Targeted Drug Delivery Systems

Studies of the unique structure of synthetic molecules will help in the development of drugs that can target diseased areas of the body.

A young researcher in the Neutron Scattering Sciences Division (NSSD) is using a broad suite of elastic and inelastic SANS to study the structure and dynamics of polyamidoamine (PAMAM) starburst dendrimers in the hope that these repeatedly branched molecules will become an effective, targeted drug delivery system for the treatment of cancers.

Wei-Ren Chen, who received his doctorate in nuclear science and engineering at MIT in 2004, is a Clifford G. Shull fellow at ORNL. Chen studies "dendritic molecules," synthetic macromolecules that can be envisioned as polymeric colloidal particles, which are globular in shape. However, dendrimers exhibit additional internal degrees of freedom, such as conformational branch fluctuations characteristic of linear chain polymers, which give rise to rich phase behavior. In addition, dendrimers have properties such as chemical uniformity, an intra-molecular cavity for accommodating exogenous materials, and functionalizable architecture, water solubility, and biocompatibility, which makes them excellent candidates for biomedical applications such as highly specific drug delivery.

"Most of the cancer drugs are very toxic, so they have to be wrapped inside some sort of vehicle when being delivered to the targeted areas inside human body," Chen explained. "It's very important to know what change takes place in the dendrimer vehicle carrying the drug when it is introduced into the body. So we developed a synergistic approach, combining various neutron scattering techniques—molecular dynamics simulations and theoretical calculations—to systematically study the underlying chemical and physical mechanisms that govern the functioning properties of dendrimers in aqueous solutions at physiologically relevant pH."

Chen works with his supervisor, Dr. Ken Herwig, and with Dr. Greg Smith, leader of the NSSD's Low-Q Group. "Wei-Ren is the intellectual driver for this. He made a proposal to ORNL's Laboratory Directed Research and Development Program and got funding for this," Herwig said. "Wei-Ren brings a unique combination of a theoretical approach to understand and interpret the data, with a very good understanding of the experimental side, and the ability to carry out precise experiments to provide the data that act as input for the theory."

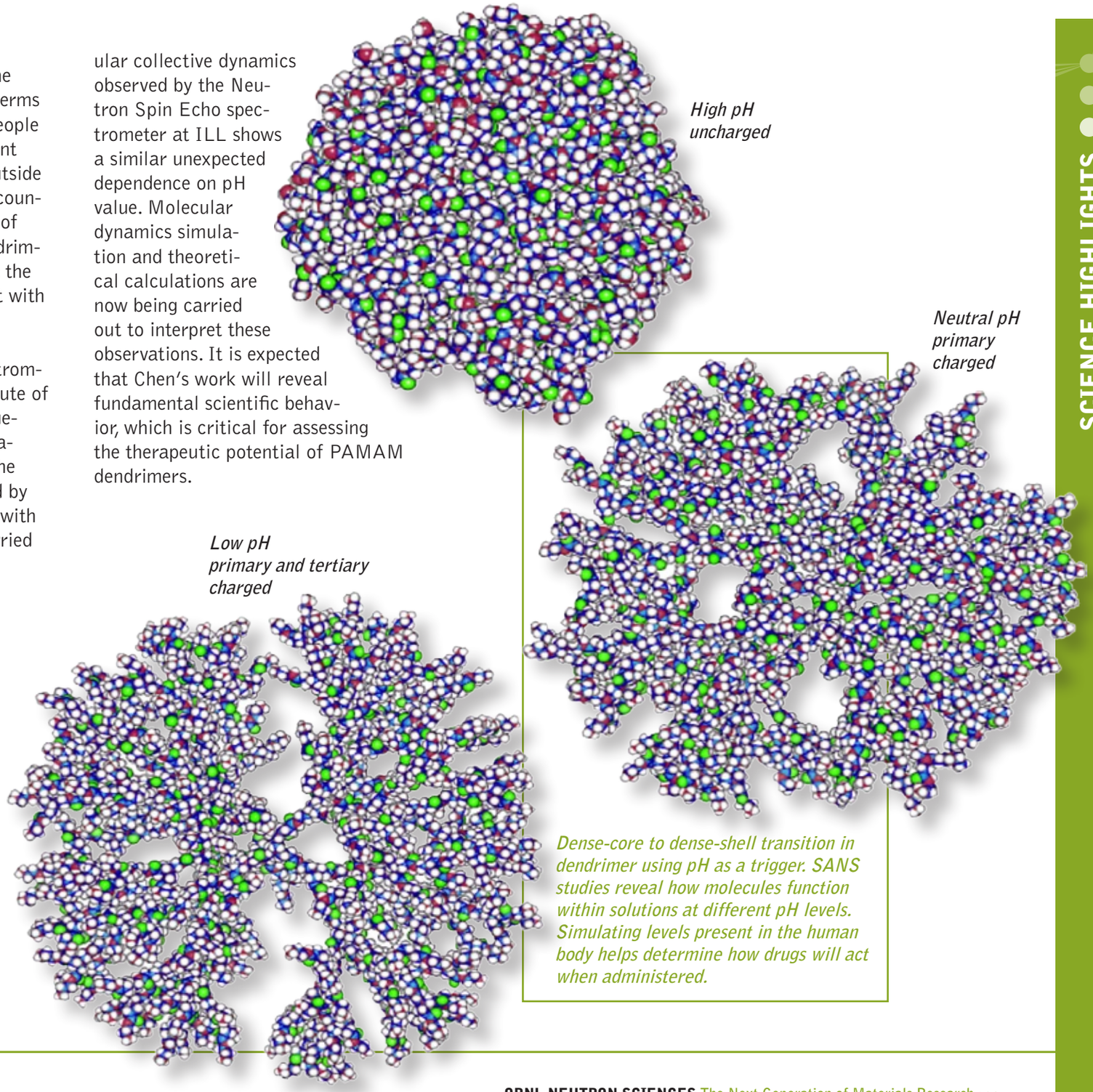
Herwig said that the research, which he calls "very, very hot in the field right now," is a broad collaboration of researchers across the United States, which Chen has been instrumental in establishing. Dr. Kunlun Hong at the Center for Nanophase Materials Sciences (CNMS) is synthesizing the isotopically labeled dendrimer, and the research group at the California Institute of Technology, led by Professor Bill Goddard, is carrying out complementary atomistic simulations to provide the microscopic information that is not accessible experimentally.

