Botanica SERBICA

Professor Dr. Draga Simić
On the occasion of her 80th birthday

Professor Dr. Draga Simić

Draga Simić was born on 16 February 1936 in Belgrade, Serbia, where she attended primary school and the First Belgrade Gymnasium. She graduated in biology from the Faculty of Natural Sciences and Mathematics, University of Belgrade, in 1959. As an excellent student truly interested in science, already during her studies she volunteered to work in the laboratory of Professor Radoslav Andjus at the Institute of Physiology of the Faculty of Natural Sciences and Mathematics. Upon graduation, she worked for four years (1959-1963) as Teaching Assistant in the Chair of Plant Physiology, headed by Professor Zvonko Damjanović, at the Institute of Botany and Botanical Garden, Faculty of Natural Sciences and Mathematics. Professor Mirjana Nešković supervised her first steps in studying the techniques of plant tissue culture. Moreover, in collaboration with Dr. I. Skreb of Zagreb University's School of Medicine, she perfected the construction of a device for measuring microrespiration. During the period 1962-63, she went through research training at the laboratory of Professor J. Brachet, Department of Molecular and Cell Biology of the Free University of Brussels, where she studied the mechanisms of amino acid incorporation into cytoplasmic and nuclear proteins of onion (*Allium cepa* L.) root tissue. In 1964 she moved to Belgium, where she obtained the position of Research Assistant in the Department of Atomic and Molecular Physics, University of Liège.

However, as nucleic acid research was the chief scientific interest of Draga Simić, she decided in 1965 to accept the position of Research Associate in the laboratory of Professor M. Errera, Department of Radiobiology of the Free University of Brussels, where she started work on her thesis. She obtained her PhD in sciences in 1969 under the mentorship of Professor M. Errera at the Free University of Brussels. Entitled „Action des Rayons Ultraviolets sur l' ADN du Phage Lambda" („Effect of Ultraviolet Rays on the DNA of Phage Lambda"), her thesis addressed the issue of photochemical changes in the DNA of lambda phage induced by UV irradiation and partially clarified the at that time still hypothetical roles of nucleotide excision and recombination in the repair of DNA damage following such irradiation. She returned to Europe after post-doctoral studies supervised by Professor P. Howard-Flanders at the Department of Radiology, Yale University, New Haven, USA (1969-1970). In the period from 1972 to 1974, Draga Simić served as Research Assistant at the Laboratory of Microbiology, University of Lille, France. At the end of 1974 she returned to Belgrade and the following year joined the group led by Professor D. Kanazir in the Laboratory of Molecular Biology and Endocrinology at the Vinča Institute of Nuclear Sciences, first as Research Associate (1975-1976) and afterwards as Senior Research Associate (1976-1980).

In 1977 Draga Simić was appointed Assistant Professor at the Faculty of Natural Sciences and Mathematics, Department of Biology. She became Head of the newly founded Chair of Microbiology at the Institute of Botany and Botanical Garden. From then until her retirement in 2003, she remained an influential member of the teaching staff of the Faculty of Biology (formerly the Department of Biology), advancing from the position of Assistant Professor to the rank of Associate Professor in 1987 and that of Full Professor in 1991.

The name of Draga Simić is inextricably linked with the development of microbiology in the educational

D. Simić with colleagues from the Institute of Botany and Botanical Garden "Jevremovac" in the early 1980s

and scientific activities of the Faculty of Biology, University of Belgrade. Although the basic elements of microbiology were present in the curriculum of General Biology from the early seventies, a modern approach to this biological discipline did not exist until Professor Simić conceptualised the independent, "self-contained" course General Microbiology in the 1977/78 academic year. Her lectures presented the latest knowledge in all fields of the biology of microorganisms, and she invested great effort and dedication in organising and carrying out the practical training of students, which was a novelty when compared to previous microbiology courses. In addition to this, as a founder and Head of the new Chair of Microbiology, Draga Simić was faced with many difficulties in her efforts to organise teaching and practical work for more than two hundred students. She therefore took steps to open a position for an assistant who would help her in her work. At the same time, she sought to obtain appropriate working space for the new Chair and additional financial resources for equipping the research and practical work with students in the laboratory. In spite of the difficulties, during the first five years the Laboratory of Microbiology was equipped with the basics and, with the commitment of Draga Simić and help of colleagues at home and abroad, the foundations were laid for modern teaching and research at the Chair of Microbiology. During that period, Professor Simić carried out intensive research in the very competitive field of DNA repair in *Escherichia coli*, studied the role of cellular proteins in induction of the SOS response and later investigated the antimutagenic effects of plant substances. Apart from these fundamental problems, applied issues of microbiology (microbiological control of different ecosystems, water treatment, production of biopesticides, etc.) were also considered.

