

Cancer Immunotherapy: Development at the Intersection of Science, Economics, and Regulation

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The human immune system represents an elegantly regulated set of mechanisms that constantly defends the body against infections and other diseases. Humans without a functioning immune system will seldom live long after being attacked by the plethora of micro-organisms to which we are routinely exposed. Equipped with a properly and well functioning immune system, we are able to fight off most infections and prevent the emergence of many diseases. It is even possible to harness the body's inherent defense mechanisms through artificial means to prevent or treat illnesses. The classic method is preventive vaccination, which trains the immune system to recognize and attack infectious agents before a clinically significant infection can occur.

The concept of prophylactic vaccines has been around for centuries, dating back to 1796 when the first vaccine was discovered and put to use by Edward Jenner (Dillman 2001). He observed that dairymaids who had been exposed to the cowpox virus through milking were protected from infection by the deadly smallpox virus. This happened because the two different viruses contain a very similar repertoire of cell surface proteins, which the immune system uses to distinguish self from foreign, and one from another. Thus prior inoculation with cowpox

trains the immune system to recognize and quickly clear any subsequent smallpox infection before the deadly virus would ever have a chance to get a foothold.

Despite this tremendous early breakthrough, vaccine research did not become a scientific and business enterprise until well into the 20th century. A series of triumphs in vaccine development for polio and many childhood diseases was interrupted in the 1980s by tort liability litigation (soon reined in by the National Childhood Vaccine Injury Act of 1986), and dampened by the extreme modesty of public reimbursement levels. In the past decade, however, a resurgence of vaccine development has brought preventative vaccines for pneumococcal bacteria (a cause of pneumonia and other other infections such as acute sinusitis, otitis media, meningitis, osteomyelitis, septic arthritis, endocarditis, peritonitis, cellulitis, and brain abscesses), hepatitis B (acute and chronic hepatitis, cirrhosis, and liver cancer), human papillomavirus or HPV (genital warts and cervical cancer), varicella zoster virus or VZV (chickenpox and shingles), and rotavirus (severe diarrhea among infants and young children). (Useful sources on the history of vaccine development include Offit 2007, IOM 2004 , and Berndt and Denoncourt 2008).

Because prophylactic vaccines generally only work against infectious agents, their scope for cancer prevention is limited. Very few cancers are known to be caused directly by infection (*Pharmaceutical Business Review* 2006), although research has long revealed tantalizing connections (see Ganem's 1999 review of Parsonnet 1999). Two preventative cancer vaccines have been approved by the Food and Drug Administration (FDA). In 2000, Engerix-B was approved to prevent primary liver cancer as a result of chronic hepatitis B infection, and in 2006, Gardasil was approved to prevent infection from some of the most common strains of human papillomavirus that cause cervical cancer (Herberman 2006; Sobol 2006). Another HPV vaccine, Cavarix, is close to approval in the U.S. (Berton 2007). But the scope for cancer prophylaxis through traditional vaccination remains limited.

Beyond Prophylactic Immune-based Approaches

In the past decade or two, biotechnology researchers successfully explored a second way to make use of the immune system (cf. Reichert 2001; Dillman 2001). The basic idea, which

dates back to the work of Paul Ehrlich a century ago, is to collect antibodies—which along with T-cells are one of the immune system’s two basic tools to kill pathogens—and inject them into the patient. In principle, sufficient quantities of the right antibody can help the body fight a variety of illnesses including rheumatoid arthritis, osteoporosis, and most notably, cancer.

The first immunotherapies to reach fruition as accepted cancer therapies were based on antibodies. Antibody-based therapies work in several ways; some require the help of the immune system, but others do not. Rituxan (rituximab), for example, is a monoclonal antibody that attaches itself to cancer cells of non-Hodgkin lymphoma (NHL), marking them for destruction by the immune system. This represents a classical function of antibodies. In contrast, other monoclonal antibodies work independently from the immune system by directly inhibiting certain proteins that are functional parts of cancer cells or by interfering with other cells that help cancer cells grow. For instance, Herceptin (trastuzumab) binds to and inhibits the HER2/neu protein, which is a growth factor receptor found at high levels in certain breast cancers, while Avastin (bevacizumab) targets the vascular endothelial growth factor (VEGF), inhibiting the formation of new blood vessels and starving the tumor of nutrients (Ferrara, et al., 2004). These approaches are considered “passive” immunotherapy because the infused antibodies have a limited duration of clinical activity and fail to “teach” the immune system to attack these targets in the future, as “active” immunotherapy would.

