



Home > Products & Technologies >

Advent of the Adjuvant: QS-21 Makes Vaccines Look Good

June 2002

by Bruce Goldman

The vaccine market is going to explode.

And when it does, it will be in large part due to the addition of a set of essential but unsung immunological tools called *adjuvants*. These immune enhancers will be vital components in making new vaccine types viable, making old ones more efficacious, and making those that are expensive to manufacture or in scarce supply go further.

A new generation of vaccines is being brought into being by giants like GlaxoSmithKline, Merck and Wyeth, says Garo Armen, PhD, CEO of New York City-based biotech Antigenics Inc. All three pharmaceutical houses are moving vaccines for a large number of indications containing Antigenics' powerful new adjuvant, QS-21™, toward or through clinical trials. "With a successful assault on such major diseases as AIDS, most hepatitis forms, and herpes, the market for prophylactic vaccines could easily double by the end of this decade," Armen says. "And the total size of the vaccine market theoretically could be as large as the entire pharmaceutical market is today, because most diseases can theoretically be treated with therapeutic vaccines, which harness the immune system to cure — rather than prevent — illnesses."

Vaccinology has expanded beyond its traditional mainstays — attenuated or killed microorganisms — to the likes of recombinant proteins and glycoproteins, synthetic peptides, and *conjugate* vaccines, in which relatively nonimmunogenic, carbohydrate-based antigens are tethered to strongly immunogenic carrier proteins. But paradoxically, the new, pared down vaccines may become less intrinsically immunogenic, even as they become safer and more precisely targeted. This is because although they contain antigens that tell the immune system's warriors and weaponry exactly what to attack, they may lack other components that kick the immune system's logistical support machinery into higher gear.

Enter the adjuvant: a substance that, although not necessarily eliciting an immune response itself, improves the immune response to a co-administered antigen. Adjuvants can work in many ways: raising antibody titers, enhancing mucosal immune responses, or making better cell responses. Considering that a vaccine may spend close to 20 years in development, research and development (R&D) expenses dwarf other aspects of its cost structure. So an adjuvant doesn't add much to the cost of a vaccine — but it can add immensely to its potency. Indeed, experimental vaccines often just won't work without one.

Clinical immunologist and public health specialist Bob Edelman, MD, a professor of medicine and pediatrics at the University of Maryland, says an ideal adjuvant would open up new worlds of prevention and treatment: "It might make for an effective vaccine against malaria or HIV. We could stop with those two." But his list also includes autoimmune diseases and a variety of

cancers.

A superior adjuvant might also extend the benefits of existing vaccines to poor responders such as older or immunocompromised people. An adjuvant that rendered lower doses more effective, moreover, would allow for cheaper vaccines in cases in which the antigen is expensive to produce (a recombinant protein, for example). It could also stretch supplies in a hurry during an epidemic or after a bioterrorist incident. *Dose sparing*, as this property is called, is of increasing importance in the development of conjugate vaccines, in which difficult chemistry limits antigen dose size, especially when several antigens must be packed into a single shot.

Adjuvant activity has been found in numerous natural products through serendipity and trial and error. One of the very first papers on the subject was written in 1925 by a French researcher who learned he could enhance immunogenicity by injecting crude products such as tapioca or bread crumbs, and chemical substances such as lecithin or *saponins* (soap-like substances isolated from plants).

That early discovery presaged one of the most promising new adjuvants in the burgeoning arsenal of vaccinology. In 1986, biochemist Charlotte Kensil, PhD, now vice president for research operations and strategy at Antigenics, came to work for what was then Cambridge Biosciences, taking on the analysis of a complex saponin extract from the bark of *Quillaja saponaria* (a South American tree) with which the company hoped to adjuvant its vaccine for feline leukemia virus (FeLV). The extract was very effective, but toxic. Looking to purify out the toxicity using high-performance liquid chromatography (HPLC), Kensil identified 23 separate peaks, or components, and set about characterizing them. Several proved irrelevant, others toxic. The 21st HPLC peak, however, yielded a saponin that was both active and nontoxic.

This substance — actually a mixture of two compounds that co-exist in a relatively constant ratio and are virtually identical in both structure and activity — was christened QS-21 (Kensil is one of the two inventors on the patent); by 1990, it was in a successfully licensed FeLV vaccine in the United States and Europe. In a restructuring move about seven years ago, Cambridge Bioscience spun off Aquila Biopharmaceuticals, which retained the rights to QS-21. Long on intellectual property but short on cash, Aquila Biopharmaceuticals was in turn bought by Antigenics at the end of 2000.

