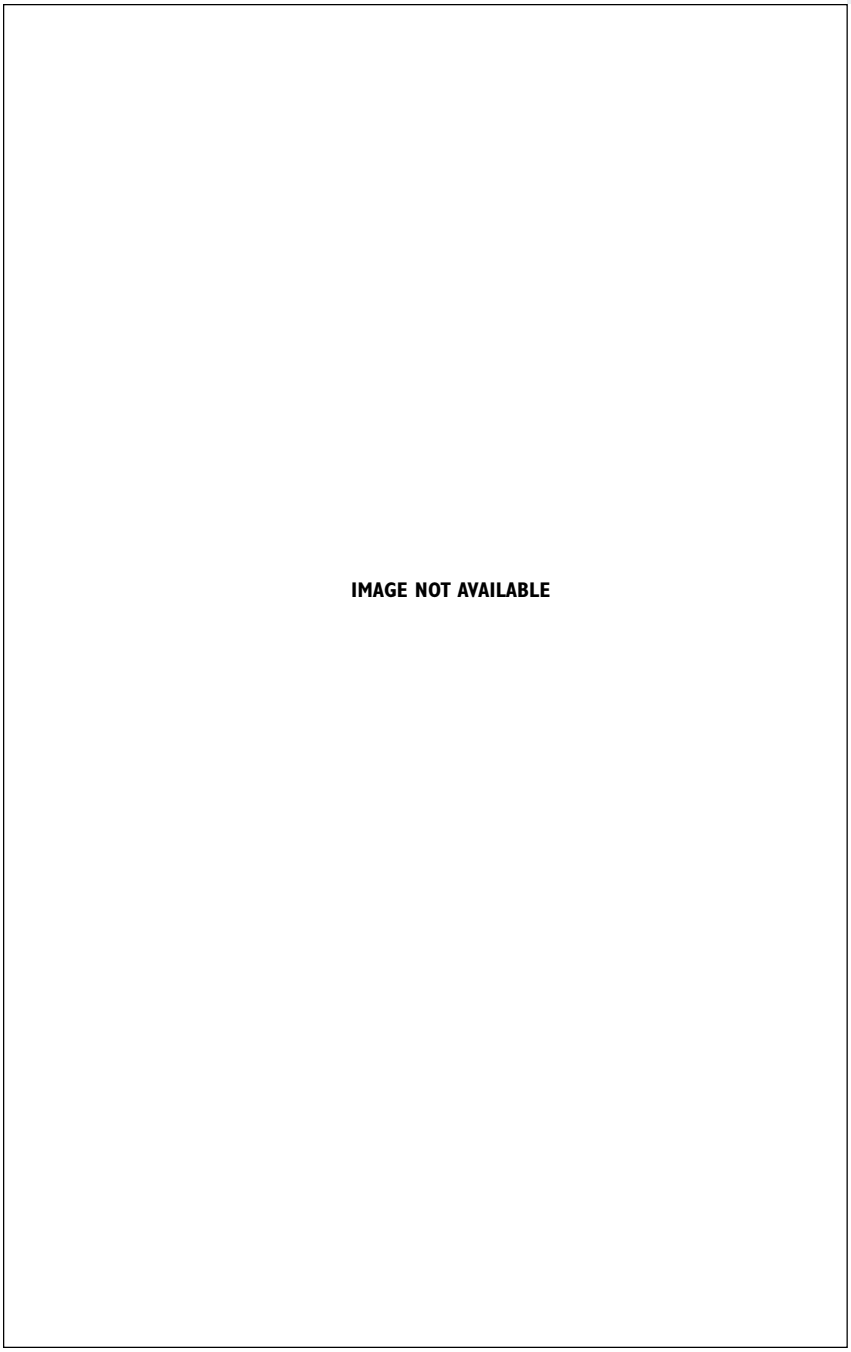
The Tangled Web: Communication in



The mysteries of the human brain have inspired countless generations of scientists, poets, and philosophers. Breathtaking in its complexity, the brain is composed of billions of individual nerve cells that are wired together to give rise to thought, emotion, consciousness, and behavior. It is the role of neuroscience to make sense of this complexity—to understand the brain's structure and function. To accomplish this goal, neuroscience draws on many different disciplines, ranging from molecular and cellular biology to cognitive psychology. In my laboratory, we combine chemistry and neurobiology to explore how nerve cells communicate and store information. Our goal is to elucidate the chemical changes that underlie phenomena such as learning, memory, and motor control. And, not surprisingly, the more that we learn about how nerve cells communicate, the more we appreciate the beauty and complexity of the brain.

To understand the workings of the nervous system, one can ask questions at three different levels: organismal, cellular, and molecular. Organismal neurobiology looks at whole organisms, such as flies, worms, and mice, and observes big-picture phenomena such as learning, memory, and behavior. At the next level, cellular neurobiology tries to explain these phenomena in terms of the interactions between cells. We know, for instance, that the process of learning stimulates nerve cells to

This Ramón y Cajal drawing of a brain-tissue section hints at the multitudinous connections made by a mere 11 nerve cells.