Simply harvesting human antibodies is generally infeasible, however valuable those antibodies might be as therapeutics (Dillman 2001). Inducing the body to generate large quantities of precisely the right antibodies against any human tissue including cancer cells is essentially impossible. On the other hand, if antibodies are induced in, and collected from mice or other animals, the human body’s natural resistance to foreign substances prevents them from working properly. Antibody therapy therefore had few uses until the development of biotechnology tools such as recombinant DNA in the 1970s and 1980s. This advance opened the possibility of identifying and creating promising humanized antibodies from animals—most typically mice—for the use against different targets implicated in different diseases. The process begins by injecting a mouse with a sample of the human target. The mouse then creates a variety of murine antibodies against the target because the target is recognized as foreign. Once the murine immune cell that produces the desired antibody is identified, the DNA from that cell is

manipulated to partly or completely humanize it so that the human body no longer treats the antibody as foreign. Then, billions of copies are grown in another organism (e.g. bacteria, yeast, or certain mammalian cell cultures), and finally, the monoclonal antibodies are infused into humans for testing. They are known as “monoclonal” antibodies because they are made by cells of a single clone, which make antibodies of a single specificity. The creation, testing and deployment of monoclonal antibodies became one the triumphs of pharmaceutical biotechnology, and it is apparently still in its early stages.

Our topic is a third immunologic approach, which essentially combines the first two. Here, the goal is to energize and teach the immune system (as vaccines do) to attack illnesses already present in the body (as monoclonal antibodies do). This is the emerging world of therapeutic vaccines or “active” immunotherapy. Again, active immunotherapies differ from passive immunotherapies in that the former trains the immune system, unlike the latter, which simply employs some aspect of immunity to realize a therapeutic end. No therapeutic vaccines have been approved by the FDA or other leading regulatory authorities elsewhere, but by 2004, dozens were in testing for a variety of conditions including Alzheimer’s disease, Huntington’s disease, multiple sclerosis, persistent viral infections, HIV, and cancer (Sela and Hillman 2004). We focus on cancer because immunotherapy raises the prospect of extraordinary therapeutic advances, and significant progress has already been reported, yet it is also an area in which immune-based therapies raise with special clarity some difficult questions in public policy and regulation.

Scientific Foundations

In general, the immune system protects us by eliminating entities that are recognized as foreign and tolerating those that are recognized as self (Pardoll 2003). When the immune system detects foreign entities, it usually attacks them by a variety of approaches, including direct killing by cytotoxic T-cells and the production of antibodies by B-cells. These T and B-cells come in unending variety, each one suited for specific pathogens even before having encountered them. Immune cells that are reactive to self, on the other hand, are almost always eliminated before they are allowed to circulate throughout the body. This prevents the immune system from

attacking normal cells, a process known as autoimmunity. In essence, the aim of therapeutic cancer vaccines is to energize the immune system to produce clones of the right T-cells and B-cells in order to attack the resident cancer cells, devoid of unwanted autoimmunity. Unlike most oncology drugs—mainly those of the cytotoxic variety, which kill both tumor and normal cells in a relatively non-specific manner—cancer vaccines offer the prospect of high specificity, low toxicity, and prolonged clinical activity (Pijpers, Faint and Saini 2005).

But while the concept of therapeutic cancer vaccination has been around for quite some time, limited success in the clinic has been achieved. Part of the problem is that cancer cells are not always recognized by the immune system as foreign (Pardoll 2003). Cancer cells are essentially immortalized self-cells that grow and divide uncontrollably. As a collection of altered self cells, tumors contain many of the same identification markers as normal cells of the tissue from which they were derived. For a long time it was thought that tumor antigens did not even exist, and it wasn't until the late 1980's that tumor antigens were first being characterized (Ribas et al 2003; Parmiani et al 2007). Because tumor cells are inherently genetically unstable, they express aberrant proteins or overexpress those that are normally repressed. This represents the therapeutic window that ultimately provides a target for recognition by effector T-cell and B-cells. The fundamental rationale for this approach lies in the exquisite specificity of both T-cells and antibodies, which allows the immune system to distinguish the most subtle differences between cancer and normal cells (Pardoll and Allison 2004).