Adjuvants on Trial

These days, the US Food and Drug Administration (FDA), rather than grant blanket approval for an adjuvant itself, reviews each vaccine-adjuvant combination as a separate package. The exception is *alum*, the only currently approved adjuvant per se. Alum — a generic term for salts of aluminum, chiefly aluminum hydroxide and aluminum phosphate — was first employed in 1926 and was effectively grandfathered in when the FDA first assumed new drug approval authority in 1938.

But Is Alum Worth Its Salt?

Oldest doesn't always mean best, says cancer vaccine specialist Phil Livingston, MD, attending physician at Memorial Sloan-Kettering Cancer Center and professor of medicine at Cornell University's medical school. In fact, he says, "as adjuvants go, alum's the weakest."

On the other hand, "Billions of doses of alum have been administered — not millions, *billions* — and it has a track record of being generally safe," says the University of Maryland's Edelman. "As a result of this long experience, we've grown to have a warm, fuzzy feeling about it, and it's

become the benchmark adjuvant against which all others are now tested.”

Alum is known to work chiefly through a *depot effect*. Small antigens, injected into the bloodstream, can quickly become degraded in the liver or filtered by the kidneys. Alum, by precipitating soluble antigens, forces them to linger longer in the area near the injection site, where antigen-presenting cells — mainly macrophages and dendritic cells — can ingest and process them, thus ensuring a greater immunologic response. An *immunostimulatory* adjuvant such as QS-21 does much more than simply prevent degradation or discharge. It may facilitate uptake of the antigen — the actual vaccine itself — into antigen-presenting cells. (Saponins such as QS-21, for example, are detergents; they may therefore render cell membranes temporarily more permeable.) Or it may induce a *cytokine* response in local tissues. Cytokines are molecular messengers that act systemically and at close range to fine-tune the immune response’s course. Under their influence, the system strikes a balance between two poles called Th1 and Th2, named for the two classes of T-helper cells. To put it somewhat simplistically, Th1 primes a cell-mediated immune response that includes the activation of killer T cells (essential for, say, combating a chronic viral infection like HIV), whereas Th2 primes an antibody response mediated by B cells, which may be adequate for fending off certain blood borne infectious organisms. Different cytokines — and different adjuvants — tend to tilt the immune system toward characteristic points on the Th1-Th2 continuum.

Edelman cautions: “You’re going to find article after article saying that ‘this adjuvant causes a Th1 response in this animal, or a Th1 response in that animal.’ What they fail to go on to say is: ‘It hasn’t been put into man yet.’ The use of adjuvants is an empirical science, and you can learn only so much from preclinical studies. I’ve grown very skeptical because I’ve been burned so many times. It really comes down to clinical trials. If you want your vaccine to work in a human, you’d better get it into a human, quickly. Otherwise you’re going to spend a lot of time with animal studies and never be able to predict what it will do in people.”

In animals *and* humans, alum tends to skew things towards Th2, says infectious disease vaccinologist Tom Evans, MD, professor of medicine at the University of California, Davis. Evans has also worked with MF59, a squalene/water emulsion manufactured by Chiron that is in a licensed influenza vaccine in Italy. “MF59 gives you better responses than alum, but it’s very Th2-skewed,” Evans says.

At the other end of the continuum sits an adjuvant class called CpG, which is still confined to early-phase clinical trials of vaccines for cancer, HIV and hepatitis B. (The term CpG denotes a category of bacterial cytosine- and guanine-rich oligonucleotide motifs found in bacterial, but not human, DNA.) A few companies are developing competing adjuvants consisting of different CpG sequence variations. “In animal studies, at least,” says Antigenics’ Charlotte Kensil, “CpG produces almost entirely Th1 cytokines.”

Right in the middle is QS-21, which, according to results of extensive testing in both animal and human studies, not only elicits both Th1- and Th2-type cytokines but also unleashes the antibodies and T cells those cytokines are supposed to bring about. For example, in a clinical trial of a melanoma vaccine reported in the July 1, 1995, issue of *Cancer Research*, researchers comparing QS-21 with monophosphoryl lipid A (MPL), which is in a licensed melanoma vaccine in Canada, reported that QS-21 elicited much higher titer and longer lasting antibody responses, in addition to recruitment of T cells.

