Strong structures in cobwebs and disease proteins

For over twentyfive years Professor Stefan Knight has been interested in how proteins can be connected to silk and fibres. His research focuses on topics such as spider silk, bacterial fimbriae, amyloid diseases such as Alzheimer’s and Parkinson’s diseases, and type 2 diabetes. By understanding the fundamental biological processes, his research team hopes to find novel applications in medicine, including new ways to treat Alzheimer’s disease and bacterial infections.

How different protein complexes are constructed, how they are built up and how they bind to different surfaces and receptors is valuable knowledge in the pursuit of new ways to treat bacterial infections. For the last twenty years, he has been studying the bacterial hairs called fimbriae. These enable bacteria to attach to the surface of a cell in the throat or urinary tract, for example, which is a prerequisite for being able to cause an infection there. It is hoped that interfering with the bacterium’s initial adhesion will enable new ways of preventing infection to be found.

“Previously, good methods for studying fimbriae directly on the surface of a bacterium were not available. But now we can produce specific antibodies against different types of fimbriae. This enables us to see when and where a bacterium uses them during the course of a disease. It is something we hope to be able to use in the future in diagnostics, and perhaps even in the development of vaccines,” explains Stefan Knight, professor at the Department of Cell and Molecular Biology at Uppsala University. Together with colleagues at New York University, they have now begun using a mouse model to examine how a bacterium that causes urinary tract infections uses its fimbriae.

Stefan Knight is also interested in spider silk, and in establishing how the spider manufactures and secretes its strong thread. The threads are very strong indeed – stronger than steel, but much more elastic. A thread as thick as a pencil would be able to support a jumbo jet, explains Stefan, and it is more than likely that Spider-Man would be able to use his spider silk to stop trains. However, Stefan is now handing over to researchers in materials chemistry so they can continue to investigate what confers elasticity and what confers strength. The goal is the large-scale production of spider silk, or new materials based on it, without the use of spiders.

Another part of Stefan Knight’s research involves a project directly linked to Alzheimer’s disease: investigating a protein domain that protects against amyloid formation.

We have previously determined the three-dimensional structure of the protein, and we have a hypothesis about how it works that is compatible with a number of observations, says Stefan Knight.

“To make further progress, structures showing how the protein binds to amyloid are needed. All structural biologists often encounter a bottleneck: obtaining the crystals of the pure protein that are required to determine its structure. This frequently takes time, sometimes years, and demands both patience and perseverance. Valuable information is hidden in the structure, including not only how the protein looks at the amino acid level, but also clues to how it functions and interacts with other molecules and substances.

“It is a tremendous feeling to be the first in the world to see what a protein molecule looks like,” says Stefan Knight. He adds that it is much more difficult today, with so many structures already elucidated compared with when he began his research twenty-five years ago. Today, the Protein Data Bank holds over 100,000 structures in its database.

X-ray crystallography and other diffraction-based techniques (SAXS, fibre diffraction) are combined with molecular biology, biophysics and biochemical computational methods.

“There is a great deal of maths, but above all, a glorious coming together of physics, maths and chemistry. Biology and medicine, too. And medicine is something that has always interested me. The possibility of helping to solve a medical problem is one of the important things driving my research,” concludes Stefan Knight.