Targeted toxins are tiny molecular mercenaries. They are designed, using recombinant DNA technology and imagination, to seek out cancer cells and kill them. Two components are needed: a molecular machine to find cancer cells, and another molecular machine to do the killing. Fortunately, evolution has done much of the work for us. We merely have picked the pieces that we need and combined them in an appropriate fashion.

To seek out cancer cells, we look to our own body for the means. Our immune system is our most powerful and flexible method for recognizing molecules, so it is an obvious place to look for a cancer-targeting molecule. Antibodies may be selected and constructed to bind to nearly any molecule on the surface of cancer cells. The trick is to find a molecule that is expressed solely on cancer cells, and not on non-cancer cells. Another option is to pick a receptor on the cancer cell surface, and then use its normal mate as the targeting molecule. Many of these pairs, such as growth factors and their receptors or interleukins and their receptors, have been employed.

To kill cancer cells, we look to nature. Plants and bacteria protect themselves with powerful toxins that kill human cells. Typically, these toxins are non-specific: they will seek out just about any human cell and kill it. The best toxins for our needs, such as ricin from castor beans (Fig. 1) or the bacterial Pseudomonas enterotoxin, are enzymes. These toxins are so powerful that a single molecule can kill an entire cell. They sneak inside cells and then wreak havoc, jumping from one molecule to the next and destroying them. This is far more effective than poisons like cyanide and arsenic, which do battle one-on-one, one toxin molecule for each of our own molecules.

By linking these two pieces, we create a targeted toxin (Fig. 2). We must pay heed to a few details. Most of these toxins have built-in targeting functions that must be disabled, so that the toxin does not attack cells indiscriminantly. Also, the targeting molecule must be carefully chosen to minimize binding to non-cancer cells. This is per-
Figure 2. Immunotoxins in action. In this illustration, the cell membrane of a leukemic B-cell is shown green, with the blood above and the interior of the cell below. An immunotoxin, composed of ricin attached to a Y-shaped antibody, is shown in red. The antibody portion binds to a cell-surface receptor, such as a CD molecule specific to the surface of B cells. The bound immunotoxin then enters the cell inside a coated pit, which is pulled into the cell by many three-armed clathrin triskelions. Ultimately, the toxin is released into the cytoplasm, where it inactivates ribosomes throughout the cell.

Perhaps the most difficult challenge—picking just the right targeting molecule for the given cancer type. The approach is showing great promise—when the appropriate components are linked together, targeted toxins provide significant clinical anticancer activity.

Additional Reading