Antigenics’ leading platform technology — personalized vaccines prepared from patients’ tumors — derives from the discovery by its chief scientific officer, Pramod Srivastava, PhD, that a species of molecules known as *heat shock proteins*, or HSPs, can be extracted from a tumor to activate a powerful Th1-type response targeted to unique antigens that characterize that tumor.

Antigenics' vaccines for kidney cancer and melanoma have progressed to Phase III trials.

QS-21's virtually unsurpassed ability to induce a vigorous antibody response, which parallels HSPs' penchant for stimulating the cell side, made the Aquila Biopharmaceuticals acquisition a logical complement to Antigenics' HSP-driven business strategy. "When it comes to activating the antibody arm of the immune system, QS-21 is *the* most powerful adjuvant out there that can be used in people, and my studies at Sloan-Kettering showed a T-cell response, too," says cancer specialist Jon Lewis, MD, PhD, who left Sloan-Kettering a few years ago to become chief medical officer of Antigenics and chairman of the company's medical board.

Stanford University's Ron Levy, MD, has conducted early-phase clinical trials of a QS-21-containing vaccine employing personalized antigens from lymphoma patients. In lymphoma, one B cell begins dividing out of control, resulting in a huge number of cells all secreting large volumes of a single antibody (the composition and structure of which differ from one patient to the next) into the blood. Levy says patients' immune systems responded to the vaccine with strong T-cell proliferation and high antibody titers specific to their personalized antigens.

"QS-21 has been extensively tested in about 3,500 patients in over 50 Phase I and II studies," says Lewis of Antigenics. "Of all adjuvants, this has by far the greatest record. It's been shown to be extremely safe and extremely potent. And now it's down to crunch time" — in other words, late-phase clinical trials.

And that's happening right now, in several indications ranging from malaria to melanoma.

Milestones in Malaria

Plasmodium falciparum, which causes more than 2 million malaria deaths annually, is a complex, multistage parasite that makes its home, by turns, in mosquitoes, human blood, and human livers — each time presenting different surface antigens. *P. falciparum* has frustrated the efforts of many medical researchers who have been working for years to develop a vaccine against it. But GlaxoSmithKline (GSK) has reported a string of successes using QS-21 in combination with two other adjuvants and an antigen GSK calls *RTS,S*: a recombinant protein from an early stage of the parasite, fused to hepatitis B surface antigen, in association with a second molecule of the identical hepatitis antigen. Besides QS-21, the adjuvant mixture contains MPL, licensed from Seattle-based Corixa, and an oil/water emulsion proprietary to GSK.

"We took the vaccine into a challenge trial in the United States in the late 1990s," says Moncef Slaoui, PhD, who, as senior vice president for business and new product development, heads the clinical R&D organization at GSK's vaccine subsidiary. In that trial, conducted in collaboration with the Walter Reed Army Research Institute and published in the January 9, 1997, issue of the *New England Journal of Medicine*, volunteers were given *RTS,S* along with one of three different adjuvant formulations, and then exposed to *P. falciparum*-carrying mosquitoes. All six immunized controls contracted malaria. So did seven of the eight who received alum plus MPL, and five of the seven given the oil/water emulsion.

But of those receiving the third adjuvant formulation — oil/water emulsion, MPL *and* QS-21, with the same antigen — five out of seven subjects resisted infection, Slaoui says. "So we brought this one into clinical trials in Africa. And we completed an efficacy trial in adults that confirmed what we'd observed in the mosquito challenge trial." In this study, published in the December 2001 issue of *The Lancet*, about 250 Gambian men aged 18–45 years got three doses of either *RTS,S* or rabies vaccine (as a control) during the malaria season. They were then monitored for 15 weeks to see if they would succumb to natural infection. Not only did the

subjects show strong antibody and T-cell responses, but the vaccine's actual efficacy in preventing infection during the first nine weeks of follow-up was an attention-grabbing 71 percent.

Antigenics' Jon Lewis minces no words: "RTS,S plus that QS-21-containing adjuvant formulation is the most significant malaria vaccine ever tested."

In the final six weeks of follow-up, the vaccine's efficacy plummeted. Then again, Slaoui notes, here the term "efficacy" means a total absence of infection. "The endpoint in our trials is very stringent: detection of parasites in the blood of vaccinated subjects or controls," he says. "As soon as any parasite presence is detected, the subject is treated. But what we don't know is whether the level of immunity that remains is still good enough to combat disease. In real life, deaths are usually accompanied by a high level of parasitemia. So I do not exclude that immunity against death or very severe disease might still be sustained well beyond three months."