In the 1985/86 academic year, Professor Simić organised the postgraduate MSc program Biology of Microorganisms, where she designed and taught

D. Simić in her office in the Institute of Botany's Chair of Microbiology

the advanced courses Microbiology and Methods in Microbiology, and organised seminars in several elective courses. Thanks to her enthusiasm, from 1987/88 the elective module Biology of Microorganisms was introduced at the undergraduate study level as well. Being the only teacher at the Chair of Microbiology until 1991, she taught several courses: Methods in Microbiology, Fundamentals of Genotoxicology (part of the course) and Viruses (part of the course), apart from which she organised seminars in Microbial Ecology and Applied Microbiology. From 1988/89 she additionally taught two obligatory one-semester Microbiology courses, which were introduced in the undergraduate study program Molecular Biology and Physiology at the Faculty of Biology and in the Biochemistry study program at the Faculty of Chemistry, both of the University of Belgrade. When the new undergraduate program Ecology and Environmental Protection was launched at the Faculty of Biology in the 1997/98 academic year, Dr. Simić taught Microbiology and Microbial Ecology, and was one of the teachers of the course Genetics and Genotoxicology. She also taught microbiology for two years at the Department of Biology, Faculty of Natural Sciences and Mathematics, University of Kragujevac.

D. Simić as Director of the Institute of Botany and Botanical Garden "Jevremovac" and her colleagues from the Institute in 1992, during the visit of Professor R. Vračar, then Rector of the University of Belgrade, and Professor Lj. Topisirović, Dean of the Faculty of Biology at the time

Since becoming a lecturer and throughout her teaching career, Draga Simić continuously developed and modernised the curricula, introducing the latest scientific information and advancements in microbiology, which in turn benefited her students, who highly appreciated her competent and dedicated transfer of knowledge. She also delivered numerous extracurricular lectures at the Petnica Science Centre (Valjevo, Serbia) and enthusiastically shared her knowledge with the general public at the Kolarac Foundation. Professor Simić supervised over 50 BSc dissertations and over 20 MSc and Specialisation dissertations. She mentored and co-mentored 6 PhD theses and participated in the commissions for review, assessment and defence of over 50 MSc and PhD theses. One of the MSc dissertations she supervised resulted in a patent registration. More than 300 published references including chapters in books and monographic publications, review articles, scientific papers and research communications have Draga Simić as an author or co-author, and there have been over 300 citations of her articles in international journals and books, as well as in scientific publications by researchers from Serbia and the countries of former Yugoslavia.

Professor Simić is the author of the university textbook Microbiology I (Mikrobiologija I) and co-author of Laboratory Exercises in Microbiology (Praktikum iz mikrobiologije), Methods in Microbiology I (Metode u mikrobiologiji I), Fundamentals of the Genetics of Prokaryotes (Osnovi genetike prokariota) and one secondary school textbook in microbiology. She contributed numerous items on microbiology to Mala enciklopedija Prosveta (Prosveta, Beograd) and is currently engaged in the major ongoing project Srpska enciklopedija as an author and member of the editorial team for biology (Matica srpska, SANU, Zavod za udžbenike, Novi Sad–Beograd, 2010, 2011, 2013).

Draga Simić was elected Director of the Institute of Botany and Botanical Garden "Jevremovac" in the period from 1991 to 1993. In 1992 she had the honour

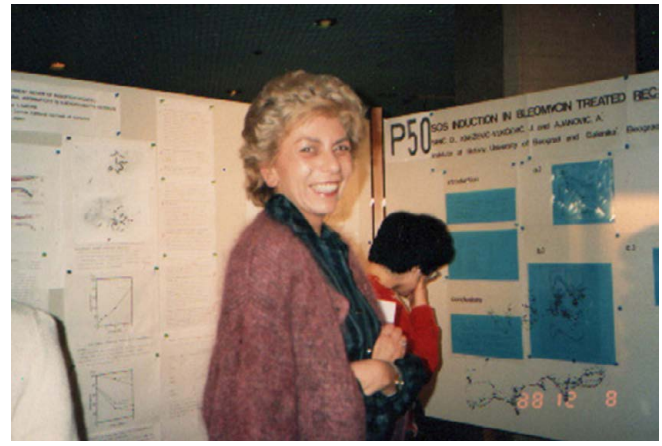
of presiding over the ceremony of celebration marking the centennial of construction of the greenhouse in the Botanical Garden „Jevremovac". This greenhouse was built in 1892 and at that time was one of the most beautiful in our part of Europe. Moreover, supported by Dr. R. Vracar (then Rector of the University of Belgrade) and Dr. Lj. Topisirovic (Dean of the Faculty of Biology at the time), she organised the preliminary project of creating the architectural design for a new building of the Institute of Botany and Botanical Garden "Jevremovac" of the Faculty of Biology. In 2002 she served as Dean of the Faculty of Biology.