Unraveling the Molecular Basis for the Brain

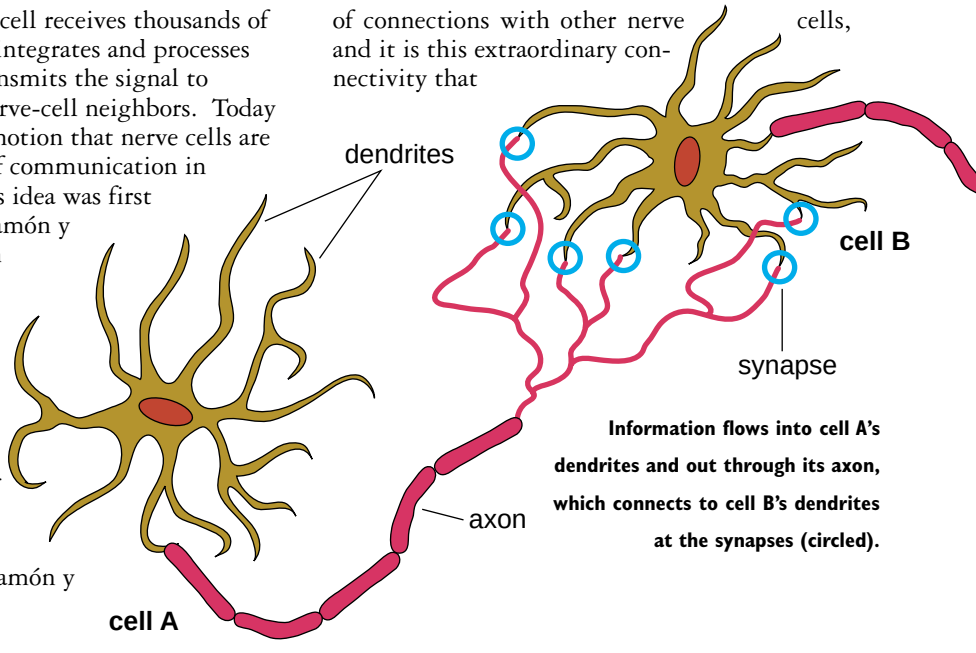
by Linda Hsieh-Wilson

seek out and maintain connections with their neighbors. Finally, molecular neurobiology attempts to explain the interaction and communication between nerve cells at the level of atoms and molecules.

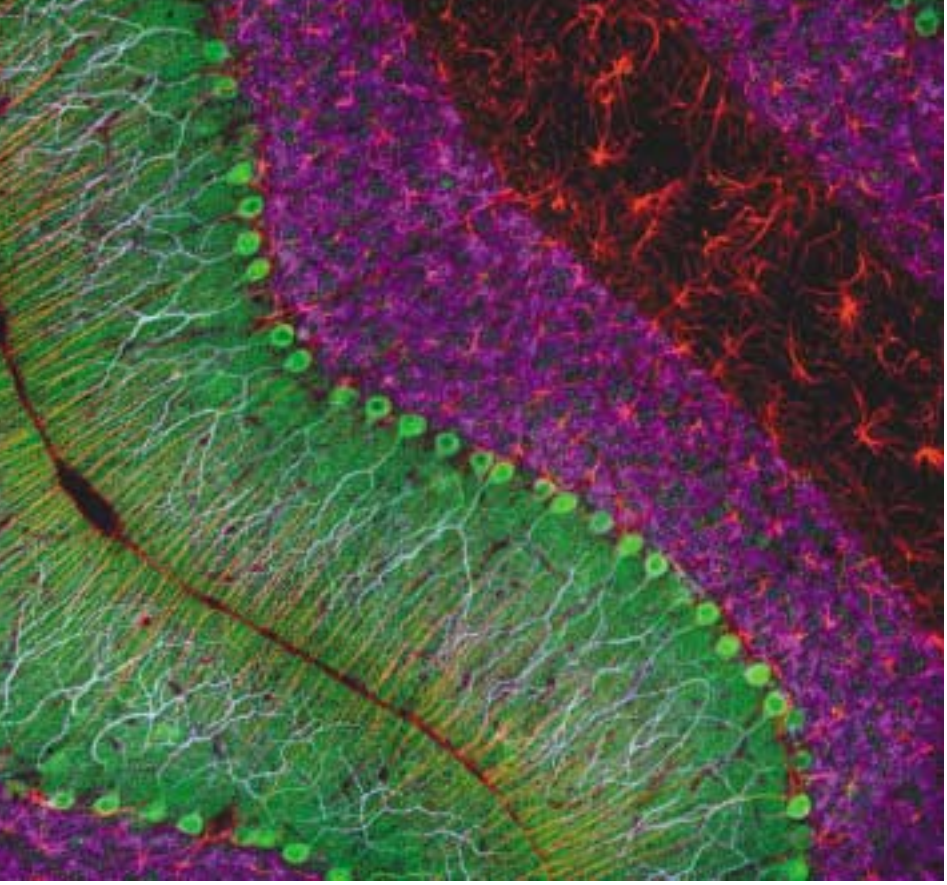
Our group is unlike most other neurobiology labs because of our strong emphasis on chemistry. As chemists, we are trained to think at the molecular level, so we feel right at home at the interface between molecular and cellular neurobiology. In addition, synthetic organic chemistry gives us the ability to design and create molecules in the laboratory. By integrating chemistry and neurobiology, we can synthesize specific molecules and test our hypotheses about their functions in the brain. Ultimately, we hope to relate events at the level of atoms and molecules to the big-picture changes that occur in disease and in normal growth and development.

While the brain is an amazingly complex organ, we can break down the complexity by considering the brain as an organized network of billions of nerve cells. Each nerve cell receives thousands of inputs from other cells, integrates and processes the information, and transmits the signal to thousands more of its nerve-cell neighbors. Today we take for granted the notion that nerve cells are the fundamental units of communication in the brain. However, this idea was first proposed by Santiago Ramón y Cajal, a brilliant Spanish neuroanatomist who examined brain structures using dyes and a microscope. He recorded his observations as sketches in laboratory notebooks—shown opposite is one of his original drawings. Each letter denotes an individual nerve cell. Ramón y Cajal discovered that each cell has branchlike extensions, and realized that these branches would allow it to reach out and interact with other nerve cells. His insight was so fundamental that it forms the foundation of modern molecular neuroscience, and he was honored with the Nobel Prize in 1906.

