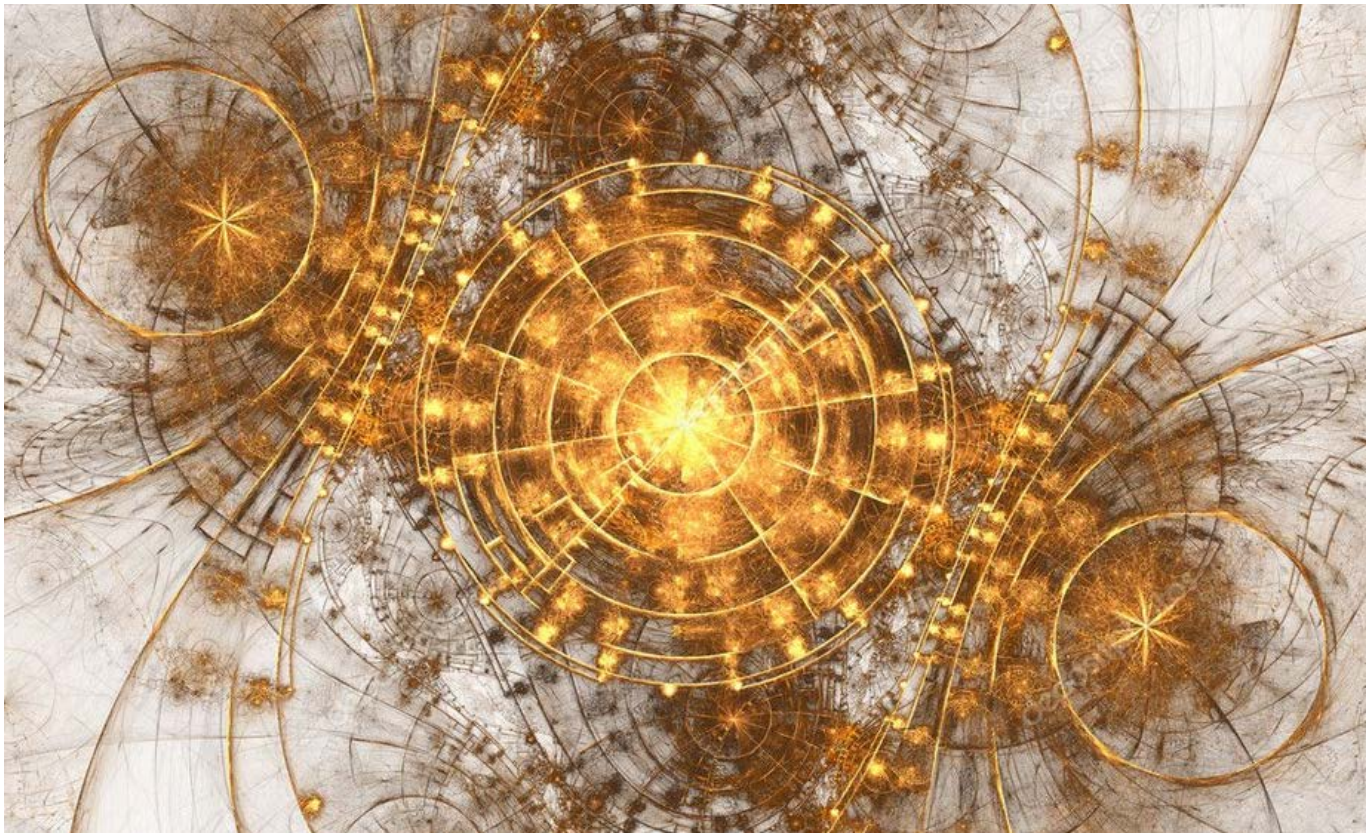
**Interview with prof. Dr. Miroslav Radman by Marin Bosotina**

# Every day we live six hours more and no one knows why!

Prof. Dr. Miroslav Radman is a Croatian biologist and a member of the French Academy of Sciences, the European Academy of Sciences and Arts, the World Academy of Sciences and the European Organization for Molecular Biology (EMBO). He gained world fame in 1989 when, by crossing two types of bacteria that did not mix for 150 million years, he discovered a molecular model of the formation of new species, more precisely, how two different species form from one species of the ancestor.

A member of the French Academy of Sciences and world-famous scientist prof. dr. Miroslav Radman described and introduced us to the process and method of aging, which is a topic to which he dedicated his scientific life as an evolutionary and molecular geneticist. In 177 papers published so far, he has described 25 original discoveries cited thousands of times, and the 12 world awards presented are a confirmation of the influence and respect he enjoys in scientific circles.



### Q: Why and how do we age?

**A:** We all age very similarly and through a whole series of evolutionary complexities: from a small invisible worm, an elephant, to a human. The aging process seems to be the same, only it takes place at different speeds in different animals. The difference in lifespan between the shortest and longest being somewhere around ten thousand times.

In general, the larger the living being, the longer it lasts - the slower the aging process. Interesting. I think there were still "living" theories about aging ten years ago. So, the challenge is great. The existence of hundreds of theories about aging means that no one knows anything about it, that theories can arise in complete freedom since there is no definition of the fundamental process of aging.

### Q: What does "ageing" actually mean?

**A:** Aging is a process that is seen in the individual: performance becomes weaker and weaker - movement, speed of thinking, and other bodily functions become weaker. At the level of the population, in this great ignorance of ageing, one of the few laws in biology still applies; Gompertz's law. This means that for every living being, with the focus being on humans, the probability of mortality increases exponentially: the older we are, the higher the probability of dying with a fifth power. So this is what the Gompertz curve looks like: if on the one hand there is age, and on the other mortality, the ageing process itself accelerates with time and is faster and faster, with the fifth power of time. If we double the age, the probability of getting sick and dying increases by about 30 or 60 times. Nothing is more dangerous to life than living! If the cause was radiation, or smoking 100 cigarettes a day, then the curve would go linearly with these toxic factors, but this goes with the fifth power . It is Gompertz's law of the mid-19th century established by an Englishman. The challenge is to understand this process, which accelerates to the fifth power with age, that is, with time, the life of everyone.