"This particular system, this generation of these dendrimer systems, is very exciting. They can be functionalized so that you can add additional groups on the out-surface of the dendrimer so that they can target particular locations, and things like viruses or cancer cells, so they can be like a Trojan horse," Herwig explained. "You functionalize the surface group with something which a virus or cell wants to attract to itself, and then you get it bound onto that substrate cell and then it delivers the targeted drug."

"The other reason there is excitement is that the dendrimer is quite adaptive in its geometry, in terms of how large you make them," Herwig said. "People are also looking at the acidity of the environment (the acidity of a dendrimer/drug preparation outside the body is very different from the acidity it encounters inside), and this is one of the key elements of Wei-Ren's research to understand how the dendrimers acquire electric charge based on how acidic the environment is and how the dendrimers interact with each other in a solvent themselves."

Chen and his collaborators use the SANS spectrometers available at the HFIR, the National Institute of Standards and Technology, and the Institut Laue-Langevin (ILL) to obtain the structural information of dendrimer solutions. They showed that the inter-dendrimer interaction is greatly influenced by their unique molecular architecture. Combined with the nuclear magnetic resonance experiment carried out at CNMS, the SANS results provide compelling evidence of the dense-core picture of the dendrimer density profile, a longstanding issue in the field of soft matter science. The findings suggest that the routinely used Stokes-Einstein relation is not valid in estimating the molecular size of ionic soft colloids, such as dendrimers.

Using a sequence of the quasi-elastic neutron scattering instruments, such as the Backscattering Spectrometer at SNS, Chen and his collaborators made the surprising discovery that the individual motions of constituent components of dendrimers show a strong dependence on the pH value of the surrounding environment. This has not been reported experimentally or predicted computationally. The intra-molecular collective dynamics observed by the Neutron Spin Echo spectrometer at ILL shows a similar unexpected dependence on pH value. Molecular dynamics simulation and theoretical calculations are now being carried out to interpret these observations. It is expected that Chen's work will reveal fundamental scientific behavior, which is critical for assessing the therapeutic potential of PAMAM dendrimers.



Dense-core to dense-shell transition in dendrimer using pH as a trigger. SANS studies reveal how molecules function within solutions at different pH levels. Simulating levels present in the human body helps determine how drugs will act when administered.