MODIFIED ZEOLITE IN MEDICINE:
DETOXIFICATION AND OTHER EFFECTS

Zeolites are aluminosilicates known for their ion-exchange properties. Properties of zeolites such as ion-exchange, intercrystalline pores that discriminate between molecules of different dimension, strong acidic sites, and active reservoirs for metal-catalyzed reactions have promoted their extensive use and fundamental zeolite research has become an area of great interest. Zeolites have high cation exchange selectivity, good resistance to temperature and ionizing radiations, and excellent compatibility with the environment, for which reasons they have been widely used in modern technology as selective adsorbents, molecular sieves, and particularly as catalysts. It is obvious that the ion sieving and other remarkable properties of
Zeolites will be utilized in the near future for the environmental and health care industries for several reasons: (a) their known biological properties accompanied with their long-term chemical and biological stability; (b) zeolites reversibly bind small molecules such as oxygen and nitric oxide; (c) they possess size and shape selectivity; (d) and the possibility of metalloenzyme mimicry. Zeolite used for medical applications in animals and humans is clinoptilolite. For example the type of clinoptilolite PMA has a similar, but finer structure which makes it active surface larger in comparison with natural raw clinoptilolite. PMA is for example, a strong inorganic cation exchanger as many other zeolites. This effect is due to negatively charged aluminosilicate structure that attracts cations. These cations consequently reside inside the empty spaces (pores and channels). As these spaces or cages are large, they easily accommodate large cations such as Na\(^+\), K\(^+\), Br\(^-\), and Ca\(^{2+}\) and even relatively large molecules and cationic groups such as water, ammonia, carbonate ions and nitrate ions. The basic structure of PMA is biologically neutral. The ion exchange process is reversible, allowing adsorption of ions and molecules which makes it useful in toxin removal from the body. This effect on body detoxification has already been documented in many studies on dietary inclusion of clinoptilolite in animal production, i.e. pigs fed with clinoptilolite experience weight gains and are less susceptible to disease than pigs fed normal which can be partially attributed to a lower toxin burden on the animal body. Moreover, addition of clinoptilolite to the aflatoxin diet reduced the adverse effects of aflatoxin. Similarly, clinoptilolite incorporated into the diet reduces deleterious effects of aflatoxin in growing chicks from 10 to 45 days of age, as it significantly reduced the negative aflatoxin effects on food consumption ratio. Heavy metals released in waste water are among the most worrisome pollution problems due to their cumulative effects along the food chain. The natural zeolites clinoptilolite, phillipsite and chabazite proved particularly useful in selectively eliminating ammonia and heavy metals such as Cd\(^{2+}\), Pb\(^{2+}\), Zn\(^{2+}\), Cu\(^{2+}\) and, partially Cr\(^{3+}\). For example, mercury is a well-known poison to human and animal health, but still widely used in many industrial processes and products (e.g. catalysis, pigments, batteries, saving lighting bulbs) and even in agriculture (e.g. antifungals). This creates serious environmental problems, pollution of aquatic systems, which leads to mercury accumulation in human body as well. Remarkable
removal rates of mercury from aqueous solutions by NaCl-pretreated pure
heulandite crystals and NaCl-pretreated clinoptilolite-containing rock samples have
been observed showing that natural zeolite materials could be used to remove
heavy metals from aqueous solutions. The same mechanism occurs in human body
upon intake of PMA. It moves through the intestine and removes toxins or heavy
metals by the ion-exchange mechanism. It is not subject to intestinal uptake and is
very stable. This prolongs its effect within the body and enforces the intestinal
barrier, known to play a pivotal role in immunity. Moreover, double activated
clinoptilolite® may exert preventive effects on the intoxication of organophosphate
poisoning as zeolite tuff containing 61% clinoptilolite has already been shown to
prevent and eliminate organophosphate poisoning. The organophosphate poison
substance can strongly inhibit enzyme cholinesterase in erythrocytes, and in the
stomach, brain and liver. This effect can be strongly diminished after pre-treatment
with zeolite (1 g/kg 5 min before intoxication). The duodenum and colon are
exceptions, where the cholinesterase activity was not significantly restored.
Detoxification effect of PMA is therefore of great importance in patients subject to
