Innovations

Cancer vaccines made to order

Antigenics L.L.C.

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The uncontrolled growth of tumor cells sets them apart from normal cells. Current chemotherapy hits the primary difference — an increased level of proliferation — with a particularly blunt sledgehammer. The associated toxicity and collateral damage is massive.

The idea of using the immune system as a more exact weapon has been around since 1893, when William Coley observed cancer regression after erysipelas infection. Perhaps, the thought goes, the immune system can be directed against individual molecular differences present in tumor cells. Early success in animal models was followed by a failure to cross-protect — animals had to be immunized with material prepared from their own tumors — and suspicions that animal models were a poor simulation of human cancers.

Slowly the field of cancer immunotherapy has revived itself. The search for tumor-specific antigens has been long and hard, and many of the therapies being tested now are tissue- rather than tumor-specific. But renewed hope is coming from the use of genomics to define tumor differences. "I think the time is right for these therapies to be taken to the clinic," says Michael Longenecker, senior vice president for research and development at Biomira Inc. (Edmonton, Alberta, Canada).

The number of companies searching for tumor-specific antigens is ever-increasing (Table 1). But Pramod Srivastava, an immunologist at the University of Connecticut and the scientific founder of Antigenics L.L.C. (New York, NY), is spurning the definition of tumor-specific antigens. "There is no reason to believe that those [tumor-specific] molecules exist," he says. Srivastava is sticking with the original observation that protection is often restricted to the animal from which the antigenic material was derived. His proposal is a personalized therapy based on, of all things, heat-shock proteins.

A nasty shock

Srivastava came to immunology with a distinctly different perspective. While others were sorting macrophages and T cells, and scanning with antibodies, he was tackling cancer immunotherapy like a good biochemist. He fractionated. But when he whittled down his protective fractions to a single protein he got a nasty surprise: the magic antigen, over and over again, was a heat-shock protein (hsp). Hsps are well known for their roles in protein folding and recovery from stress, but not for growth promotion and carcinogenesis. Could Srivastava have been so wrong?

If every cancer is different, why not try a personalized vaccine?

"It was extremely depressing," he says. "I entered the winter of my discontent, not knowing where to go from there. I kept looking for where I had gone wrong." Quickly he looked for, and failed to find, variations between hsp genes in normal and cancer cells. Hsps were such unlikely candidate tumor promoters that "it was clear there had to be a contaminant," he says. But nothing was visible on gels. "By deduction I argued it was peptides," says Srivastava. "At the time I was attacked a lot because I had no data about the peptides."

But the data came. In 1993, Srivastava found that the critical ingredient was, indeed, peptides. Most of the peptides are identical between normal and cancer cells, but a critical few differ. Srivastava believes that the high mutation rate in cancer cells generates random changes in a random assortment of proteins. Most of the changes are not related to the process of transformation and are unique to each cancer. But rare divergent peptides, when bound to and presented by hsps, can be detected as immunogenic by immune cells. This presentation route is potent because antigen-presenting cells have specific receptors for the hsps and, as Srivastava found in 1995, the cells' intracellular trafficking directs the peptides onto products of the major histocompatibility complex (MHC), ready for display to the rest of the immune system.

Presumably this complicated pathway has not evolved for the benefit of cancer immunologists. Rather it may be a primitive early warning system — the original signal that cell lysis and death are occurring. "It's a bit like blood — if you see it on the floor something bad has happened," says Srivastava. After first evolving to deal with stresses to single prokaryotic cells, hsps may have become an intercellular alert signal for multicellular organisms. As the most abundant intracellular proteins, hsps are certainly well suited to the job, and their peptide-binding means that they can carry the antigens of invading infectious agents with them.

Making a product

In 1997, Srivastava prepared doses of the hsp gp96 from mouse tumors. When given back to the donor mice, the gp96 (with peptides still attached) reduced by tenfold the number of metastases from a large tumor. If the large mass was removed first, otherwise untreated mice died of micrometastases, but additional gp96 treatment resulted in symptom-free survival in 80% of the mice.

Before Antigenics could start treating people they needed an efficient means of producing a personalized therapy. In the current

Table 1

Some of the other companies investigating cancer immunotherapy.

