The cancer vaccine roller coaster

Bruce Goldman & Laura DeFrancesco

The cancer vaccine field is littered with promising products that failed to show clinical efficacy. Could it finally be on the verge of a first US approval?

If any field epitomizes the boom and bust cycles of biotech, it would be cancer vaccines. Over the years, numerous tumor immunotherapies have gone through rounds of early-stage successes, only to fail in phase 3 clinical trials. Experts point to many reasons for the failures, from "jumping the gun" before enough was known about the biology or the therapies to letting business considerations—going for low cost and short time lines—trump science; what Peter Bross, chief of clinical evaluations at the US Food and Drug Administration's (FDA's) Center for Biologicals Evaluation and Research calls companies simply not doing their homework. Put these problems together with poorly designed clinical trials of heterogeneous cancer patient populations with late-stage disease, add a lack of familiarity of the regulatory authorities in assessing tumor vaccine products, mix in manufacturing scale-up headaches and the resulting recipe is all but toxic to investors. As Bruce Booth of Atlas Ventures (Waltham, MA, USA) puts it, realizing the potential of cancer vaccines is "full of complexity."

But some researchers and analysts are keeping the faith, hoping that a more comprehensive understanding of tumor immunology will lead the way to more fruitful approaches (**Table 1**). Several promising phase 3 programs are nearing completion, so 2009 may well be the year of the cancer vaccine. "There have been other technologies that failed in their first iteration…. As long as modifications are made and something new comes out of it, I think you'll generate interest," says Reni Benjamin, senior biotech analyst at Rodman and Renshaw (New York).

In the meantime, the question is whether there is enough money to support the approach in the coffers of biotechs or coming from the pharmaceutical industry, which has been burned repeatedly (**Table 2**). And what lessons from the ever-growing list of failures—and some possible successes—will inform future practitioners in the field?

Bruce Goldman is a freelance writer living in San Francisco, and Laura DeFrancesco is Senior Editor, Nature Biotechnology.

Beginnings

Cancer vaccinology is predicated on the notion of awakening the immune system to the presence of cancer by presenting it with antigens associated with tumor cells. Once the immune system is roused, the concept is that it would be capable not only of mounting a sustained bodywide search for similarly suspicious cells, but also of retaining a memory of the abnormal antigens, permitting a renewed, rapid assault should the tumor recur.

The notion that the immune system could be enlisted to launch an attack on an existing tumor has been around at least since the late 1800s, when the New York City–based physician William Coley noticed that metastases at several sites regressed in a sarcoma patient after she developed a bacterial incision-wound infection. Coley's attempts to exploit this discovery were handicapped by the then-crude state of knowledge. But to this day, remnants of this approach can be seen in the use of general immune stimulants, like attenuated bacteria (e.g., mycobacterial components in Bacille Calmette Guerin, BCG) and interleukins, in treating bladder cancer and melanoma, respectively, as well as their inclusion in combination therapies in literally hundreds of clinical trials.

The discovery and identification of tumor-associated antigens, which now number in the hundreds (see **Table 3** for some examples), stimulated a second approach to cancer vaccines, an approach still highly visible among the therapies being tested today. Roughly half of ongoing clinical trials enlist a tumor-associated antigen or collection of antigens (**Fig. 1** and **Table 4**). Many such trials have ended in failure, which we now know is because these antigens muster only weak immune responses because they are normal human proteins merely overexpressed on tumor cells (to which the patient would be tolerant) or they too closely resemble such proteins or they elicit only a weak response from the patient's compromised immune system. It is now known that multiple costimulatory signals are needed to generate a robust T-cell response against a tumor-associated antigen; if these signals are not supplied, T-cell anergy and peripheral tolerance follows. Such tepid immune responses are not nearly what would be needed to eradicate advanced cancers, which early on accounted for most patients treated in clinical trials. Contemporary trials using tumor-associated and more promising tumor-specific antigens now use various immune stimulatory molecules, such as granulocyte macrophage colony stimulating factor (GM-CSF), and generalized adjuvants, such as keyhole limpet hemocyanin (KLH), to boost the response.

Many approaches have explicitly tried to engage cell-mediated immunity either using isolated antigen-presenting cells (APCs) or attempting to stimulate them *in situ* (**Fig. 2**). Techniques were developed for extracting dendritic cells, a major APC, loading them up with tumor antigens in various ways and reintroducing them into patients. Early attempts here failed, and in some cases, actually led to poorer outcomes than if the individual had been untreated, as immature dendritic cells, it was later learned, were as likely to suppress the immune system as to stimulate it. Methods for characterizing the right types of dendritic cell and other APCs are now being worked out, and it's become clearer how to activate these cells through cytokines, such as GM-CSF, to optimize antigen presentation (one such immunotherapeutic candidate in late-stage

Table 1 Selected early stage cancer vaccine programs

Company (location)	Product	Composition	Indication	Trial phase
Antigen Express (Worcester, MA, USA; a subsidiary of Generex Biotechnology, Toronto)	Her-2/neu breast cancer vaccine	Her-2/neu epitope peptide conjugated at N terminus to the C terminus of the key moiety of the MHC class II–associated invariant chain (Ii protein) containing a four–amino-acid (LRMK) modification	Breast cancer	Phase 2
Apthera (Scottsdale, AZ, USA)	NeuVax	Immunopeptide (E25) from Her-2/neu administered together with GM-CSF	Early-stage breast cancer	Phase 1/ 2
Argos Therapeutics (Durham, NC, USA)	AGS-003	Autologous dendritic cells loaded with total RNA from resected tumors	Renal cancer	Phase 2
Immunocellular Therapeutics (Los Angeles, CA, USA)	ICT-107	Autologous dendritic cells treated with tumor-specific peptides from 6 antigens expressed on glioblastomas	Brain cancer	Phase 1
Immunotope (Doylestown, PA, USA)	IMT-1012	Peptide vaccine containing 12 tumor-associated peptides discovered through proteomics, including A-kinase anchor protein 9, midasin (MIDAS-containing protein RAD50), talin 1, vinculin vimentin and centrosome-associated protein 350	Advanced ovarian and breast cancer	Phase 1
Pevion Biotech (Bern, Switzerland)	Pevi-Pro	Influenza virosomes expressing three Her2/neu epitopes	Breast cancer	Phase 1
Vaxon Biotech (Paris)	Vx-001	A peptide vaccine comprising the cryptic peptide human telomerase reverse transcriptase ($TERT_{572}$) and its HLA-A*0201-restricted modified variant ($TERT_{572Y}$)	NSCLC	Phase 1

Table 2 Selected deals in the cancer vaccine sector

Date	Company (location)	Partner (location)	Product	Deal terms	Status
12/08	Oncothyreon	Merck KgaA	Stimuvax for NSCLC	$13 million for manufacturing rights	Phase 3
11/08	Argos Therapeutics	Private investment	RNA-loaded autologous dendritic cells (and other immunotherapies)	$35.2 million for series C funding	AGS-033 for renal cell carcinoma in phase 1/2
4/08	Cell Genesys	Takeda (Osaka)	GVAX for prostate cancer	$50 million up front, plus milestones worth up to $270 million	Collaboration terminated after GVAX trial stopped (12/08)
3/07	Oxford Biomedica	sanofi aventis (Bridgewater, NJ, USA)	TroVax (allogeneic modified vaccinia strain Ankara expressing 5T4 (OBA1) antigen) for renal cancer	$690 million in royalties and milestones	Phase 2 vaccinations stopped due to excess deaths (7/08), analysis continues of vaccinated patients
12/04	CancerVax	Merck/Serono	Canvaxin for melanoma	$25 million cash up front, $12 million equity purchase; equally share development costs, up to $253 million in milestones	Partnership terminated (11/05); CancerVax merged with Micromet in 2006
4/03	Biovest	Accentia	BiovaxID (autologous idiotypic determinant from B-cell lymphoma conjugated to KLH and combined with GM-CSF) for non-Hodgkin's lymphoma	$20 million; Accentia owns 81% of Biovest	Phase 3
7/01	IDM Pharma (Irvine, CA, USA)	sanofi aventis	Uvidem (autologous dendritic cell vaccine loaded *ex vivo* with tumor antigens derived from resected tumor) for melanoma	$33 million	Partnership terminated (1/08)

clinical trials, Dendreon's Provenge (Seattle; sipuleucel-T) for prostate cancer, may prove to be among the first therapeutic cancer vaccines to receive FDA approval; **Box 1**).