Building on Ramón y Cajal's observations, neuroscientists have learned that nerve cells have evolved to gather, process, and transmit information. Below is a close-up drawing of two nerve cells. Information flows from one cell to the next, and usually in one direction only. Cell A receives signals through branchlike extensions called dendrites. The cell processes the information and transmits a message that travels out the main extension, called the axon. The far end of the axon then splits into tens of thousands of tiny branches, which contact the dendrites of neighboring cells. While this diagram accurately depicts the flow of information, it is an oversimplification. In reality, each nerve cell in the brain makes thousands of connections with other nerve cells, and it is this extraordinary connectivity that



Information flows into cell A's dendrites and out through its axon, which connects to cell B's dendrites at the synapses (circled).



This microphotographic slice through a rat's cerebellum (a portion of the brain involved in muscular coordination) has been stained with fluorescent tags that bind to specific proteins. The green ovals sprouting blue dendrites are a type of nerve cell called Purkinje cells. Granule cells, another type of nerve cell, show up in the purple layer. The red cells are astrocytes, which are essential to brain function but are not nerve cells. (Image courtesy of Tom Deerinck and Mark Ellisman, National Center for Microscopy and Imaging Research, UC San Diego.)

underlies higher brain functions. Importantly, although Ramón y Cajal made his discoveries more than a century ago, we still don't truly understand how nerve cells talk to one another and keep all of the information straight.

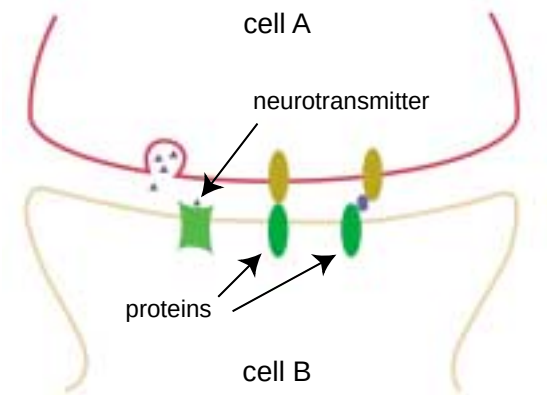
To appreciate fully the power of the brain, we need to consider the nerve cell in the context of billions of other nerve cells. A simple back-of-the-envelope calculation makes the point. The human brain has roughly 100,000,000,000 nerve cells. If each cell makes 1,000 connections with other cells, and each connection processes information at the rate of 100 operations per second, then we're talking about computing power that is still unmatched today. In fact, this simple calculation suggests that our brains are between 10 and 10,000 times faster than the world's fastest supercomputer. At the current rate of development, computing power should surpass the human brain around the year 2015. All this, of course, is little consolation to Gary Kasparov!

Up until now, I've been describing the function of the brain on a cellular and an organismal level. However, we also know something about how communication occurs at the molecular level. Cell A communicates with cell B through a combination of chemical and electrical signals. When cell A sends a message to cell B, an electrical impulse goes zipping down the axon, much like a current through a wire. At the axon's terminal, the electrical impulse reaches a gap, called the synapse, between the two cells. For years, neuroscientists believed that the electrical impulse simply jumped the gap, like a spark between two electrodes. We now know, however, that the electrical signal induces the release of small molecules called neurotransmitters that diffuse across the synapse. Upon reaching cell B, the neurotransmitters initiate a new electrical signal and the message continues on its way.

But there's more to the story than just neurotransmitters. Over the years, scientists have discovered that a variety of molecules—including carbohydrates, proteins, and neurotransmitters—populate the synapse, and the interactions among these molecules control how the nerve cells behave. The modes of interaction vary widely: in one case, for instance, we may find a small molecule that binds to a large protein molecule while, in another case, we may find a small molecule that bridges two large proteins. These binding interactions are highly specific, much like a lock that recognizes only a particular key. It's clear that if we want to understand the flow of information through the synapse, we must study the structure and function of the molecules at the synapse and learn how they interact with one another.

My laboratory focuses on two types of molecules at the synapse: fucosyl sugars and glycosaminoglycans. While both are sugars, they have very different chemical structures. In particular, fucosyl sugars are small and simple whereas glycosaminoglycans are complex polymers, composed of a number of simple sugars strung together like beads on a necklace.

You may recall from organic chemistry that sugars are composed of carbon, hydrogen, and



A variety of molecules populate the synapse. The molecules interact in many different ways, three of which are shown here. In addition to the neurotransmitters, which diffuse across the synapse to bind to proteins on the surface of cell B, proteins on the surface of cell A can reach out to bind to proteins on cell B, and small molecules can bridge the gap between two proteins on opposite sides of the synapse. These interactions modulate the strength of the connection between the two cells and are associated with learning and memory.

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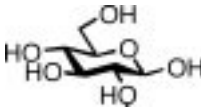
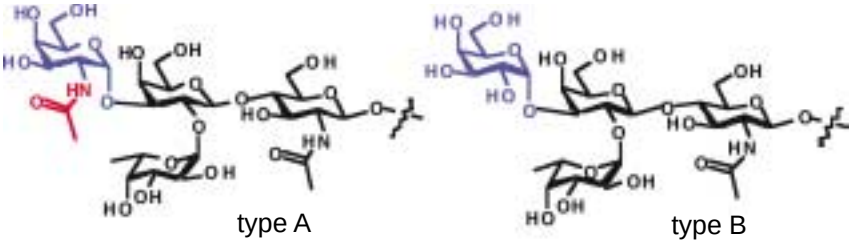
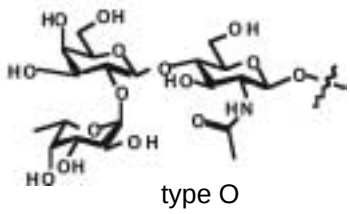


Above: A molecule of glucose, a simple sugar having five carbon atoms in its ring. (The carbon atoms are represented by the points where two or more line segments intersect; the heavier line segments indicate the part of the ring that sticks out in front of the plane of the page.)

