Mysteries of the Cell

We live in the golden age of genetics, but the fundamental unit of biology is still arguably the cell. The scientists gathering next week in Denver for the American Society for Cell Biology’s annual meeting need little reminding of that, but as they detail their latest insights and data, it’s useful to reflect on how much of the cell remains unexplained or unknown. To that end, our news staff, aided by Science Editor-in-Chief Bruce Alberts and editors Stella Hurtley and Valda Vinson, have polled some of our Board of Reviewing Editors and other biologists to identify the cell’s lingering mysteries. The handful we highlight here range from basic questions, such as how does a cell know its size, to more obscure, perplexing puzzles. And if those aren’t enough to inspire you, we’ve noted another batch of cellular mysteries that could provide fodder for future Ph.D.s—or Nobel Prizes. —JOHN TRAVIS

Do Lipid Rafts Exist?

The contention that molecular platforms known as lipid rafts sail on the cell’s outer, or plasma, membrane has kept researchers debating for more than a decade. Although many scientists argue that rafts either don’t exist or have no biological relevance, their supporters insist the idea remains afloat.

Cell biologist Kai Simons, now at the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden, Germany, and his colleague Elina Ikonen christened the term “lipid raft” in a 1997 Nature paper that detailed the concept. At the time, the main model of the plasma membrane portrayed it as a sea of lipids through which proteins drifted with little or no organization. But the duo proposed that two kinds of lipids, cholesterol and sphingolipids, huddle together in the membrane, producing stable formations they called rafts. One line of evidence for that concept, the team noted, was the goop left behind in test tube studies when certain detergents dissolve the plasma membrane. This so-called detergent-resistant membrane oozes with cholesterol, sphingolipids, and select membrane proteins.

Rafts serve the cell, the hypothesis suggested, because they gather in one place the proteins necessary for a particular task, such as importing material or relaying a message across the plasma membrane. Proposed passengers on the rafts included glycosylphosphatidylinositol (GPI)-anchored proteins, which adhere to the outer layer of the plasma membrane and perform functions such as receiving signals and helping cells stick together.

The idea roiled the cell biology community. “Right away, there were two camps,” Simons says. “One camp didn’t believe a word.” But plenty of scientists hopped aboard. More than 3000 papers later, the activities attributed to lipid rafts include promoting drug resistance in cancer cells and serving as escape hatches for viruses such as the ones that cause flu. Possibly the most debated hypothesis invoked rafts to explain the activation of the T cell receptor, the cell surface protein that spurs these immune cells to action when a pathogen is on the loose in the body. Incorporating the receptor into a raft helps switch it on, studies have suggested, possibly by allowing the receptor to hobnob with other proteins necessary for stimulating the T cell or because those proteins need the raft environment to work.

Members of both camps concur that the raft concept was compelling and galvanized investigation into membrane organization. “The raft hypothesis is brilliant in some ways,” says biophysical chemist Jay Groves of the University of California, Berkeley. “My personal opinion is that the very idea of rafts enriches scientific research,” says biophysicist Sarah Keller of the University of Washington, Seattle, “whether or not rafts exist in either specific cases or more generally.”

But how solid is the proof there are rafts? Skeptics abound, and they’ve scored some hits on the original raft evidence. Membrane biologist Michael Edidin of Johns Hopkins University in Baltimore, Maryland, says the field has fallen victim to what he calls the “sins of detergent extraction.” Too many researchers have assumed that detergent-resistant membranes are genuine rafts, even though studies reveal that extraction can disrupt their composition. “The idea of these isolatable islands of raft lipids is probably not viable,” says membrane biologist Ken Jacobson of the University of North Carolina, Chapel Hill.

According to the raft hypothesis, certain lipids naturally sort themselves to create the organized pockets of proteins that make up rafts. But many researchers don’t buy that mechanism for inducing order in the membrane. It is too passive, especially when the plasma membrane is constantly churning, says Satyajit Mayor, a membrane biologist at the National Centre for Biological Sci...
How Does a Cell Know Its Size?

From short and heavy to tall and thin, people come in various sizes — and so do their cells. An egg cell dwarfs a sperm, for example, and both are dainty compared with some of our neurons that stretch to more than a meter in length. But within specific cell types, cells actually stick to “a fairly narrow range of sizes,” says cell biologist Marc Kirschner of Harvard Medical School in Boston.