# We are not all the same

### Q: What happens to our cells that causes them to age?

**A:** Now, the most popular theory is that these are mutations, changes in genes, that these changes (mutations) accumulate over time, which is why bad proteins are produced. We know that aging is a very complicated phenotype - therefore, a set of all the characteristics of a given organism, be it a simple little worm or a complex man or an elephant. What biologists call a phenotype are all characteristics of that organism, and we know that these characteristics are the result of biological functions, and those are proteins, not genes. Genes determine which proteins will be synthesized.

When a gene is damaged then the protein will also be damaged because the gene encodes a protein. However, what got out of mind is that the function can be damaged without damaging its gene. We can take cars as an example, after all, they die exponentially. Like humans, cars made on the same day, cloned by robots - the same models on the same production chain made robotically, will not stop working on the same day or after the same

number of kilometers - because they are not quite identical, and will not be identical based on the way of life of that car. It all depends on who drives it, how often, on what terrain and whether you look after it.

This is how we treat our organism individually: someone lives a healthy life; focuses on maintaining a good diet, refrains from smoking, and then there is someone who lives excessively - there is an overlap, or as the English say "nature-nurture" which means nature (genetics) and living conditions both affect ageing. I think the reason for this conversation is that we can now be sure enough that in my institute we obtained a complex image, first on bacteria, then on yeast, then on small red cells and then on human cells and directly on a biopsy of human skin or tumors, an ageing mechanism that agrees with everything we know so far and that promises a lot.

**Q: Why?**

**A:** If aging was at the level of genes, and you have genes on the other side of DNA, and if aging occurs due to a mutation in a gene, then the mutation will cause the dysfunction of the protein it encodes because the protein carries that same mutation. There is no way for such a cell. It is too rare for a new mutation to return the sequence to its original one. However, if we are right, then aging is at the level of protein damage, not genes.

# Ageing - a process that can be reversed?

The damage to proteins that is most common is corrosion, that is, oxidation. As well as oxidation of cars, the bacteria and human cells are also susceptible to oxidation. Namely, the biological material can oxidate just like all other materials. I think that molecules are even more sensitive. If the cause of aging is damage to proteins, then there is hope: if we break down this damaged protein, send it to the trash in some way and synthesize a new one from the correct gene, we have returned the same protein to function. If this is aging, this increase in the risk of all diseases related to aging and death is in principle a reversible process; it means that in principle aging could and would be reversible. Certain interventions, lifestyles or taking something could not only stop aging but even "walk" it backwards. However, a few years ago, it was shown in mice that if the bloodstream of two genetically identical mice is connected, and one is young the other old (note: they must be genetically identical because their immune system would cause problems), within a week, visibly and by all measurements, the older mouse is rejuvenated for the equivalent to ten days, while the young mouse is only slightly older.

The old mouse rejuvenates a lot, and this lasts as long as they are connected as long as the bloodstream is connected. So the question of whether ageing is reversible? It is. But what happens if the connection between such a rejuvenated and old mouse is broken? It seems that the rejuvenated mouse from that moment will not only age but will age faster. As if there is some memory in the body. He (the rejuvenated mouse) rejuvenates by all criteria - even the hypertrophied heart returns to normal, the telomeres at the end of the chromosome increase, the bone density... everything improves. The mouse simply rejuvenates. However, after that, when that connection is broken, when a mouse that was two and a half years old rejuvenated by one year, the question arises whether he will continue to live like a one-year-old mouse? No. In a few weeks, he will return to his real age.