With side effects shown not to have been an issue for adults, GSK has been moving down the age bracket first to adolescents, and then to very young children. Trials addressing two different age groups between one and seven years of age are now reasonably far along. "There will be a long follow-up period for safety, but the active part of immunizing the children is mostly completed," says Slaoui. "Our objective is to assess whether the immune response and the efficacy induced by this vaccine in children is as good and/or as short-lived as was shown in adults. And if it is also short-lived, we would like to improve on the design to make it effective for at least six months or a year, or longer.

"We're very satisfied with our access to QS-21," Slaoui continues. "We're using the three-adjuvant formulation in other vaccines, primarily ones that are very complex to develop and that require very strong immune responses." Vaccines for hepatitis B and non-small cell lung cancer are already in Phase II studies; a vaccine using a glycoprotein called gp120 (the dominant coat protein in HIV) entered the clinic in January. Still other candidates are in preclinical development.

A 600-Fold Stretch

Interestingly, Ron Levy's lymphoma vaccine experiments at Stanford compared both QS-21 as a stand-alone adjuvant with GSK's three-adjuvant cocktail and found QS-21 alone to be just as good as the mix in eliciting an immune response, and no more reactogenic. "There was no significant difference in side effects," Levy says. In neither case was pain upon injection much of a problem.

So, what if gp120 were to be tested with QS-21 alone, instead of in an adjuvant mix?

UC Davis' Evans is principal investigator of GSK's 80-subject, ongoing Phase I trial of its HIV vaccine: gp120 plus its QS-21-containing, three-adjuvant combination. Before coming to UC Davis, Evans was at the University of Rochester, where he was principal investigator for a 37-subject, National Institutes of Health (NIH)-funded Phase II study of a version of QS-21 plus gp120 produced by VaxGen, a San Francisco-based biotech.

"While gp120 is an obvious target for a preventive immune response, it's not very immunogenic," says Evans. "It doesn't elicit much antibody, and the antibodies it does elicit don't tend to be the ones we're looking for."

Then there's the cost. Capacity constraints are already a problem with bacterially produced

recombinant proteins. But glycoproteins such as gp120 can't be made in bacteria. They have to be produced in mammalian cells, and the yield is always low. "If VaxGen's gp120 is successful, there will be a huge production problem," Evans says. "There's no way they can make enough even for the domestic market, let alone developing countries."

A previous trial had shown no useful QS-21 effect on the immune response at good-sized doses — 100 to 600 micrograms — of VaxGen's gp120. In contrast, the trial that Evans ran was designed to look at not whether QS-21 boosted a *maximum* dose of gp120, but whether QS-21 could reduce the necessary dose of gp120 and, therefore, permit decreased manufacturing costs.

Evans and his colleagues found that when the dose of gp120 was dropped to 30 or 3 micrograms, addition of QS-21 not only elicited antibody titers equivalent to those generated by high doses of the antigen, but aroused T cells, too. "QS-21 was a phenomenal adjuvant," Evans says.

But unlike Levy's lymphoma patients, these subjects complained of significant early pain at the injection site.

A study co-authored by Antigenics' Kensil and several others and published in *Vaccine* last year indicated that adding either polysorbate 80 or cyclodextrin to QS-21 significantly reduced injection pain. (Polysorbate also stabilizes QS-21, giving it a longer shelf life, Kensil says.)

"We did a 60-subject follow-on study in which we added polysorbate 80," says Evans. "But this time we took the dose of gp120 from 3 micrograms all the way down to 0.5 micrograms. And we learned that 0.5 micrograms of gp120 given with QS-21 elicited at least as good or better antibody and T-cell responses than 300 micrograms given with alum — a 600-fold dose reduction. And our *neutralizing* antibody responses — the ones that really count — were at least as good as we got lower, and trending towards being *better*: the lower the dose, the better it looked. The data are irrefutable. This is the most impressive dose-sparing effect that's been seen to date."

Polysorbate 80 diminished the injection pain, Evans says, but not enough for VaxGen, which decided to conduct its ongoing, 5,000-person Phase III efficacy trial in North America and Europe with a formulation containing alum but not QS-21.

