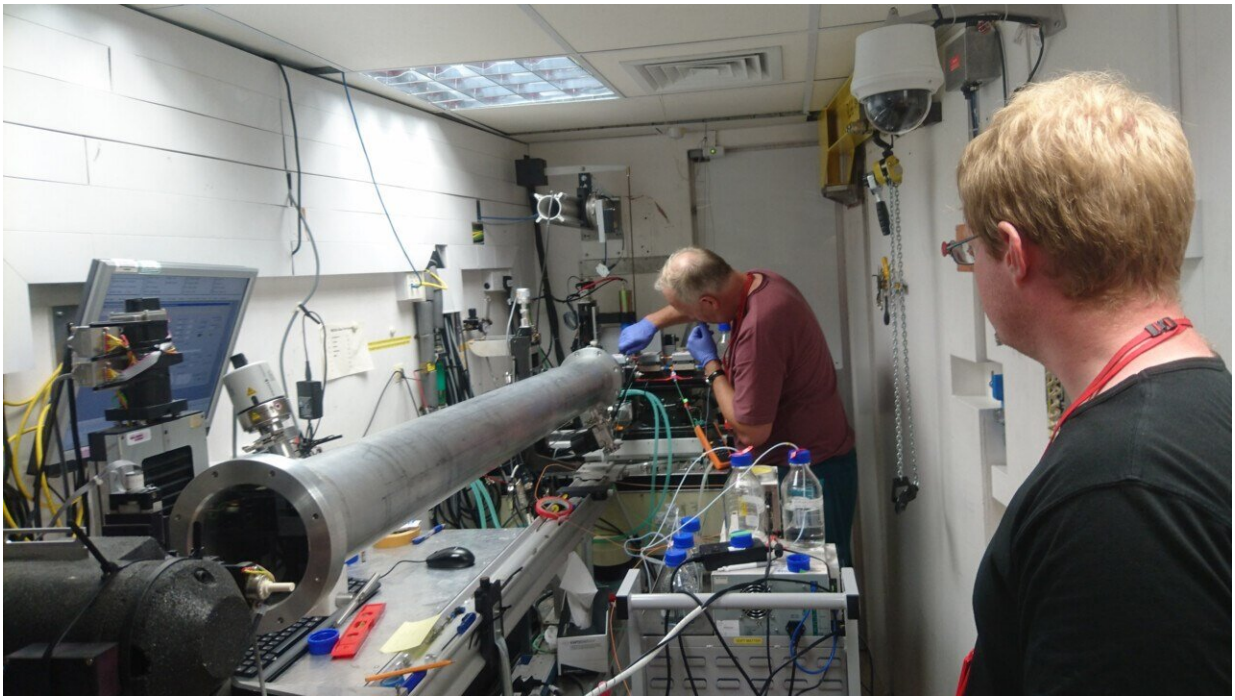
Breakthrough in the understanding of a protein with a key role in cancer

April 27 2021



Professor Gerhard Gröbner and research engineer Jörgen Åden are changing a sample at SURF, a neutron reflectometer at ISIS, a national research structure at Harwell in England. Credit: Tobias Sparrman

The neutron reflexometry method has given scientists an atomic-level insight into the behavior of Bcl-2, a protein that promotes cancerous cell growth. The new study was carried out by Umeå chemists in collaboration with the research facilities ESS and ISIS and is published

in *Nature Communications Biology*.

Elevated function of the cell-protecting membrane protein Bcl-2 can promote cancer and cause resistance to cancer treatment. Developing an understanding of the way it does this could inform the development of anti-cancer drugs.

It may seem counter-intuitive, but cell death is crucial to overall health, and is managed by a series of proteins from the Bcl-2 family. These proteins work together at the membrane surface of intracellular organelles—the mitochondria—to determine a cell's wellbeing. However, overproduction of the cell-protecting Bcl-2 members can interrupt this delicate balance and inhibit signals for cell death. This can cause cancerous cells to continue to grow, and not respond to cancer treatment.

However, how cell-protecting and cell-killing proteins of the Bcl-2 family interact with one another in their intracellular membrane environment is not fully understood, since a picture of their structure and behavior in this environment was not available.

In this study, the researchers used the novel combination of neutron reflectometry (NR) and NMR spectroscopy to study full-length human Bcl-2 protein located in its unique membrane environment, providing insight into the key structural and dynamic features.

Also partner in the research collaboration is European Spallation Source (ESS), an international Big Science facility currently under construction in Lund, Sweden, that will use neutrons for materials research within e.g. structural chemistry. Dr. Hanna Wacklin-Knecht, ESS and Physical chemistry Division at Lund University, has contributed with expertise to optimize samples and experiment conditions as well as providing the deuterated lipids for the follow-up studies on the function of Bcl-2s that

have been conducted later.

"The project with Professor Gröbner is an excellent example of how close collaboration with the research facilities ESS and ISIS helps new research groups to use neutrons in their pioneering research and prepares them to become early users of ESS. The collaboration was made possible thanks to the Swedish Research Council's specially targeted project grants to promote neutron research in Sweden," says Hanna Wacklin-Knecht, ESS Life Scientist.

The NR experiments were performed in collaboration with Dr. Luke Clifton at the ISIS Neutron and Muon Source research facility in Oxfordshire, England on one of the leading instruments in the world for this type of experiment. These studies made it possible for the Umeå researchers to determine the relative distribution of Bcl-2 protein across the membrane. The results showed that the protein is in the membrane rather than on the surface, as previously thought.

The NMR experiments looked at individual protein segments and their behavior in the membrane, and suggest that the part of the protein that acts as a molecular switch is on, or close to, the membrane interface. However, the main protein body that blocks cell-killing partners is restricted within the membrane. The researchers' results have led to a significant breakthrough in the understanding of how Bcl-2 exerts its cell-protective function at the membrane level by simply inhibiting cell-killing proteins there.

"We have discovered the location and behavior of the Bcl-2 protein in its native membrane. It is a breakthrough, not only in understanding the molecular cell-protecting function of Bcl-2, but also its notorious role in cancers, thereby making this protein a prime target in the hunt for novel cancer therapies," says Professor Gerhard Gröbner, Department of Chemistry at Umeå University.

In future experimental studies, Gerhard Gröbner hopes to discover how the position of Bcl-2 in the membrane is related to the way that it prompts cell death.

"Together, we now plan to unravel the active state of Bcl-2 protein when caught in the act of binding cell-killing proteins at the membrane."

More information: Ameeq Ul Mushtaq et al. Neutron reflectometry and NMR spectroscopy of full-length Bcl-2 protein reveal its membrane localization and conformation, *Communications Biology* (2021). DOI: 10.1038/s42003-021-02032-1

Provided by Umea University