oxygen atoms arranged in a ring. Many people are familiar with sugars as a form of energy, such as glucose or fructose, or as a means of structural support, as in the case of cellulose, which is found in plants. Most people, however, are not aware that sugars also play a critical role in controlling cell-cell recognition. For example, shown below are the three sugars, called blood-type antigens, that determine whether your blood type is A, B, AB, or O. These sugars decorate the surfaces of red blood cells and have very subtle chemical differences. All of them share a basic core structure of three different sugar units, but antigen types A and B contain a fourth sugar unit, galactose, shown in blue. The type-A blood antigen looks a lot like the type-B blood antigen except that it has an *N*-acetyl group, shown in red, in place of a hydroxyl (OH) group. This is a powerful example of how a very subtle chemical change can have a profound impact on human biology—if you have type-A blood and receive a transfusion of type-B blood, this tiny four-atom change can be devastating. Your immune system recognizes the blood as foreign to your body and destroys the offending cells, causing their remains to clump in your blood vessels and wreak havoc.



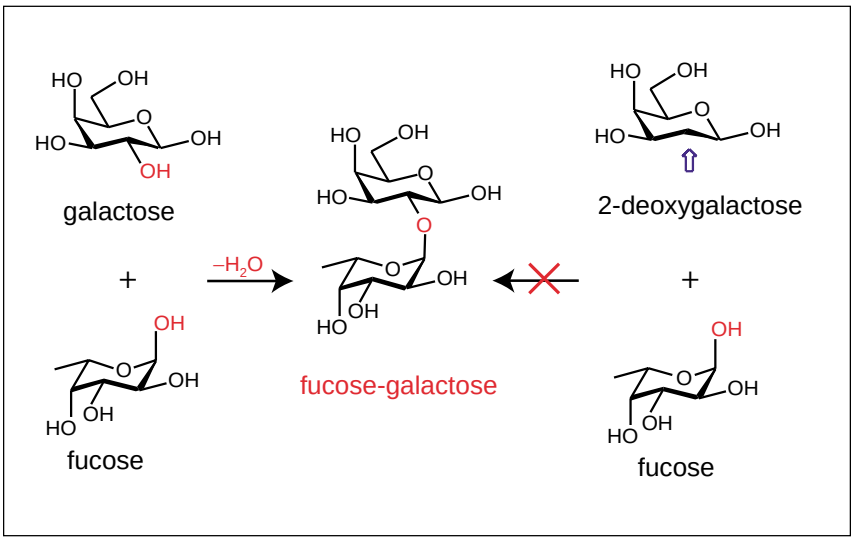


The blood-type antigens share a three-sugar core (black) made of one molecule each of fucose, galactose, and *N*-acetylglucosamine. Type-A blood differs from type-B blood by only four atoms (red), and both differ from type-O blood by one galactose molecule (blue). (People with Type-AB blood have both the A and B antigens.)

In addition to the sugars that determine your blood type, there are hundreds of other sugars that modulate the interactions among cells in your body. For example, sugars control the ability of viruses such as influenza, which causes the flu, to enter and infect your cells. Sugars are also involved in tissue inflammation, which is often a byproduct of injury or disease, and in cancer metastasis. Finally, sugars help nerve cells to grow, establish, and maintain connections—steps that are critical for proper brain development, learning, and memory.

While sugars help to transmit information across the synapse, other molecules also play important roles. In our case, for example, the fucosyl sugars and glycosaminoglycans are chemically linked to large proteins. Proteins are long polymers made up of amino-acid building blocks arranged in varying orders. Tryptophan is an amino acid that you may be familiar with—it is found in high concentrations in turkey, and is the culprit that makes you sleepy after a large Thanksgiving meal. Chemists depict proteins as long, linear chains, but in reality, they fold up into well-defined, three-dimensional structures that endow them with biological functions. For instance, you may have heard of the protein called amylase, which is a digestive enzyme found in saliva that breaks down starches. Another example is hemoglobin, which binds to oxygen molecules and ferries them throughout your blood.

A major project in our laboratory is to understand the role of fucose in the brain. Fucose is a simple sugar that is attached to proteins at the synapse and is frequently associated with other sugar molecules. Several lines of evidence have recently converged to suggest that fucose is important for modulating the transmission



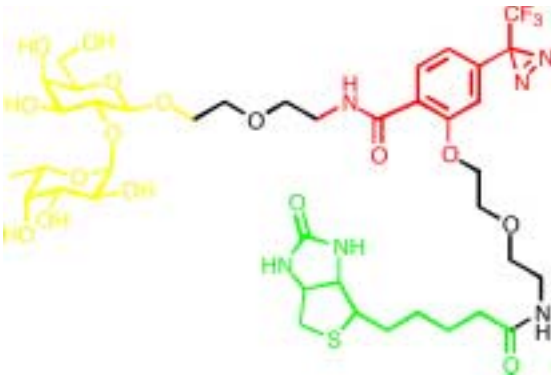
Fucose and galactose (left) link together in the brain to strengthen nerve-cell connections. Each sugar molecule contributes a hydroxyl (OH) group, shown in red, which combine to expel a water molecule and leave an oxygen atom behind as a bridge. Fucose and 2-deoxygalactose (right) cannot link, because the latter is missing the vital OH group at the blue arrow. No linkage, no memory.

of signals between two or more nerve cells. For example, fucose is highly concentrated at the synapse, and repeated nerve-cell firing increases the levels still further. And fucose may be involved in learning and memory because disrupting a critical fucose-containing linkage causes amnesia in lab rats. Fucose is often linked to another sugar called galactose. The linkage, shown in red in the diagram above, is created when hydroxyl groups on the two sugars combine and expel a water molecule. Rats given 2-deoxygalactose (which is identical to galactose in all respects except that it lacks the critical hydroxyl group) cannot form this linkage, and develop amnesia.