The rationale for therapeutic cancer vaccination is perhaps even more evident when we consider the immune system's inherent capacity to control and shape the progression of cancer. There is growing evidence that, by holding the expansion of transformed (i.e. cancer) cells in check, the immune system plays a significant role in maintaining small, potentially cancerous lesions in a state of dormancy (Koebel, et al. 2007). This state of dormancy can be thought of as equilibrium between tumor elimination and tumor escape. If, for example, resident tumors develop a dampened immunogenicity (i.e. become less recognizably "foreign"), or if the immune system is attenuated by the cancer cells or by some other force, then cancer cells escape immune surveillance, and the process becomes characterized by persistent tumor growth (Koebel et al 2007; Melief 2007; Jones 2007). The natural role that immunity plays in controlling tumor

progression suggests that harnessing the potential of the immune system may be very useful in treating cancer.

Most often, however, the net result is that our immune system naturally tolerates and essentially ignores most tumors (Pardoll 2003). Developers of therapeutic cancer vaccines aim to change this by heightening awareness and breaking tolerance. Harnessing the inherent capacity of the immune system to fight cancer represents a promising approach to therapy; one that has the potential to convert cancer from a relentlessly progressive disease to one that is chronic and controllable, or perhaps ultimately curable.

Approaches to Therapeutic Cancer Vaccines

Therapeutic cancer vaccines can be either autologous or allogeneic (National Cancer Institute 2006). Autologous vaccines are created for a single patient by using the patient's own tissue (e.g. the patient's tumor cells or immune cells) to produce an individualized therapy. Allogeneic vaccines, on the other hand, are off-the-shelf mass-produced therapies, created by using generalized tumor-associated antigens that are common to the particular cancer. While the initial immune response will be specifically directed against the generalized tumor-associated antigen, allogeneic vaccines have shown the capacity to cross-prime and activate the immune system to recognize the patient's own tumor antigens on subsequent vaccine deliveries (Bernstein 2006a). On the other hand, autologous vaccines offer efficacy and specificity advantages of being formulated for each patient and do not necessarily require an in-depth knowledge of the exact antigens involved. However, they present commercial disadvantages, such as high cost and low scalability of manufacture, logistical complications, and a more complex regulatory approval process (Danson and Lorigan 2006; Hoos et al 2007). . For these reasons and because of recent advances in genomics and proteomics, some analysts have predicted that allogeneic vaccines will dominate the preclinical pipeline (*Pharmaceutical Business Review* 2006). Nevertheless, autologous vaccine candidates represent about half of the Phase III projects currently in clinical development.

Autologous and allogeneic vaccines can be further categorized based on the methods used for presenting cancer antigens (i.e. the target) to the body's immune system (National

Cancer Institute 2006). The basic types include antigen/adjuvant vaccines, whole cell tumor vaccines, anti-idiotypic vaccines, DNA vaccines and viral vectors, as well as dendritic cell vaccines and adoptive T-cell transfers (National Cancer Institute 2006). Each offers its own relative advantages and disadvantages.

Antigen/adjuvant vaccines were some of the first investigated. In immunology, an adjuvant is an additive that enhances the effectiveness of a medical treatment by acting as a non-specific stimulator of the immune response. Because an adjuvant can cause and enhance an immune response by itself, it is hoped that, in responding to the antigen-carrying adjuvant, the immune system will also attack the patient's tumor cells that express the antigen. Whole cell tumor vaccination employs a similar approach, but they use entire killed tumor cells, which contain a more complete repertoire of surface antigens, and are usually genetically modified to make the cells more immunogenic. This may provide for a broader and more effective attack on the tumor by the effector immune cells. Tumor-specific idiotypic vaccines are also similar to the antigen/adjuvant approach. These vaccines consist of antibodies that mimic tumor-associated antigens that are coupled to an adjuvant. Vaccination with these tumor-specific idiotypic antibodies essentially amplifies the mass of tumor antigens, making it easier to train the immune system to recognize and mount a response against the tumor.

