

Perspectives on Research

jur interviews Assistant Professor Vera Gubernova

Vera Gubernova is an Assistant Professor of Biology at the University of Rochester

jur: Could you tell us about your educational background, how you first got involved in research, current research interests, and outside interests?

Gorbunova: I wanted to be a scientist for as long as I can remember; it's hard to say when exactly. As a high school student, I was interested in animal behavior, which I think is a common path for biology students. We start as animal lovers, and then as we learn more, become interested in molecular questions. I did research projects at the St. Petersburg Zoo and other observations of animals, and then I decided to apply to the Biology Department at St. Petersburg State University, which is where I did my undergraduate studies; I was involved in several independent studies as an undergraduate. I would highly recommend that undergraduates go out there and find a laboratory that sounds interesting to you and get involved in research. For me, undergraduate research experience was extremely useful. It broadened my horizons and gave me first-hand experience. I learned a lot about science and also about myself in science, and how the experiments are done. Even now, I remember some experiments I have done as an undergraduate, and this knowledge is still very useful. After St. Petersburg University, I moved to do my Masters and Ph.D. degrees in Israel at the Weizmann Institute of Science, which was a great experience as well. Living in Israel was exciting; I had an opportunity to travel and see historical places, many of them just unbelievable. Also, the research environment at the Weizmann Institute was great. I moved to do my postdoctoral work in Canada at McGill University, and then moved to the Baylor College of Medicine in Houston. So as you can see, I had an opportunity to travel and live in several different countries, which is great advantage of a scientific career.

My current research interests are related to the mechanisms of human aging and the role of DNA repair and genomic instability in the aging process. As for my outside interests, I enjoy hiking and wilderness camping. I love camping in the north up in Canada, in places so remote that we do not see people for days and can feel at one with nature.

jur: How did you become interested in studying the mechanisms of aging?

Gorbunova: The first time I started thinking about this area of biology was when I was an undergraduate student taking a human genetics course; our professor invited a guest lecturer, and he talked about human cells in culture. He explained that cells taken from human body and put into culture do not divide indefinitely, but stop proliferation after undergoing approximately 60 population doublings. Then, it was calculated that if you take highly proliferative tissues in the human body, 60 population doublings is just enough to provide cells for 120 years of life, which is a maximum human lifespan. I was fascinated by this observation, and it got stuck in my mind. At the Weizmann Institute, I looked around for my Ph.D. project, but no one was involved in aging studies, so I chose to study DNA repair in plants. Then when choosing a field for my postdoctoral studies, (and this is usually the field in which you will stay for the rest of your research career), I remembered the excitement I felt about the puzzle of aging. I find aging fascinating because this is a fundamental biological process, as all living organisms age, and at the same time aging is highly relevant to human health. There are many areas of research that are hard to explain to general public, while aging is something that interests everybody.

jur: Your recent research has to do with the differences in telomerase expression between human beings and mice. Although mice experience tumorigenesis, how often does this occur in comparison to tissue regeneration, and how do you measure telomerase activity in rodents?

Gorbunova: Telomerase is an enzyme that elongates the ends of human chromosomes. When cells replicate, their DNA the very end of the chromosome cannot be completely replicated. To deal with this problem, cells have a special enzyme called telomerase, which helps maintain the very ends of chromosomes. If there is no telomerase around, the telomeres get shorter and shorter with every cell division. This process is actually behind the mortality of human cells in culture, because their telomeres get shorter and shorter, and when they get critically short, the

cells stop dividing. In somatic human cells telomerase is not expressed, and that is why somatic cells arrest their replication after sixty generations. One might wonder why humans don't become extinct; the reason is that telomerase is expressed in our germ cells, so for every new generation, chromosomes have complete telomeres and maintain constant length of telomeres from generation to generation. But in somatic cells, telomere shortening prevents cells from replicating too much when you don't want them to. Such unwanted replication happens in tumorigenesis. Senescence or telomere shortening is one mechanism that arrests cell replication before there's a tumor that has grown too large. This is what happens in humans. In mice, the picture is very different. Mice express telomerase in all of their cells. If you put mouse cells in culture they won't stop after sixty generations: they just continue. Mice in the wild are killed by predators, but if you put them in a protective environment up to 90% die of cancer, while in humans, cancer mortality is about 25%, considerably less. In humans, most cancers develop in the older years past the middle age; in mice, the same thing happens when they are two years old. So obviously the chances of mice getting cancer are much greater. They are missing this important support mechanism of repressing tumor growth: their cells keep dividing. One might wonder why mice do not repress telomerase and do not have the same protection as humans; perhaps there are some benefits of having telomerase expressed. For example, it helps cells divide more actively in case of injury, to quickly regenerate tissue. In mice, it may be more important to have efficient wound healing rather than protection from cancer because cancer is not a big issue in the wild, while for humans it is a bigger issue, and it becomes important to protect ourselves from cancer.