# In search of this memory

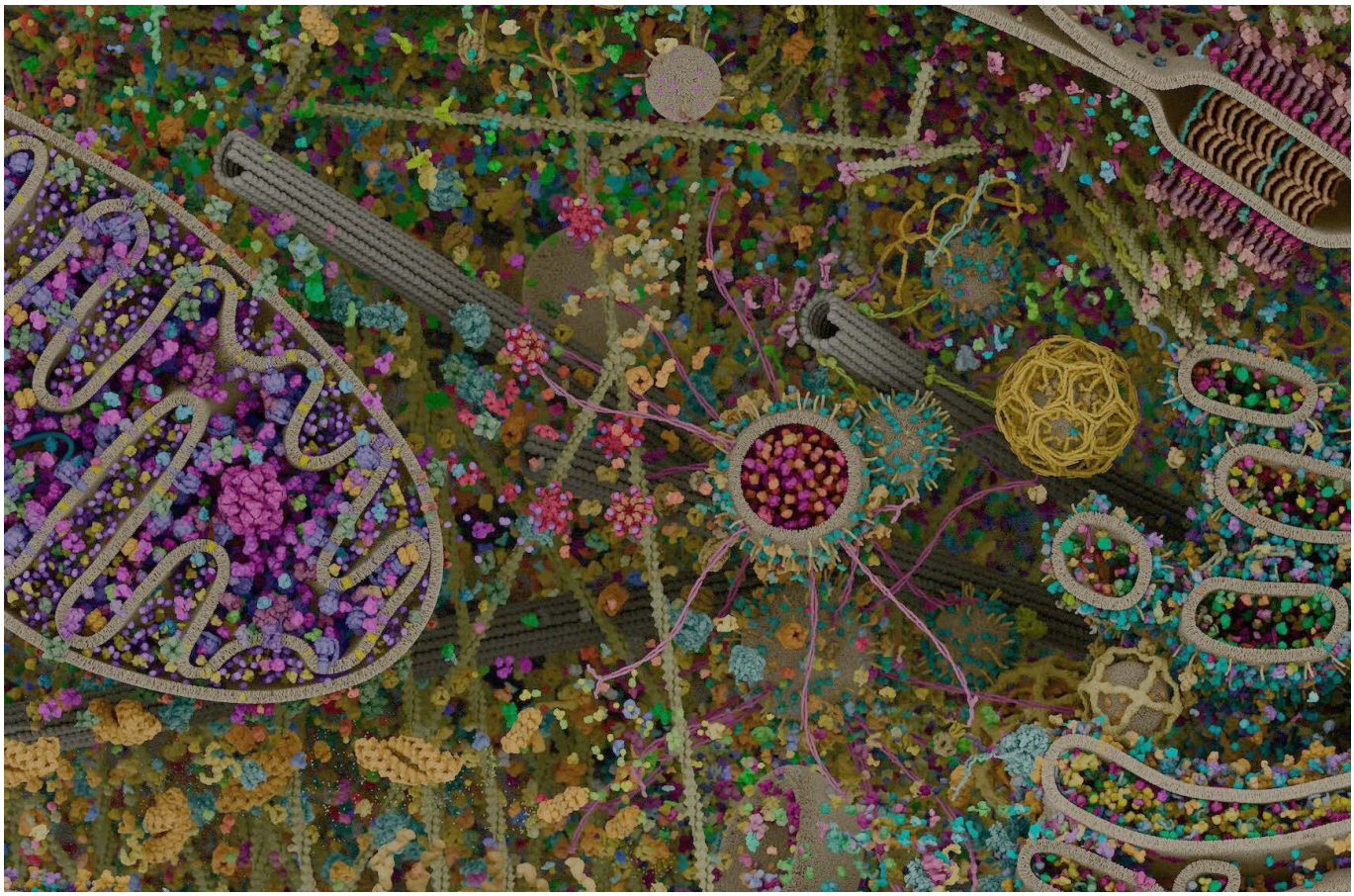
So now the question is: where is the memory? This is very interesting: where is the memory of his real age that we erased during that parabiosis? A two-and-a-half-year-old mouse has been rejuvenated by all measures, including mental activity, such as navigating a maze. How is it that there has been no permanent rejuvenation, that is, why does this connection have to remain permanent for youth to be maintained?

The best hypothesis we have so far is that during aging at the gene level, DNA is modified (in both mice and the vast majority of all animals). So, small methyl groups seem to print DNA text and say this is fine, this is fine… and when you look at these modifications, it's not a change of text, it's not a mutation, it's a modification of a cytosine base. If the modification in the liver looks like this, then the same genes, and we know that our cells carry the same initial DNA, it may look like this in the brain. Thus, these modifications activate and deactivate genes, they silence genes that are not needed in the liver but are needed in the brain. Now, when cells divide and proteins are damaged, then those carrier proteins, which replicate DNA, must be faithfully transferred to a new chain of modification. But they are no longer effective and certain modifications are lost, new ones are added by mistake. When this happens at the DNA level, then this protein renewal is no longer true. I will try to simplify it.

If we take only one gene that produces only one protein in a lot of copies, which, say, oxidizes, and in cells, the damage of each protein is quantitatively measured, why is reversion possible? Because we know that these damaged proteins go in a special trash can where they break down into pieces, amino acids, which are then recycled in the synthesis of new proteins. Thus, the fresh protein will be synthesized again. This constant renewal, when it happens in a fast and efficient rhythm, makes us young. The same cell with the same genes, although slowing down regeneration, will begin to accumulate damaged proteins. When we look at the accumulation of damaged proteins, then on the Gompers

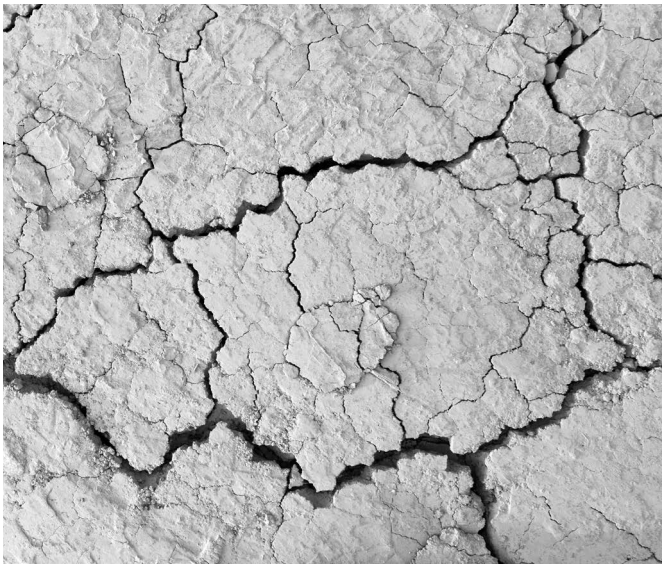
curve we see that damaged proteins also accumulate exponentially in cells as we age. So, we now conclude that the most likely, basic, fundamental chemistry of aging is protein corrosion that is not purified. Cleansing is done by special proteins. Since all functions in life are performed by proteins, they also perform the cleansing. When the cleansing system is damaged, then the cleansing will be less efficient, that is, fresh proteins will also be needed to create new ones. It's protein renewal: they need both cleansing and renewal to keep the protein fund clean and functional.