Just in the past five years, information has surfaced, pointing to a whole new problem with cancer immunotherapy—active immunosuppression in the tumor microenvironment. Tumors have been long suspected to evade immune detection by, for example, Darwinian evolution of cells whose defining surface antigens are suppressed or creating positive pressure gradients that make it harder for circulating immune cells to penetrate them (**Fig. 3**). But now, it has emerged that in addition to evasion, tumors actually can induce local immunosuppression through the stimulation of regulatory T cells or the recruitment of myeloid-derived suppressor (MDS) cells. The former, primarily through their production of transforming growth factor (TGF)-β, inhibit $CD8^+$ cytotoxic T cells (CTLs), T helper 1 (T_H1) cells and natural killer (NK) cells, which are the main mediators of immune surveillance against tumors. MDS cells, a mixed population of relatively immature myeloid cells, also suppress cellular immune responses primarily by producing arginase 1 and nitric oxide synthase 2A.

One means of potentiating the power of cancer vaccines and unleashing the immune system, according to leading academics, would be to counteract tumor-mediated immune suppression. This could be accomplished by targeting the regulators of the regulators, so to speak. For example, several molecules have been identified (e.g., CTL antigen 4, CTLA-4) that engage with regulatory T cells. Animal studies have shown that blocking such interactions, either with monoclonal antibodies (mAbs) or gene knockouts abrogates immune suppression. Indeed, several dozen clinical trials, according to the US National Institutes of Health (http://www.clinicaltrials.gov), are currently underway using mAbs against CTLA-4 in combination with chemotherapy or vaccines.

Table 3 Examples of tumor-specific antigens

Tumor-specific, shared antigens
Cancer only
MAGE-3
NY-ESO-1
TRAG-3
Expressed in some normal tissues
WT-1
PRAME
SURVIVIN-2B
Overexpressed in cancer
Her-2
MUC-1
Survivin
Mutated, unique
p53
α-actinin-4
Malic enzymes

Source: GSK

Immunotherapy's many faces

Cancer immunotherapy means different things to different people. In the case of cancers that are known to express viral antigens (e.g., cervical cancer and some melanomas that express human papilloma virus), immunotherapy takes the form of a classic immunoprotective, prophylatic vaccine like smallpox or polio where a viral antigen is presented to the immune system. In those cases where cancers overexpress a particular endogenous surface antigen (e.g., Her-2 in some breast cancers or CD-20 in some lymphoma cells), mAbs directed against those surface markers (Genentech's Herceptin (trastuzumab) and Genentech's and Biogen-Idec's Rituxan (rituximab), respectively) provide passive immunity, which can keep a tumor in check for a while. There are many such mAbs for various cancers under development. As currently applied, these mAbs are not preventive but rather therapeutic, though Herceptin has been approved for ever earlier stages in breast cancer, where it might, at least in theory, protect against recurrences by preventing metastases from taking hold.

Active immunotherapies, on the other hand, are designed to incite the individual's own immune system to mount a response to an antigen or group of antigens exclusive to or predominantly associated with the patient's tumor. They can take the form of peptide/protein vaccines or cellular vaccines.

The former type of vaccine generally falls into two categories. The first is based on shared peptide or protein antigens that occur commonly in a particular cancer or group of cancers (epidermal growth factor receptor (EGFR) vIII, for example, which is found in 30–40% of glioblastomas, or MAGE-3, which is expressed on many lung tumors). The proteins can be injected directly or expressed on attenuated virus particles, or nonproliferative bacterial or yeast cells (**Box 2**). An alternative approach is to isolate antigens from an individual patient and present these back to the person in a form designed to elicit immune surveillance, such

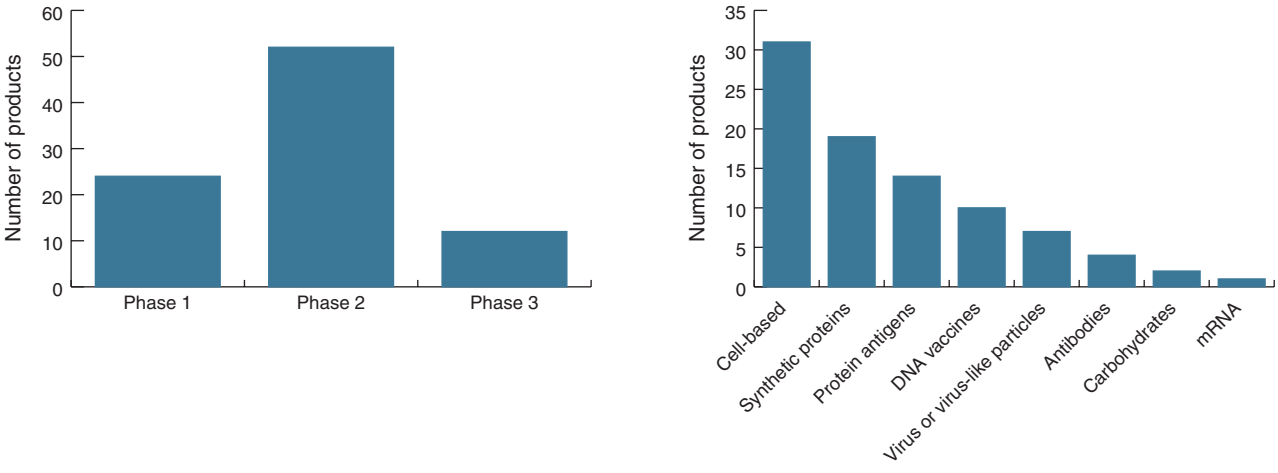

Figure 1 Cancer vaccine types. (Source: Tufts Center for the Study of Drug Development)

as vaccines designed to stimulate responses against antibody idiotypes found on lymphomas or the use of heat shock proteins to present unique tumor peptides (**Box 3**).

Cellular cancer vaccines can also be divided into two broad groups: allogeneic or autologous. The former, so-called 'off-the-shelf' vaccines, are usually collections of tumor cell lines, administered as aggregates to present several potential tumor antigens to the patient's immune system. Autologous whole cells, on the other hand, are isolated from, and returned to, individuals after some *ex vivo* manipulation to activate or induce maturation of APCs. An example of this type of vaccine would be a product based on isolation of APCs from a patient that is engineered to express some soluble factor (or factors) that generates an immune response to a common antigen (e.g., prostate-specific antigen in the case of prostate cancer, or p53/telomerase more generally (**Box 1**)).

Compared with cellular vaccines, peptide vaccines have the advantage of being similar to existing vaccine approaches used for decades in immunization programs against infectious agents. Such vaccines are less tricky to manufacture on a large scale than cellular vaccines. In 2002, for example, the FDA placed a hold on CancerVax's (Carlsbad, CA, USA) phase 3 trial of cellular vaccine Canvaxin because of manufacturing concerns. What's more, the longer clinical history and widespread use of peptide/protein vaccines means that regulators are more familiar with their oversight and less likely to raise issues unanticipated by product sponsors.