DNA vaccines, on the other hand, use a nucleic acid sequence that will typically produce one or more cancer antigen proteins, one or more costimulatory molecules, or some combination of all of the above (National Cancer Institute 2006). Costimulatory molecules are important mediators that initiate and maintain the activation of certain immune cells, and can therefore be used for the purpose of enhancing tumor immunotherapy (Ward and Kaufman 2007). In many cases, the DNA is delivered to the target cells via a weakened or replication-deficient virus, which serves as a vector. These replication-deficient viruses can infect cells, but cannot spread thereafter. In addition, these viruses can be genetically engineered to more selectively infect rapidly dividing cancer cells, as opposed to normal cells. The virus also inherently elicits an immune response which may help jump start the process of generating antitumor immunity. In other models, the DNA can be delivered by targeted biodegradable spheres, which themselves do not incite an immune response. In either setting, heterologous prime-boost protocols are now more often being used (Rice, Ottensmeier and Stevenson 2008). In general, two different

vaccines are used, where the priming vaccine activates effector and memory cells, and the boosting vaccines expand the response. This method elicits immune responses of greater magnitude and breadth than can be achieved by priming and boosting with the same vector. However, determining the right combination, dose and schedule can be a challenge, as it seems to be the case, regardless of the treatment modality (Ramaswamy 2007). Overall, the expression of the cancer antigens and the costimulatory molecules in DNA and viral vaccines will help better activate the pre-existing—but resting—effector immune cells that will specifically attack the tumor.

The use of specialized antigen-presenting immune cells known as dendritic cells represents another promising method for therapeutic vaccination (National Cancer Institute 2006; Flanagan 2007). In this procedure, blood is drawn from the patient, and the dendritic cells are isolated and subsequently stimulated by one or more tumor-associated antigens or the patient's own tumor cells. The dendritic cells are then grown and multiplied in culture, and finally reintroduced back into the patient. These antigen-experienced dendritic cells will now present the tumor antigens to the effector immune cells that are specific for that antigen, activating them to attack the tumor (Banchereau and Steinman 1998; Flanagan 2007). A similar approach involves activating these effector immune cells—generally T-cells—in culture, and reintroducing these cells back into the patient (Gattinoni et al 2006). This method is known as adoptive cell transfer. Whereas dendritic cell vaccines aim to activate tumor reactive effector immune cells in the patient (*in vivo*), adoptive transfers aim to activate these cells in the laboratory, outside of the patient (*ex vivo*).

A remarkable variety of therapeutic vaccines are now in all stages of preclinical and clinical testing for cancer (for example, Schlom, Arlen, and Gulley 2007 provide a detailed examination of selected vaccines for prostate cancer). Some candidates in late-stage clinical development include: Dendreon's Provenge for prostate cancer (an autologous dendritic cell vaccine); Cell Genesys's GVAX Prostate Cancer Vaccine (an allogeneic whole cell tumor vaccine) as well as the GVAX Lung Cancer Vaccine (an autologous whole cell tumor vaccine); AVAX's M-Vax for melanoma (another autologous whole cell tumor vaccine); Antigenics's Oncophage for a variety of cancers (an autologous product akin to whole cell and antigen/adjuvant vaccines) Favril's Specifid—formerly FavID—and Genitope's MyVax for

follicular non-Hodgkin's lymphoma (both autologous idiotype vaccines); Oxford BioMedica's and Sanofi Aventis's TroVax for a variety of solid tumors (an allogeneic viral vector DNA vaccine); and the National Cancer Institute continues to explore variants of their TRICOM vaccine (triad of costimulatory molecules with tumor antigens; another allogeneic viral vector DNA vaccine) for a number of different cancers (National Cancer Institute 2006; Bernstein 2006a; Fox 2007b).