We recently completed a very interesting project that deals with this question. We decided to test the common theory in the field that humans repress telomerase activity in somatic tissues because they are long-lived, and mice do not because they are short-lived. We were interested in whether this correlation would be true for a broader range of animals, or if it is really connected to something else, like body mass. Humans are larger than mice, and have many more cells; if every cell can mutate, then humans have a higher chance of one cell becoming cancerous and forming a tumor. So, we took a collection of different rodents, some of which are very long lived (like squirrels, which live up to twenty three years, and beavers, which live up to twenty five years) and others that are short lived (mice generally only survive three years). Interestingly, we didn't see any correlation with life span, but rather with body mass. This suggests that in humans evolved telomerase repression not because they are long-lived, but because they are large. As to how we measure telomerase activity, there are biochemical assays that allow us to do it. We prepare extracts from animal tissues and mix it with radiolabeled primers that resemble telomeres. If there is telomerase in the extract, it will extend the primer, which is then visualized using X-ray film. It was quite an experience to collect the wild animal samples, as it goes beyond the normal lab routine where we purchase mice from commercial vendors - you can't purchase beavers in the same way, so we had to do a lot of collaboration with people from different areas. I am very thankful to my colleagues who contributed animal samples to this project.

jur: Some of your research deals with DNA double-strand breaks. What future do you see for understanding DNA double-strand breaks, and how has characterization allowed you to investigate ways in which DNA repair can be improved?


Gorbunova: Double-stranded breaks are very dangerous types of DNA lesions. It can lead to loss of large chromosome segments, or if repaired incorrectly can lead to chromosomal aberrations like translocations, where fragments are located in the wrong places. These types of aberrations are often found in aging organs or tissues. Chromosomal aberrations are also found in cancer cells. Our laboratory has shown that the process of repairing DNA breaks becomes less efficient and more error-prone with age, so we are now trying to pinpoint exactly what processes lead to this, what proteins are affected, and why it becomes less efficient with age. Once we understand this, we can look for a way to prevent age-related decline of DNA repair, or even to make the repair more efficient, which will help to slow down aging and prevent cancer.

jur: What kind of applications could potentially result from your research or related research, and what kind of impact do you expect to have on your field?

Gorbunova: Ultimately, we would like to extend human lifespan, and this would have an impact on all of society, not only on the aging field; but we are not there yet. Medicine focuses on specific diseases, and many diseases are associated with age, like cardiovascular diseases and cancer. So if we could find out how to slow down the whole aging process, we could at the same time prevent age-related diseases. It would be a global approach where instead of going after each disease individually, we could cure them all of them at once. Some may argue that we don't need more elderly people straining the economy,, which is a huge misconception about the aging field. If we find a way to slow down aging, we would increase not only lifespan, but health span as well, so that people would stay healthy for a longer time. There is no problem with the economy here; people will just keep their active lives longer. Currently in my laboratory, we are looking for ways to counteract age-related genomic instability; as I already said, this would help fight cancer and also help prevent changes in gene expression and other changes that reduce fitness with age.

There is another interesting implication from the telomerase study that I just told you about. We got very fascinated with squirrels, as we found that they have extremely high telomerase activity in their somatic cells. Telomerase activity in the squirrel is about four times higher than that in human cancer cells, and squirrels still manage to live for twenty years without developing cancer. We are now working to identify the mechanisms that protect squirrels from developing cancer despite the high telomerase activity. It is believed that cancer in humans originates from stem cells gone bad. Since stem cells maintain low levels of telomerase activity, it will be very important to find mechanisms that prevent stem cells from turning cancerous.

Another aspect in which we are very interested is how large animals deal with cancer. For example, take a whale: it is huge, and it has so many more cells than humans. Every cell has a chance of getting a mutation and becoming cancerous, so you



would expect a whale to get cancer pretty quickly; yet whales live for a hundred years or so. Perhaps they have other tumor-suppression mechanisms that even humans don't have, and it would be nice to find out what these mechanisms are and whether they can be activated in humans.

We're also interested in the comparative aspects of aging. For example, what makes a mouse short-lived while a squirrel is long-lived? Understanding the mechanisms that determine longevity of the species would help to manipulate human lifespan.

jur. How can undergraduates get involved in research in your field? What can they expect? Do you have any advice for up-and-coming biologists?

Gorbunova: I must say that I enjoy being at the College Biology Department. In my previous position at the Baylor College of Medicine, there were only graduate students around, and it was a little less vibrant than here. Every semester two to four undergraduates work in my lab on independent research projects; and they contribute significantly to our research. There are also summer opportunities, like Reach funding, DeKiewit fellowships, the GEBS summer program, etc. So there are many ways undergraduates can enter the field. It's very exciting to have enthusiastic young people around.

What can they expect when entering the field? Expect to have a lot of fun, because research is a lot of fun. They will be involved in research in an active laboratory using the most modern techniques. In the aging field, they will be working on problems that have relevance to medicine and basic science at the same time. In our laboratory, we do a lot of cloning; we culture human cells, and we even collect samples from wild rodents, so there is some field work as well. In general, research is a very exciting field, and I enjoy every minute of it. Even for me, it's sometimes strange to call it a job because a job is presumably something tedious, but what you do in research is so exciting, unlike a typical job. It is amazing we're getting paid for what we do.

What I love about biology is that you can ask very basic questions about life, and at the same time it can be very useful in applied medicine to make people's lives better. Biology is a rapidly developing field that is now on the rise and tremendous resources are being put in it, so if you chose biology you made a wise choice. For students starting research, my advice is to be prepared to learn, because we always learn new things. Be prepared that some of your experiments won't work right away; there will be some disappointments, but overall, research is extremely rewarding.