The perilous path

Cancer vaccines represent a relatively small portion of the oncology drugs in commercial development. The Tufts Center for the Study of Drug Development (Boston) reports that only one-fifth of oncology biologic therapeutics in company pipelines are vaccines (**Fig. 4**).

Table 4 Selected cancer vaccines in late clinical trials

Company (location)	Product	Description	Indication	Trial phase
Whole-cell-based autologous cells (personalized)				
Avax Technologies (Philadelphia)	M-Vax	Autologous cell vaccine in which patient tumor cells are treated with the hapten dinitrophenyl	Metastatic melanoma with at least one tumor to create vaccine	Phase 3
Dendreon	Provenge	Autologous dendritic cells exposed *ex vivo* to fusion protein combining prostate alkaline phosphatase and GM-CSF	Asymptomatic, metastatic hormone-refractory prostate cancer	Phase 3
Geron (Menlo Park, CA, USA)	GRNVAC1	Autologous dendritic cells transfected with mRNA for human telomerase and a portion of lysosome- associated membrane protein (enhances antigen presentation)	AML in remission	Phase 2
IDM Pharma	Bexidem	Autologous interferon-γ-activated macrophages (monocyte-derived activated NK cells).	Superficial bladder cancer	Phase 2/3
	Uvidem	Autologous dendritic cell vaccine loaded *ex vivo* with tumor antigens derived from resected tumor	Melanoma with M1a or M1b stage disease and/or in-transit lesions; stage III and IV melanoma	Phase 2
	Collidem		Colorectal cancer	Phase 1/2
Introgen Therapeutics (Austin, TX, USA)	INGN 225	Dendritic cells treated with an adenovector carrying the human p53 gene	Advanced metastatic SCLC Breast	Phase 2
MolMed (Milan)	M3TK	T cells bioengineered to express MAGE 3 tumor antigen	Metastatic melanoma	Phase 2 (enrollment halted)
Northwest Biotherapeutics (Bethesda, MD, USA)	DC-Vax Prostate	Dendritic cells loaded with recombinant prostate-specific membrane antigen (PSMA)	Hormone-dependent, nonmetastatic prostate cancer	Phase 3
	DC-Vax Brain	Dendritic cells loaded with tumor extract	Newly diagnosed glioblastoma multiforma requiring surgery, radiation and chemotherapy	Phase 2
Prima Biomed (Sydney, Australia)	CVac	Dendritic cells primed with a mucin-1 and a mannan-fusion protein adjuvant	Late-stage ovarian cancer	Phase 2
Whole-cell-based allogeneic tumor cells (off-the-shelf)				
Cell Genesys	GVAX pancreatic	Two allogeneic cultured cancer lines, irradiated and bioengineered to secrete GM-CSF.	Metastatic pancreatic cancer	Phase 2
	GVAX leukemia	One allogeneic leukemia cell line irradiated and bioengineered to secrete GM-CSF	Newly diagnosed AML, chronic CML and myelodysplastic syndrome	Phase 2
NovaRx (San Diego)	Lucanix	Four non-small cell lung cancer cell lines carrying antisense oligonucleotides against transforming growth factor β-2	Advanced NSCLC	Phase 3

Table 4 Selected cancer vaccines in late clinical trials (continued)

Company (location)	Product	Description	Indication	Trial phase
Onyvax (London)	Onyvax-P	Three human cell lines representing different stages of prostate cancer	Hormone-resistant prostate cancer	Phase 2
Unique-antigen-based (personalized): purified peptide or protein				
Antigenics	HSPPC-96 Oncophage	Heat shock protein vaccine purified from autologous tumor cells	Recurrent glioma	Phase 2 (investigator-initiated trial)
			Resected renal-cell carcinoma (RCC)	Phase 3 (completed)
Biovest International	BiovaxID	Tumor-specific idiotype conjugated to keyhole limpet hemocyanin, plus GM-CSF	Mantle cell lymphoma Indolent follicular B-cell non-Hodgkin's lymphoma	Phase 2 Phase 3
Shared antigen (off-the-shelf): purified protein or peptide				
Apthera (Scottsdale, AZ, USA)	NeuVax	Immunogenic peptide derived from the Her-2/neu protein plus GM-CSF	Early-stage Her-2-positive breast cancer	Phase 2/3
CellDex	CDX-110	A 14-amino-acid segment of a mutated EGFR	Glioblastoma multiforme	Phase 2/3
Cytos Biotechnology (Schlieren, Switzerland)	CYT004-MelQbG10	Modified fragment of the Melan-A/MART-1 protein coupled to the carrier QbG10	Advanced-stage melanoma	Phase 2
Generex Biotechnology	Ii-Key/HER2/neu cancer vaccine	Peptide vaccine containing Ii-Key modified Her-2/neu protein fragment	Node-negative breast cancer	Phase 2
GlaxoSmithKline Biologicals (Brussels, Belgium)	MAGE-A3 antigen-specific cancer immunotherapeutic	Liposomally packaged cancer vaccine against MAGE-3 antigen	Metastatic MAGE-A3-positive melanoma NSCLC following surgery	Phase 3 Phase 3
IDM Pharma	IDM-2101	Nine CTL epitopes from four tumor-associated antigens, including two proprietary native epitopes and seven modified epitopes and one universal epitope (a source of T-cell help)	NSCLC	Phase 2
Immatics Biotechnologies (Tuebingen, Germany)	IMA901 IMA910	Peptide vaccine comprising multiple fully synthetic tumor-associated peptides	Renal cancer Colorectal cancer	Phase 2 Phase 1/2
Norwood Immunology (Chelsea Heights, Australia)	Melanoma cancer vaccine	Melanoma-specific peptides gp100 and MAGE-3	Melanoma	Phase 2
Oncothyreon	Stimuvax	Liposomal vaccine containing a synthetic 25–amino-acid-peptide sequence from MUC-1	Stage III NSCLC	Phase 3
Pharmexa (Hoersholm, Denmark)	GV1001	Recombinant protein vaccine targeting human telomerase reverse transcriptase, plus GM-CSF	Pancreatic Liver Lung	Phase 3 Phase 2 Phase 2

AML, amyotrophic lateral sclerosis; CML, chronic myelogenous leukemia.

Although modern cancer vaccine development dates back to the 1980s, none has been approved in the United States (though there are five products on the market elsewhere; **Table 5**). Thus, the rate of approval of cancer vaccines lags far behind other biologics—as of 2006, seven of twelve vaccines in phase 3 clinical trials had entered clinical study a decade earlier.

To date, an estimated 7,000 people have participated in late-stage clinical trials of active cancer immunotherapies. These have largely been an exercise in frustration, as candidates—including a few that looked quite good in early trials—have fallen by the wayside in pivotal phase 3 trials. Some recent losers that have gone quietly into the night:

- PANVAC (Therion Biologics, Cambridge, MA, USA), an off-the-shelf vaccine consisting of attenuated poxvirus carrying genes encoding two tumor-associated antigens (carcinoembryonic antigen and mucin 1, MUC-1) and three immunostimulatory molecules (intracellular adhesion molecule 1, B7.1 and lymphocyte function–associated molecule 3) for use in advanced pancreatic cancer, failed to meet clinical endpoints after promising early trials, leading the company to close its doors and file for bankruptcy protection in December 2006.