The Prospect of Combination Therapy

Experience has shown that combination therapy is almost always necessary to treat complex, multifactorial disease such as diabetes, HIV infection, and coronary heart disease, as mono-therapy is often insufficient to achieve therapeutic benefit or is inferior to combination therapy. In the case of cancer, it has been widely recognized that there are good scientific reasons why cancer treatment will usually require the simultaneous use of two or more agents (Hanahan and Weinberg 2000; National Cancer Institute 2003). In the transformation from a normal cell to a cancerous cell, cancers acquire and rely on a variety of mechanisms, including: self-sufficiency in growth signals; insensitivity to growth-inhibitor signals; evasion of apoptosis (i.e. programmed cell death); limitless replicative potential; sustained angiogenesis (i.e., the growth of new blood vessels to supply nutrients); and tissue invasion and metastasis (i.e. distant spread) (Hanahan and Weinberg 2000). This multiplicity of defenses makes cancer difficult to treat by a single agent. The drug cocktail approach to treating cancer has become the norm as more and more drugs are being developed and approved to treat these various mechanisms (Ramaswamy 2007).

The need for combinations may be even more pressing for immunotherapy than for traditional cytotoxic agents. This is because energizing the immune system is more akin to operating a rheostat than it is a simple on/off switch (Riley and June 2005). The immune system is elegantly regulated by both separate and overlapping cascades of complex interactions, involving various checkpoints that work at distinct points in the evolution of the effector immune response. The best anti-tumor response will probably be generated by combination strategies that affect these multiple checkpoints (Pure, Allison and Schreiber 2005). That is why there has been an increasing trend in therapeutic vaccine development towards the use of multiple antigens, adjuvants, and costimulatory molecules in single vaccines, while taking advantage of the intrinsic ability of a variety of immune cells to attack cancers.

We emphasize that by combination therapy, we mean immune-based therapeutics combined with chemotherapeutic drugs, as well as combinations of immune-based therapeutics (particularly active immunotherapies). Immune-based therapies include both active (e.g. therapeutic vaccines) and passive (e.g. monoclonal antibodies) varieties, whereas chemotherapies include mainly cytotoxic agents (e.g., alkylating agents, anti-metabolites, etc). As we noted, clinicians and researchers are leaning strongly toward attacking cancers from several angles by a variety of methods in the hopes of obtaining synergistic and clinically significant results.

A Note on Economic Issues

The scientific challenges in developing practical and useful immune-based therapeutics for cancer are daunting. Progress has been rapid, however, and success in related areas such as monoclonal antibodies is very encouraging. But many of the core scientific challenges in creating immune-based therapeutics raise serious economic and regulatory problems. We turn first to economics, and then to FDA regulation. On economics, we are fairly optimistic, as can be seen by briefly examining a few obvious issues.

Financial Risk

The economics of any novel approach to treating diseases is always daunting. Given the scientific challenges in attacking cancer through the immune system, one might reasonably doubt whether cancer immunotherapy will ever be a practical tool and therefore, whether the expenditure of billions of dollars in research funding is likely to yield commensurate payoffs (cf. Pardoll and Allison 2004 at 888). There is a parallel in the development monoclonal antibodies, however. There, too, the scientific difficulties in harnessing the immune system were formidable. What was needed in the way of science extended far beyond an understanding of either antibodies or the pathogens to be attacked. A series of longshot investment were launched to exploit advances in basic research. Nonetheless, monoclonal antibody therapy remained shrouded in scientific doubt almost until the time when success was achieved (Dillman 2001 at p. 298, and Reichert 2001). Numerous maps are now used against cancer, rheumatoid arthritis, M.S., and other conditions, and many more are in testing.

Intellectual Property for Combination Products

Immune-based cancer therapeutics are almost always “biologics,” i.e., complex proteins rather than identifiable and easily synthesized small molecules. Biologics also typically involve numerous patents rather than just one or two, although biologics patents tend to be more easily challenged. Most important, there is no established regulatory pathway for the introduction of “generic” biologics, in contrast to the Hatch-Waxman mechanism for traditional small-molecule pharmaceuticals. Thus patent life alone is usually not a threat to therapeutic vaccine development despite long development times (pre-registration clinical trials of Provenge began in 1999 and still underway). On the other hand, combination therapeutics typically involve intellectual property held by multiple firms. This raises serious problems of coordination among firms. This problem is hardly unique to immune-based therapeutics, however. Indeed, the coordination of diverse pieces of I.P. is a widely discussed problem. Despite manifold theoretical problems, workable arrangements including patent pools have permitted I.P.-based research to proceed on many fronts (Barfield and Calfee 2007).