However, Evans wants to do his own follow-on Phase II study of gp120 with lower doses or other formulations of QS-21 than were used in previous studies to strike a balance between decreased reactogenicity and robust immunogenicity. "QS-21's the best adjuvant I've ever evaluated. Unless you use something like it, these antigens can't be manufactured on a large enough scale to allow you to deliver them worldwide," he says. "But if, all of a sudden, you can cut the dose you need to give by 100-fold, which QS-21 does, you now have effectively increased your manufacturing capability by 100-fold."

Learning to Growl at Sugar

A vaccine that's dynamite for one population may be a dud for another. This is certainly the case with vaccines composed of complex carbohydrates. Take, for example, the only currently approved vaccine for prevention of pneumococcal disease in adults. *Pneumococcus*, short for *Streptococcus pneumoniae*, is surrounded by a polysaccharide capsule. The vaccine works by generating antibodies that bind to the invading microorganism's capsule, allowing the bacteria to be effectively eliminated.

“Young adults respond quite vigorously to polysaccharides,” says infectious disease specialist John Treanor, MD, of the University of Rochester School of Medicine. “But efficacy seems to decrease as you get older.”

Tissue-localized infections such as bacterial pneumonia are bad enough. But in addition, says Treanor, “the risk of *invasive* pneumococcal diseases such meningitis and bacteremia also goes up quite dramatically once you start getting beyond age 50. Rates among otherwise healthy people over 65 are about 10 or 20 times higher — in fact, maybe more like 100 times higher — than among adults in general. And antibiotics are not that effective, particularly because a lot of the mortality occurs within the first 48 hours, before you have a chance to do anything with antibiotics. So the elderly are the real target for an improved pneumococcal vaccine.”

The vaccine consists of purified capsular polysaccharides from 23 different bacterial strains, adsorbed to alum. “There are on the order of 90 or so distinct serotypes, or antigenic structures, of the pneumococcal capsule,” says Treanor, “and they’re fairly distinctive from one another, so in general, an antibody that recognized one would not recognize a different one. You need to include an example of the polysaccharide of each strain of epidemiological importance. Fortunately, 85 percent of all of invasive pneumococcal disease in adults is accounted for by the 23 serotypes contained in the vaccine.”

The immune systems of kids under two years of age don’t respond to naked polysaccharides. A similar type of conjugate vaccine against *Haemophilus influenzae* (another polysaccharide-coated microbe) had generated very robust antibody and T-cell responses in kids, so Wyeth (formerly known as American Home Products) developed a vaccine made of pneumococcal polysaccharides conjugated to immunogenic carrier proteins. “But instead of trying to conjugate just one polysaccharide to a carrier, as with *H. influenzae*,” says Treanor, “with pneumococcus you’ve got to conjugate as many serotypes as you can. There’s a limit to the amount of polysaccharide you can get on a carrier. So you’re constrained as to the number of serotypes you can include in your vaccine.”

In February 2000, the FDA approved Wyeth’s pared down, seven-serotype conjugate vaccine adjuvanted with alum. That vaccine, called Prevnar, proved extremely effective among children. “We’d actually been hoping Prevnar could rev up some arm of immune responsiveness that doesn’t occur with the elderly,” says Treanor, referring to his role as principal investigator for a Phase I trial among healthy adults 65 years of age or older, conducted at the University of Rochester over the course of about a year. “But when we tried it, it didn’t work. There was essentially no difference between Prevnar and polysaccharide vaccine alone. Prevnar was no better — and in some cases, worse.

“Then we added QS-21 to it. QS-21 seemed attractive because the amount of polysaccharide used in those conjugate vaccines is considerably less than the amount that’s given with standard polysaccharide, and QS-21 seems to have a good dose-sparing effect and had had quite a big effect with several protein antigens—in particular, with gp120,” says Treanor, who worked closely with Evans while the latter was still at Rochester.

Of the 30 enrollees in Treanor’s trial, 10 were inoculated with the standard polysaccharide vaccine, 10 received Prevnar alone, and 10 were given Prevnar along with QS-21 and polysorbate 80 — a combination Antigenics calls *Quilimmune-P*.

“Quilimmune-P was significantly better,” says Treanor. Only one person out of the 10 getting the polysaccharide vaccine, versus *five* out of the nine who were injected with Quilimmune-P, had antibody responses to at least six of the seven serotypes contained in the conjugate vaccine — a result that attained statistical significance even with this small number of subjects.

