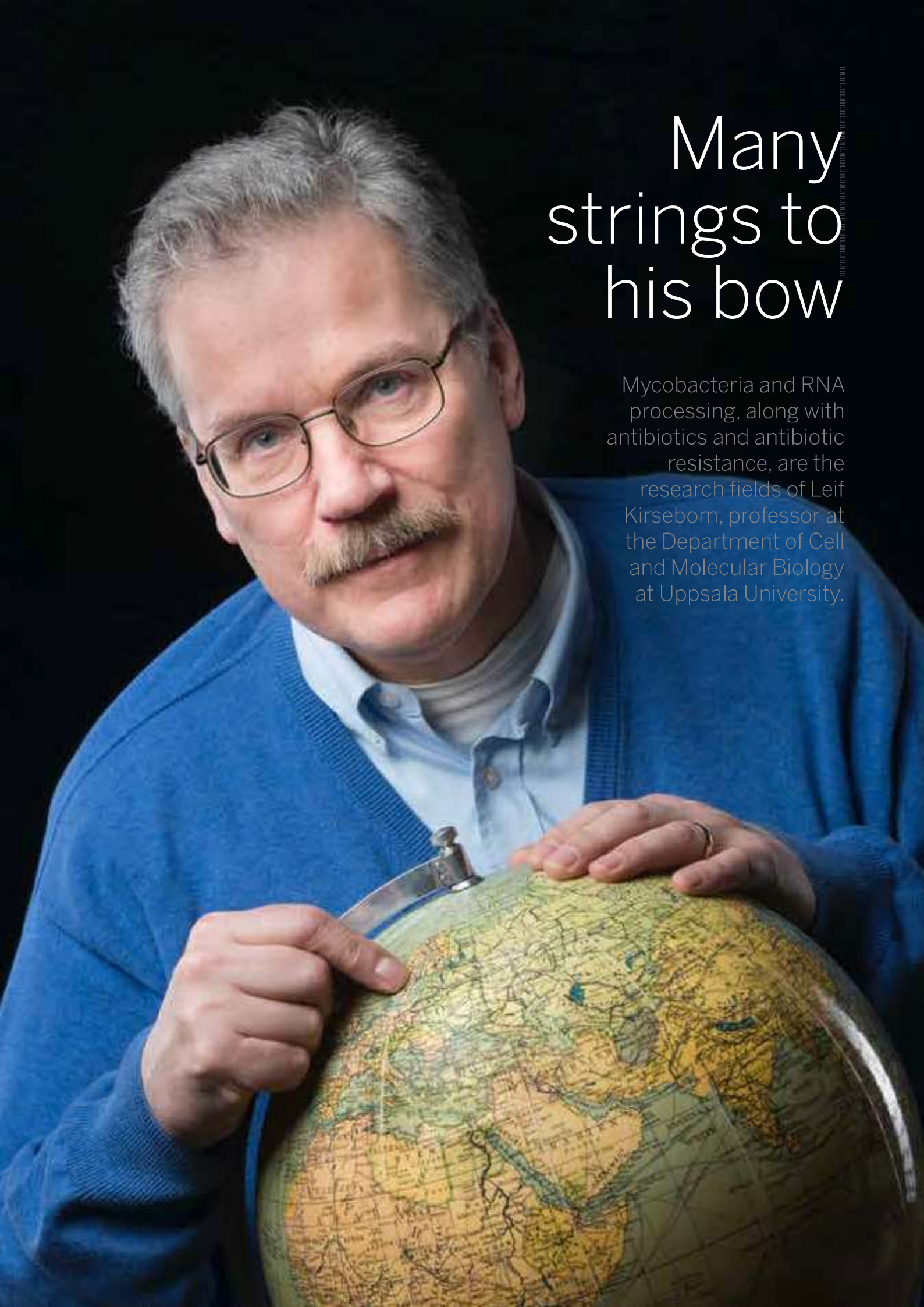

Many strings to his bow

Mycobacteria and RNA processing, along with antibiotics and antibiotic resistance, are the research fields of Leif Kirsebom, professor at the Department of Cell and Molecular Biology at Uppsala University.

Mycobacteria are found in diverse environments such as groundwater, tap water, soil, animals and humans. They are hardy and can withstand temperature changes, for example, and survive in water containing disinfectant. Several mycobacteria cause serious diseases, the one causing tuberculosis (TB) being the best-known of them. Other examples of mycobacterial diseases afflicting animals and humans include chronic diarrhoea in cattle, Johne's disease, leprosy and the skin disease Buruli ulcer. Many people carry latent TB, and show no symptoms of the disease. It is estimated that a third of the world's population is infected, with about ten million new cases of TB diagnosed every year and about two million people dying annually from the disease. Treatment takes a long time, and the increasing incidence of resistant strains makes mycobacterial infections like TB difficult to treat.