It happens when we are young because there is little damage and little mortality. As the repair and cleansing system is damaged, there is an increasing accumulation of damaged proteins and this function suffers. There are more and more of them in the cell, including one that will modify, that will say that some gene must not be expressed or that it will be silenced by mistake. Now, if it is silenced, even when the proteins are cleared in parabiosis, what is recorded remains, what is remembered, what is a bottleneck, and it is this error at the DNA level that is not a mutation but that the gene is said not to be expressed or will be very rarely cleaned. That way the proteins will not be able to regenerate even though everything was well done. Renewal becomes deficient and therefore it is necessary to constantly take this factor from the blood of a young mouse. I note that these findings have been published in very serious journals such as Nature and Cell. If it goes back to a low level of GDF, then I think I explained to you: the bottleneck is the memory of the changes that have taken place in DNA and which are then called epigenetic. It is not a mutation, it does not create the wrong protein, but it causes the formation of too few good proteins. So, the thing is in quantity and that is why it is called the epigenetic effect. I think that somewhere is the bulk of the picture of aging that we have today and that is enough to start constructing an optimism of intervention. In principle, aging is reversible. If we do not allow it because we prevent it from the beginning, by prevention, we prevent oxidative damage, then we can see where it is because there are ways to do it. And then the curve shifts. This is our project.



# We all die in a similar way

After the first part of the interview with Professor Miroslav Radman, the world's top molecular geneticist, a sequel follows in which he reveals and explains his key findings and results of genetic research that have aroused great interest and praise from the profession and the general public:



### Q: If we prevent the oxidation of certain proteins, we can slow down aging in that area. Can you explain this for us in more detail?

**A:** You ask on what basis do I claim that the chemistry of aging is the same in the little worm, the mouse, and the human? Based on the following: if instead of years, 3 years for a mouse, 90 years for a human, 3 months for a fly, maybe two and a half weeks for a small worm, we put the age fraction on the age curve, that means from 0 to 1, on the one hand, the beginning of life, and on the other end, 100 years for man, 3 years for mice, 2 and a half weeks for worms and oxidation by protein, and without any other normalization, simply by stating the number of oxidized proteins relative to the non-oxidized protein, we will get different data for man and that will be 90 years. We will have the same curve, exponential for worms, flies, mice and humans, if we put a fraction of life instead of chronological age. Here we can conclude that by quantitative measurement of protein oxidation we measure the fraction of life, i.e. aging. When it comes to humans, we know that these values will never be at the same point because we are not clones and do not live identically. So for a given age, the man will be younger because there will be deviations on the Gompertz curve. Someone will have more oxidation than his age, and someone less. In that case, based on the curve, we will say, for example, "Sir, you are five years older than your age" or "Sir, you are 7 years younger than your chronological age." Therefore, if the measurement of the chemistry of aging, i.e. protein oxidation, is quantitative, the data will monitor the quality of the organism. We will find out the actual biological age, not the chronological one (date of our birth).

# Formation of molecular patches

**Q: Can predispositions be determined concerning dying (in relation to disease and illness, not accidents)? Is it within our capabilities to predict what someone will die from? Lastly, can a predisposition to an illness/disease be seen?**

**A:** That would conclude this story now with a single image, or drawing, from which we can get an image, and includes methods in which individual proteins in two-dimensional analysis give one thick dot called a spot, which will be multiple copies of the same protein. Thus, in this method, we disperse different proteins by molecular weight and electric charge. We can see two thousands of them and that's about as many as one specialized organ, like the liver or skin, will make them. This has been known for a long time, but now we have a method by which we can see it because a fluorescent signal appears for oxidative damage. When oxygen is attached to this protein molecule and it is done often, then the protein point will give a protein signal, which is how we are able to see it. But we will also get a strong, red signal indicating that the protein is oxidatively damaged. So, one protein will be damaged and the other will not, one will be badly damaged, the other weakly, etc... And then what will we see? We will see that in different individuals the damage to all proteins is not identical. One group will always be damaged, we will have something in common and something related to the individual. The damage will be somewhere for me, and for my neighbor, it's going to be somewhere else. We can see the protein in question in two individuals and we can make a prediction, for example, say "This protein is much more sensitive in me than in my neighbor. What does this protein do? It is important in kidney function, so it's no wonder my grandfather and my father had kidney problems. Let's check my proteins!" - "What can we do?" - We can make a diagnosis perhaps at birth. There will be very little damage, but we can cause it with peroxide or with a little radiation and damage to the umbilical cord cells artificially. It will turn out like in an old black and white film: it will show points that are more and those that are less sensitive. After that, a predictive

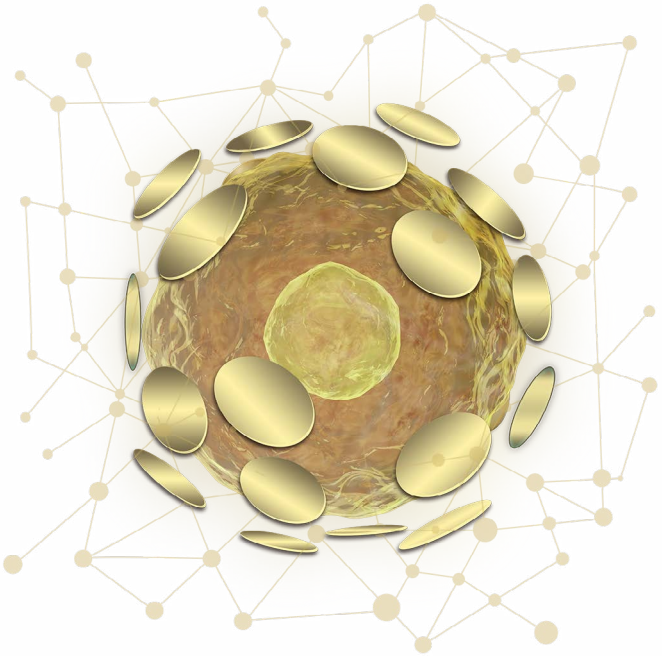
prognostic diagnosis can be made to get an answer to the question of what will happen to that baby, who will go on to win the Olympic gold medal at the age of 25 with a heart or kidney at the age of 60 or 70 years. So this is a dream that opened up the sequencing of the complete human genome and which, to read 3 billion letters of the human genome, cost $3 billion. It was thought that individual predispositions for the disease, which would be acquired in old age according to Gompers' curve, would be seen directly from it. However, it turned out that we did not have enough knowledge about that. But now this analysis comes into play, revealing that interindividual differences in people of the same age show this predisposition. So, this is a predisposition of proteins to oxidation, which leads to a person's predisposition to a disease, say Parkinson's disease. This opens the door to predictive and prognostic diagnostics, preventive activity by which with the repeated measurements we can monitor whether it has changed the situation in the cells or not. It is also possible to realistically plan new pharmacology where it is known exactly what polyformisms, differences in proteins between healthy people, are going to cause problems, and how/why a protein that is sensitive in one person oxidizes and causes an earlier disease. We also learn how molecules can be designed to prevent just this polyformism; this protein from oxidizing. So we expect that we will need to develop just a few hundred molecules that will be like molecular patches that will protect sensitive molecules in individuals, and that will first need to be diagnosed and identified, then taken from a series of those drugs that will be either simple molecules or maybe designed mini protein parts that will lie down and repair or protect the structure. To conclude, is it just a crazy dream?