- Theratope (Biomira, Edmunton, AB, Canada; now Oncothyreon, Seattle), an off-the-shelf vaccine, consisting of a synthetic mimic (STn-crotyl) of the tumor-associated, *O*-linked epitope of MUC-1 (STn-serine), tethered to an immunostimulatory protein (KLH) and delivered along with an adjuvant from Seattle-based Corixa (Detox-B, an oil droplet emulsion containing monophosphoryl lipid A and cell wall skeleton from *Mycobacterium phlei*) for use in metastatic breast cancer, showed no improvement in either time to progression or overall survival. The company hasn't completely abandoned the target; in partnership with Merck KGaA (Darmstadt, Germany), it has developed a "more sophisticated" approach for eliciting a T-cell response, according to Marita Hobman, director of intellectual property

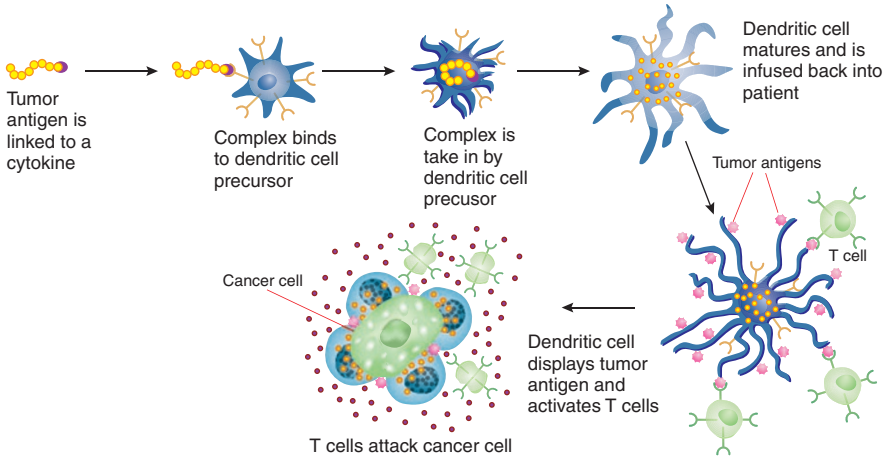

Figure 2 Dendritic cells that attack cancer. (Source: National Cancer Institute)

management and business development at Oncothyreon.

- Canvaxin (CancerVax, now MicroMet, Munich), an off-the-shelf mix of three irradiated melanoma cell lines bearing over a dozen defined tumor-associated antigens, plus an adjuvant (BCG) for use in stage III melanoma, yielded worse outcomes in treated patients than in controls, unlike earlier trials in which patients had been more carefully selected for human leukocyte antigen (HLA) alleles correlating with better outcomes. After Canvaxin failed, CancerVax merged with Micromet, which is developing passive immunotherapies using mAbs against various tumor antigens.

- GVAX (Cell Genesys, S. San Francisco, CA, USA), an off-the-shelf, whole-cell vaccine, consisting of infusions of cells from existing prostate cancer lines engineered to express GM-CSF for use in hormone-refractory prostate cancer, yielded excess deaths in treated patients versus controls, leading to abandonment of the trial.

Although there is a clear preponderance of off-the-shelf vaccines in this group of failures, the fate of individualized vaccines has not necessarily been much better. Two companies with vaccines targeting antibody idiotypes associated with tumors—Favrille (San Diego) and Genitope (Fremont, CA, USA)—both shut down their trials when their products failed to reach statistical significance, essentially ending their programs in late 2008.

Getting it right

A cancer vaccine has to jump through several hoops, says Johns Hopkins University

Box 1 A whole-cell vaccine nears approval?

Dendreon is developing a whole-cell-based candidate, Provenge, for metastatic, hormone-resistant, prostate cancer (HRPC). The vaccine is a patient-specific, vaccine produced by incubating an individual's own blood, enriched for dendritic cells and other APCs with a recombinant fusion protein composed of prostatic acid phosphatase (PAP) and GM-CSF.

Although not tumor specific, PAP is highly tissue specific. Although expressed in the majority of prostate tumors, PAP is only minimally expressed in tissues other than the prostate gland, says Dendreon's Frohlich, who is chief medical officer. It is immunologically distinct from acid phosphatases found in other tissues. Because HRPC patients' prostates have already been surgically removed or irradiated, autoimmunity doesn't pose much of a practical problem.

The question of whether tolerance to this antigen can be broken was addressed in a preclinical study performed by Dendreon investigators and published in 2001 (ref. 2), in which their product induced autoimmune prostatitis in rats (a clear sign of immune mobilization against the antigen). This convinced Dendreon that it could raise an immune response in a clinical setting as well. A phase 1/2 trial published in 2000 (ref. 3), demonstrating strong antigen-specific T- and B-cell responses to the approach, was consistent with this finding.

That year, Dendreon launched two trials of Provenge, each with about 120 asymptomatic patients. As Frohlich explains, it was then believed that asymptomatic patients would progress more slowly than symptomatic patients, buying time for the initially subtle effects of immunotherapy to kick in before the disease reached a stage that was intractable to immunotherapy.

In the interest of getting a fast readout, Dendreon had picked as its primary endpoint time to progression (TTP)—assumed to be a reasonable surrogate for survival. But Dendreon was to find out otherwise. During the course of the trial, medical opinion leaders decided that overall survival is a better endpoint than TTP, which carries a subjective component. However, the trial continued with the previously agreed upon endpoint of TTP.

This proved ironic. When the first trial was unblinded, TTP had missed statistical significance ($P = 0.05$) by the barest of margins, ($P = 0.052$) whereas overall survival analysis demonstrated a 41% reduction in the risk of death, with a high level of statistical significance ($P = 0.01$).

But survival was not a prespecified primary endpoint. And whereas an outside advisory committee voted 13–4 for approval, in April 2007, the FDA instead insisted on another trial to confirm the survival results.

In the aftermath of the FDA's failure to approve Provenge despite clear signs of efficacy, angry patient advocates peppered the agency with letters of protest. But proponents of strict adherence to trial protocols liken the argument that a therapy ought to be approved on the basis of an unplanned analysis to moving the goal posts[4].

Dendreon is soldiering on with a new 512-patient trial with the primary endpoint of survival. Preliminary results, announced in October 2008, demonstrated a 20% reduction in the risk of death in the treatment arm, only slightly less than the 22% reduction, which the company believes is necessary to achieve statistical significance. Final results are due later this year, and if Provenge makes the grade, it may yet turn out to be the first whole-cell-based active cancer immunotherapy approved by the FDA. But many years, many tens of millions of dollars, and perhaps more than a few lives might have been saved had the Dendreon's phase 3 trial not been marred by an unfortunate choice of an endpoint.

oncologist Hyam Levitsky, co-inventor of GVAX and member of the board of the cancer vaccine company Antigenics (New York). "In an existing tumor, the body has already been exposed to those antigens, so there may already have been an initial immune response. But very often, the immune system is defeated and rendered tolerant to the antigens that the vaccine is targeting. A successful vaccine has to overcome this tolerance, and that's not trivial." Moreover, Levitsky says, the vaccine frequently has to work in what can be a hostile environment. "The tumor has essentially taken over and altered the landscape, stealing various attributes of the normal immune system to turn down immune response."

The antigens to use in a vaccine to circumvent the challenge of breaking immune tolerance without generating autoimmunity should be tumor specific. But such antigens are rarely found, says Jeffrey Weber, head of the Comprehensive Melanoma Research Center at the H. Lee Moffitt Cancer Center (Tampa, FL, USA). "These are few and far between. You can discover any number of mutated, tumor-specific antigens, but you seldom find any that turn up on more than 5% of tumors of any given type." And even when you find one, he says, that doesn't mean it will be highly immunogenic.

