VACCINES

Know your enemy

Vaccines are arguably our greatest medical achievement. But to what extent can they help prevent cancer?

BY MICHAEL EISENSTEIN

Cancer operates like a well-disguised saboteur. Occasionally it slips up by displaying unusual proteins, tripping immunological surveillance systems that are checking for abnormal growth. For decades now, scientists have tried to exploit this vulnerability with therapeutic vaccines — injections of tumour-associated proteins that essentially hang a ‘Wanted’ poster, helping immune cells recognize and kill cancer cells.

After a string of expensive and dispiriting defeats, therapeutic cancer vaccines recently registered their first big win. In April 2010, the US Food and Drug Administration (FDA) approved Provenge (sipuleucel-T) — a mixture of a patient’s own cells incubated with a protein expressed by 95% of prostate tumours. This was not an unequivocal victory, however. “On average, patients live about four months longer,” says Martin Kast, a cancer vaccine specialist at the Norris Comprehensive Cancer Center at the University of Southern California (USC) in Los Angeles. “It certainly measures up to many chemotherapeutics, but there’s still a long way to go.”

The problem is that as cancer develops, it disrupts the immune system to prevent an effective counter-attack. Accordingly, Kast and other researchers have been refocusing their efforts towards developing cancer vaccines as

preventative measures, before cancer sets its traps. “You don’t wait to get polio before taking the polio vaccine — you vaccinate prior to the engagement of the pathogen,” says Vincent Tuohy, an immunologist at the Cleveland Clinic in Ohio. With therapeutic vaccines “we were asking the immune system to go in and heroically eliminate this large and mature tumour load, and that’s a problem. If you want to get rid of a disease, you do it prophylactically”.

CATCHING CANCER

So far, the best examples of anticancer vaccines are those that thwart cancer-causing infections. For example, vaccination against the hepatitis B virus (HBV) offers lasting protection against liver cancer: an estimated 54% of hepatocellular carcinoma (HCC) cases are attributable to HBV. A 20-year study in Taiwan demonstrated that vaccination reduces the risk of developing HCC by roughly 70% (ref. 1).

Vaccines against human papillomavirus (HPV, see main image) can potentially have even greater impact. HPV is responsible for almost all of the half-a-million cases of cervical cancer worldwide, as well as 60,000 cases of anal, genital and throat cancer. The two FDA-approved vaccines, Gardasil (Merck,

approved 2006) and Cervarix (GlaxoSmith-Kline, approved 2009), both demonstrate remarkable efficacy in preventing infection by HPV strains 16 and 18, which account for the lion’s share of HPV-associated cancer. “I’m optimistic that we’re going to have long-term protection,” says John Schiller, head of the Neoplastic Disease Section at the National Cancer Institute in Bethesda, Maryland, and a co-inventor of both vaccines.

At least a dozen other strains of carcinogenic HPV elude these vaccines, however. The reach of a vaccine is determined by its valency, which is the number of different targets it presents to the immune system. Gardasil is effective against four strains of HPV, Cervarix two. Merck is looking to up the ante: its V503 vaccine, now in a phase III clinical trial, covers nine strains. Meanwhile, Schiller is developing an ‘omnivalent’ vaccine, derived from a different viral protein, which could offer complete protection. In tissue cultures, Schiller says, this vaccine “prevents infection by all the HPV types we’ve ever tried”. Schiller anticipates that such a broad antiviral vaccine could be routinely given to younger patients of both sexes, greatly expanding coverage — as of 2008, only 18% of girls aged 13 to 17 years in the United States had received a full course of HPV vaccinations. Sanofi-Pasteur is likely to advance such an omnivalent approach into clinical trials in the near future.

Scientists are also starting to make progress in developing vaccines against *Helicobacter pylori*, a bacterium linked to 60% of the one million or so cases of stomach cancer worldwide. In 2008, a team led by Peter Malfertheiner, a gastroenterologist at the Otto-von Guericke Universität in Magdeburg, Germany, showed that a candidate vaccine — now under development at Novartis — was both safe and capable of raising a strong immune response against selected proteins². “These antigens are key players in the pathogenesis of *H. pylori* infection,” says Malfertheiner, “and we found a very significant systemic response.” His team plans to expose healthy volunteers to a moderately virulent strain of the bacteria to test the vaccine’s protective capacity.

FRIEND OR FOE

Most cancers — including major killers such as lung and colorectal cancer — are not caused by infections. In these cases, prophylactic vaccines must target essential proteins that the tumour needs to thrive. Fortunately, the past decade has seen great progress in both cataloguing tumour proteins and developing genetically modified mouse models that closely mimic human cancer progression. Pier-Luigi Lollini, a molecular oncologist at the University of Bologna in Italy, reports early promising results from vaccinating mice against HER2/neu, a protein over-expressed in many breast tumours³. “We can prevent

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tumour onset, and the ongoing carcinogenic process fuelled by *HER2*, in mice for most of their adult life," says Lollini. His focus is purely on animal studies, but colleagues Guido Forni and Federica Cavallo are pursuing a parallel *HER2/neu* vaccine strategy in humans that could soon enter clinical trials.