There was no significant difference in side effect profile in these three treatment arms. Treanor presented the data in May 2002 at a Baltimore meeting of the National Foundation for Infectious Diseases Vaccine Symposium.

"Having proved the principle that adjuvanting the vaccine would be useful, the next logical step is to try to expand the coverage by putting in more serotypes," says Jon Lewis of Antigenics. "Pevnar doesn't have enough serotypes in it to be ideal for older people because the range of serotypes responsible for invasive disease is broader in adults than it is in children." But in a conjugate vaccine, more different antigens means smaller doses of each of them. The constraints of chemistry call for careful calibrations of QS-21's dose-sparing capabilities on a serotype-by-serotype basis, a task likely to require partnering with a large pharmaceutical company.

Throwing the Book at Cancer

Dose sparing is not an issue with cancer patients, says Phil Livingston of Sloan-Kettering. "For cancer, you always go for the maximum antigen dose," he says.

A group led by Livingston has been conducting Phase I and II clinical trials of QS-21 in conjugate vaccines for melanoma, and breast, ovarian, prostate and non-small cell lung cancers. In these vaccines, carrier proteins are linked to up to five or six different antigens — some of them peptides and others *gangliosides* (complex lipopolysaccharides found in normal tissue such as nerve, spleen and thymus) — that tend to be overexpressed on tumor cells. "It's hard enough to raise a high-titer antibody response to a polysaccharide antigen in any indication," Livingston says. "But on top of that, all those overexpressed carbohydrate antigens on cancer cell surfaces are *self*-antigens — they're also present to some extent on normal cells — so the immune system has been trained to ignore them. That's why conjugate vaccines are so important in the cancer world."

(Vaccines targeting overexpressed self antigens differ from Antigenics' heat shock proteins in that the latter, rather than having to overcome immunotolerance, confer immunogenicity to mutant antigens that are *unique* to the tumor.)

"Really potent adjuvants are clearly necessary, too," continues Livingston. "You just don't get a detectable response *without* the adjuvant." In a study reported in *Vaccine* in 2000, he and his colleagues compared 19 new adjuvants, included in a conjugate cancer vaccine, for their ability to induce two subclasses of immunoglobins — IgM and IgG — and to trigger production of both Th1 and Th2 cytokines. "QS-21 was right at the top," Livingston says.

A couple of years ago, Livingston licensed a melanoma vaccine he'd designed — an overexpressed ganglioside called GM2 conjugated to a carrier protein and mixed with QS-21 — to Progenics Pharmaceuticals. The Tarrytown, NY, company has brought the formulation along to a Phase III trial in the United States. But preliminary results of that trial, in which the vaccine went head to head with interferon-alpha, have been lackluster. "QS-21's not the problem," says Livingston. "It did what it was supposed to do. The patients are making antibodies. The ones who have the highest titer have the best prognosis."

Progenics has started a European trial of the QS-21-adjuvanted, single-ganglioside conjugate with somewhat earlier-disease patients. But Livingston says, "I just don't think a single antigen is enough. While every melanoma seems to express GM2, only a subset of them — about a quarter or a fifth of melanoma cell lines — have enough so that you can get killing of the cell, even with the best antibodies."

Livingston's hopes lie with a multi-antigen, ganglioside conjugate vaccine. "We really need to use multiple antigens so that we can kill *everybody's* melanoma cell lines *in vitro*. There are 10 times more GD3 [another of Livingston's experimental gangliosides] than GM2 molecules on the surface of melanoma cells." GD3 is only weakly immunogenic, but recently Livingston's lab found ways to induce a good antibody response against GD3 using QS-21.

"We'd like all of our partners to go in that direction," says Armen, Antigenics' CEO.

"GlaxoSmithKline's malaria trials also are just using a single RTS,S antigen. But their melanoma trial is using a multi-antigen approach."

Risk and Reward

"Cancer patients will gladly take the risk of strong reactions because their alternative is, simply, death or worsening disease," says the University of Maryland's Bob Edelman. But when a disease resides in the central nervous system (CNS), the line between efficacy and immune overstimulation is extremely fine.

After QS-21 came out as the winner in Elan Corporation's animal tests of a host of adjuvants, the Ireland-based pharmaceutical firm anointed QS-21 as the only adjuvant for the company's clinical trials of AN-1792, the first ever immunotherapeutic treatment for a neurological disorder. AN-1792's relevant antigen is the peptide A-beta, which has been strongly implicated in formation of plaques that accumulate in the brains of Alzheimer's disease patients. The idea is that training the immune system to attack A-beta may result in a lower burden of Alzheimer's-associated plaque — and, it is hoped, slow, arrest or even reverse the course of the disease.