Professor Simić also undertook a number of social obligations. She was a member of many professional and scientific boards of the Faculty of Biology, member of the Faculty Council and the University Council, and member of the Professional Board for Biology of the University of Belgrade. In addition, she has been President of the Serbian Biological Society and was two-term General Secretary of the Union of Genetic Societies of Yugoslavia. In January of 2014 she was awarded the Platinum Diploma in recognition of her active participation in the development and affirmation of the Serbian Biological Society and its journal Archives of Biological Sciences. Draga Simić is a member of the Serbian Association of Microbiologists, the Serbian Genetics Society and the American Microbiological Society (AMS). She was a member of the International Genetics Federation (IGF), the Society of Molecular Biology and the European Environmental Mutagen Society (EEMS), where she served as consultant for Yugoslavia. She was also a member of the organising and/or scientific committees of national and international conferences.

Finally, she has been a member of the editorial boards of several scientific journals: Bulletin of the Institute of Botany and Botanical Garden Belgrade, Archives of Biological Sciences, Genetika and Botanica Serbica, the international peer-reviewed botanical journal of the Institute of Botany and Jevremovac Botanical Garden. She also reviewed many papers for national and international scientific journals.

A lifetime commitment to DNA repair studies

Almost the entire scientific career of Draga Simić has been dedicated to the field of molecular radiobiology, especially to the study of DNA repair in *E. coli*. Her research began in the field of plant physiology, but in 1964 she started investigating the effects of ionizing radiation on proteins, nucleohistones and DNA irradiated in the solid state. Using the method of electron-spin resonance, she obtained considerable information about the radioresistance of these molecules, alone or in complex, localised the parts of the molecules where free radicals were induced and determined the effect of temperature and metal ions on their radioresistance. The results of these studies, published in several papers in the period of 1965-66, showed an astonishing analogy with results obtained *in vivo*.



D. Simić in front of her poster presented at the International Conference on Antimutagenesis in Ohito, Japan, 1988

From 1966 the scientific interest of Draga Simić turned to the study of photochemical damage in DNA induced by UV radiation, using phage lambda of *E. coli* as a model. The obtained results were an integral part of her PhD thesis. By combining different methods (sedimentation of DNA in neutral and alkaline sucrose gradients, electron microscopy, radiochromatography, alkaline denaturation), she showed unequivocally that pyrimidine dimers are the major types of induced lesions and the essential cause of biological inactivation of DNA. By tracking the fate of irradiated phage DNA during superinfection of *E. coli* strains defective in DNA repair, she demonstrated the complementary roles of recombination and nucleotide excision in the repair of pyrimidine dimers: while excision corrected the damage before replication, recombination was operational during or after replication. Furthermore, DNA containing a small number of dimers is repaired mainly by recombination, while excision begins in the presence of a large number of lesions. In a review paper written together with her mentor, Professor M. Errera, published in 1969, she discussed available data on DNA damage induced by radiation, as well as biochemical and other aspects of mutations in *E. coli* that led to increased radiation sensitivity. Her own results in this exceptionally competitive line of research greatly contributed to the general knowledge of DNA repair mechanisms.

Her work on these issues was temporarily suspended during her post-doctoral studies at the Yale University, where she joined the laboratory of Professor P. Howard-Flanders. Her vast experience in physico-chemical and biochemical studies of biomolecules was of great value for examination of the complex formed between the DNA of phage lambda and the bacterial membrane. Some results of these investigations laid the groundwork for further research that confirmed the important role

With Professor F. Sobels during the International Conference on Antimutagenesis in Ohito, Japan, 1988

With Dr. M. Alačević during a refreshing respite at the Congress of Croatian Geneticists, Island of Brač, Croatia, 2005

played by the DNA-membrane complex in regulation of the replication and transcription of phage DNA. She also brought her expertise to the Laboratory of Microbiology, University of Lille, where she isolated, characterised and classified bacteriophages of the symbiotic nitrogen-fixing bacterium *Rhizobium meliloti*. Unfortunately, later technical difficulties did not allow further in-depth exploration of this subject.

Back in Belgrade, Draga Simić returned to the study of DNA repair mechanisms in *E. coli* and through these studies developed a team of young scientists to carry on this research. Her scientific interest focused on the regulation of cellular responses to DNA damage, especially the role played by the RecA protein and recombination pathways in induction of the SOS response. To be specific, damage to DNA in *E. coli* causes the induction of physiological responses, called SOS functions, which are regulated by products of the *recA* and *lexA* genes. After DNA damage, the RecA protein, activated by the SOS signal, allows degradation of the LexA repressor and a repressor of phage lambda to occur, which leads to increased expression of *recA* and other SOS genes and induction of the SOS functions (mutagenesis, Weigle-reactivation, cell filamentation, induction of phage lambda, etc.). In a comparative study of several SOS functions induced by treatments which differently damaged DNA, Draga Simić obtained important new information, namely that an increased amount of RecA protein is not necessary for induction of prophage lambda, except when the RecA-mediated recombination is required to repair DNA lesions induced by the treatment. This finding led her to further explore the participation of alternative pathways of recombination repair in *E. coli* in generation of the SOS signal. The molecular nature of the SOS signal was unknown at that time, when it was presumed to be formed by DNA damage processing during the repair process. Studies on the physiological, biochemical and genetic levels published by Professor Simić during the 1980s contributed to insight into the distinct roles of alternative recombination pathways, RecBCD or RecF, in the repair of different types of DNA lesions and SOS signal generation.

