ACCADEMIA NAZIONALE DEI LINCEI

**APERTURA ANNO ACCADEMICO 2009-2010**

13 novembre 2009

**PROF. IRA H. PASTAN**

**PREMIO INTERNAZIONALE "ANTONIO FELTRINELLI" 2009 PER LA MEDICINA**

# *Recombinant Immunotoxins: a New Cancer Therapy*

In normal human development, there is a genetic program that determines how many cells are contained in each organ. In cancer, these genetic controls are damaged so that certain cells begin to multiply without restraint. Until the 1960's, cancer treatment involved surgical removal of these cells or destruction of them by x-ray.

With the rapid development of the field of organic chemistry, many novel organic compounds were produced, and a few of these were found to be selectively toxic to some types of cancers. But many other cancers did not respond, and raising the dose in order to make the effects of the compounds stronger damaged normal cells, producing undesirable side effects. One way to circumvent toxicity to these normal cells was to find a therapy directed specifically to the cancer cells. Antibodies, which are produced by the immune system to fight off infection, have the potential ability to do this.

It was not possible to make specific antibodies that would react with cancer cells until 1975 when Kohler and Milstein discovered a method to make monoclonal antibodies—antibodies that would react with just one protein. This

discovery created great excitement in the field of cancer therapy and ultimately led to the development of such monoclonal antibodies as Rituxan, which specifically binds to a protein present on the surface of many Lymphomas and Leukemias. The binding of Rituxan to this protein induces the death of a large number of Lymphoma or Leukemia cells and provides great benefit to the patient. And because CD20 is not present on most normal cells, toxic side effects are minimal. Several other antibodies have now been developed that selectively kill different types of cancer cells. But unfortunately, though they do selectively bind to them, most antibodies do not actually kill the cancer cells.

It was quickly realized that a poison could be delivered to the cancer cell by combining it with a monoclonal antibody, and there are now major efforts to do this. But because the number of antibodies that can bind to these cells is small, it is necessary to attach a very powerful poison to it in order to deliver sufficient amounts to kill the cell. Protein toxins made by bacteria and plants are among the most toxic substances we know, and are therefore attractive candidates for this job. We call these proteins, in which antibodies are attached to toxins, **immunotoxins**.

Early efforts in this field involved attaching purified protein toxins to monoclonal antibodies by using chemical linkages. Unfortunately, this approach had several drawbacks and proved unsuccessful. We now use modern recombinant DNA techniques of gene splicing to produce novel chimeric proteins that contain just a small portion of an antibody (called an Fv) attached to a piece of the toxin. The FV binds to the cancer cell, and the toxic portion enters the cell and kills it. We named these new agents **recombinant immunotoxins** to indicate that they are made by **recombinant** DNA techniques: they contain a portion of an antibody made by the **immune** system as well as a portion of a protein **toxin**.

We are currently developing two recombinant immunotoxins, one for hematopoetic malignancies and the other for solid tumors. The first of these, named BL22, targets the CD22 protein that is present on many lymphomas and leukemias. BL22 has produced many complete remissions in drug resistant Hairy Cell Leukemia, but it has shown only low anti-tumor activity in other B cell malignancies where CD22 expression is lower than in Hairy Cell Leukemia. We have used protein engineering to improve the activity of BL22, and this new form of BL22 has just entered clinical trials in chronic lymphocytic leukemia, lymphoma and acute lymphoblastic leukemia in children.

The other immunotoxin is named SS1P and targets the mesothelin protein, highly expressed on mesothelioma, lung, pancreatic and ovarian cancer. We have already shown that SS1P can be given safely to patients with mesothelioma and ovarian cancer, and in addition we have observed modest anti-tumor activity. Based on laboratory studies which show that SS1P is much more active when combined with chemotherapy, we have begun treating mesothelioma patients with chemotherapy and SS1P. The initial clinical results look promising.