Financing and Conducting Trials of Combination Products

The launching of clinical trials of combination products also raises a problem of coordinating efforts among separate and possibly competing firms. Although the opportunities for mutual misunderstandings and for mutually self-defeating strategies are legion, they can be overcome when the payoffs from success are large. An example is the ongoing (and very expensive) series of clinical trials for Vytorin, an approved combination of Zetia (ezetimibe) and Zocor (simvastatin), funded by its competing manufacturers, Schering-Plough and Merck, respectively. Also relevant are combinations of therapeutics and diagnostics from different manufacturers. A striking example of research funded by multiple firms is the recently announced plan by Abbott, Genentech, Hoffmann-La Roche, and OSI Pharmaceuticals, Inc. to develop a gene test to assess the clinical benefit of Genentech's cancer drug Tarceva (Abbott press release, Mar. 7, 2008).

Regulation

We think that the ability to surmount scientific challenges remains the principal barrier to success in immune-based cancer therapeutics, but the regulatory environment also threatens to impede progress substantially. Most regulatory issues arise from simple fact that active immunotherapies work quite differently from traditional cytotoxic drugs or even from the passive administration of monoclonal antibodies.

Taking Advantage of Baseline Safety

Chemotherapeutic drugs typically kill cells by impairing some aspect of the cell cycle, exploiting the propensity of cancer cells to grow and divide rapidly unconstrained by normal cellular control checkpoints (Mandel 1978). These drugs can significantly reduce tumor burden, but do so at the cost of killing some fraction of normal cells, which lends to the adverse side-effect profile of these agents. In other words, fighting cancer with cytotoxic chemotherapies is akin to a war of attrition. And while monoclonal antibodies offer a far greater degree of specificity than cytotoxic agents, they, too, have a limited duration of action.

The immune system goes about its job in a fundamentally different way. Therapeutic vaccines enlist the cells of the immune system to target cancer cells with great specificity, avoiding many of the unwanted side-effects associated with the relatively non-specific killing accomplished by most chemotherapy agents (Hoos et al 2007). Although the potential for serious safety problems remain, many and perhaps most immune-based therapeutics can be expected to enter regulatory review with a relatively benign safety profile compared to traditional cytotoxic and even passive immune-based products. Because oncology drug approval has often involved a search for substantial demonstrated benefits to offset serious expected side-effects, a somewhat different approach is necessary for the kind of therapeutics under examination here.

Clinical Endpoints

As an “active” immunotherapy, vaccines initiate a dynamic immune response that offers the prospect of prolonged antitumor activity. In the clinic, these vaccines appear to benefit patient to a variable degree, but often do little in terms of shrinking the tumor size (Pijpers, Faint and Saini 2005). This has given rise to a small but vigorous literature on how to measure progress with immunotherapies in clinical trials. Commonly used efficacy endpoints, which tend to be based on quantitative tumor assessments(see FDA 2007), may not adequately reflect patients’ clinical benefit (i.e. survival and quality of life). This raises two issues. One is what to measure. Numerous clinical trials of cancer vaccines have revealed statistically significant survival advantage but failed to achieve predetermined efficacy levels in terms of tumor regression (Schlom, Arlen and Gulley 2007; Arnst 2007a). An example is Dendreon’s Provenge, an autologous dendritic cell vaccine for prostate cancer, which in a 13-4 vote an FDA advisory committee recommended for approval on the basis of an excellent safety profile and a survival benefit that approached statistical significance. The FDA staff denied approval because the trial had missed its primary endpoints and asked Dendreon to perform additional trials (*Nature Biotechnology* unsigned editorial 2008). This situation is apparently fairly common. Schlom, Arlen and Gulley (2007) describe numerous clinical trials of cancer vaccines in which traditional clinical trial markers such as tumor regression have significantly diverged from other relevant measures such as overall patient survival. Hence prolonged disease stabilization and overall

patient survival might be a more relevant endpoints for cancer vaccine trials than any measurement of tumor regression (American Association for Cancer Research 2007).

