Bench to Bedside

These stories describe NIGMS-funded medical research projects. Although only the lead researchers are named, science is a team sport, and it's important to recognize that many researchers work together to carry out these studies.

Frogs Fighting Cancer

You might be surprised to learn that a carnivorous amphibian from Africa is helping scientists fight cancer. It's true—a clawed frog with the Latin name *Xenopus laevis* is teaching researchers about the genetics of Fanconi anemia, a rare, inherited condition that increases susceptibility to some forms of cancer.

Molecular biologist **Maureen Hoatlin** of the Oregon Health and Science University School of Medicine in Portland and her collaborator **Karlene Cimprich** of Stanford University in California used *Xenopus* eggs as incubators to understand how various genes and proteins might be involved in Fanconi anemia.

MICHAEL REDMER

Even though the enzymes that copy DNA as our cells grow and divide are extremely accurate, mistakes sometimes occur. Fortunately, repair proteins detect and fix virtually all of the errors. Researchers suspect that in the case of Fanconi anemia, a part of this DNA repair machine may be faulty.

The scientists showed that normal versions of the Fanconi anemia proteins do, in fact, prevent the accumulation of DNA errors in frog egg extracts. They think the proteins probably perform the same protective role in human cells.

That's because frog egg cells perform many of the same biochemical functions that human cells do.

Since *Xenopus* eggs are easy to grow and manipulate, scientists can use them to study DNA replication in a way that's difficult to do with mammalian cells. That quality is especially useful for Fanconi anemia research, because cells naturally stockpile the Fanconi proteins and others in preparation for the firestorm of DNA copying that occurs soon after an egg is fertilized.
—*Sarah Goforth*

Marking Multiple Sclerosis

Multiple sclerosis (MS)—a chronic, often disabling disease affecting the brain and spinal cord—can be notoriously difficult to diagnose.

In MS the immune system attacks the protective coverings of nerves. These coverings, called myelin sheaths, normally speed electrical signals between nerves and organs. As the sheaths erode, however, people with MS can develop serious problems with movement, vision, and speech.

For the more than 10,000 Americans who will develop MS each year, spotting the disease promptly offers a chance for early treatment.

With that goal in mind, neurologist **Avindra Nath** and pharmacologist **Robert Cotter**, who both work at the Johns Hopkins School of Medicine in Baltimore, Maryland, searched for chemical markers of the disease in the fluid that surrounds the brain and spinal cord.

The researchers used a lab technique called mass spectrometry that can find a single type of protein in a complex mixture like spinal fluid. They examined this fluid in 29 people who had either MS or pre-MS symptoms and then compared the proteins found in their samples to the proteins found in spinal fluid taken from people with other conditions that impair neurological function.

Nath and Cotter discovered a single protein that was a lot more common in those with MS. If further studies confirm the protein's link to the disease, the work could lead to a simple test to diagnose MS much earlier than is currently possible.—*S.G.*

Vitamin B12 Explained

Without enough vitamin B12, people can get sick with anemia or other illnesses. B12, which helps keep red blood cells healthy, is also a key ingredient in the building blocks of DNA.

We get the vitamin through our diet, either in animal protein containing the vitamin or in certain fortified foods like breakfast cereals. Strict vegetarians are at risk for illnesses caused by too little B12, as are people in countries where meat is scarce and nutrient-fortified foods aren't available.

B12 deficiency can also be a problem for older adults, whose bodies are sometimes less able to absorb the vitamin from food. Some studies even suggest a lack of B12 may contribute to Alzheimer's disease.

Researchers have studied vitamin B12 for decades, and the determination of its complicated structure earned English chemist Dorothy Crowfoot Hodgkin the 1964 Nobel Prize in chemistry. In addition, for years scientists have been studying how B12's elaborate chemical structure is assembled inside cells.

Yet some mysteries remain, and a big step toward solving them comes from the discovery of bacteria that can't synthesize B12 normally.

In the course of research to understand how bacteria cause disease, biologist **Graham Walker** of the Massachusetts Institute of Technology in Cambridge found that the bacteria he was studying were not behaving as expected.

Following up on this surprising observation, Walker learned that the bacteria were a mutant strain missing a key gene that is essential for B12 synthesis. He's now investigating whether B12 plays a role in bacteria-host interactions that can lead to infections in people.—*S.G.*

Genes Affect Breast Cancer Drug Benefit

A common treatment for breast cancer is tamoxifen, which works by blocking the hormone estrogen from fueling tumor growth. But some people don't benefit from the drug, and new research shows that their genetic make-up plays a role.

Clinical pharmacologist **David Flockhart** of the Indiana University School of Medicine in Indianapolis discovered that of the roughly 210,000 people who develop breast cancer each year, about 10 percent have a genetic trait that causes them to metabolize, or break down, tamoxifen differently than others.

Because the drug is less effective in people with this trait, they have twice the chance that their cancer will return.

Finding this genetic link to drug response means that doctors could soon test a person's genes to predict response to tamoxifen and adjust prescriptions accordingly.—*S.G.*

Mechanical Ventilation Protocol - Inflammation and the Host Response to Injury

In patients with ALI or established ARDS (PaO_2/FiO_2 ≤300 or PaO_2/FiO_2 ≤300, respectively, with bilateral pulmonary infiltrates) aim for the following within 24 hrs of meeting criteria:

- Initial tidal volumes may be set at 8 mL/kg predicted body weight (PBW); tidal volumes should be reduced by 1 mL/kg at intervals of <2 hours until the tidal volume =6 mL/kg.
  Tidal volume calculations are based on predicted body weight as follows:
  For males: PBW (kg) = 50 + 2.3 [height (inches) – 60]
  For females: PBW (kg) = 45.5 + 2.3 [height (inches) – 60]
- PaO_2 55-80 mm Hg or SpO_2 88%- 95%. FiO_2/PEEP ratio should be ≤5 and PEEP must be ≤35 cm H_2O
- pH 7.25-7.45 with RR <35 and $PaCO_2$ ≥25. HCO_3 infusion may be given if necessary. If pH < 7.15 then Vt may be increased by 1 mL/kg to pH ≥7.15 and target plateau pressures (see below) may be exceeded
- Plateau pressures (PP) ≤30 cm H_2O. Reduce Vt to no less than 4 mL/kg. If Vt <6 mL/kg and PP <25 then increase Vt until PP= 25-30 or Vt = 6 mL/kg

Patients not meeting ALI/ARDS criteria can be ventilated using the mode, rate and tidal volume chosen at the treating physician's discretion.

RONALD MAIER

Setting Standards

Emergency room doctors are famous for their ability to improvise under pressure. But the same creativity that allows doctors to cope with chaotic circumstances can actually work against efforts to determine which treatments are most effective.

That's where establishing standards of care for clinical research comes in. Setting guidelines for specific medical treatments can reduce the number of variables in research that involves patients, enabling physician-scientists to more clearly understand the impact of interventions.

Such standards are already in place for many medical situations. Yet the treatment of patients with severe burns or other critical injuries varies widely from ER to ER. This confounds research to determine the best treatments for individual patients, whose bodies may react to injury, and respond to treatment, differently.

Recognizing this problem, a large team of scientists and doctors working to improve the care of severely injured patients banded together to develop a set of standardized treatment procedures.

As a result of this effort, doctors across the country can follow the same procedure for a given situation, advancing the research that ultimately improves patient care. In a step in that direction, the team has developed treatment summaries that fit on index cards and can be downloaded from the Internet for use as a bedside reference.

The team members acknowledge that, over time, the guidelines may need to be adjusted to reflect new research findings.—*S.G.*