In the early 1990s Draga Simić initiated a new line of research in the relatively new field of antimutagenesis/anticarcinogenesis, dealing with the detection of inhibitors or modulators of genotoxic agents and determination of their mechanisms of action. Professor Simić applied her knowledge of DNA repair and its biological consequences to the construction and validation of a new *E. coli* K12 test system for detection of antimutagens and their mechanisms of action. The assay was designed to measure several end-points at the DNA level: spontaneous and induced mutagenesis on different genetic backgrounds, SOS induction and homologous recombination. It was initially intended to detect agents which prevent mutations by modulating DNA repair and replication, but was later amended to allow detection of the antimutagenic effect of antioxidants.

Extensive searching for antimutagens from different medicinal and aromatic plants promoted sage (*Salvia officinalis* L.) as a possible source of bioantimutagens, and basil (*Ocimum basilicum* L.) as a potent source of antioxidants. Detailed studies of sage and basil extracts containing monoterpenes with *E. coli* K 12 and appropriately modified standard mutagenicity tests in conjunction with the comet assay revealed that the bioantimutagenic effect of sage monoterpenes is predominately based on the stimulation of „error-free“ DNA repair mechanisms, while the protective effect of monoterpenes from basil mainly involes the inhibition of oxidative DNA damage. These studies resulted in a large number of scientific papers and conference lectures, as well as in many BSc, MSc and PhD dissertations mentored by Professor Simić. The scientific communities in different countries, especially Japan, showed great interest in our research in the field

D. Simić with her closest associates, Professors J. Knežević-Vukčević and B. Vuković-Gačić

of antimutagenesis/anticarcinogenesis, which resulted in invitations to deliver lectures at several conferences (ones organised in the Japanese cities of Ohito in 1988, Okayama in 1996 and Shizuoka in 2001). A review of hers published as a monograph by the journal Topical Issues in Applied Microbiology and Biotechnology illustrates the outstanding contribution of Professor Simić to knowledge of the complex molecular mechanisms of mutagenesis inhibition.

The studies of antimutagenic effects of plant substances that she initiated were successfully continued by her younger colleagues from the Chair of Microbiology, and current research extends to other biological properties, such as antimicrobial, cytotoxic and pathogen adhesion-inhibition activities. More recently, antimicrobial substances from *Bacillus* strains effective against plant pathogenic bacteria are also under study. In 2013 the Centre for Genotoxicology and Ecogenotoxicology was established within the framework of the Chair, and it is currently performing microbiological and genotoxic monitoring of river waters in Serbia.

Concluding this overview of the prosperous and creative career of Draga Simić as a scientist and teacher, let me emphasise that she founded the Chair of Microbiology at the Faculty of Biology, University of Belgrade, and pioneered DNA repair and antimutagenesis studies in Serbia. Her work greatly influenced the research orientation of many authors in the country. During her professional career, she collaborated with many prominent names in the field of DNA repair, scientists such as P. Howard-Flanders, M. Errera, R. Thomas, M. Radman, R. Devoret, M. Alačević and P. Sobels. She inspired us, her younger colleagues at the Chair of Microbiology, to follow the highest criteria in teaching and research, for which we are grateful. And finally let me guess that after devoting so many years of fruitful efforts to them, Draga Simić is pleased that the Nobel Prize has finally been awarded for studies of her favorite subject, DNA repair.

It is certainly noteworthy that apart from an outstanding mastery of specific scientific disciplines, Draga Simić had a remarkably wide field of scientific knowledge and interests. Due to this particular quality, she was a greatly appreciated participant in and contributor to discussions, formal and informal, primarily among her colleagues, molecular biologists and geneticists, but also among botanists specialising in plant physiology, ecology, biochemistry and evolution. A person lively and gregarious in her time off from professional duties, fond of theatre and cinema, and keenly appreciative of contemporary literature, Draga Simić holds a special place in our pleasant memories of various professional and social meetings.

On behalf of all of us who have had the privilege of working with Professor Draga Simić, I wish her good health and many happy days with her grandchildren in the years to come.

Professor Jelena Knežević-Vukčević,
Head of the Chair of Microbiology

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