun*** 61, 591-597
    c. Osman F, Jarrous N, Ben-Asouli Y, **Kaempfer R** (1999) A *cis*-acting element in the 3'-untranslated region of human *TNF-α* mRNA renders splicing dependent on the activation of protein kinase PKR. ***Genes Dev*** 13, 3280-3293
    d. Ben-Asouli Y, Banai Y, Pel-Or Y, Shir A, **Kaempfer R** (2002) Human *interferon-γ* mRNA autoregulates its translation through a pseudoknot that activates the interferon-inducible protein kinase PKR. ***Cell*** 108, 221-232
    e. Cohen-Chalamish S, Hasson A, Weinberg D, Namer LS, Banai Y, Osman F, **Kaempfer R** (2009) Dynamic refolding of *IFN-γ* mRNA enables it to function as PKR activator and translation template. ***Nature Chem Biol*** 5, 896-903
    f. Ilan L, Osman F, Namer LS, Eliahu E, Cohen-Chalamish S, Ben-Asouli Y, Banai Y, **Kaempfer R** (2017) PKR activation and eIF2α phosphorylation mediate human *globin* mRNA splicing at spliceosome assembly. ***Cell Research*** 27, 688-704
    g. Namer LS, Osman F, Banai Y, Masquida B, Jung R, **Kaempfer R** (2017) An ancient pseudoknot in *TNF-α* pre-mRNA activates PKR, inducing eIF2α phosphorylation that potently enhances splicing. ***Cell Reports*** 20, 188-200
    h. **Kaempfer R**, Ilan L, Cohen-Chalamish S, Turgeman O, Namer LS, Osman F (2019) Control of mRNA splicing by intragenic RNA activators of stress signaling: Potential implications for human disease. ***Front Genet*** 10, 464
    i. Namer LS, Harwig A, Heynen SP, Das AT, Berkhout B, **Kaempfer R** (2023) HIV co-opts a cellular antiviral mechanism, activation of stress kinase PKR by its RNA, to enable splicing of *rev/tat* mRNA. ***Cell & Bioscience*** 13, 28
    j. **Kaempfer R** (2023) Positive regulation of splicing of cellular and viral mRNA by intragenic RNA elements that activate the stress kinase PKR, an antiviral mechanism. ***Genes*** 14, 974

3. ***Cytokine gene regulation.*** In the early 1980s, I pioneered the molecular biology of cytokine gene expression, even before cDNA cloning.
    a. Efrat S, Pilo S, **Kaempfer R** (1982) Kinetics of induction and molecular size of mRNA species encoding human interleukin-2 and γ-interferon. ***Nature*** 297, 236-239
    b. Efrat S, **Kaempfer R** (1984) Control of biologically active *interleukin-2* messenger RNA formation in induced human lymphocytes. ***Proc Natl Acad Sci USA*** 81, 2601-2605
    c. Lebendiker MA, Tal C, Sayar D, Pilo S, Eilon A, Banai Y, **Kaempfer R** (1987) Superinduction of the human gene encoding immune interferon. ***EMBO J*** 6, 585-589
    d. Gerez L, Arad G, Efrat S, Ketzinel M, **Kaempfer R** (1995) Post-transcriptional regulation of human *interleukin-2* gene expression at processing of precursor transcripts. ***J Biol Chem*** 270, 19569-19575.

4. ***Cytokine genes and disease.*** The early focus on molecular biology of inflammatory cytokine gene expression allowed me to investigate how it is disturbed in diseases. This laid the foundation for our later work on superantigen toxins. The Pentagon (USAMRMC, DARPA) recruited me into biodefense research based on this expertise which provided essential tools.
    a. Gerez L, Madar L, Arad G, Sharav T, Reshef A, Ketzinel M, Sayar D, Silberberg C, **Kaempfer R** (1991) Aberrant regulation of *interleukin-2* but not of *interferon-γ* gene expression in Down Syndrome (trisomy 21). ***Clin Immunol Immunopathol*** 58, 251-266
    b. Gerez L, Madar L, Shkolnik T, Kristal B, Arad G, Reshef A, Steinberger A, Ketzinel M, Sayar D, Shasha S, **Kaempfer** R (1991) Regulation of *interleukin-2* and *interferon-γ* gene expression in renal failure. ***Kidney International*** 40, 266-272
    c. **Kaempfer R**, Gerez L, Farbstein H, Madar L, Hirschman O, Nussinovich R, Shapiro A (1996) Prediction of response to treatment in superficial bladder carcinoma through pattern of *interleukin-2* gene expression. ***J Clin Oncol*** 14, 1778-1786
    d. Gerez L, Shkolnik T, Hirschmann O, Lorber M, Arad G, **Kaempfer R** (1997) Hyperinducible expression of the *interferon-γ* (*IFN-γ*) gene and its suppression in Systemic Lupus Erythematosus (SLE). ***Clin Exp Immunol*** 109, 296-303