"Like other bacteria, mycobacteria have an exceptional ability to manage and adapt to different environmental circumstances. They can form biofilms, which can be thought of as bacterial communities, and grow as single cells or as filaments. Under certain conditions, they can change their cell morphology. And like many other bacteria, mycobacteria can form resistant spores to enable them to 'hibernate'. We know very little about the mechanisms that mycobacteria use to control changes in cell morphology. Neither do we know whether and how cell morphology affects mycobacterial infectiveness," says Leif Kirsebom.

His research group was the first to show that a close relative of the TB bacterium could form spores, contrary to the prevailing view. This was a major, but disputed and controversial, discovery.

"This was huge for us and for the whole research field, because it opens up entirely new opportunities to understand how mycobacteria spread and 'hibernate'. Ultimately, it might reveal more about latent infections," says Leif Kirsebom.

The opposition they encountered did not cause undue concern, he says, because that is how it is in research at times. Since this result was published in 2009, other research teams too have demonstrated that mycobacteria sporulate, supporting the finding. The research team is studying Mycobacterium marinum, which causes a TB-like disease in fish and is a close relative of the TB bacterium. In the experiments, fish are fed with infected larvae to enable study of the mycobacterial genes that are switched on and off, and their roles when the bacteria grow in the fish's cells. Also being studied are the changes to the mycobacterium's cell biology during aging and when subjected to stressors such as antibiotics, oxidative stress and heat stress. And how a restricted oxygen supply affects bacterial gene expression.

"We use an in vitro model called the Wayne model to study the changes in gene expression and cell morphology during oxygen starvation. After 12 days, the expression of some genes is more than 100 times higher, though the bacteria are no longer growing and dividing," says Leif Kirsebom.

The team is also in the final phase of a very extensive sequencing project. The DNA from all 150-160 mycobacterial species will be sequenced. It is hoped that this will help answer interesting questions such as what is a species, and which genes are of interest with regard to infection.

"This might have a bearing on how we treat mycobacterial infections. Like other mycobacterial infections, tuberculosis is generally pretty difficult to treat. This makes it even more important to get it right, and to be able to choose the right treatment regimen. The sequencing information might offer some guidance here," says Leif Kirsebom.

The second arm of his research is about understanding the biology of RNA and its role in various cellular processes. For more than 30 years, he has been studying cellular processes involving tRNA or, to be more precise, the processing of tRNA and the function of the endoribonuclease RNase P. The main model system has been E. coli, though other bacterial systems have been used. A particular interest has been the involvement of bivalent metal ions in the function of RNase P and its catalytic RNA. Leif Kirsebom's research team has shown that antibiotics can block this cleavage, because they compete with bivalent metal ions for the same site on the RNA. With the need to overcome antibiotic resistance growing day by day, knocking out RNase P might be one way to stop the growth of bacteria. Protein synthesis is stopped, and so the bacteria die. This type of inhibitor could be thought of as a metal mimic. This led to Bioimics, the name of the company started by Leif and fellow researcher Anders Virtanen in 2001. There they help combat antibiotic resistance by searching for molecules that bind to RNA and inhibit its function. When it comes to researching RNA processing, Leif has returned to where he once began in the late 70s, he says.

"I have come full circle, back studying RNase P in vivo, but now with far more modern and powerful techniques. These enable us to do new types of experiments that we could not do previously. Rather than this being the final word, however, I believe it will open up a new chapter for RNase P."

Alongside his research, Leif Kirsebom is also director of Uppsala Biomedical Centre, and is adviser to the Vice-Chancellor for Internationalization at Uppsala University. He is deeply involved there in the university's international relations. During 2016, he and other representatives from Uppsala University and five other Swedish universities are ensuring that Swedish research is disseminated and promoted in Indonesia and Brazil. The focus is on areas such as life sciences, sustainable development, higher education and innovation. The objectives include meeting global challenges, creating new co-operations and ensuring the development of existing ones, and strengthening partnerships between companies and universities through innovation.

"Meeting people from other cultures is very instructive. We have so much to learn from each other, and from seeing how different countries solve their various problems. Programmes in both research and education are important aspects, and Sweden has much to contribute in these areas," says Leif Kirsebom.