different poisoning, i.e. organic metals, heavy metals or toxic drugs. In particular,
patients undergoing anti-infectious therapy with nucleoside analogues or
chemotherapy often develop painful neuropathies due to increased levels of toxins
and free radicals in the body. This simultaneous malfunction of peripheral nerves in
the body cannot be cured at the moment and the condition is treated by palliative
approach. PMA may be used in these cases as an adjuvant drug of choice either for
acute states as for chronic conditions as it might substantially decrease the level of
toxins and free radicals thus preventing the damage of nerves and/or increase the
body natural capability of tissue recovery. In particular, polyneuropatic pain caused
by ammonia has been observed in patients suffering from cancer. For example,
ammonia/ammonium concentrations increase in the gastric mucosa due to infection
with H. pylori, Ammonia acts as a promoter in a rat model of gastric cancer induced
by N-methyl-N-nitro-N-nitrosoguanidine (MNNG). Similarly, colon cancer has been
associated with high-protein diets poor in fibres and carbohydrates when
undigested proteins reach the colon and are fermented by microflora into toxic
compounds such as phenol compounds, indoles, cresol, amines and ammonia.
Double activated clinoptilolite eliminates very efficiently ammonia by ion exchange process. Such mechanism might act preventively and contribute to the therapeutic effect in such patients. The ultimate mechanisms of PMA action in states such as polyneuropathies thus, involve direct detoxification effects (it is a ‘scavenger’ for toxic compounds and free radicals) and increase of cellular antioxidant capacities, i.e. superoxide dismutase enzymes activity (SOD). Indeed, it is known that the activity of SOD1 and SOD2 are completely dependent on minerals (Cu, Zn and Mn). Moreover, activated clinoptilolite protected the cells by radical oxygen species (ROS)-induced cell death. The mechanism underlying this effect included reduction of the mitochondrial ROS production following a pro-oxidant stimulation. Indeed, they observed increased activity of SOD enzymes in the hippocampus of treated mice involved in the study. This study is important as it confirms previous data on detoxification effects of PMA. The detox-mechanism involves reduction of oxidative stress which enables physiological regeneration of each cell and prevents damage of biological structures. Altogether, PMA positively influences the mineral metabolism, adds to the antioxidant status of cells, lowers the levels of ROS and increase the activity of SOD enzyme. This effect synergistically contributes to lowering of cellular damage (i.e. those of neural cells) and consequently prevents and alleviates neuropathic pain. Decrease in ROS levels was also documented for PMA and it proved efficient to lower the damage of neurons in other diseases, i.e. Alzheimer disease. Indeed, on an Alzheimer mice model the authors showed that a reduction in amyloid levels and plaque load Alzheimer were observed in animals treated with activated clinoptilolite in comparison with control mice. Moreover, PMA has antimicrobial effects as reported previously. This effect might be attributable to adsorption of microbes on the mineral surface. It proved efficient for various urological patients who needed long-term use of indwelling balloon catheter for lower urinary tract obstruction and for neurogenic bladder. Moreover, PMA might have a positive impact in Diabetes Mellitus patients as well. Our previous, unpublished data brings out results on clinoptilolite effects on alloxan-induced diabetic mice model. Results proved that natural clinoptilolite might prevent or alleviate some late complications of diabetes, including development of polyneuropathies. Although natural, finely ground clinoptilolite did not significantly
decrease the blood glucose levels in studied animals, there were some indications that clinoptilolite managed to adsorb small amounts of glucose, as it was already proven that natural purified clinoptilolite hydrothermally transformed by use of FeSO$_4$ causes selectivity for glucose adsorption. Clinoptilolite showed positive effects on many diabetic symptoms. For example, non-treated diabetic mice had 1.92 mM/L Ca$^{2+}$ in sera, whereas clinoptilolite-treated diabetic mice had higher Ca$^{2+}$ concentration in sera ranging from 2.15 to 2.3 mM/L. Furthermore, Fe$_2^+$–containing natural clinoptilolite interacts with glucose forming an iron-glucose complex in the clinoptilolite. The mechanism of action of the Fe$_2^+$-clinoptilolite-glucose interaction is a strong adsorption governed by the reactive characteristics of glucose.
CURRICULUM VITAES PROF. KRESIMIR PAVELIC