5. ***Novel anti-inflammatory molecules that attenuate costimulation.*** For many years, it was known that superantigens induce a cytokine storm by binding directly to MHC-II molecule and T cell receptor outside the cell. I discovered that the costimulatory receptor CD28 is a direct and critical receptor for superantigen toxins. This surprising discovery led to our design of novel antagonist peptides. Such a peptide, derived from the CD28 homodimer interface, proved effective not only against superantigen toxicity but also against Gram(+) as well as Gram(-) infections and polymicrobial sepsis, with clear therapeutic benefit. My recent work shows that the peptide attenuates formation of intercellular B7-2/CD28 and B7-1/CD28 synapses, thereby reducing costimulatory signaling that is key to T-cell activation and the induction of a harmful cytokine storm by diverse pathogens. This unexpectedly broad reach of therapeutic activity is only now becoming evident.
    a. Arad G, Levy R, Hillman D, **Kaempfer R** (2000) Superantigen antagonist protects against lethal shock and defines a new domain for T-cell activation. ***Nature Medicine*** 6, 414-421
    b. Arad G, Levy R, Nasie I, Hillman D, Rotfogel Z, Barash U, Supper E, Shpilka T, Minis A, **Kaempfer R** (2011) Binding of superantigen toxins into the CD28 homodimer interface is essential for induction of cytokine genes that mediate lethal shock. ***PLoS Biology*** 9, e1001149
    c. Ramachandran G, Tulapurkar ME, Harris KM, Arad G, Shirvan A, Shemesh R, DeTolla LJ, Benazzi C, Opal SM, **Kaempfer R***, Cross AS* (2013) A peptide antagonist of CD28 signaling attenuates toxic shock and necrotizing soft tissue infection induced by *Streptococcus pyogenes*. ***J Infect Dis*** 207, 1869-1877
    d. Bulger EM, Maier RV, Sperry J, Joshi M, Henry S, Moore FA, Moldawer LL, Demetriades D, Talving P, Schreiber M, Ham B, Cohen M, Opal SM, Segalovich I, Maislin G, **Kaempfer R**, Shirvan A (2014) A novel drug for treatment of necrotizing soft-tissue infections: A randomized clinical trial. ***JAMA Surg*** 149, 528-536
    e. Ramachandran G, **Kaempfer R**, Chung C-S, Chahin AB, Palardy JE, Parejo NA, Chen Y, Whitford M, Arad G, Hillman D, Shirvan S, Shemesh R, Ayala A, Cross AS, Opal SM (2015) CD28 homodimer interface mimetic peptide acts as preventive and therapeutic agent in models of severe bacterial sepsis and Gram-negative bacterial peritonitis. ***J Infect Dis*** 211, 995-1003
    f. Levy R, Rotfogel Z, Hillman D, Popugailo A, Arad G, Supper E, Osman F, **Kaempfer R** (2016) Superantigens hyperinduce inflammatory cytokines by enhancing the B7-2/CD28 costimulatory receptor interaction. ***Proc Natl Acad Sci USA*** 113, E6437-E6446
    g. **Kaempfer R**, Popugailo A, Levy R, Arad G, Hillman D, Rotfogel Z (2017) Bacterial superantigen toxins induce a lethal cytokine storm by enhancing B7-2/CD28 costimulatory receptor engagement, a critical immune checkpoint. ***Receptors Clin Investig*** 4, e1500

h. **Kaempfer R** (2018) Bacterial superantigen toxins, CD28, and drug development. ***Toxins*** 10, 459

i. Popugailo A, Rotfogel Z, Supper E, Hillman D, **Kaempfer R** (2019) Staphylococcal and streptococcal superantigens trigger B7/CD28 costimulatory receptor engagement to hyperinduce inflammatory cytokines. ***Front Immunol*** 10, 942

j. Kunkl M, Amormino C, Caristi S, Tedeschi V, Fiorillo MT, Levy R, Popugailo A, **Kaempfer R**, Tuosto L (2021) Binding of staphylococcal enterotoxin B (SEB) to B7 receptors triggers TCR- and CD28-mediated inflammatory signals in the absence of MHC class II molecules. ***Front Immunol*** 12, 723689

k. Kunkl M, Amormino C, Spallotta F, Caristi S, Fiorillo MT, Paiardini A, **Kaempfer R**, Tuosto L (2023) Bivalent binding of staphylococcal superantigens to the TCR and CD28 triggers inflammatory signals independently of antigen presenting cells. ***Front Immunol*** 14, https://doi.org/10.3389/fimmu.2023.1170821

l. Popugailo A*, Rotfogel Z*, Hillman D, Levy M, Turgeman O, Levy R, Arad G, Shpilka T, **Kaempfer R** (2023) The homodimer interfaces of costimulatory receptors B7 and CD28 control their engagement and pro-inflammatory signaling. ***J Biomed Science*** *In revision*

Complete List of Published Work:
https://www.ncbi.nlm.nih.gov/pubmed/?term=kaempfer+r