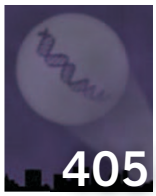
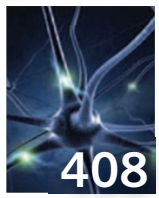
Channeling hope:
Targeted cystic fibrosis drugs move closer to the clinic



Mutant hero:
Reverse mutations can have life-saving consequences



Seizing insight:
Epilepsy and autism share intriguing overlap

Nuclear leak reinforces need for drugs to combat radiation

Last month, in the aftermath of Japan's 9.0-magnitude earthquake and subsequent tsunami, evacuation centers surrounding the crippled Fukushima Daiichi Nuclear Power Station stockpiled nearly a quarter-million doses of potassium iodide as a preventative measure against radiation poisoning. These pills protect people from the long-term risks of thyroid cancer associated with chronic radiation exposure, but they do little to guard against the ill effects of high-dose radiation toxicity.

Unfortunately, no drugs are currently approved to treat the extreme radiation sickness that plant workers or emergency personnel may experience. Yet, thanks to investment from the US government, several candidate compounds might soon be available in the event of another nuclear catastrophe.

The Project BioShield Act, passed by Congress in 2004, and the Pandemic and All-Hazard Preparedness Act, signed into law two years later, allotted billions of dollars in funding for research into medical countermeasures to be used in the case of nuclear, chemical and biological attacks. These government awards include more than $500 million for the treatment and prevention of so-called acute radiation syndrome (ARS), the extreme radiation sickness associated with exposure to high doses of ionizing radiation over a short period of time.

In addition to terrorism, nuclear plant disasters are a leading cause of ARS. The 1986 explosion at Ukraine's Chernobyl plant, for example, caused 134 confirmed cases of ARS, accounting for almost one third of the reported incidences of the disease worldwide (*Health Phys.* **93**, 462–469, 2007). As *Nature Medicine* went to press, engineers in Japan were making headway in containing leaks at the Fukushima site and seemed to have averted a meltdown. But radiation at the plant had already spiked to dangerous levels, forcing hundreds of exposed emergency workers to temporarily evacuate.

If any of these workers are diagnosed with ARS, their treatment options currently are limited to antibiotics, blood transfusions and fluid supplements that deal with the symptoms of the disease. Physicians also sometimes administer cancer drugs that help the immune system rebound, but these drugs must be given in medical facilities. Now, however, researchers are developing biologics and small molecule drugs that be used in the field to stem radiation's ill effects.

One of the lead candidates—a drug called CBLB502 being developed by Cleveland BioLabs of Buffalo, New York—binds an immune protein called Toll-like receptor 5 to activate a cell survival pathway. In unpublished data from rodent and monkey models, the drug, which is derived from a protein found in the flagella of *Salmonella* bacteria, remained "very efficacious" up to 48 hours after exposure, according to Cleveland BioLabs' chief scientific officer Andrei Gudkov.

The US Food and Drug Administration (FDA) granted the compound fast-track status in July 2010, and, backed by a $15.6 million award from the US government, the company has already tested CBLB502 in 150 healthy volunteers in two phase 1 safety studies. According to spokesperson Rachel Levine, the company plans to submit an approval application by the end of next year.

Meanwhile, the Pennsylvania-based biotech Onconova is advancing its own compound, Ex-RAD, which works by inhibiting proapoptosis proteins such as p53 as well as downstream regulators of cell death. According to Ramesh Kumar, Onconova's president and CEO, the small molecule has been tested for safety in more than 50 people, with few adverse effects reported.

Fresh blood

Instead of trying to block cell death, some companies are developing treatments that simply replace the cells lost to radiation. For example, the California-based biotech Cellerant Therapeutics has a system based on blood progenitor cells that can form mature infection-fighting and clotting blood cells upon infusion by intravenous drip. Importantly, these cells—dubbed CLT-008—do not produce the mature T cells that cause immune reactions, so just one product can be stored to serve as a temporary therapy for all ARS-affected individuals. What's more, unlike many other ARS drug candidates, CLT-008 seems to work up to a week after exposure. "By that time, you'd actually have a chance to evacuate people out of the city," notes Mark Whitnall, head of the radiation countermeasures program at the Armed Forces Radiobiology Research Institute in Bethesda, Maryland.

Asahi Shimbun via Getty Images

Public exposure: Radiation drugs needed.

Other products in development include Osiris Therapeutics' Prochymal, a stem cell therapy derived from adult bone marrow for the treatment of organ damage resulting from radiation exposure, and Aeolus Pharmaceuticals' AEOL-10150, a small molecule that reduces oxidative stress and inflammation associated with radiation exposure. Both companies have government contracts that exceed $100 million.

Notably, all of these experimental ARS treatments are being developed under the FDA's 'animal rule', which provides a path to drug approval for life-threatening agents where human efficacy trials aren't ethical or feasible. This regulatory route still requires safety testing in humans, large-scale efficacy studies in animal models and a good understanding of the drug's mechanism of action. But the exact requirements of the rule—which was introduced in 2002—remain unclear to many drug developers. "The mechanism is very vague," says Kumar.

What's more, even after these drugs gain approval, another hurdle remains for companies to make money. "Who are the eventual buyers and consumers of this drug?" Kumar asks. "That is a bigger question."

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