You may be wondering how one knows when a rat has amnesia. As it turns out, a number of years ago a neuroscientist named Tassoni and his colleagues at the University of Florence, Italy, conducted a fairly simple memory experiment. The rat was placed in a box whose interior was illuminated on one side and dark on the other. The box was constructed such that the rat received a mild electric shock when it ventured into the dark section. In contrast, the illuminated section did not give shocks. Conditioning the rat taught it to associate the dark section with the shock, so that, after a period of time, the scientists could turn off the shock and the animal would continue to avoid the dark section because it remembered the jolt. The interesting result from our perspective was that rats treated with 2-deoxygalactose (but not galactose, 2-deoxyglucose, glucose, or fucose) after conditioning showed no preference for either section, presumably because they couldn't form the essential fucose-galactose linkage. In another study, rats treated with 2-deoxygalactose were unable to maintain long-term potentiation (LTP), which is a widely used model for learning and memory. Taken together, these experiments strongly suggest to us that fucose-containing molecules at the synapse may play an important role in learning and memory.

My lab has developed a model that may explain fucose's role at the synapse. The figure below shows the synaptic cleft between cells A and B. We know that proteins on cell A's side of the synapse contain fucose, and we believe that fucose is binding to proteins on the surface of cell B, thereby acting as a chemical bridge across the synapse. This binding event should activate the cellular machinery in cell B and instruct the cell to synthesize more proteins. One can envision a positive feedback loop, in which the proteins synthesized in cell B are transported to the cell surface, where they interact with the fucose units from cell A to stimulate still more protein synthesis. This model is consistent with the observation that fucose levels increase at the synapse with repeated nerve-cell activity. The model is also consistent with current theories about the chemical basis of long-term memory. In particular, neuroscientists have observed that new protein synthesis is required to form long-lasting memories. By changing the concentration of specific molecules at the synapse, it is believed that certain connections between nerve cells are

Our model for how fucose could act as a chemical signal: A fucose molecule attached to a protein on cell A's side of the synapse can bind to another protein on cell B's side. This stimulates cell B to make more of the fucose-binding protein, enhancing the cell's sensitivity to fucose and strengthening the connection.



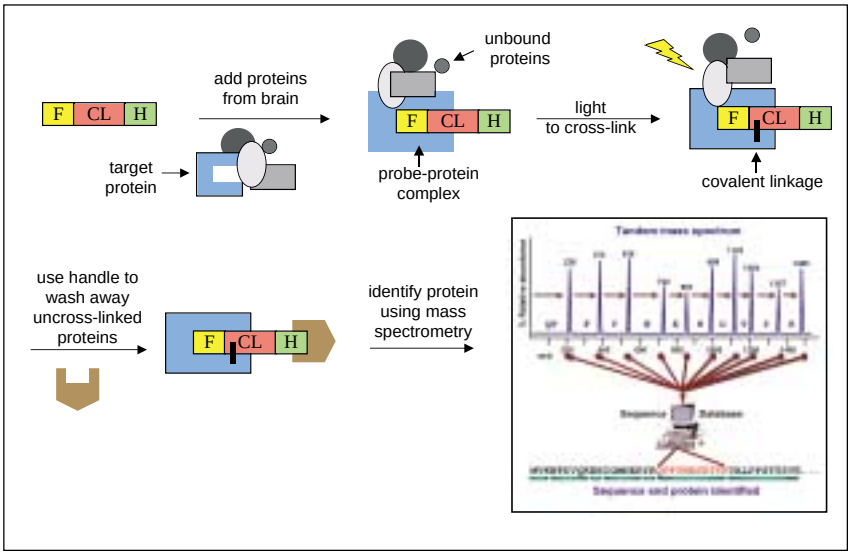
The fucose "harpoon." Upon irradiation with ultraviolet light, the diazarine group (N=N) is converted to nitrogen gas (N_2), which escapes. The molecule left behind is highly reactive and attaches chemically to nearby proteins, allowing us to harpoon them for further study.

enhanced and grow stronger over time.

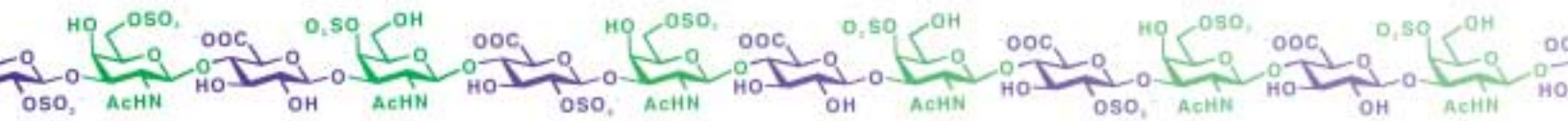
To test whether our model is correct, we need to identify the protein partners that recognize fucose at the synapse. Recently, my research group designed and synthesized a chemical probe that acts as a "molecular harpoon" to help us to isolate and identify these proteins. The chemical structure of our probe is shown above, and it has three basic elements. The first element is a fucose-galactose group (yellow) that interacts with the target protein. The second element is a chemical cross-linker (red), a member of the diazirine family that is the "harpoon" piece of our probe. Diazirine molecules become very reactive when exposed to ultraviolet light. Thus, once the probe is bound to the target, we can zap the solution with ultraviolet light and form a permanent covalent bond between the probe and the protein. The third and final element (green) is what I call a "chemical handle" because it allows us to isolate the protein-probe complex from a mixture of thousands of other proteins. We are using biotin (which, incidentally, is one of the B-vitamins) as the handle, because biotin binds specifically, and very tightly, to a protein called streptavidin. We can buy streptavidin already bound to resin particles that have the consistency of fine sand. So when we want to isolate the streptavidin-biotin-probe-protein ensemble, we simply let the resin sink to the bottom of our centrifuge tube and rinse away all of the other proteins that remain suspended in solution.