Personal Data

Born July 19, 1952. in Slavonski Brod, Croatia - Croatian citizen

Krešimir Pavelić (1952) medical doctor, professor of molecular biology, Head, Department of Biotechnology, University of Rijeka, former director and establisher of Division of Molecular Medicine, Ruder Bošković Institute, Former Secretary General of the European Molecular Biology Conference (EMBC), EMBO member, member of Croatian Academy of Sciences and Arts and many others international scientific organisations, former vice-president of European Molecular Biology Conference, EMBC, Delegate of Croatian Academy of Sciences and Arts in European Science Foundation, Former President of the National Scientific Council, Republic of Croatia, former member of the parliamentarian committee for national scientific awards, expert for molecular medicine of the Trans radical party in the European Parliament. Krešimir Pavelić is ex officio member of the Council of the European Molecular Biology Laboratory. He has published 280 scientific papers in world top scientific journals and several invited review papers and chapters in prestigious journals and book published by American and European publishers. He significantly contributed to the understanding of biology of the transformed cell.

Degrees

M.D. School of Medicine, University of Zagreb, Croatia - July 1975.


Ph.D. Thesis "Combined chemotherapy and immunotherapy of mice with malignant tumors". School of Medicine, University of Zagreb, 1979.

Assistant Professor (Research Associate) Ruder Bošković Institute, Zagreb, April 1980.

Associate Professor (Senior Research Associate), Ruder Bošković Institute, Zagreb, October, 1981.

Full Professor (Senior Scientist), Ruder Bošković Institute, Zagreb, March, 1985.

Teaching and Research Experience

Research Assistant, Ruder Bošković Institute, Department of Biology and Medicine, University of Zagreb 1975-1979.

Research on the tumor immunology and experimental cancer chemotherapy.

Assistant Professor, Ruder Bošković Institute, April 1980.
Elucidation of the physiological and cellular mechanisms underlying induction of tumor associated hormonally active substances which are involved in regulation of tumor growth.

**Senior Research Associate**, Ruđer Bošković Institute, October 1981.

Growth factors and positive feed back mechanism of tumor growth. Autocrine tumor growth regulation.

**Full Professor**, Ruđer Bošković Institute, 1985.

Growth factors and oncogenes in embryonal and tumor growth, cancer genetic.

**Professor of Anatomy and Physiology**, School of Pharmacy and Biochemistry, University of Zagreb 1982-1989.

**Professor of Molecular Biology**, School of Pharmacy and Biochemistry, University of Zagreb, 1990-2007.

**Professor of Molecular Biology**, Department of biotechnology, University of Rijeka, 2007-present.

**Teaching - Postgraduate Studies**

**Postgraduate Study in Oncology**, School of Medicine, University of Zagreb, 1977-present

Hormones and cancer, growth factors, oncogenes, new approaches in anticancer therapy, new diagnostic procedures

**Postgraduate Study in Predclinical and Experimental Pharmacology and Clinical Pharmacology**, School of Medicine, University of Zagreb, 1987-1989

Molecular pharmacology

**Postgraduate Study in Endocrinology**, School of Medicine, University of Zagreb, 1988-1989

Growth factors

**International Postgraduate Study in Diabetology**, School of Medicine, University of Zagreb, 1988-1989

Growth factors, hormones and cancer

**Postgraduate Study in Neurology**, School of Medicine, University of Zagreb, 1993-1994

Cancer genetics

**Postgraduate Study in Medical Genetics**, School of Medicine, University of Zagreb, 1994-present

Molecular genetic, cancer genetic
Postgraduate Study in Cytology, School of Medicine, University of Zagreb, 1994-present
Molecular genetic of cancer

Postgraduate Study in Medical Microbiology, School of Medicine, University of Zagreb, 1994/1995
Principles and application of recombinant DNA technology in medical microbiology

Postgraduate Study Biomedicine, School of Medicine University of Rijeka, 1996-present
Molecular oncology

Postgraduate and Postdoctoral Study, School of Medicine, University of Zagreb, 1998-present
Molecular Oncology

Selected Executive and Administrative International Functions
Secretary General, European Molecular Biology Conference (EMBC), 2008-2013.

Ex Officio Member, EMBO Council 2008-2013.
Member, Standing Committee, European Medical Research Council, European Science Foundation 2004-present
Delegate, European Molecular Biology Conference, 2001-present
Delegate, European Molecular Biology Laboratory, 2006-present
Member, Strategic Working Party EMBC/EMBO, 2004-present
Member, Nahrstoff Akademie Salzburg, scientific board, 2003-present
Member of Executive Committee, European Association for Cancer Research 1999-2003

Selected Executive and Administrative Domestic Functions
Member, Senat, University of Rijeka, 2016-present
President, National Scientific Board Republic of Croatia, 2007-2012.
Head, Department of Biotechnology, University of Rijeka, 2008-present
Director, Division of Molecular Medicine, Ruđer Bošković Institute, 1993-2009.
President, Governing Council, Institute for Medical Research and Occupational Health 2005-2011.


President, Scientific Council, Department of Experimental Biology and Medicine, Ruđer Bošković Institute, 1986-1988.


Member, Senat, University of Zagreb, 1987-1992.

Member, Scientific Council of the University of Zagreb (Board of deans) 1987-1992.


Head, Laboratory of Molecular Oncology, Division of Molecular Medicine, Ruđer Bošković Institute, 1991-1997.