In practice, cancer antigens targeted by active immunotherapies have more often been tumor associated: overexpressed on tumors, but nonetheless present at lower frequencies in normal tissues. In trials of vaccines based on these antigens, the necessity of breaking tolerance—for example, by pairing the selected antigen with a powerful adjuvant—has clashed with the need to avoid an excessive immune assault on healthy tissues where the antigen also resides. "You can vaccinate the hell out of somebody against melanoma self-antigens that are overexpressed on cancer, and you won't induce severe side effects—or any immune response to speak of," says Weber. "But if you administer the same vaccine along with one dose of anti-CTLA-4 antibodies, you can induce life-threatening autoimmune colitis or skin rash or hepatitis."

Another problem plaguing trials of cancer immunotherapies has been the intractability of the cancers targeted. In theory, any cancer should be amenable to immunotherapy, but in practice, only a few cancers have received most of the attention, at least historically. Melanoma, which early on was found to have tumor-specific antigens, has been targeted frequently using the protein or peptide approach—mostly without success, as no really tumor-specific melanoma antigens have yet been exploited, only tumor-associated antigens. But those cell-based approaches, in which autologous proteins or extracts are used for priming, require access to a sufficient tumor mass. This more or less excludes melanoma or even breast cancer, where the tissue tends to be fibrotic and where tumors tend to be diagnosed increasingly early, while they are still relatively small.

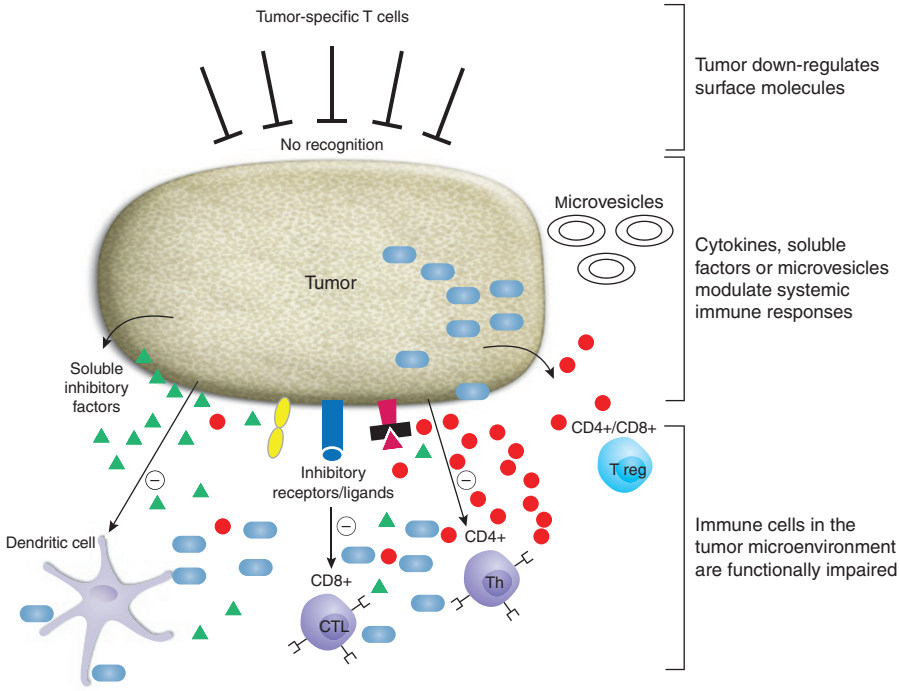

Figure 3 Tumor cell's interactions with the immune system. (Reprinted from Whiteside, T.L. Immune suppression in cancer: effects on immune cells, mechanisms and future therapeutic intervention. *Semin. Cancer Biol.* **16**, 3–15, 2006, with permission from Elsevier.)

Recognizing that the immune response takes time to develop, some vaccine developers have turned to slow-growing prostate cancer or kidney tumors, where the time to progression is longer. And then, of course, greater prevalence of certain tumor types, such as lung, create a large patient pool with which to populate clinical trials, whereas the dearth of decent treatments for these indications speaks most loudly to the need for ramped-up clinical experimentation.

Certainly, the tendency to use individuals who are in advanced cancer stages has made proof of clinical efficacy more difficult to achieve. Of course, individuals with late-stage disease, who have often been treated with other therapeutic agents that have failed, tend to be more available. And sponsoring companies prefer this population because they expect that positive treatment effects will be observed more quickly in advanced-stage patients than in early-stage or fully resected ones. But decades' worth of clinical trials of cancer vaccines conducted across multiple tumor types not surprisingly suggest that immunotherapies are more likely to work best in patients with earlier-stage, less-aggressive tumors[1] or in individuals whose tumor burden has been reduced to the microscopic level by surgery or chemotherapy.

"It's at this level of microscopic disease where I think cancer vaccines are most likely to succeed," Levitsky says. "Well over 50% of the common cancers can be treated into a state of minimal residual disease. What we lose patients to is typically not the inability to get the disease into that minimal state, but rather the inability to completely eradicate the residual component." All too often, a seemingly excised tumor returns. "From a public-health point of view," he says, "the impact of an effective immunotherapy—delivered at the point of minimal residual disease—that could wipe out the last traces of a tumor, would be truly staggering. Ironically, that's probably the most difficult time to demonstrate efficacy in a clinical trial."

Standard measures of a cancer therapy's efficacy—tumor shrinkage or growth arrest—are worthless for patients with minimal residual disease. How can you score tumor shrinkage if the patient no longer appears to have a tumor?

Box 2 Pharma perseveres with off-the-shelf vaccines

Off-the-shelf vaccines have the advantage that they can be produced in bulk, making them more attractive to big pharma than individualized vaccines that are tailored to each patient. One such vaccine, CDX-110, developed by John Sampson at Duke University (Durham, NC, USA) and Amy Heimberger at MD Anderson Hospital (Houston), has been in-licensed by Celldex Therapeutics (Phillipsburg, NJ, USA, which merged with Avant Immunotherapics, Needham, MA,USA, in late 2007) and has attracted the attention of Pfizer (New York).

The vaccine targets EGFRvIII (a 14-amino-acid segment of a mutated EGFR) that not only appears solely on glioblastoma cells, but also has never been expressed in any other kind of cell at any time in development. Its biological activity is clearly germane to the tumor's aggressiveness, so knocking it out should directly impair the tumor's viability. It is located on cell surfaces, making it accessible to attack. And, because it's a mere peptide rather than a full-sized protein, it's simple to manufacture.

EGFRvIII is found on 30–40% of glioblastomas, an aggressive form of brain cancer, which even when surgically excised, irradiated and exposed to chemotherapy, typically recurs within six months. The mutant receptor is characterized by a 267–amino acid deletion within its extracellular domain, which changes the molecule's configuration, locking it into a perpetual signaling mode that drives relentless cell replication. Thus its 100% tumor specificity: no cell with elevated expression of this mutant receptor could possibly be normal. In addition, the deletion creates a novel splice junction, which CDX-110 spans.

The dearth of effective therapies for glioblastoma makes it possible to test the new vaccine as a front-line therapy in patients who have just had their tumors thoroughly resected. In a phase 2 trial (ACTIVATE), 22 patients with EGFRvIII-positive glioblastomas were given standard treatment, followed by serial injections of the vaccine. Time to progression (TTP) more than doubled to more than 14 months compared with 6.4 months for a set of EGFRvIII-positive historical controls. Overall survival improved commensurately, proving surprisingly enduring, with about two-thirds of the injected patients surviving for two years, more than one-third for at least three years and a fifth still alive after four years. In a second phase 2 study (ACT II), in which 23 subjects received the vaccine simultaneously with chemotherapy, patients' median TTP reached 16.6 months, and median survival time 33.1 months—a point at which, historically, all EGFRvIII-positive patients would long since have died.