Once we have isolated the target protein using our molecular harpoon, we still have the challenge of determining what we've found. Fortunately, there's an instrument, called a mass spectrometer, that identifies molecules based on their size and charge. In the case of very large molecules such as proteins, we must first break the protein up into smaller fragments. Then we use the mass

"Tandem mass spectrum" diagram reprinted from *Current Opinion in Chemical Biology*, Vol. 2000, No. 4, Gygi and Aebersold, "Mass Spectrometry and Proteomics," p. 490, copyright 2000, with permission from Elsevier Science.



How to harpoon a protein and render its identity. The yellow-red-green rectangle is the fucose (F)–cross-linker (CL)–handle (H) probe.



A glycosaminoglycan is a polymer of simple sugars that alternate with each other. Shown here is chondroitin sulfate, which consists of alternating D-glucuronic acid (blue) and *N*-acetylgalactosamine (green). The polymer can be up to 200 sugars long.

spectrometer and a computer to sort the fragments and identify the amino-acid sequence that corresponds to each fragment. As a final step, we compare the amino-acid sequences of our fragments to DNA-sequence databases that contain genetic information for many organisms, including humans, mice, and rats. Once we find a match for our fragments in the databases, we know the identity of our target protein.

Lori Lee, a second-year graduate student in my laboratory, has just completed the synthesis of our chemical probe, and we hope very shortly to learn which proteins at the synapse bind to fucose. We are very excited about this because, if we're successful, we will begin to have a molecular-level understanding of the complex processes by which nerve cells communicate. If you think back to the example of the blood-type antigens, just four atoms meant the difference between a successful blood transfusion and a serious health hazard. With our experiments to unravel the identity of fucose-binding proteins at the synapse, we hope to bring the same molecular-level perspective to our understanding of the brain.

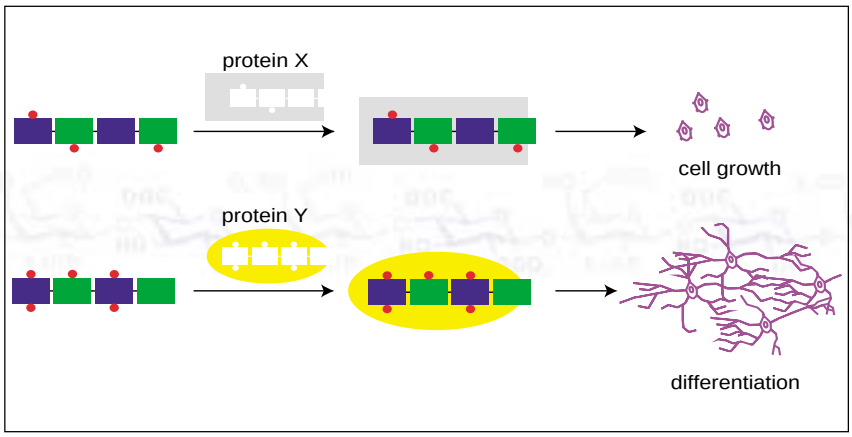
Another area that my lab has been exploring involves a class of molecules called glycosaminoglycans. Glycosaminoglycans play a variety of important roles throughout biology—for example, heparin is a glycosaminoglycan that's used after surgery to prevent blood clotting. Glycosaminoglycans are also involved in Alzheimer's disease, cancer, and angiogenesis, which is the process by which blood vessels develop and link up with one another. Our interest in glycosaminoglycans stems from the fact that, like fucose, they are found at the synapse, are important for proper brain development, and play a critical role in learning and memory. It is believed that, like fucose, glycosaminoglycans are also involved in establishing connections between nerve cells. However, the molecular mechanisms of this process remain poorly understood.

Whereas fucose is a relatively simple sugar, glycosaminoglycans are complex polymers, having a repeating A-B-A-B-A structure composed of alternating sugar units. There are several different kinds of glycosaminoglycans found in nature, and each is characterized by different sugar units. For example, chondroitin sulfate is composed of alternating D-glucuronic acid and *N*-acetylgalactosamine units. Another glycosaminoglycan, heparan sulfate, is composed of alternating L-iduronic acid or D-glucuronic acid and *N*-acetylglucosamine units. Both chondroitin sulfate and heparan sulfate are found in the brain, but they play very different roles. So, at the first level, we see that nature can encode different biological functions by using different sugar sequences.

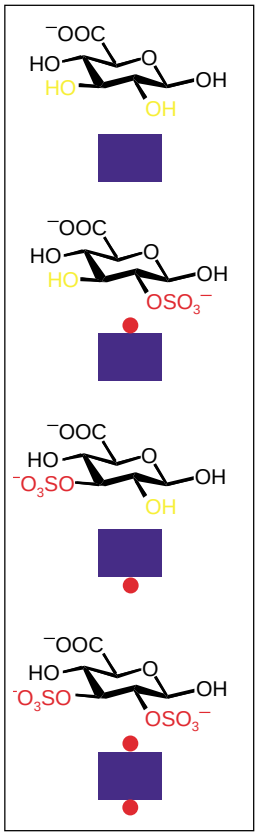
However, nature has taken the chemical diversity of glycosaminoglycans one step further. Even a single sugar molecule can take many different forms. If, for example, we look at a typical simple sugar, we see that there are five different hydroxyl (OH) groups arrayed around a six-membered ring. If we attach a second chemical group to one of these five hydroxyl groups, the resulting molecule is different than if we attach that same chemical group to one of the other hydroxyl groups. These two molecules have the same number of atoms, the same electrical charge, and the same molecular weight. But, importantly, they are chemically distinct. They have different three-dimensional shapes, so they interact with the outside world in completely different ways. A simple example may make the point more clearly: If you look at your right hand and your left hand, you'll see that they have the same number of fingers and are roughly the same size and shape. We all know, however, that no matter how hard you try, you cannot fit a left-handed glove on your right hand. Sugars are much the same and, for this reason, they are both fascinating and challenging to study.