Biologists have puzzled over how cells know when they’ve reached the right size. “The question has been there for a long time. The answers haven’t,” Kirschner says. Researchers have finally begun to identify potential size-sensing mechanisms within cells, but they admit there’s still a lot to learn.

When a cell does deviate from the norm, it may signal a malfunction: Skewed cell size is a hallmark of some diseases. Take small-cell carcinoma, a type of cancer that usually sprouts in the lungs, in which tumor cells are so puny that they barely have room for any cytoplasm.

“Cell size control doesn’t just happen by itself,” notes cell biologist James Umen of the University of Washington in St. Louis, Missouri. “To understand how cells manage their dimensions, researchers have been searching for a ‘sizer’ that enables cells to gauge how big they are. The challenge for cells is ‘how do you make a measuring stick?’” says cell biologist James Moseley of Dartmouth Medical School in Hanover, New Hampshire.

It might not be as hard as you think. Instead of inventing specialized measurement tools, cells may take advantage of existing mechanisms and reactions that serve other purposes, says biomedical engineer David Odde of the University of Minnesota, Twin Cities. Possible measuring sticks, his work suggests, include an activated enzyme that is gradually switched off as it travels through the cell and microtubules, fibers that are continually extending and shrinking within the cytoplasm. “Any cellular reaction which has diffusion in it can sense spatial scales by the time it takes” for something to cross the cell, explains biophysicist Petra Schwille of the Technical University of Dresden in Germany.

Researchers have uncovered the best evidence for a sizer in single-celled organisms. In papers independently published in 2009, Moseley and colleagues and a second group from the University of Lausanne in Switzerland identified one way that certain kinds of yeast cells measure themselves. A so-called fission yeast cell lengthens as it grows, until it reaches a point at which it splits in the middle to form equal-sized daughter cells. The groups found that this behavior depends on Pom1, a protein whose concentration is high at the ends of the elongated cells but falls off toward the center. As the yeast cell lengthens, the amount of Pom1 at its midsection dwindles until too little remains to block a molecular circuit that curbs mitosis. Voilà! The cell begins to divide.

Research by microbiologist Petra Levin of Washington University in St. Louis and colleagues suggests that at least some bacteria have a size sensor. The size at which most bacteria divide depends on how well they are eating. If food is abundant, they reproduce at a larger mass than when meals are scarce. Levin’s group identified a molecular circuit, which includes the enzyme UgfP, that senses food availability, helping the cell decide when to split. The cell’s mass also influences this decision, suggesting that the cell has a system to gauge how big it is, although how the cell does this remains uncertain.

A yeast or bacterial cell is typically an individualist, relying only on itself. But in multicellular organisms like humans, cells integrate into tissues and organs. Some researchers argue that cells in such organisms don’t need any kind of internal size-sensing mechanism. External controls, such as growth factors released by other cells, dictate how big a cell becomes.

To resolve the issue, some researchers are trying to determine if there are so-called checkpoints that prevent a cell from starting to divide if it isn’t the right size. So far, the evidence for size checkpoints is contradictory.

David and Goliath? This tussle between immune cells (red) and a cancer cell illustrates that cells come in a range of sizes.

—MITCH LESLIE
and indirect. Cell biologists have attempted to find them by measuring an aspect of how individual cells enlarge—whether their growth is linear or exponential. For linear growth, a cell would enlarge at a constant rate until it divides. But for exponential growth, the increase would be proportional to the cell’s girth. In the latter case, the small but natural variations in size between two cells resulting from division would rapidly expand to create a population of cells with large size differences. So if cells are growing exponentially, researchers reason, they must have a checkpoint to rein in growth and keep themselves within the observed narrow size range.

Determining what type of growth various kinds of cells actually undergo can be extremely difficult, however. The disparity in growth rates between a linearly growing cell and an exponentially growing one will be only about 6%, Kirschner notes.

Four years ago, cell biologist Alison Lloyd of University College London and colleagues gauged how quickly nervous system cells enlarged. Their results suggested that growth in these cells was linear. “Do mammalian cells have a checkpoint? We say no, the cell doesn’t need it,” Lloyd says.

In a _Science_ paper published 2 years ago (10 July 2009, p. 167), Kirschner and colleagues applied a statistical approach to reach the opposite conclusion about immune system cells. The next year, Kirschner teamed up with Scott Manalis of the Massachusetts Institute of Technology (MIT) and colleagues to weigh individual cells, herding them one by one onto the microscopic equivalent of a scale. Again, they found that the cells, which included bacteria and immune cells, displayed exponential growth, suggesting that checkpoints are operating. The identity of the molecules that detect the size of the cells remains unclear, however, Kirschner says.