# We are all descendants of only 7 or 8 great-grandmothers

By analyzing human diversity, we looked at what happened 150 or 180 thousand years ago, at a time when the human species was almost extinct. This is very recent for evolution - a time when the human species was almost extinct and there was only one small population left in sub-Saharan Africa. It is estimated that about 10,000 individuals remained then, about as many as there are tigers today. There were so many of us, our ancestors, and that is very few. Genetic analysis of DNA, i.e. mitochondria: small energy machines in which radicals are created, has shown that we, 7 billion people, are the descendants of only 7 or 8 great-grandmothers! That small population in the sub-Saharan region was made up of several thousand people. The survivors produced offsprings who are the descendants of less than a dozen great-great-great-grandmothers. However, in just 150,000 years, there has been a major explosion. We are talking about one very recent event, which was the almost complete extinction of the human species. Yet not only did this species not become extinct, but it exploded and thrived from a population of a few thousand to 7 billion people. We are genetically relatively homogeneous.

There are indeed some tens of millions of different letters between you and me, however, most of those differences are in 98% of the DNA that doesn't encode for proteins, so it doesn't matter to us in this story. But when viewed in proteins, there is a large penalty for mutation, and differences in proteins are very, very rare. We have studied how in those 150,000 years when some of our ancestors from Central Africa moved to Australia, Europe, the North, or America, there was an accumulation of these small differences. So, there were migrations to different continents, and since there were no planes or cars, people did not mix, so the resulting mutations remained local, where those people were. This is how the so-called polyformism came about. Today we can ask ourselves, do we all die similarly in the absence of some great epidemics? Do we all, the heirs of the recent ancestor from which the Indians, Indians, Europeans and of course the African population arose, have the same style of dying? The answer is: we have! Cardiovascular, neurodegenerative, infectious disorders, cancer, everything related to immune system defects is related to this predisposition of individual proteins and individual polyformism. We discover how many of these mutations there are, the difference in the sensitivity of individual protein human diversity in Europe, Africa, Asia, Australia and America. And they overlap in just a hundred differences that are probably inherited from that small population of 150,000 years ago. They used to die as we do today (if they weren't eaten by a wild animal or some awful bacterium or virus), but drugs are being designed that will neutralize and alleviate the individual predispositions that exist in a hundred molecules, no more. I was afraid that there would be 100 thousands of them, and there are only a hundred of them. It's optimism, and the other is that this goes hand in hand with surprise and good news - imagine having a hundred molecular cures for all diseases. Today we have thousands and thousands of cures for a hundred diseases. This would be the solution to all the aging-related diseases. There are about a hundred and we would need those 100 molecules for them.

# New protein medicine



Here, I will end with unpublished results that surprised us, and in a way amazed us. We almost came to some philosophical pleasure watching those results. And they came from the remnants of the skin after cosmetic surgery, which, fortunately, as far as experiments are concerned, there is enough in the world, even in Croatia. That human skin that would otherwise go in the trash, gave information about what the man was about, whether he was sick, old, young, whether he smoked, whether he was fat, thin... everything could be monitored by looking at his proteins. Thus, not only could predisposition be seen, but differences in the analysis of skin proteins of smokers and non-smokers were grouped, which were sufficiently visible, but also those between very fat and only large or thin. So, even a lifestyle can be seen on proteins, not just a genetic predisposition which is one fatality that you can still act on by correcting not a gene, but a defect in the protein level of that gene, which is crucial and is a new protein medicine. Likewise, when you look at the skin, we have seen that over time the number of these oxidized proteins in man grows, there are more and more of them, to create one specific curve. However, when you identify a protein, which you must discover by a complicated method, we come to this conclusion: we all age individually as humanity. Given these small differences in some proteins between two individuals, damage occurs that will be typical for diabetes, Parkinson's disease, or various other types of disease. So, when you watch people die, they die from a hundred types of tumors, cardiovascular accidents, brain, heart, etc. In the aging of each person, a certain percentage of each of these major diseases can be seen, which ultimately kill people, with the proviso that, given the protein damage, for example, in my case, the winner will be one species, e.g. cardiovascular, and in my neighbor, who is the same age as me, it will be Parkinson's disease: he will start to shake, and I won't.

When we look at what is going on, then every human being is an individual at the level of these protein defects: old as humanity, but in different proportions. Maybe someone is already 75% cardiovascular, 30% cancer, 45% Alzheimer's, 10% Parkinson's ... and then at a given moment in the first line that is most advanced as damage, it is diagnosed as death - a man died of a heart attack. However, if he had not died of heart disease, he would have died of pancreatic cancer in two and a half years, etc.