It is useful to keep the image of your right and left hands in mind while you consider the

Different sulfation patterns could be ignition keys, turning on various proteins that control the cell.



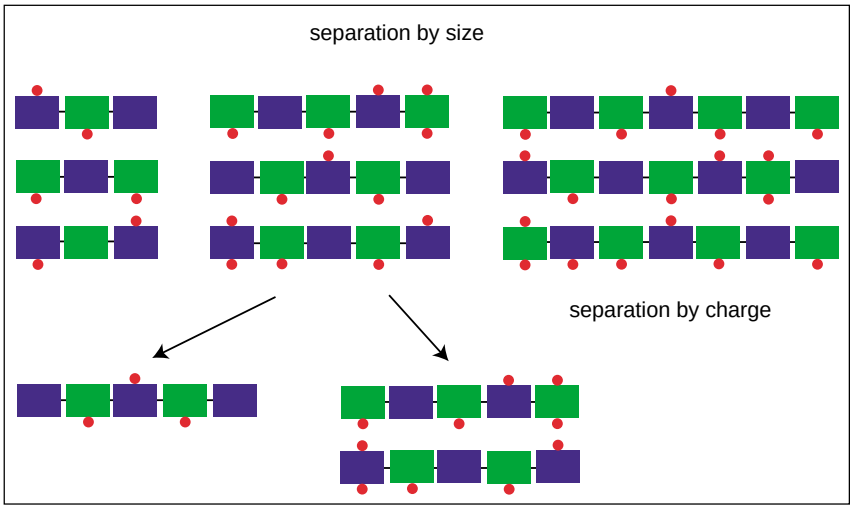
next level of complexity exhibited by the glycosaminoglycans. I have shown the chemical structure of D-glucuronic acid in the drawing below and, for simplicity, as a blue square below the structure. In your body, however, D-glucuronic acid may be chemically modified with sulfate (OSO_3^-) groups at either or both of the 2- and 3- positions, depicted schematically as red circles above and below the blue square. Thus, sulfating D-glucuronic acid generates four different chemical structures: one molecule with no sulfate groups (top), two molecules, each with a single sulfate group at either the 2- or 3-position (middle), and one molecule with sulfate groups at both the 2- and 3-positions (bottom). Similarly, sulfation of *N*-acetylgalactosamine also generates four different structures. The result is that every sugar unit along the polymer chain can have any one of four different chemical structures. So if you consider a simple, four-unit molecule of chondroitin sulfate, you have four possibilities in the first position times four more in each of the second, third, and fourth positions, for a total of 256 different compounds.



Nature has done something remarkably clever here. It's taken a relatively simple polymer and built up diversity by adding sulfate groups along the chain. This strategy has tremendous implications in the body because naturally occurring glycosaminoglycans can be up to 200 sugar units long. Taking into account all the possible ways to sulfate 200 sugars, we end up with a number of possible compounds that is greater than Avogadro's number (6.022×10^{23})!

You may be wondering what is the biological significance of so much chemical diversity. Evidence suggests that the sulfation pattern of a glycosaminoglycan determines whether particular proteins can interact with it. Protein binding, in turn, controls a variety of other downstream biological events, including the ability of cells to grow, communicate, and differentiate into other types of cells. Each of these processes requires the presence of distinct proteins in a defined sequence of events. We and others believe that the "instructions" for these biological events may be encoded, in part, by the sequence and sulfation pattern of glycosaminoglycans. I like to think of glycosaminoglycans as molecular fingerprints because, while they may look similar, no two are identical. Glycosaminoglycans provide a powerful means to encode biological information—nature can use different fingerprints to direct different functions.

There's an intriguing similarity in the way that nature encodes information in the structures of both glycosaminoglycans and DNA. It is well established that nature stores the genetic information of all organisms in the sequence of As, Ts, Cs and Gs, strung along the backbone of DNA's famous double helix. We believe that glycosaminoglycans also encode information through their structure and patterns of sulfation. In particular, we suspect that the position of the sulfate groups along the sugar backbone tells other molecules at the synapse, such as proteins, where to go and what to do. Our goal, of course, is to use chemistry to unlock this sulfation code.



It's easy to separate glycosaminoglycans by their size and then by their charge. However, the two five-sugar sequences at bottom center have equal numbers of sulfates, giving them the same charge. They may be indistinguishable in the lab, but their different sulfation patterns are easily recognizable in the body.

While biochemical studies have clearly demonstrated the functional significance of sulfation, efforts to advance a molecular-level understanding of glycosaminoglycans have been hampered by difficulties in obtaining well-defined chemical structures. Until recently, glycosaminoglycans could only be isolated from natural sources as very complex mixtures of compounds. This was problematic because the same factors that make glycosaminoglycans interesting to study (namely, subtle variations in size, chemical structure, and patterns of sulfation) make them nearly impossible to purify in the lab. Two different glycosaminoglycans that are readily distinguished by a protein in your body may appear virtually identical to state-of-the-art analytical instruments.