His group and Lloyd’s could both be right, Kirschner suggests: The two teams studied different kinds of cells that might behave differently. Umen agrees. Fast-growing immune cells might be more like yeast, relying on their own size-measuring mechanism, whereas nervous system cells mainly heed external cues, he speculates.

Although researchers have made some progress toward understanding how dividing cells sense and control their size, that issue is part of a broader question, says molecular biologist David Sabatini of MIT. Most of the cells in our bodies don’t divide, yet they can continue to grow. How these cells sense when they are big enough to stop expanding is also a mystery, he says. Biologists who want to decipher cell size control still have some big questions to answer.

—MITCH LESLIE

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**How Does the Cell Position Its Proteins?**

If you think air traffic controllers have a tough job guiding planes into major airports or across a crowded continental airspace, consider the challenge facing a human cell trying to position its proteins. The latest analyses suggest that some of our cells make more than 10,000 different proteins. And a typical mammalian cell will contain more than a billion individual protein molecules. Somehow, a cell must get all its proteins to their correct destinations—and equally important, keep these molecules out of the wrong places. While research addressing this challenge has already produced a Nobel Prize, biologists stress that the mystery of how cells place their protein repertoire is far from solved.

Protein localization within the cell wasn’t always recognized as a fundamental puzzle. Before the advent of powerful microscopes and tools to label individual proteins, scientists typically considered cells simple bags of freely diffusing molecules. People were taught, says cell biologist James Wilhelm of the University of California, San Diego, “that the cytoplasm is a homogeneous goo.”

As organelles were discovered and specific proteins were found to be localized to them and to other cellular compartments, there came a need to explain how the molecules get to specific homes. Enter cell biologist Günter Blobel of Rockefeller University in New York City, who with colleague David Sabatini theorized in 1971 that proteins intended for the endoplasmic reticulum carried among their amino acids a localization, or sorting, signal. In work that won him a Nobel Prize in 1999, Blobel subsequently proved that conjecture, identifying sorting signals that direct newly synthesized proteins to various organelle membranes. “The concept that a sequence on a protein carried information relevant to its final destination was novel. ... It was very speculative,” says cell biologist Karl Matlin of the University of Chicago, who is writing a history of that period.

Nobel Prize—case closed on protein localization? Not so fast. Many proteins operate outside organelles but still need to find specific homes or molecular partners within the relatively vast spaces of a cell. So does the cell have other ways to concentrate proteins in the right spots? Undoubtedly, biologists say. “The Blobel hypothesis in a sense kept blinders on people for a long time,” notes developmental biologist Henry Krause of the University of Toronto in Canada. “The common perception was that proteins knew how to get places.”

Biologists are finding other tricks cells use to place newly minted proteins, but another emerging story is that a cell begins to position proteins even before they are made. Starting in the mid-1980s, a few biologists began to gather evidence that cells localized proteins by directing the corresponding messenger RNAs (mRNAs) that encode their production to a specific destination, so the proteins are manufactured where they are needed. One of those pioneers, Robert Singer, now at Albert Einstein College of Medicine in New York City, initially showed that fibroblast cells position the protein beta-actin’s mRNA to facilitate cell movement. Other scientists followed, revealing mRNA localization in fruit fly and frog eggs and in various animal neurons, for example. But a perception lingered that these cases were...
rare or oddities. “It was awfully lonely for a decade or so,” Singer recalls, noting that a meeting on mRNA localization he organized in 1994 drew only about 30 scientists.

There are seemingly obvious advantages to mRNA localization for positioning proteins. Efficiency, for example. Rather than requiring a cell to move many copies of a protein, Singer notes, “one mRNA could make thousands of proteins, and in the right place.” Localizing mRNAs could also prevent dangerous, unintended interactions as proteins move through a cell. “It seems easier to sort the information for a molecule than the molecules themselves,” Wilhelm says.

It’s increasingly clear that cells agree with Wilhelm. He, Singer, and others point to a 2007 study by Krause’s group as some of the first compelling evidence that mRNA localization is pervasive. In that work, the scientists labeled RNA with fluorescent tags and systematically observed the positioning of more than 3000 different types of mRNA during early fruit fly development. More than 70% exhibited clear localization. That’s a “staggeringly large number,” Singer says. “It’s almost as if every mRNA coming out of the nucleus knows where it’s going.”