An 80-patient Phase I trial completed about a year ago showed an excellent safety profile, and Elan's randomized Phase II trial was fully enrolled at about 375 patients within six hours of its announcement — the fastest recruitment in clinical trial history. But after all patients had received at least two shots, more than a dozen of them developed symptoms of CNS inflammation, some quite severe. Fortunately, most patients' symptoms resolved with the cessation of dosing.

Although press reports suggest that the AN-1792 trial has been abandoned, that's not the case. Patients are still being carefully monitored not only for inflammatory symptoms, but also for signs of efficacy. Should any beneficial effect of the vaccine be found among Phase II patients (and there have been a few such reports, albeit guarded and purely anecdotal), a series of issues will have to be addressed.

First, correlation of benefit to inflammation will have to be sought on a patient-by-patient basis. If such a correlation does exist, the question becomes: Can the inflammatory CNS reaction be separated from the targeted immune response? It's possible that a rejiggering of the vaccine formulation or dosing schedule can eliminate the connection. "An overwhelming number of factors control immune response in humans," says Edelman. "It depends on the type and dose of antigen, the dose of the adjuvant, the number of injections, and amount of time *between* them." Certainly, given the total absence of any adverse reaction in Phase I, it's a safe bet that trial records will be carefully combed for any signs of difference in the design and execution of Elan's Phase II versus its Phase I trials.

But to the extent inflammation appears to be a necessary concomitant to T-cell and B-cell activation, vaccine developers and regulators alike will have to answer another, more Hobbesian question: "Is the risk-to-reward ratio favorable?" The cytokine interleukin 2 (IL-2), to name a

precedent, received FDA approval for the treatment of renal cell carcinoma, another severe disease. This is despite the fact that only 12 percent to 15 percent of patients' tumors responded to IL-2 and IL-2 *directly* kills about 3 percent of the patients. The FDA approved it simply because no other effective agent was available. And to date, there's no available drug that can arrest or reverse the course of Alzheimer's disease.

Sudden Demand for Short Supplies

A globalized society confers many benefits on its participants, but it does not come without its risks. Among those risks is the potential for the rapid spread of natural epidemics—and, more recently, of diseases deliberately sowed by bioterrorists. Recognizing these realities, the federal government has been turning its funding attention to ways of meeting the sudden need for increased supplies of vaccines for diseases thought to have been brought under control, as well as for those that recur with every passing season — influenza, for instance.

The current influenza vaccine is less than optimally effective in elderly and, even in younger individuals, may fail to provide full protection. Nor, according to Phil Wyde, PhD, of Baylor University's school of medicine, does alum pass muster as a helpful adjuvant for the influenza vaccine. But in animal studies of that vaccine conducted by Wyde, QS-21 has shown the kind of dose-sparing potential reminiscent of Tom Evans' HIV trials in which, at ultra-low doses of gp120, QS-21 achieved an immune response so strong that, to get the same reaction with alum, would have required an antigen dose 600 times as large. As was the case with the human gp120 trials, in Wyde's mouse studies this effect was apparent only at low doses of antigen.

"Every year for the last several years there's been an influenza vaccine shortage," says Jon Lewis. "According to the National Institutes of Health, there's now also a pneumonia vaccine shortage. We've shown that when we add QS-21 to the pneumonia vaccine, we get an immune response from older patients, and that's tough to do."

In mouse studies, QS-21 has induced a solid immune response to tetanus toxoid, the active antigen of tetanus vaccines, also in short supply now. And in a study conducted by U.S. Army researchers at Walter Reed and reported in 1998 in *Vaccine*, QS-21 plus an antigen from bacteria responsible for anthrax fully protected *Rhesus* monkeys against aerosol blasts containing almost 100 times the amount that would be expected to kill half of them. What's more, the vaccine wiped out all traces of bacteria in the monkeys' blood — a performance besting that of alum, MPL, and even the currently licensed human anthrax vaccine.

"QS-21 holds a huge potential, in both a quantitative and qualitative sense, for increasing our prophylactic and therapeutic vaccine stores," says Garo Armen, Antigenics' CEO. "I think we've just started to scratch the surface of this potential."

Bruce Goldman is a freelance scientific writer who lives in San Francisco.