Company	Technology and status of trials
StressGen Biotechnologies Corp.	Mycoplasma Hsp fused to human papilloma virus antigen, in phase II trials for treatment of anal and cervical dysplasia.
Corixa Corporation	Lysed melanoma cells plus an adjuvant, now approved for use in Canada.
Therion Biologics Corporation	Gene therapy with carcinoembryonic antigen for colorectal and lung cancer, melanosome antigens including tyrosinase for melanoma, PSA for prostate cancer, and mucin for breast cancer. Partnership with Pasteur Mérieux Connaught.
Biomira Inc.	Synthetic mimic of altered mucin carbohydrate in phase III trials for breast cancer. Mucin peptide vaccine (against epitope exposed by altered carbohydrate metabolism) in phase II for small cell lung cancer.
ImClone Systems Incorporated	Ganglioside mimic in phase III for small cell lung carcinoma.
Genzyme Molecular Oncology	Gene therapy with melanoma antigens in phase I/II.

procedure, a patient's tumor sample is rushed by courier to Antigenics, where it is passed, in a ten-hour procedure, through a blender, a centrifuge, an affinity column and an ion-exchange column. The final preparation of hsps and associated peptides is 80–95% pure. This preparation is then administered to the patient over the following weeks.

Immunizing with such a poorly defined set of peptides raises concerns about reproducibility. "That has regulatory implications," says Biomira's Longenecker. "Big pharma won't touch that." Srivastava says that regulatory agencies "have not encountered a procedure like this but they have been extremely helpful and cooperative. They have been extremely understanding about the novelty of it."

Meanwhile, human studies are tending to confirm findings in animals that the treatment does not induce its own problems. "We do not break tolerance or induce tolerance," says Srivastava. "We're immunizing with the whole gemish of molecules but we only get a specific response. The prospect of doing harm is not there based on the human data thus far."

Srivastava notes that the immune system is constantly exposed to self peptides without generating autoimmunity. Of course, it also fails to generate immunity to the tumor antigens without the help of the immunization procedure. This failure may be a result of immunosuppressing factors produced by many tumors, and the inaccessibility of hsps trapped inside the tumor cells. Once the hsps are administered as a treatment, they become a highly efficient natural adjuvant. "The receptor [for hsps] makes it possible," says Srivastava. "That is the magical element."

Antigenics is now in phase I and II trials for treatment of a number of different cancers, and financing of further trials will be helped by the company's successful public offering on February 4. Early trial results have been promising. For now the choice of cancer type reflects issues such as the relative inadequacy of current treatments and the logistics of patient recruitment. But Srivastava's long-term plans are more ambitious. "Once we've proven that it works, we'll essentially expand to every tumor type," he says. "Experimental work suggests there is no limitation."

The search for the ultimate antigen

Antigenics is in a crowded field (Table 1), but its methods are unique. "The whole Antigenics approach is based on the idea that each person's cancer has its own antigenic signature," says cancer immunologist Drew Pardoll (Johns Hopkins University, Baltimore, MD). "In most mouse models that seems to be the case. The jury is still out for human cancer."

Other companies are immunizing with specific antigens, but "ultimately the antigens that will be most useful have not really been identified," says Pardoll. "Most of the vaccines in play don't use true tumor-specific antigens," he says, relying instead on tissue-specific antigens, or antigens from viruses associated with the cancer. In fact, Pardoll says, "true tumor-specific antigens are unlikely [to exist]. But the prospects for getting antigens that are highly expressed in tumors are pretty good. I'm optimistic there will be a pretty good [therapeutic] window."

Genzyme Molecular Oncology (Framingham, MA) is using high-throughput methods to identify promising antigens — after harvesting T cells from tumors they test the T cells for binding to a combinatorial library of peptides. Bruce Roberts, Genzyme's senior director for gene therapy, agrees that the search for specific mutations is largely a waste of time. "I think the thing that is more reliable is the upregulation of proteins," he says. "Cancer cells will figure out a way to switch on a protein that will give them a growth advantage," he says, and the poor regulation of that switch can create an excellent target. Thus the Her2 protein is found in normal epithelial cells, but its gross overexpression in some breast cancers makes the tumors susceptible to Herceptin, a humanized monoclonal antibody made by Genentech, Inc. (South San Francisco, CA).

Perhaps there are single antigens that will make good targets, and perhaps the only viable approach will be individualized therapy. For the consumer, at least, it is heartening that both approaches are being pursued vigorously.

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