This raises a second problem, which is that preferred endpoints—especially survival—may require clinical trials lasting for years instead of months, at substantial or even unacceptable costs in human and other terms (Bernstein 2006a; DiMasi and Grabowski 2007). Prospectively designed endpoints are essential, of course, in order to minimize bias and facilitate assessment. But focusing on a single criterion for all therapeutics, cancer types, and disease stages can bring classic paradigm paralysis (Schlom, Arlen and Gulley 2007).

Much of the tension between trial length and the search for clinical endpoints could be alleviated in two ways. One is for the FDA to give far more weight to the preferences of patients and their physicians. The second, which would work toward the same end, would be to reinvigorate the “accelerated approval” pathway, with its emphasis on incomplete information at approval time supplemented by post-approval findings.

Clinical Trial Design for Combination Therapy

The FDA's regulatory system is geared toward single-agent drug approvals (Tuma 2007). This is consonant with a longstanding paradigm of cancer therapeutics development in which drugs are initially developed as single agents, tested either alone or in combination with a standard treatment, and only subsequently used and perhaps tested in varied combinations (Pardoll and Allison 2004). Regulatory approval of combinations of therapeutic agents has usually required definitive demonstrations of the independent contribution of each component for fixed combination products (Hoos et al 2007). This traditional approach may work poorly for immune-based therapeutics, as single agent or single-component vaccines will usually prove inefficacious as immune-based therapies. Rather, they will usually have to be combined with conventional chemotherapy, and/or with agents that affect the host immune system, and/or with other vaccine therapies (National Cancer Institute 2003; Pure, Allison and Schreiber 2005; Schein and Scheffler 2006; Arnst 2007b).

The different approaches create very different therapeutic and regulatory scenarios. Multi-component vaccines are an example. Here, the goal is to overcome tolerance to tumor antigens and generate a significant antitumor response in the face of numerous checkpoints,

which the immune system uses to prevent autoimmunity and to appropriately control immune responses against pathogens and other entities recognized as foreign (Petricoin 2005; Pure, Allison and Schreiber 2005). However, failure of a multi-component vaccine may cast doubt about any one of its individual components, when in fact any one of those components may be better suited for use in a different combination.

Combining vaccines with conventional chemotherapy is another approach. Relevant here are two interesting phenomena that have been observed in the clinic (Schlom, Arlen and Gulley 2007). First, therapeutic vaccines initiate a dynamic process of host immune responses that may be exploited in subsequent therapy. There is evidence that patients who receive a vaccine—and mount an immune response—tend to have an enhanced outcome to subsequent therapies. And second, certain standard-of-care therapeutics—including conventional chemotherapy and radiation therapy—can actually alter the phenotype of tumor cells, rendering them more susceptible to subsequent immune-mediated lysis. Choosing the right combination, dose, and schedule for these therapies is crucial. In addition, it is important to keep in mind that active immune-based therapies require an intact and functioning immune system. Unfortunately, many of the cancer patients enrolled in clinical trials have late-stage disease, and thus the capacity of their immune system is limited (Sosman, Weeraratna, and Sondak 2004; Bernstein 2006a; Hoos et al 2007; Miller 2007). A high tumor burden and failing immune system practically guarantee a poor response to therapy. Together, these factors greatly complicate the development and approval process of cancer vaccines.

Biomarkers and Adaptive Clinical Trial Designs

The past few years have seen considerable discussion of how to modify clinical trial design to accommodate faster drug testing and approvals (Singer 2005). Of particular interest is the adaptive clinical trial approach, which employs Bayesian statistical methods to exploit information as it accumulates during a trial (Berry 2006; Gottlieb 2006; Fox 2007a). This is of special importance for immune-based therapeutics, which are best tested against relatively early-stage cancer and often in combinations or sequences about which the science is relatively new at the start of trials (cf. Berry 2006). Hence there concerted private and public efforts to develop better ways to predict clinical benefits from the immune responses mounted by patients (Abrams

et al 2005; Pijpers, Faint and Saini 2005; Goldberg 2007; Goulart 2007). In any case, adaptive trials may help to identify patients who are best responding to treatment, allowing clinician-researchers and drug developers to provide better care while making better decisions about drug development.