So, each of us ages at the level of individual functions of which there are thousands and thousands, but humanity gives a victorious disease, one that kills. A lot of people die from a heart attack or colon cancer, but we were surprised that in the aging of a single individual, we could see (in percentage) how close it is to death from cancer or some other disease. Because we are such close descendants of such close grandparents from just 150,000 years ago. With this small poetic image, which is again not fatal, I act in the hope that we have finally found the cause of aging and diseases that are only part of the aging process, and that we will not be able to see the fate of a person's health and then sit idly by. A vision of influencing one's destiny that is more effective than "eat healthy food, don't smoke." That's good advice, of course, but it opens perspectives toward a much more effective intervention that will make it possible that perhaps in 30-40 years, centenarians will be biologically and mentally in the form in which today's 50-year-olds are. Then the social, political, cultural and economic consequences will be very interesting.

# All we are capable of doing is the result of a combination of the work of about a million proteins

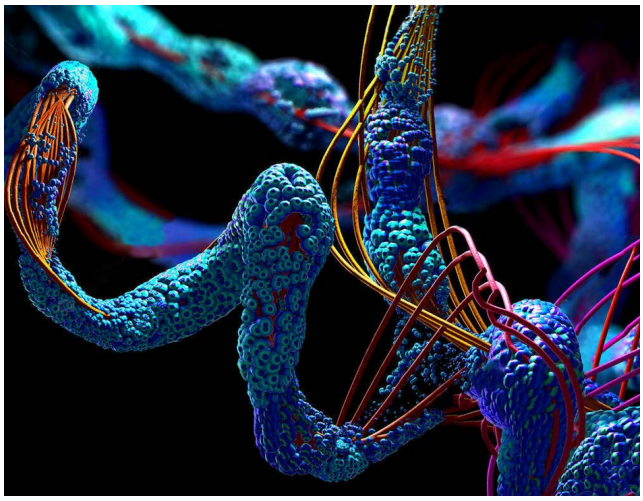
**Q: What is now, with a healthy lifestyle and genetic predisposition as it is, the impact of antioxidants on all proteins, on the whole process plus GDF11 factor - are they as an isolated factor acting on our DNA structure to recognize that gene and activate production protein, that is, how much therapy based on it has a future? How much do these antioxidants prevent oxidative processes? Can I improve my quality of life in general?**

**A:** As for intervening in the very process of aging and getting sick from the disease of aging, we have a couple of terribly simple approaches. It's about how to prevent this chemistry from happening at this speed, how to slow it down. Perhaps it would be easier to imagine that we are learned mice, that we are in the position of a mouse, then our project would be aimed at achieving human lifespan. How to live as long as possible? How to live 30 times longer?

# Antioxidants as the main protectors of proteins

We as humans can ask the same question: how to live longer, like some species that are simpler than ours but more long-lived? How to intervene in the aging process in terms of prevention, treatment, and the reversal of the disease? It is first necessary, of course, at the level of basic chemistry, to reduce oxidation. Oxidation comes from our oxidative metabolism which to man is like gasoline for a car - without it, there is no life. In mitochondria, it is the burning of sugar with the help of oxygen. Now, one percent of that oxygen is in forms we call ROS, which is a common name for oxygen radicals. It is not ordinary oxygen but its aggressive form, hence ephemeral, short-lived molecules of unstable oxygen that then bind to anything. Either it will be iron rust or rust of my protein or DNA.

Of course, so-called antioxidants are used, which have an enormous number of panoply and without them, we would not be able to live 90 years. A goji plant that grows at 4,000 feet above sea level and with so much ultraviolet light that creates damage and radicals would never have survived at that altitude without strong pigments. And that's why we profit now. We take evolutionary products such as resveratrol from black grape seeds or goji herbs from China, one in which evolution has selected great protection, similar to the some bacteria we have long studied. How can these



cells, in terms of protein, remain intact after a million absorbed radiation doses (rad), which is two thousand times the dose that is fatal to humans? How is that possible? They synthesize small molecules that are like magnets for radicals and instead of damaging the protein, there is an antioxidant that will neutralize them. This is the simplest approach. There are at least 4-5 types of elemental radicals that are different but convert to each other: superoxide to peroxide, peroxide to hydroxyl, and the latter is by far the most aggressive. How do we work effectively when we measure antioxidant cocktails? For example, this super-resistant bacteria has a whole range, it is one cocktail of different molecules that neutralizes all radicals at once and that is why it is so effective. Can we use that? Yes. However, the sooner the better. I say this because pre-tumor, premalignant conditions are neutralized in relation to cancer with the help of apoptosis, cell suicide, and this takes place with the help of radicals. If I were to take super-effective antioxidants at my age to neutralize all free radicals then the premalignant cells I certainly have in my body would benefit from fitness and start growing more efficiently as a tumor. So, global antioxidants themselves need to work on prevention, which should probably start at a young age. And this second approach is suitable even for the treatment and reversal of disease because it will simply protect a specific protein. It will not necessarily work to reduce radicals, but it will work to protect that most fragile protein. So, there is optimism a bit modulated concerning the moment of finding the right cocktail of antioxidants...

# Protein protection slows down the ageing

We talked mainly about proteomics, protein analysis in aging and diseases, and we read newspapers, watched TV, genomics is everywhere, gene analysis in diseases in aging. Fortunately, there is no conflict. For the first time, there is a wedding of genetics and proteomics, a dialogue between these two approaches to disease analysis and aging, and that is the approach by genes and the approach by proteins, although we know that the function of genes is to synthesize proteins. And after all, life is a function, and death its cessation.