Thanks to this and similar work, many biologists are taking a new look at mRNA localization. And to an extent, history is repeating itself. Much as Blobel did with proteins, biologists are now identifying specific short RNA sequences—Singer calls them Zip Codes—that direct mRNA strands to various parts of the cell. Even proteins that have sorting signals of the type Blobel studied may also have mRNAs with built-in Zip Codes. “It looks like the RNA is localized first,” Krause says.

Krause suspects that cells needing to position proteins turn to RNA in additional ways. He speculates that certain RNA strands serve as focal points within the cytoplasm around which specific complexes of proteins form.

Clifford Brangwynne of Princeton University may have uncovered something along those lines while probing how cells position something so-called P granules, poorly understood assemblages of proteins and RNA that help specify germ cells during development in nematodes. Once the fertilized worm egg breaks symmetry, P granules move to one half of the single-cell embryo, from which germ cells will arise. In 2009, Brangwynne reported that P granules behave like liquid droplets within cytoplasm—the drops can fuse to one another, drip out of dissected cells, and “wet” the surfaces of organelles such as the nucleus—and that specific RNA-binding proteins control localized “condensation” of these drops.

The biophysicist suspects that cells often use this strategy to condense RNAs and proteins into dynamic “microworxes” that encourage molecular interactions, perhaps between an enzyme and its substrate, for example. “People usually think about cellular organization being accomplished largely by membrane-bound compartments, which are bathed in a homogeneous cytoplasmic fluid,” he says. “The work by us and others in this area is beginning to paint a picture in which this cytoplasmic fluid is actually highly structured, which is useful for putting things in the right place at the right time.”

Cell biologist Timothy Mitchison of Harvard Medical School in Boston has recently collaborated with Brangwynne and found that nucleoli, RNA-protein bodies in a cell’s nucleus, similarly represent such droplets. “It’s fair to say Cliff has discovered a new state of biological matter,” he says.

It’s clear that biologists have a long way to go before they fully understand the protein traffic control system within a cell. A Nobel Prize doesn’t mean a mystery is solved, Blobel says with a laugh. “There’s a lot left to be learned.”

How Do Hungry Cells Start Eating Themselves?

Hungry cells take recycling to the extreme. When a cell runs out of raw materials, it sprouts an internal membrane that encapsulates some of its contents and breaks them down for reuse. The process is called autophagy: literally, “self-eating.” Cell biologists have long wondered where this membrane comes from. Now, they might be close to an answer.

To devour part of itself, a cell initially fashions the equivalent of a mouth: a membrane pocket known as a phagophore. The expanding phagophore swallows a portion of cytoplasm, trapping proteins and even organelles such as mitochondria. After it closes, this membrane receptacle, now termed an autophagosome, docks with the cell’s version of a stomach—the lysosome—which digests the delivery, recycling the material it contains.

Even in good times, when nutrients are plentiful, cells rely on autophagy to rid themselves of worn-out or defective organelles and molecules. More and more evidence suggests that when this self-cannibalism goes awry, cellular—and overall—health suffers. Faltering autophagy might promote a range of illnesses, from neurodegenerative disorders such as Huntington’s disease to diabetes, and it could also spur aging.

Since researchers discovered autophagy in the 1950s, they’ve worked out many of its molecular details, but the origin of the autophagosome membrane has slipped through their grasp. And that’s frustrating because determining where the membrane comes from could give a boost to researchers who hope to combat diseases by managing autophagy.

The autophagosome “wasn’t following the rules,” says cell biologist Jennifer Lippincott-Schwartz of the National Institute of Child Health and Human Development in Bethesda, Maryland. Most organelles, she explains, hew to a “like from like” rule. A new mitochondrion, for example, is born when an existing one cleaves. But autophagosomes apparently don’t spring from other autophagosomes. That leaves two options. Proteins inside the cell could build the phagophore from scratch, synthesizing fresh membrane in the cytoplasm. Alternatively, the cell could borrow lipids from another location;
membrane swapping among other organelles is common in cells. A cell teems with potential sources of existing membrane. The endoplasmic reticulum (ER), a membranous network that helps synthesize proteins and lipids, pervades the cytoplasm, for example. Even the plasma membrane that wraps the cell could contribute to building the autophagosome.

Some recent work suggests that the ER, which manufactures most of the membrane lipids for the cell, donates membrane to nascent autophagosomes. A group from Finland and another group from Japan have observed autophagosomes or phagophores attached to the ER, as if they were being born. As one of the papers put it, a portion of the ER serves as a “cradle for autophagosome formation.”