This jump in long-term survival is puzzling, as EGFRvIII-positive glioblastomas typically contain large numbers of EGFRvIII-negative cells—a status that ought to shield them from the vaccine. One possible explanation says Sampson, is that EGFRvIII-positive cells are stem cells for the tumor, another possibility is that EGFRvIII-positive cells either make other tumor cells more proliferative or harder to kill. Chuck Baum, senior vice-president and head of the oncology development at Pfizer (New York), which licensed the rights to the vaccine in April, 2008, suggests that part of the apparently powerful effect CDX-110 has on even EGFRvIII-negative tissue may be due to a phenomenon called 'epitope spreading': as tumor cells lyse, they release their internal contents into the surrounding medium, giving local APCs access to previously occult tumor antigens (e.g., mutant intracellular proteins). "You can get a broadening response with time, and eventually end up with a more effective immune response than the one you started with," Baum says.

Avant and Pfizer are working on a large phase 2/3 trial, with preliminary results expected by mid-2009. With the aggressive lethality that characterizes glioblastoma, those results shouldn't be long in coming. "It's not going take 20 years to find out if the vaccine worked," says Heimberger.

Another vaccine in the pipeline that targets an antigen that is both tumor specific and present in enough patients' tumors to allow an off-the-shelf, mass-produced vaccine is GlaxoSmithKline (GSK) Biologicals (Brussels) MAGE-3 (melanoma antigenic epitope 3). Since October 2007, the vaccine-producing division of the pharmaceutical giant has been recruiting non-small-cell lung cancer (NSCLC) patients for a large phase 3 clinical trial. The 400-center study, spanning 33 countries, will be the largest-ever in lung cancer and, for that matter, the largest-ever study of an active cancer immunotherapy for any indication.

Vincent Brichard, senior vice-president for cancer immunotherapeutics at GSK, says that about 40% of all NSCLC tumors express MAGE-3, which is expressed only transiently during fetal development. In adults, MAGE-3 expression is confined to the testes, opaque to immune surveillance so that tolerance doesn't develop.

This makes it possible to conceive of an off-the-shelf immunotherapy targeting the widely shared antigen. The GSK approach uses the entire 360 amino acid–long MAGE-3 protein to maximize the number of epitopes. GSK's vaccine bolsters the T-cell immunogenicity of its recombinant MAGE-3 protein by packaging it in liposomes, which Brichard says enhances delivery to APCs and by administering the vaccine with an adjuvant mix that has been optimized to produce a potent T-cell response to MAGE-3. This immunostimulatory potion combines GSK's own adjuvant, monophosphoryl lipid A (MPA), with QS-21, a complex lipid mix licensed from Antigenics, and CpG oligonucleotide (a Toll-like receptor 9 agonist developed by Coley Pharmaceutical Group, a Canadian biotech purchased in late 2007 by Pfizer).

QS-21 is also known to induce a strong antibody response. Antibodies could conceivably play a role against even an intracellular molecule such as MAGE-3 to the extent that lysed tumor cells release entire, undegraded protein molecules that could be targeted by antibodies. The resulting antigen-antibody complexes would, in turn, be highly available for uptake by APCs.

At the annual meeting of the American Society of Clinical Oncology in Chicago in June 2008, GSK presented the results of a randomized, 182-patient phase 2 trial of MAGE-3. Early-stage NSCLC patients who had had their tumors completely resected and then received several injections of the MAGE-3 vaccine had roughly one-third the recurrence rates of those given placebo injections, results mirroring those from several other MAGE-3 tests.

GSK's huge phase 3 trial—whose primary endpoint, like that of the recent phase 2, is disease-free survival—departs from its phase 2 counterpart in two respects: first, about half of the patients in the trial will receive chemotherapy before vaccination, a regimen never tested in phase 2 (Brichard notes, though, that the trial's large size leaves plenty of statistical power for an independent analysis of those eschewing chemotherapy). Second, there has been a change in the adjuvant mix's composition—the addition of CpG —since the phase 2 trial. Brichard says the new mix proved more immunostimulatory compared with the earlier formulation in another head-to-head trial, but it is into such small cracks that surprises can flow.

An alternative is to monitor recurrences or, more accurately, deaths among treated versus untreated patients. But that can take a long time. In renal-cell carcinoma, for example, the median time to recurrence for patients who have had their tumors fully resected and show no signs of residual tumor is 6.8 years.

Further complicating cancer immunology trials is the fact that each approach tends to be novel, creating trial-design and regulatory issues. A designated antigen can be either tumor associated or tumor specific, and tumor-specific antigens can be shared by many patients or unique to each patient. Shared antigens offer the prospect of off-the-shelf vaccines, with attendant economies of scale. But they also often lack tumor specificity, thus incurring the drawbacks of immune tolerance.

Whereas the failed Biomira vaccine, Theratope, is an example of a highly purified, well-defined antigen with a single epitope, CancerVax's Canvaxin candidate was a whole-cell mixture with multiple antigens, some of them undoubtedly not even identified, let alone characterized. The former approach runs the risk of eliciting too narrow an immune response. The latter may trigger unwanted cross-reactions, says Weber, and the difficulty of assessing its potency in any given person poses regulatory issues.

The roughly 30 different active cancer immunotherapies now in late-stage clinical trials (**Table 3**) also differ in their methods of manufacture and the indications for which they're being tested. Trial designs differ greatly, too. Among the variables: early- versus late-stage disease trade-offs, different endpoints and widely divergent timelines due to differential prognoses in different indications.

"Any therapy that's totally novel and first in class is a double-edged sword," says Mark Frohlich, senior vice president of clinical affairs and chief medical officer of Dendreon. "On the one hand, there's a lot of excitement from patients and regulators who want to approve something that's new and different. On the other hand, if it's a new product, those same regulators also need to make sure they're doing everything to ensure public safety and establish a solid precedent." Frohlich speaks from experience, having undergone an epic regulatory ordeal with Dendreon's cell-based prostate-cancer vaccine Provenge (**Box 1**).

For all these reasons, clinical trials of active cancer immunotherapies are high-stakes

Box 3 Personalized vaccines—a viable option?

Oncophage, a personalized vaccine developed by Antigenics, consists of an extract containing heat-shock protein-peptide complexes prepared from an individual patient's excised tumor. This approach is based on work by company co-founder Pramod Srivastava, now director of the University of Connecticut's Center for Immmunotherapy of Cancer and Infectious Diseases (Farmington, CT, USA), showing that APCs have receptors for heat shock proteins. This provides a pathway whereby unique tumor-specific antigens (the products of random mutations in rapidly dividing cancer cells) could become immunogenic. In principle, this preparation can target any tumor type, but in practice, its application is limited to tumors of sufficient size to obtain enough material.

In several early-stage trials involving individuals with advanced disease over several indications, there were striking cases of complete tumor regression as well as instances of partial shrinkage or stable disease, although the overall results were unspectacular. Given the virtual absence of side effects, Antigenics forged ahead, launching phase 3 trials in advanced metastatic melanoma[5] and renal-cell carcinoma (RCC)[6].

The melanoma trial proved difficult, as excised tumors were often too small to produce enough vaccine and subsequent clinical development was halted. But subjects with early-stage disease who got ten or more injections saw a big survival improvement over controls receiving currently approved treatments.