Member, Council of the School of Medicine, University of Zagreb, 1991-1992

Member, National Board for Biomedicine, Ministry of Science and Technology, Republic of Croatia, 1995-1998.

President, Section of Molecular Genetic, Croatian Society of Human Genetic, 1995-1997.

Member, Croatian Association of the Club of Rome, 1995-present.

Assistant Director General, Ruđer Bošković Institute, 1999-present

Member and vicepresident, National Board for Scientific Awards, Biomedicine, 2001-2005.

Member, Gouverning Board, Agency for Science and High Education, Ministry of Sciences, Education and Sports, 2005-present

Member, National Scientific Board, 2004-2012.

President, Gouverning Board, Institute for Medical Research and Occupational Medicine, Zagreb, 2005-2011.

Evaluator and panel member European Science Foundation

Evaluator and panel member Portugese Foundation for Science and Technology (2014-present)

Current Membership in Scientific Societies

Croatian Immunological Society

Croatian Cancer Society

Croatian Genetical Society
Croatian Physiological Society
Croatian Association of Human Genetics
Croatian Endocrinological Society
European Association for Cancer Research
International Stress Management Association
European Society of Human Genetics
Croatian Bioethical Society

**Visiting Research Fellow**

Roswell Park Memorial Institute, Buffalo, N.Y. U.S.A. November 1978.

*Visiting Professor,* Roswell Park Memorial Institute, Grace Cancer Drug Center, Buffalo, N.Y. U.S.A. 1984-1986.

*Visiting Professor,* University of Hamburg, University Clinic Eppendorf, Institute for Physiological Chemistry, Hamburg, Germany, (three months) 1988.

*Visiting Professor,* University of Cincinnati, College of Medicine, Department of Pathology and Laboratory Medicine, Cincinnati, OH, U.S.A. (6 months) 1990.

*Visiting Professor,* Mayo Clinic and Foundation, Division of Developmental Oncology Research Rochester, MN. U.S.A. (3 months) 1991.

**Honors and Awards**

*University of Zagreb May Prize* for research performed by students for 1972 and 1973.

*Drago Perović Prize* for students of the School of Medicine, University of Zagreb for 1973.

*Federal Prize for Young Scientists* (under 30) for 1978.

*Vuk Vrhovac Prize* for research in diabetology (Diabetology Section of Croatian Medical Association) for 1982.


University of Hamburg Fellowship 1988.


*Yamagiwa-Yoshida Memorial Award,* International Union Against Cancer, 1993.

Croatian Academy of Medical Sciences, Annual award "Ante Šercer" for best scientific paper published in 1996.

Croatian Government State Award for 1998.
Membership in Academies

Member of European Molecular Biology Organization (EMBO), 2002.
Member of Croatian Academy of Sciences and Arts, 1992.
Member of Croatian Academy of Medical Sciences, 1994.

Membership in the Editorial Boards in Scientific Journals

*Libri Oncologici*, Zagreb, Croatia, member of editorial board, since 1992.
*Pathology Oncology Research*, Budapest, Hungary, member of editorial board, since 1996.
*Medical Science Monitor*, member of editorial board since 2002.
*Balcan Journal of Medical Genetics*, member of editorial board since 2002.
Journal of Oncology, Hindawi publishing Group, member of editorial board, May 2008.
MD - Medical Data, Mostart, Zemun, Serbia, June 2011.
Acta Medica Academica, Journal of Department of Medical Sciences of Academy of Sciences and Arts of Bosnia & Herzegovina, Sarajevo.
Archives of Industrial Hygiene and Toxicology, Zagreb, Croatia
Advances in Genetic Engineering and Biotechnology, Boston, MA, USA member of editorial board since July 2014

External Reviewer for International Scientific Organizations

European Science Foundation
ESF-EMBO Symposia Review Panel
Portuguese Foundation for Science and Technology, periodic evaluation of R&D Units

Grants Awarded (Principal Investigator)


2. *Development of Technology for Production of Fetal Calf and Newborn Calf Serum for Cell Culture System*. Ministry of Science, Technology and Information, Republic of Croatia, Zagreb, 1983. Grant No. V-511/1-83

4. Differentiation and Growth Control of Normal and Tumor Cells. Ministry of Science, Technology and Information, Republic of Croatia, Zagreb, 1986-1990. Grant No. 2.04.01.02.01


10. National Cancer Research Program, Ministry of Science and Technology, Republic of Croatia, 1997- present, Grant No. P-9811

11. Molecular Genetic Basis of Metastasis, Ministry of Science and Technology, Republic of Croatia, 1997- present, Grant No. P-1104