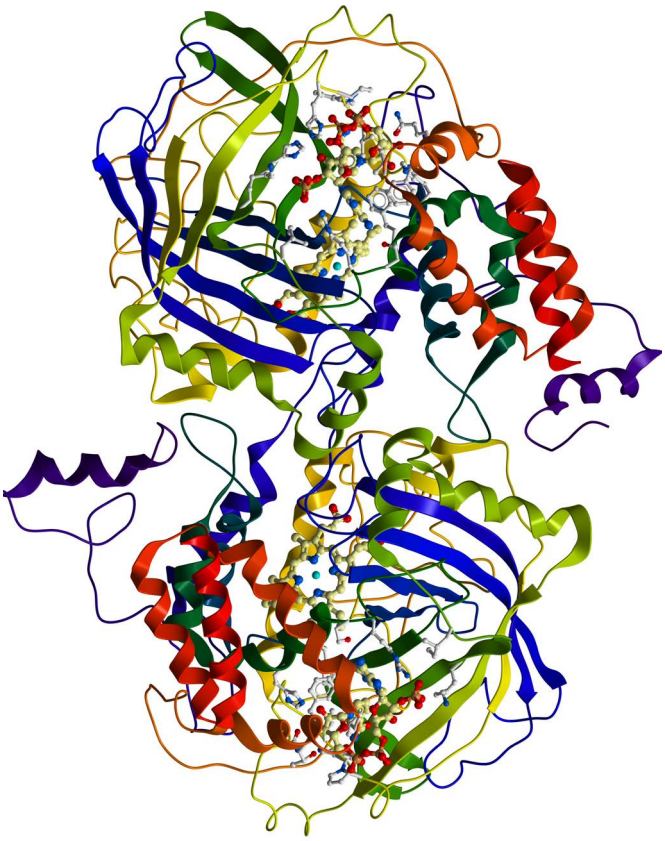
It is very significant and we were very pleasantly surprised to see that in aging and some specific diseases such as cancer, impaired function occurs directly through protein damage. Once we established which proteins these were, we saw that the genes for these oxidatively damaged proteins were already known from a list of inherited rare congenital diseases called syndromes, of which there are thousands. So, what appears in the human population as an individual defect that causes disease at birth and is called a syndrome, we find in all healthy people. In the process of aging and the onset of age-related diseases, we find this same functioning damage, but which occurs over time as it occurs at the protein level and not directly at the gene level. In this case, dozens and dozens of proteins relevant to the fight against the disease appear to us as damaged. In healthy people who age, at the age of 70-80, we suddenly see that each of them is known as an individual mutation in rare congenital syndromes, rare diseases. So, what I just mentioned: we age as if in different proportions we get a whole range of diseases that are known to us as age-related diseases or as rare congenital diseases, syndromes. It has come to the point that there is nothing new, these are the same known functions. I can see them in a population of a million people as a rare congenital disease or I can see them as damaged proteins in every person who has lived to be 80 years old. This is one of the most interesting observations we have come to and will once again direct us to an intervention to restore and protect proteins damaged by mutation or oxidation.

# Life makes a difference

### Q: Newborns with congenital diseases have contributed to research in this area?

**A:** This is perhaps just another way of saying that aging diseases and aging itself are at the level of protein functioning and vital functions which is the appearance of mutations that are barely detected at first, and with aging and increasing oxidative damage become stronger and stronger mutations. It's like taking a radio and starting from a barely audible signal and slowly amplifying it; It's aging. It may not be a coincidence that the differences in proteins between healthy people are called "silent polyformism". And it's like that because all those kids in the same class are running and thinking fast. However, differences start to appear when they are 50, 60 or 70 years old. They are all very similar when they are small. This can also be seen in identical twins: they are very similar at birth, but with age, the differences increase in them as well. Not because they have different or the same genes, but because they lived differently. Protein damage was not identical because they lived under different conditions. The older they are, the more different monozygotic twins are, not to mention in the human population where we are not clones as two identical twins, but we have a huge number of these silent differences that are increasingly manifested by increasing oxidation. Much like when we developed black-and-white photos by ourselves: the time we spent holding the image in the developer is like ageing, as the passage of life. After all, if we keep the picture long enough, everything will turn black, and that is death. It's even oxidation, but in black and white photography it's bromine, while here it's protein oxidation.

**Proteins are functions and if you take all the variations of proteins, and it is estimated that the human body has about a million proteins and only 23 thousand genes, then they are read in different ways so that there are about 100 thousand gene messages. But we don't just have 100,000 proteins, but because of physiological modifications and chemical decorations, there are about a dozen different ones. Of those 100,000 basic proteins, by protein decorations, we have about a million.**



So the human phenotype, all we are capable of doing is the result of a combination of the work of about a million proteins. And when I say physiological modification, it is acetylation, phosphorylation, etc., that will necessarily interfere with this toxic, undesirable modification which is oxidation or carbonylation. This can only be imagined because we have not yet been able to do any of this, but it is almost evident that previous protein oxidation will reduce the precision and efficiency of this physiological modification of proteins and that full protein decoration will either protect them or expose them to full oxidation. So, the whole field opens that we know nothing about except that it will be an interesting and complicated game.

# Do not be afraid of knowledge or change!

### Q: What makes us what we are, as the human species?

**A:** I would like to look very briefly at the long debates, especially in France where the population, unlike, say, the population in California, is very critical and afraid of change. They are even afraid of desirable changes because, for example, I would love to live 200 years, and if I were 200 years old and in shape, I would love to live 500 years. But when it comes to intervention in longevity, people's fear of all the changes is very interesting, including these desirable ones, how to be healthy and able to work and in full shape at 100 years old. They see this as a problem. I think this is the only way of cultural evolution and problem-solving with science and all other mental human activities because technologies have become so complicated that we only become Doctor of Science at the age of 30, a surgeon only at the age of 30 and even more begins to operate competently on the brain or heart. If longevity were like it was a few centuries ago, when people lived only 30 years, then our scientists or pilots would not be able to work. Just when they got their degree they would die.