In the RCC trial, initiated in 2000, more than 700 patients whose tumors had been resected were randomized to either Oncophage or the current standard of care, which consists of 'watchful waiting' as there are no approved, effective treatments for such patients. As reported in *The Lancet* last July[6], an analysis triggered in November 2005 by the accumulation of a specified number of inidivduals whose disease had progressed found no statistically significant difference between treated and untreated patients for either relapse-free survival or overall survival. Disturbingly, though, the independent review committee also determined that 40% of the patients originally logged by principal investigators in the multicenter trial as having had recurrences, in reality had residual disease before treatment began. Excluding these patients from the analysis diluted the power of the study, which would have run much longer had these classification errors not been made. "One of the reasons the trial did not meet its endpoints relates to the fact that the data were evaluated prematurely," says Christopher Wood of MD Anderson, who was the principal investigator and author of the *Lancet* paper.

In March 2007, study investigators conducted a second analysis of more mature data, using an RCC classification system that hadn't existed when the Oncophage trial had begun. Vaccinated patients classified as "intermediate stage" in this new system (a subset consisting of stage 1–3b, which overlapped but was not equivalent to the older system's "early stage" group) enjoyed a statistically robust ($P = 0.026$) relapse-free survival benefit, suffering recurrences at just over half the rate of untreated patients—as well as a trend toward statistically significant improvement in overall survival ($P = 0.126$).

"What needs to be done, and hopefully will be done," Wood says, "is another trial that focuses on that earlier-stage group. But the amount of money to do that would be enormous, because you're narrowing down the population even further, so it would be hard to accrue. And because they're earlier-stage disease, recurrences are less frequent, so it could take ten years before you reach statistical significance."

The direct costs of the seven-year phase 3 trial exceeded $60 million, says Garo Armen, Antigenics' CEO. "That, plus the necessary maintenance of our manufacturing, quality control, quality assurance and manufacturing-related research functions throughout the trial, came to $250 million."

Armen says about 500 trial patients will continue to be followed up for relapse-free survival and overall survival for another three years, at a cost to the company of $1.5 million. Meanwhile, in April, 2008, Oncophage was approved in Russia, where a large number of the phase 3 patients had been recruited. Antigenics has also filed with the European Medicines Agency (EMEA) for approval in Europe. The EMEA policy of granting conditional approval would allow Oncophage to be launched commercially in Europe provided Antigenics commits to conducting

(continued)

Box 3 Personalized vaccines—a viable option? (continued)

a full-sized confirmatory phase 3 trial. Such an option is not available in the United States.

Like Antigenics's Oncophage, BiovaxID, developed by Biovest International, (Worcester, MA, USA) a majority-owned subsidiary of Accentia Biopharma (Tampa, FL, USA), is personalized and targets antigens that are both tumor specific and unique to each patient. But its construct is entirely different. The vaccine's lead indication is indolent follicular non-Hodgkin's lymphoma, in which a particular cancerous clone of antibody-producing B-lymphocytes proliferates.

The BiovaxID concept began in the Stanford University laboratory of Ron Levy and was pushed forward by Larry Kwak, who took the idea with him to the National Cancer Institute (NCI), where a phase 2 trial was initiated in 1995. Kwak now heads the lymphoma division at MD Anderson and consults for Biovest.

All the constituent cells of a B-cell lymphoma produce antibodies with identical idiotypes characteristic of the cancerous cells' hyperproliferative common ancestor. Those malignant B-cells also carry the idiotype on their surfaces. BiovaxID is an anti-idiotype vaccine consisting of hybridoma-produced identical copies of those overabundant (and, therefore, easily characterized) antibodies conjugated to the immune stimulant KLH. The vaccine is administered along with GM-CSF.

In 1999, favorable phase 2 results led the NCI to initiate a double-blind phase 3 trial, which Biovest took over under a Cooperative Research and Development Agreement. In the trial, 76 patients in remission following standard chemotherapeutic regimens, received serial BiovaxID injections. Importantly, only subjects who had sustained a complete remission after chemotherapy were included, because previous studies showed that patients in complete remission mount a better immune response (humoral and/or cellular) compared to those who do not, which also correlates with clinical outcome, according to Angelos Stergiou, chief medical officer and head of clinical research at Biovest.

This summer, Biovest reported that BiovaxID treatment prolonged disease-free survival by over one year, from 30.6 months for control subjects to 44.2 months for BiovaxID-treated subjects, ($P = 0.047$). The announced results will be formally presented at the next American Society of Clinical Oncology Conference in Orlando and will be submitted for peer review. In addition to seeking approval in the United States, the company is approaching regulatory agencies in other countries and plans on launching a compassionate-use program, referred to as Name-Patient Program, for BiovaxID, in parts of Europe early in 2009, according to Stergiou..

The apparent BiovaxID success follows failures of two other nearly identical candidates, advanced by Genitope (Fremont, CA, USA) and Favrille (San Diego), to reach statistically significant results in phase 3 trials over the past year. Like BiovaxID, these were anti-idiotype vaccines conjugated to KLH and delivered with GM-CSF, but Stergiou speculates that the method of preparation of the antibody may be the difference. Both Genitope and Favrille produced their antibodies as recombinant proteins rather than using the hybridoma methodology employed by Biovest.

Another potentially big difference is that in the BiovaxID trial, all vaccinated patients were in a state of complete remission. The other candidates' protocols, in contrast, allowed patients in partial remission—with visible tumor masses—to remain under study. Although this sped enrollment, it may have hindered efficacy.

BiovaxID's approach could, in theory, be applicable to other non-Hodgkin's lymphomas as well as multiple myeloma. But, as a personalized vaccine treatment that must be produced batch by batch for each patient, even the most efficiently manufactured product is likely to be expensive for patients—although Stergiou refuses to put a price tag on the vaccine at the moment.

propositions. Putting a novel approach through its paces among those most likely to benefit—patients who are least ill and for whom obtaining statistically significant results will thus presumably take the most patience—is a costly venture. Even the most sponsor-friendly phase 3 cancer immunotherapy trials—a modest 300-patient study of an easily manufactured, mass-produced off-the-shelf vaccine, in an indication with fast clinical readouts—and associated surgeries, imaging assays and so forth are going to cost about $20 million, according to one knowledgeable company official. With more and larger trials of personalized, more technology-intensive vaccines, the cost soars to hundreds of millions.

The way forward

All segments of the sector—immunologists, entrepreneurs, even regulators—appear to agree that the entrée into cancer vaccines was premature. Thomas Okarma, CEO of Geron (Menlo Park, CA, USA), which has a product in trials, calls early attempts at vaccines "immunological kindergarten." In addition, certain assumptions about the immune system may not be correct. Early failures with cancer vaccines led to the belief that tumors could not generate an immune response, according to Eli Gilboa, at the University of Miami, Florida. In fact, he says, "It appears [tumors] can [generate an immune response] for a time, but they have elaborated mechanisms for avoiding the immune system. Focusing more on how to mitigate tumor-induced immune suppression will be key going forward."

A second assumption that is proving false is that chemotherapy and immunotherapy are incompatible. According to Gilboa, evidence is emerging that some forms of chemotherapy are not incompatible, but in fact can synergize immunotherapy.

Another area of agreement is that we have reached the end of the single-agent era. Key to confronting the two main issues facing vaccine developers—the ability of tumors to induce tolerance and the hostile microenvironment in tumors—are combination therapies, but this creates certain problems, according to Robert Schreiber, cancer researcher at Washington University School of Medicine (St. Louis). "Most companies are locked into using their own products and therefore do not like to use combination therapies. And the FDA is particularly leery of trying too many combinations at once," he says. Schreiber sees a role for university-industry partnerships in getting around this potential logjam. "Once a successful regimen has been identified, there will be many companies that come knocking at the door. Since large-size clinical trials are very expensive, I see a great opportunity for industry and academia/foundations to pair up at this time," he says.