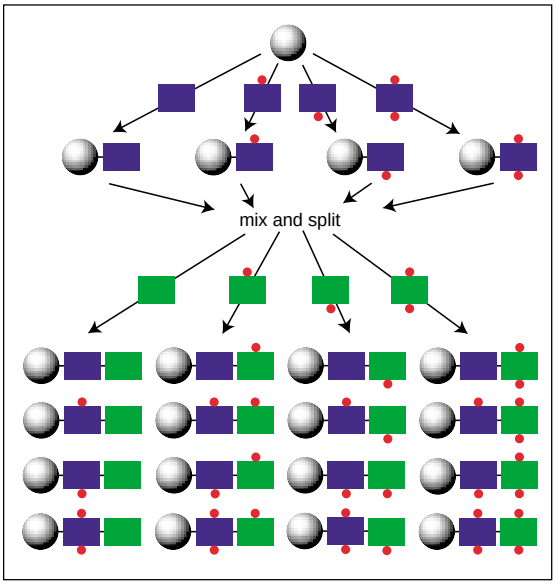
Using the tools of synthetic chemistry, however, we can build predetermined glycosaminoglycan structures in the laboratory. We start with chemically pure building blocks and link them together in an ordered fashion. By choosing the structure of each building block, we can dictate precisely the sequence and sulfation pattern of the resulting polymer. In addition to synthesizing single glycosaminoglycans, we are also developing methods to make large populations of diverse ones. This is important because, in many cases, we have very little structural information about the glycosaminoglycan involved. We may know, for example, that a particular protein binds to a chondroitin sulfate molecule that is at least six units in length, but we do not know which six units are involved or in what sequence. If every unit has four different possibilities, then we have 4^6 or 4,096 different compounds from which to choose. That's a lot of molecules!

Fortunately, chemists have devised two technologies, called solid-phase synthesis and combinatorial chemistry, which allow us to make large numbers of compounds rapidly and simultaneously. To understand the advantage of solid-phase synthesis, it is helpful to understand how chemists ordinarily make molecules. If a chemist wants to create a chemical bond between two molecules, she prepares appropriate building blocks, mixes them together in solution, and may add special solvents, reagents, or catalysts to accelerate the reaction. Once the reaction is complete, she purifies and isolates the desired product. This process of chemical synthesis forms the basis of modern organic chemistry and is the foundation of the pharmaceutical, chemical, and agribusiness industries, among others. The chief drawback is that purifying the intermediates can be time-consuming and expensive.

Nearly 30 years ago, however, Bruce Merrifield of Rockefeller University devised an alternative approach. Merrifield and his coworkers were synthesizing peptides—small polymers of amino acids—and their revolutionary insight was to anchor one end of the polymer to a solid, insoluble support, such as a glass or polystyrene bead. (You can actually see these beads under a microscope, and pick them up with tweezers.) By reacting the growing polymer chain with the right set of chemicals, one could perform a desired reaction and, at the end, the excess reagents and the by-products could be removed by filtering and washing the beads. Merrifield's invention was a fundamental leap forward, and he was awarded the Nobel Prize in chemistry in 1984. Solid-phase synthetic techniques have since been applied to many other molecules, including DNA, carbohydrates, and many classes of smaller compounds.

The second major innovation we use is called combinatorial chemistry—a simple, yet ingenious extension of solid-phase chemistry. If our chemist wanted to synthesize a collection of 16 related compounds using traditional synthetic organic methods, she would need to conduct 16 separate reaction sequences and purify 16 different products. Using a solid-phase approach, however, she can simply divide her beads into four portions and react each portion with a different building block.

Glycosaminoglycans that are readily distinguished by a protein in your body may appear virtually identical to state-of-the-art analytical instruments.



Combinatorial chemistry enables all possible sequence combinations of any given length to be made in a minimal number of steps, as the two-sugar library above shows. (The gray spheres represent the beads.)

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15 — Doug Cummings;
16–23 — Linda Hsieh-Wilson

If she were to stop there, the result would be four different compounds. If, however, she pours the four sets of beads back into one flask, stirs them thoroughly, and pours out the mixture into four new flasks that she reacts with a new set of building blocks, then she will generate 4×4 (or 16) different molecules. Accordingly, she would need to run only eight reactions to produce the 16 compounds, and the purification of the final products would be that much simpler.

In chemistry, we call a collection of related molecules synthesized in this way a "library" of compounds. The figure above shows the combinatorial synthesis of a 16-compound glycosaminoglycan library. All the possible sulfation patterns are represented, and each bead contains a unique compound that can be isolated and characterized. In my laboratory, Sarah Tully and Sherry Tsai, two second-year graduate students, and Connie Wang, an undergraduate, have been working on methods to synthesize a chondroitin sulfate library. The construction of this library is a major undertaking, but our group has already successfully synthesized the building blocks. At present, we're optimizing the chemical steps needed to link the blocks to one another and to the beads.

With the library in hand, we can begin to identify the specific sulfation patterns that are responsible for the biological activity of glycosaminoglycans. We've begun to study several proteins whose binding to glycosaminoglycans has been implicated in nerve-cell growth and differentiation, and we expect to find out what governs these interactions. In addition, we want to understand how specific glycosaminoglycans influence cellular behavior, such as nerve-cell growth and regeneration. Finally, we'd also like to correlate specific sulfation patterns with physiological changes in brain function and development. Whether specific glycosaminoglycans are associated with development, aging, and neurodegenerative disease is a wide-open question at this time.

I hope that you'll agree that the intersection between chemistry and neurobiology is an incredibly exciting place to be. As one of the last great frontiers of scientific exploration, neuroscience requires the energy, creativity, and insight of people from a variety of different disciplines. Together, we're working to build a framework of understanding that stretches from molecules and genes to learning, memory, and perhaps even consciousness itself. Unraveling the many mysteries of the human brain will carry us well into the next century. Without a doubt, however, the adventure will continue to captivate the imagination of scientists and nonscientists alike. □

Assistant Professor of Chemistry Linda Hsieh-Wilson earned her BS from Yale in 1990, and her PhD from UC Berkeley in 1996, both in chemistry. After a postdoctoral appointment in neurobiology at Rockefeller University, she joined the Caltech faculty in the fall of 2000. Since then, she has been named a Beckman Young Investigator by the Arnold and Mabel Beckman Foundation, and has received a Research Innovation Award from the Research Corporation. This article was adapted from a 2001 Alumni Seminar Day talk.