However, other studies point to the Golgi apparatus, a membrane-rich organelle whose job is to put the finishing touches on new membrane from the ER, as the birthplace. Daniel Klionsky, a cell biologist at the University of Michigan, Ann Arbor, and colleagues revealed in Cell this summer that autophagy in yeast requires so-called SNARE proteins carried by membrane-enclosed capsules, or vesicles, released from the Golgi apparatus. These vesicles could supply fresh membrane to the growing phagophore. “We think the Golgi is a major source [of the lipids],” Klionsky says.

Lippincott-Schwartz’s evidence backs yet another option. Famished mammalian cells obtain their autophagosome membrane from the outer membrane around mitochondria, she and her colleagues concluded last year in Cell. Using live cell imaging, the researchers watched fluorescently labeled autophagosomes grow right next to the outer mitochondrial membrane, and they appeared to be connected to the organelle. The team also followed tagged lipids appearing on mitochondria and then on autophagosomes.

Then there’s the cell’s plasma membrane, recently, and unexpectedly, implicated in autophagosome formation by David Rubinsztein of the Cambridge Institute for Medical Research in the United Kingdom and colleagues. The team’s original goal was to track down the molecular partners of a protein present on young phagophores. They discovered that the protein latches onto another protein that helps engineer endocytosis, a process in which a cell imports material through pockets in the plasma membrane. That molecular link suggested that endocytosis feeds membrane to the autophagosome. When the researchers halted endocytosis, the number of autophagosomes in cells dropped by about 30%.

Five papers support four sources of autophagosome membrane—some people might call those results inconsistent. Yet many researchers say the field is moving toward an inclusive explanation. “What we have learned is that everybody was right,” says cell biologist Ana Maria Cuervo of Albert Einstein College of Medicine in New York City. In other words, the cell might draw material for the autophagosome membrane from many sources. That would make autophagosomes unique, with cells building essentially the same structure at several different locations. “There’s no precedent for this kind of mechanism,” Klionsky says. “It’s hard for people to digest,” Lippincott-Schwartz adds.

Why would a cell need multiple sources of autophagosome membrane? It could come down to supply. “There may be such a huge demand for membrane that you have to mobilize it from every place you can,” Klionsky says. Or cells might turn to different sources in certain situations. For instance, they might choose mitochondrial membrane when starving and ER membrane when they need to clean up the cytoplasm. Researchers say the field is poised to start answering questions like these. “I think that there will be a lot more clarity in the next few years,” Rubinsztein says. —MITCH LESLIE

**Does a Gene’s Location In the Nucleus Matter?**

Viewed under the right kind of microscope, a cell’s nucleus resembles a plate of spaghetti. The noodles—chromosomes—appear to be tossed in Alfredo sauce. Yet the sauce is not a smooth cream but chunky, from a variety of subnuclear bodies, each with its own unique chemical makeup. And the randomness of each noodle’s placement is an illusion, says Victor Corces, a cell biologist at Emory University in Atlanta. “The picture that is emerging is that the chef took a long time to arrange the spaghetti in a specific pattern.”

How that pattern in the nucleus and those subnuclear bodies affect gene activity and other cellular functions is an enduring mystery in biology, one that won’t be unraveled soon. “We are at the very beginning of solving this problem,” Corces says.

Yet it’s an important challenge. Changes in the structure within the nucleus may drive differentiation of cells. And in many diseases, including cancer, the nucleus becomes reorganized.

The first reports suggesting that the nucleus was more than a glob of chromosomes actually date back more than a century. Only in the past 2 decades, however, have new technologies begun to truly reveal the workings of its internal structures. The nucleus has compartments composed of RNA and proteins and designated places for each chromosome.

It stands to reason that all this order influences when and how genes work, but pinning down links between their activity and their location within the nucleus has for the most part eluded researchers’ best efforts. “Cells seem to care about where DNA and proteins are within the nucleus,” says Jason Brickner, a cell biologist at Northwestern University in Evanston, Illinois. “The question is why and how.”

As early as 1885, Austrian biologist Carl Rabl suggested that chromosomes had designated spots in the nucleus. Not until a century later did German researchers Thomas and Christoph Cremer indirectly demonstrate the existence of these chromosome territories, as Rabl’s contemporary Theodor Boveri dubbed them. And finally in 1988, a method to
fluorescently label different chromosomes provided clear visual proof.