12. Establishing of toxicological and antitumoral effects of potential agents against tumors. Ministry of Science and Technology, Republic of Croatia, 2001- present, Grant No. 00981499


SR&D contracts with international industrial partners (2009-2014)

Coorganizer of International Conferences

- 1st International Conference on Signal Transduction

  8-11 October 1998, Cavtat-Dubrovnik, Croatia
• 2\textsuperscript{nd} International Conference on Signal Transduction
  26-31 May 2000, Cavtat-Dubrovnik, Croatia
• 3\textsuperscript{nd} International Conference on Signal Transduction
  May 2002, Cavtat-Dubrovnik, Croatia
• 4\textsuperscript{th} International Conference on Signal Transduction
  May 2004, Cavtat-Dubrovnik, Croatia
• 1\textsuperscript{st} International Conference on Mechanisms of Action of Nutraceuticals
  14-19 October, 2001, Cavtat-Dubrovnik, Croatia
• 2\textsuperscript{nd} International Conference on Mechanisms of Action of Nutraceuticals. October, 2002, Krems, Austria
• 3\textsuperscript{rd} International Conference on Mechanisms of Action of Nutraceuticals
  November, 2004, Maggie Walley, North Caroline, USA
• 2\textsuperscript{nd} EMBO Sectoral Meeting on Molecular Medicine
• 2\textsuperscript{nd} International conference on regenerative orthopaedics and tissue engineering. 20-22, 09. 2012, Opatija, Croatia. (Co-president).

\textbf{Books}

\textbf{Author}

- Pavelić K., \textit{Kako pobijediti rak}, Globus, Zagreb, 1989
Editor


International Initiatives

- K. Pavelić: Initiator of Croatian membership to European Molecular Biology Laboratory as organization’s 19th Member State, 29.06.2006.

Invited speakers at international meetings

- 5. Pavelić K.: Induction of tumor cell differentiation in different human cell lines. Institut for Physiological Chemistry, University Clinic Eppendorf, University of Hamburg,11.2.1988., Hamburg, Germany
- 9. Pavelić K.: Immunohistochemical detection of C-MYC oncoprotein in paraffin-embedded tissue. University of Cincinnati, College of Medicine, 17.8.1990., Cincinnati, Ohio, USA


15. Pavelić K.: Expression of nm23 gene in human tumors. *College of Medicine, University of Cincinnati*, 30.3.1994., Cincinnati, Ohio, USA


21. Pavelić K.: Molecular genetics of malignant insulinomas. *International Conference on Disease of Pancreas, Biliary Tract and Duodenum*, 07.05.1999., Ljubljana, Slovenia


29. Pavelić K.: Molecular genetics in oncology. SEE – Conference on Molecular Medicine, 6-8.12. 2001., Skopje, Macedonia


65. Pavelić K.: Casting Lights on Molecular Events Underlying Tumor Invasion and Metastasis: What can be Seen from the “Oomics” point of View? 7th Slovenian Meeting of the Slovenian Biochemical Society with International Participation. Maribor, Slovenia. 26.-29. 09. 2007


83. Pavelić K: The ex-post evaluation of the impact of research projects and funding programmes. Workshop, European Research Council „The ex-post evaluation of the impacts of research projects and funding programmes”, Brussels, Belgium, 29-30.11. 2012,


89. Pavelić K: Medical application of clinoptilolite. Applicazioni della zeolite in gastroenterologia e oncologia. Medical Meeting Gli Dei, Pozzuoli, Italy, 29.04. – 1.05.2014.

90. Pavelić K: Medical application of clinoptilolite in oncology: cellular and molecular mechanisms. Hospital Cardarelli, Oncology Department, Napoli, Napoli, Italy, 30.04.2014.

91. Pavelić K: Toxicology of modified clinoptilolite and possible effect on polyneuropatic pain developed after chemotherapy of colon tumor. Novara, Italy, 17.07. 2014.


See under list of pubblication:
List of publications in international peer reviewed journals and books


90. GRAZIO S., FRKOVIĆ-GRAZIO S., ČABRIJAN T., ZIAČIĆ-ROTVIĆ V., GOLDONI V., PEČINA-SLAUS N., KAMENJICKI E., PAVELIĆ K., Freshly frozen subsequently AMeX processed breast carcinoma tissue - a


257. KOLUNDŽIĆ R, TRKULJA V, MIKOLAUCIC M, KOLUNDŽIĆ M, KOLUNDŽIĆ M, KRALJEVIC S, PAVELIC K: Association of interleukin-6 and transforming growth factor-β1 gene polymorphisms with


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