With chemotherapy, we search for weaknesses in cancer cells and attack them where they are most vulnerable. Since cancer cells are dividing at an abnormally fast rate, many drugs target the processes of cell division. Cancer cells often communicate (or do not communicate) in odd ways, which provides other sensitive spots for treatment. The best drugs are those that attack features that are unique to cancer cells. We rarely reach this ideal, but with L-asparaginase, we get close.

Our cells require a steady supply of the amino acid asparagine to build proteins. Most cells use the enzyme asparagine synthetase (Fig. 1, top) to make their own asparagine. The enzyme takes aspartate and adds an amine, forming the characteristic amide group of asparagine. Thus, most cells can make their own supplies of asparagine and do not need to obtain it in their diet. Some blood cells, however, rely instead on the blood for their supply of asparagine.

**Figure 1.** Asparagine synthetase (top) is a large enzyme composed of two identical subunits. The one shown here is from bacteria. It connects an ammonia molecule directly to aspartate to form asparagine. Our own enzyme uses glutamine to provide the amine instead of ammonia. L-Asparaginase (bottom) purified from bacterial cells is used for chemotherapy. This enzyme is composed of four identical subunits. The active sites grip asparagine (red) and use a well-placed threonine amino acid (green) to perform the cleavage reaction. The enzyme is also active with glutamine, cleaving its amino group off at a slower rate.
trusting that there will always be enough and not bothering with making their own.

L-Asparaginase therapy takes advantage of this fact. L-Asparaginase (Fig. 1, bottom) performs the opposite reaction: it takes asparagine and pulls off its amine, releasing aspartate and ammonia. It is normally involved in balancing the levels of amino acids for use in protein synthesis. However, if a large dose of this enzyme is introduced into the blood, it will circulate and continually break down all the asparagine that it finds, ultimately starving the cells that rely on the blood-borne supply.

L-Asparaginase is a remarkably effective therapy for those specific cases where blood cells become cancerous, such as in acute lymphoblastic leukemia. The enzyme cuts off the supply of asparagine in the blood, and the cancer cells die as they become unable to build their proteins. However, the use of a large protein as a drug poses several challenges. Our immune system is designed to destroy large, multisubunit proteins, so L-asparaginase is rapidly cleared from the blood in a day or so. Also, the immune system occasionally responds too strongly to a large influx of foreign protein, leading to allergic reactions. These problems may be addressed in part by hiding the enzyme from the immune system, for instance by covering the enzyme with a coat of neutral polyethylene glycol molecules.

**Additional Reading**