Most cancer proteins are, to a certain extent, produced by healthy cells and as such enjoy a privileged 'self' status that protects them against immunologic attack. By incorporating carefully selected adjuvant molecules that enhance the immune response, vaccines can break this inherent tolerance and turn immunity against these self-proteins — without the nasty effects seen in autoimmune diseases. For example, a 2010 study by Tuohy and colleagues showed striking success in a mouse model of breast cancer by targeting the milk protein α -lactalbumin⁴. This protein is normally expressed only during late pregnancy and lactation, but Tuohy notes that expression is also common in newly formed tumours. "One of the things they do is make inappropriate proteins like α -lactalbumin," says Tuohy. In fact, vaccinated mice achieved 100% protection against breast cancer, provided they were dosed before tumours began to develop. Tissue damage and inflammation were limited to the breast tissue of nursing animals. This should not be a problem for humans, as the highest risk breast cancer patients are generally past childbearing age. "97% of women 'retire' their breasts from lactation after 40, and that's exactly the age range where 95% of breast cancers occur," says Tuohy.

Some researchers contend that broader protection could be possible with vaccines that target many different tumours. "You could potentially come up with multi-antigen approaches that cover 90% or even almost 100% of populations of different tumour types," says Mary Disis, head of the Tumor Vaccine Group at the University of Washington in Seattle. Immunologist Olivera Finn's group at the University of Pittsburgh has worked extensively with one such candidate, mucin-1

(MUC1). "About 80% or more of all human cancers aberrantly express this protein," says Finn. "The immune system sees that abnormal expression and generates a response." This response on its own is too weak to prevent cancer onset, but Finn and colleagues have developed a MUC1 vaccine that prepares the immune system in advance of tumour formation. Early trials have demonstrated a strong and potentially protective immune response in more than 50% of patients. Finn's group is conducting a clinical trial of MUC1 in Pittsburgh with patients at high risk for colorectal cancer — one of the few prophylactic cancer vaccine trials currently underway.

TRIALS AND TRIBULATIONS

Prophylactic cancer vaccine trials face numerous obstacles, including the long-term endpoints needed to determine prevention in cancer-free individuals. Schiller's work with cervical cancer vaccines has benefited from the fact that lesions arising from HPV infection are a powerful predictor of cancer risk. Gardasil and Cervarix "haven't formally been demonstrated to prevent the cancer," he says, but preventing 98% of HPV-associated lesions represents a "good surrogate marker for protection".

Finn and other researchers are using similar pathological features to select individuals likely to acquire malignancies in the near term. Finn's MUC1 colon cancer prevention trials, for example, focus on patients with advanced adenomatous polyps — unusual lumps on the colon wall. Such growths, explains Finn, represent "the latest stage of premalignant changes, most proximal to colon cancer". Likewise, Kast's team at USC vaccinates mice shortly after they develop precancerous growths in their prostate⁵. This approach straddles the line between therapy and prevention: the vaccines flag existing abnormalities but nevertheless train the immune system to block the advance of full-blown cancer. Timing appears to be the crucial element that separates a failed therapeutic vaccine from a successful prophylactic

one. "If you vaccinate early on, before there is actual cancer but while carcinogenesis is underway, you have a chance," says Kast. Results from his studies in mice are promising. "Instead of dying between 6 and 12 months, most mice were still alive at 1.5 years, and they were dying of old age, not prostate cancer."

Even with a head start from preselecting high-risk patients, human studies will be a lengthy and expensive slog — a major deterrent for many companies and funding agencies. This is especially problematic for infections such as *H. pylori*, which primarily affects the developing world. "The calculation of the cost-benefit ratio is critical," says Malfertheiner. "The developing world does not have the money to buy vaccines, whereas the developed world has good therapeutics that can treat infection." Even existing vaccines such as Gardasil remain a costly proposition for poor nations, although improved formulation and low-cost generics may address this in the near future.

Exposure for cancer vaccines also remains a problem. The first dedicated conference, scheduled for March 2011 at Arizona State University in Tucson, was abruptly cancelled in February. "We were described as being too far ahead of the curve," says Kast. However, a symposium on preventative cancer vaccines in April 2011 at the annual meeting of the American Association for Cancer Research in Florida should help stimulate interest. For researchers, promising results from early stage multi-antigen studies speak for themselves. "When I first got into the field of tumour immunology 15 years ago, I remember saying, 'I don't think I'll ever see a vaccine to prevent cancer,'" recalls Disis. "I may have to eat my words." ■

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VACCINE-PREVENTABLE CANCERS

Current vaccines against human papillomavirus and hepatitis B virus have already made an impact on the incidence of certain cancer types. Future vaccines can potentially prevent millions of different cancer cases.