# Ageing starts prematurely

The bottleneck in cultural evolution is a biologically healthy person who has as much time available as possible to be productive given what he has learned in the first 30-40 years of life, not to start having symptoms of Alzheimer's disease at 60 years old. There is now a conflict of interest between the cultural evolution that would accompany a biologically healthy person who creates even at 100 years old, with all the knowledge she has gathered individually and that no one else has gathered because no one else has lived her or his life. There is also a biological curve that begins to decline exponentially at the age of 60-65. Functional libraries of knowledge called Miroslav Radman or bearing some other name are being destroyed, with biological degradation coming too soon. That is why I think that prolonging a healthy human life would lead to a revolution, to an explosion of cultural evolution and humanity as we wish, where many of the problems we solve today in the most primitive, shameful ways would be analyzed and solved more healthily. People should not be afraid of knowledge. When knowledge comes then problems are solved in a far more cultural way. When it was not known what color blindness was, during the Inquisition, when a man was asked to say what was green and what was red, and he did not want to say, they would kill him. The moment we know it's a mutation in a gene, we're kind to that person, we don't think he's a liar or a thief. And so it will be for other human characteristics. If you ask French women, who currently live an average of 84 years, if they would like to live as their great-grandparents in the mid-19th century did, only 42 years on average, they would, of course, say they don't want to. Why would a great-great-granddaughter say she would live to be 84 when she can live to be 160? And this conservatism has arisen due to a lack of imagination related to the change in living conditions in an unpredictable way. It strikes me that the culture I love is afraid of change, even the desirable ones.

# Emotion is the best proof that we are alive

I will end with a personal story. It's easy to tell these stories when you have the data but to get to them, go down to the lab, figure out a way to identify the dots, and say "It's glucose-6-dehydrogenase" or something, it's a huge job. For that, you need to find people, money, space, teach them to think, think with them and finally write a paper. It's an extensive job. We are not masochists: I sit down for coffee, look at the sunny sea in the distance and ask myself "Miroslav, you are over 70 years old, why do you bother? Why do you do what you do, what drives you? Why are we doing what we are doing?" Of course, the answer is: "We need power for money" because someone wants to be a billionaire, the president of the state, so they share power. But what will you do with power? A biologist would answer, "So that as a man I can fertilize thousands and thousands of women, leave my genes!" But then the question arises: what do you need it for? What do you get out of it? I have concluded for myself that when I am not hungry, when I am not starving, that the Roman saying of panem et circenses, bread and games, is very appropriate because it is interesting that after bread come games. Even today, we see how important they are, and it is not about games. At least for me, it's about arousing emotions. I work to feel. And what do I need feelings for? We have already wondered why I need money, more than what I can spend? What will power do to me and why the pleasure of power over other people at all, if you do not enjoy others conducting you the way they want, it's simple - emotion as a feeling is the best proof that I am alive. When there is no emotion, then, as the Americans say, "one game in town", you are either alive or dead. When you're dead, there's none of this.

So, we need to have constant proof that we are alive. For me, it goes through emotion. And then I thought, Descartes says, "Cogito ergo sum," I mean so I did. I think Rene screwed up a bit because even he didn't think during orgasm, and he certainly didn't doubt if he was alive during that time. Emotions are very strong. I work and deal with these problems because of gusto, because of emotion, because I know that while I feel, I am certainly alive. It seems to me that this is so for everyone: for the murderer and Hitler and Stalin and the rapist and for this one who has to cut someone's throat to provoke emotion in him, with his pathologies and bitter fate, and he says: "I'm cutting someone's throat, so I'm alive, he's not." I think we have that in common and not to mention the emotions of Mozart, it's all about emotion. Mother Teresa also worked for her emotions, not for money, power, but very strong emotions.

There are all kinds of them in human variation, but I think it's noble, it somehow made my life easier. So, I do this for emotions, because of feelings, and then you have to be smart and say, "Should I search for emotions?" I feel, so I'm alive. Do I need a billion euros or a Nobel Prize? Is it necessary to me or is it just a waste of time? The wisdom is to get emotions in the cheapest way. Have as many of them as possible in the cheapest way. That doesn't mean you need to be a beggar, because those aren't some emotional conditions, but neither are those where you have a hundred billion of any currency and worry about how to invest, how many lawyers to take, so you cheat and the like. Nor is it the most direct way to emotion.

I think that perhaps the main challenge of getting to know each other will be to discover how our brain works. What is the chemistry of emotions? What is the chemistry of the brain? We are making progress in this knowledge, but what is the chemistry of emotions? And after all, when we get to them, will it be justified if we provoke them artificially, with the help of drugs?

If the feeling is important, will it be fatal to get it chemically because we won't have to do anything about it? Now we need to live long and do various things for emotions to appear. We know that something that repeats identically decreases in intensity. But in all that challenge, I think we still have time, that we don't need to break our heads over, neither we nor our children. We will talk about that when we are sufficiently satisfied with the knowledge about ourselves because for now, we are pathetically inefficient. Flight into space is a beauty, DNA analysis is the same, but we still don't know how to control the blood sugar of diabetics in any effective and painless way. I hope that the science of human biology will progress faster so we will avoid a lot of conflicts as in that case with color blindness. When we know that people are not guilty, a sense of shame and guilt that is destructive and causes even wars indirectly must contribute to morality and ethics. Not because it is moral in itself, but because knowing how we function will free us from frequent feelings of guilt and sometimes shame. That would be a nice contribution to the science and culture of mankind.