Many proteins inside the nucleus also have their designated homes. The nucleolus, a mass of proteins and RNA where the cell’s ribosomes are made before export into the cytoplasm, was big enough to be seen with 19th century microscopes. But about a dozen other structures—Cajal bodies, speckles, paraspeckles, PML bodies, and more—populate the nuclear interior, new techniques developed over the past half-century have shown.

Several studies have indicated that the specific location of a gene in the nucleus makes a difference to its activity. In 2008, three groups showed that they could sometimes dampen or enhance the expression of different genes by tethering their DNA to the nuclear periphery. Other work has demonstrated that active genes generally tend to reside near the edges of chromosome territories, while silenced ones lie deep inside them.

A gene’s location with respect to other DNA in the nucleus is also proving important to its activity. In 2002, Job Dekker at the University of Massachusetts Medical School in Worcester and colleagues developed a technology called chromosome conformation capture that has since revealed an extensive 3D network of chromosomal loops that bring distant genes and regulatory DNA into close proximity, possibly affecting gene expression.

A spate of recent techniques that allow researchers to follow the shifting locations of proteins and genes have begun to provide more clues to the importance of the internal structure of the nucleus. “We can also move things around in the nucleus and ask what effect does that have on gene expression,” says David Spector, a cell biologist at Cold Spring Harbor Laboratory in New York. Such work has led to an appreciation of the dynamics of the interior of the nucleus. Chromosomes, for example, can move about 0.5 micrometers in any one direction.

Yet for the most part, links between gene function and nuclear structure are still just correlations. A cell biologist may find that a gene is active if it’s in a certain location in the nucleus or next to a certain body, but it’s hard to say more than that at the moment. And as for diseases in which the structure of the nucleus is altered, “we need to determine if the changes in nuclear organization are a cause or a result” of a condition, Spector says.

Instead of controlling whether a gene is on or off, nuclear location may play a role in more fully activating a gene and making gene transcription and RNA processing more efficient, researchers suggest. A cell that can, say, activate its stress-response genes a little more quickly could have a survival advantage, favoring the evolution of specialized nuclear bodies that facilitate such efficiency.

To pin down the role of nuclear organization, “we have to do more in vivo biochemistry,” says Angus Lamond of the University of Dundee in the United Kingdom. Additional bodies and structures within the nucleus may also need to be isolated and characterized. And individual genes need to be better followed in living cells. These advances are on the horizon, biologists say.

“The field has made enormous progress in the past 20 or so years, and the technologies are now in place to allow us to really break this [field] open in the next 10 to 15 years,” Spector says. “It’s a very exciting time in nuclear cell biology.”

—ELIZABETH PENNISI

Despite past cell biology success (see page 1048), Günter Blobel of Rockefeller University isn’t content to rest on his laurels. In terms of the cell, “the number of things we don’t know is staggering,” he says. The biologist is now tackling what he considers the “biggest mystery” in the cell: how the nuclear pore complex, which Blobel calls the cell’s “largest and most versatile transport structure,” handles shuttling ions, proteins, RNAs, and ribosomes in or out of a nucleus. Below are a few more mysteries suggested to us that could keep cell biologists working long hours.

Where am I? In complex animals, cells specialize, forming many different tissues and cell types. But to behave appropriately, cells must know exactly where they are in a multicellular organism, and details of this cellular GPS are unclear.

By a nose. Many kinds of cells detect and migrate toward (or away from) tiny gradients of chemicals in their environment. How “cellular noses” operate with such sensitivity remains to be sniffed out in most circumstances.

Follow me. How do groups of cells migrate? Cell-cell adhesion often suppresses cell migration, but there are many instances in development and at other times when cells move en masse.

Complex question. After decades of work on the issue, cell biologists are still arguing about how newly synthesized proteins move across the membranes of the Golgi apparatus. Two main models dominate, but the technology needed to settle the question isn’t quite ready.

The vault’s secret. Still dismissed as unimportant by many biologists nearly 3 decades after their discovery in the cytoplasm of many kinds of cells, barrel-shaped protein particles dubbed vaults contain RNAs of unknown function inside. Like several other strange RNA-protein particles in the cell, what vaults do remains a riddle.

Long-distance chatter. Neurons project long axons to talk to distant colleagues, but biologists have observed in vitro that other cell types also create lengthy extensions, known by various names such as cytomes or membrane nanotubes, to connect with distant cells. What these apparent links do remains unresolved (Science, 15 April, p. 312).