As for cell-based therapies, the jury is still out on whether autologous vaccines will be the ticket or whether there is a place for allogeneic, off-the-shelf ones. Logistics (read 'cost') seems to dictate that only allogeneic vaccines will be

Table 5 Approved and marketed cancer vaccines

Company (location)	Product	Description	Indication	Status
Antigenics	OncoPhage	Heat shock protein vaccine purified from autologous tumor cells	Renal cell carcinoma	Approved in Russia Granted fast track status by US FDA
Biovest International	BiovaxID	Tumor-specific idiotype conjugated to keyhole limpet hemocyanin, plus GM-CSF	Various B-cell–related cancers	Compassionate use in France, Germany, Italy, Greece, Spain and the UK. Granted fast track status by US FDA
Corixa (acquired by GSK in 2005)	Melacrine	Lysate from two melanoma cell lines, Detox adjuvant (proprietary) with monophosphoryl lipid A and mycobacterial cell wall skeleton	Melanoma	Approved in Canada
CreaGene (Seoul)	CreaVaxRCC	Autologous monocytes treated with GM-CSF and IL-4 to create immature dendritic cells activated with tumor extracts plus cytokines	Metastatic renal cell carcinoma	Approved in Korea
Genoa Biotechnologia (Brazil)	Hybricell	Autologous monocytes treated with cytokines and converted to dendritic cells that are fused with patient-derived tumor cells	Various cancers	Approved in Brazil
Vaccinogen (Frederick, MD, USA)	OncoVax	Metabolically active, irradiated, autologous tumor cells with BCG	Colon cancer	Approved in Europe, available in Switzerland Granted Fast Track status by FDA
Mologen (Berlin)	dSlim/Midge	Genetically modified allogeneic (human) tumor cells for the expression of IL-7, GM-CSF, CD80 and CD154, in fixed combination with a DNA-based double stem loop immunomodulator (dSLIM).	Kidney cancer	Orphan drug status granted by EMEA in 2006
Center of Molecular Immunology (Cuba)	CimaVax EGF	EGF conjugated to rP64k	Lung cancer	Cuba, Peru

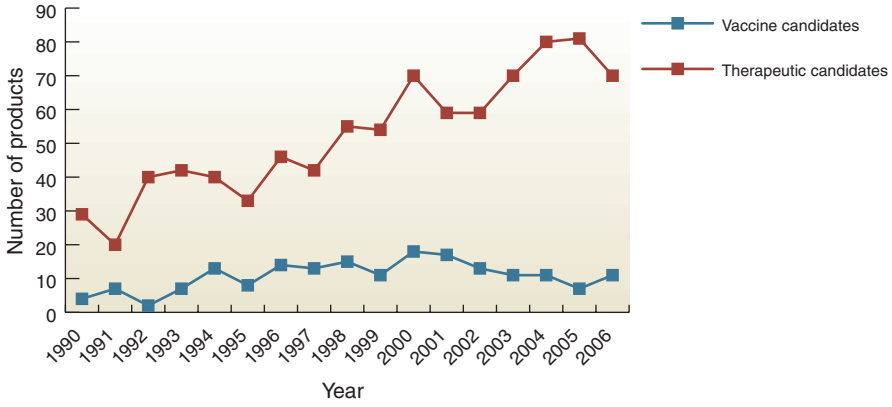

Figure 4 New cancer therapeutics and vaccines entering clinical study per year from 1990 to 2006. (Source: Tufts Center for the Study of Drug Development)

commercially viable, although the evidence to date suggests that it may not be a clinically viable approach.

Even non-cell-based personalized vaccines raise a host of regulatory issues. Is each vaccine a different product? Do vaccines produced for different patients have different immunogenicities? Different cross-reactivities? Different potencies?

The answer might rest in finding more shared, but tumor-specific, antigens, which are in the minority among products in trials today. And down the road, advances in related fields might provide cancer vaccinologists with the tools they need to create off-the-shelf vaccines. For example, Geron, which has an autologous vaccine in trials now, is using this as a proof of concept according to Okarma. The company also has in place the technology for making dendritic cells from stem cells, which would enable the company to prepare an off-the-shelf, activated dendritic cell, something not available at present.

Keith Wonnacott, chief of FDA's cell therapies, joins the chorus of immunologists and academics optimistic that some cancer vaccine will succeed. "We anticipate success, and that lessons will be learned. Much of what has gone on has been helpful. We would love to see success," he says. Whether that optimism is justified, only time will tell.

1. Choudhury, A. *et al. Adv. Cancer Res.* **95**, 147–202 (2006).
2. Valone, FH, *et al. Cancer J.*, **7**, S53–61 (2001).
3. Small, E.J. *et al. J. Clin. Oncol.* **18**, 3894–3903 (2000).
4. Allison, M. *Nat. Biotechnol.* **26**, 967–969 (2008).
5. Testori, A. *et al. J. Clin. Oncol.* **26**, 955–962 (2008).
6. Wood, C. *et al. Lancet* **372**, 145–154 (2008).

Corrected after print 7 June 2010.

Erratum: The cancer vaccine roller coaster

Bruce Goldman & Laura DeFrancesco

***Nat. Biotechnol.* 27, 129–139 (2009); published online 7 February 2009; corrected after print 7 June 2010**

In the version of this article initially published, the Mologen product description in Table 5, page 139, was incomplete and its status incorrectly stated to be compassionate use in India. The product description should have read: Genetically modified allogeneic (human) tumor cells for the expression of IL-7, GM-CSF, CD80 and CD154, in fixed combination with a DNA-based double stem loop immunomodulator (dSLIM). The status should have read: Orphan drug status granted by EMEA in 2006. The error has been corrected in the HTML and PDF versions of the article.

Erratum: Irish bioethics council axed

Cormac Sheridan

***Nat. Biotechnol.* 28, 112 (2010); published online 5 February 2010; corrected after print 7 June 2010**

In the version of this article initially published, a researcher at University College Cork was incorrectly named. His name is Tom (not Barry) Moore. The error has been corrected in the HTML and PDF versions of the article.

Erratum: Never again

Chris Scott

***Nat. Biotechnol.* 28, 131 (2010); published online 5 February 2010; corrected after print 7 June 2010**

In the version of this article initially published, Art Levinson is incorrectly described as a founder of Genentech, Sandra Horning as senior vice president of global clinical development and Richard Scheller as chief of operations. Their titles should have read: CEO Arthur Levinson moved up to the board of directors…. Sandra Horning…took over as senior vice president, global head, clinical development, hematology/oncology. Executive vice president, research, Richard Scheller…. The errors have been corrected in the HTML and PDF versions of the article.

Erratum: Resuscitated deCODE refocuses on diagnostics

Mark Ratner

***Nat. Biotechnol.* 28, 192 (2010); published online 8 March 2010; corrected after print 7 June 2010**

In the version of this article initially published, it was reported that deCODE had "shuttered its Emerald Biosciences and Emerald Biostructures drug discovery operations"; in fact, the companies were sold to investors. In addition, the correct name of Emerald Biosciences is Emerald BioSystems. The error has been corrected in the HTML and PDF versions of the article.

Erratum: Biotech in a blink

Ken Garber

***Nat. Biotechnol.* 28, 311–314 (2010); published online 8 April 2010; corrected after print 15 April 2010**

In the version of the article originally published, Michael Tolentino was misquoted to the effect that bevasiranib had been shown to persist indefinitely in post-mitotic cells. Tolentino actually stated that the RNA-induced signaling complex persists. The error has been corrected in the HMTL and PDF versions of the article.