This point becomes clear when one compares cytotoxic chemotherapy, from which a significant number of patients are expected to benefit, but only incompletely, with immunotherapy, where a likelier outcome is that a certain (perhaps modest) percent of patients will benefit, but dramatically (Bernstein 2006a). Identifying the subset of patients who respond to therapy is important for both patients and drug developers. Another important consideration is that it may take weeks, or even months, for a patient to develop an antitumor immune response, during which time, the extent of the tumor may even progress (Bernstein 2006a; Hoos et al 2007; Miller 2007). Thus, it is important to allow time for the immune system to kick into full gear. Taking these issues into consideration, regulators can more clearly outline their expectations, and together with drug developers, more efficient clinical trials can be designed that will meet those expectations.

Overcoming FDA Risk-aversion in New Drug Approvals

Of signal importance are the bureaucratic incentives of the FDA staff who preside over cancer drug testing and approval. Notwithstanding the long-running public debate over Vioxx, SSRI antidepressants, and other drug safety issues, there is little persuasive evidence of FDA neglect of drug safety in recent years (Calfee 2007). On the other hand, the biased incentive structure facing FDA staff insures that too much weight will be given to safety and not enough to benefits. FDA staff members know that if they commit what is often called a Type I error — the approval of a drug that turns out to be insufficiently safe once marketing begins — their error will usually become known (a “public error”), often arousing impassioned criticism. On the other hand, a Type II error — the failure to permit marketing of a drug that would in fact provide benefits in excess of harms — is typically detected by relatively few people (a “private error”). The natural effects of this arrangement became apparent in a stream of research on the “drug lag” of the 1960s and 1970s, when FDA approvals trailed far behind those in European nations, with no offsetting benefit in terms of safer drugs (Peltzman 1973, 1974; Wardell and Lasagna 1975;

Katin and Brown 1995; Bakke, et al. 1995). The FDA's recent rejection of its advisory committee's advice on approving the autologous vaccine Provenge seems to illustrate the continuing force of these incentives.

This reasoning helps explain why the FDA seems to be taking little account of the likelihood that therapeutics vaccines are substantially safer than cytotoxic drugs (Hoos, et al. 2007). The major adverse toxicity interaction, if any, is likely to be manifest as a late autoimmune event, and patients usually do not experience the dangerous and unpleasant side-effects that unavoidably accompany chemotherapy. Moreover, the FDA seems to give little weight to the fact that relatively benign therapeutic vaccines are typically designed for acutely lethal illnesses rather than chronic diseases. For example, immunotherapies for chronic arthritis are essentially evaluated similarly to those for pancreatic cancer, which is a characteristically aggressive tumor for which nearly all patients die within two years of diagnosis (Pardoll and Allison 2004). This leads to an imbalance in risk-benefit judgments in regulating the development of novel approaches to treat lethal cancers (Anand 2007; Nature Biotechnology unsigned editorial 2008).

Conclusions: Prospects for a Breakthrough

The path toward immune-based cancer therapeutics such as therapeutic vaccines is reminiscent of the path blazed by monoclonal antibodies a decade or so earlier. The payoffs from success would be extraordinary, but the challenges in exploiting arguably the most difficult of immune-based approaches to cancer treatment are daunting. The basic properties of these therapies raise numerous economic issues such as R&D funding, the coordination of intellectual property, and multiple ownership of agents to be tested in combination or in sequence. Even more difficult, however, are the ways in which FDA regulation may, and perhaps does, stand in the way of rapid testing and approval of promising therapeutics. If the FDA can adapt to certain elements--the central role played by combination and sequential therapy, the necessity (in some cases) of running trials against early-stage cancer, and the benefits of adaptive trial design and other non-traditional methods--while also working to overcome the excessive risk-aversion that is endemic to it as a institution, we may see important changes at the FDA (such as the

invigoration of accelerated approval) and perhaps, a succession of dramatic new cancer treatments.

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