Researchers Get Creative in Solving MoAb Problems

About 10 years ago, Stanford University's Ronald Levy, M.D., reported he had successfully used monoclonal antibodies to eradicate a patient's B-cell lymphoma. Since then a variety of monoclonal antibodies have been tested in hundreds of cancer patients, with findings that generally do not come close to Levy's.

The problems encountered in these early clinical trials have fueled the production of a new breed of monoclonal antibodies. Armed with radioisotopes, toxins, more human features, or more effective targets, many of these "New Age" monoclonals are faring better than their predecessors.

The Problems

A major drawback to MoAbs has been their bulky size and dispersal via the blood, which prevent them from substantially penetrating solid, poorly vascularized tumors.

"Monoclonal antibodies are not active 'magic bullets,' but passive jellyfish floating through the bloodstream," said James L. Mulshine, M.D., of the National Cancer Institute's Biomarkers and Prevention Research Branch. "The chance of one meeting up with the appropriate tumor antigen is small. At least 99.99% of the MoAbs are degraded or cleared without ever finding their desired target," he added.

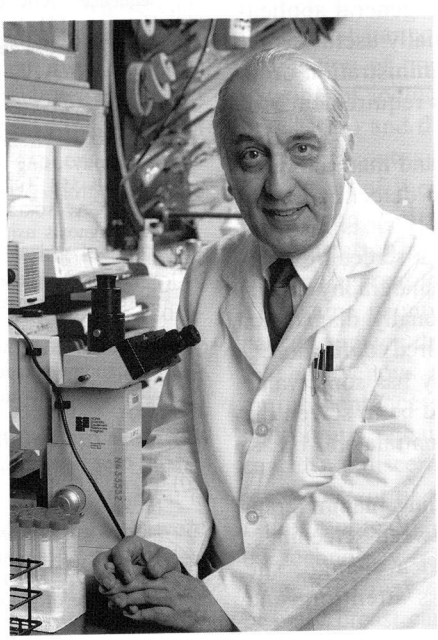
Monoclonal antibodies are also poor killers on their own, according to Thomas A. Waldmann, M.D., chief of NCI's Metabolism Branch. "They know where to go, but don't know what to do when they get there," he said.

Because most MoAbs are of mouse origin, they usually spur an immune reaction in patients, reducing their effectiveness. The specificity of monoclonals is also limiting, as many tumor cells may sport different antigens or receptors than the one targeted by a monoclonal.

The Solutions

One new technique that holds potential for boosting the ability of MoAbs to do harm is to target them to tumor growth factor receptors. By gumming up these receptors, monoclonals might prevent tumor cells from getting the growth factors they need to survive and divide.

Researchers have also started to arm monoclonals with radioisotopes.



Dr. Thomas A. Waldmann

Radiolabeled monoclonals can home in on and kill cancer cells by themselves, without additional help from the immune system. Such killing can also potentially spread to neighboring cancer cells not targeted by the antibody.

Waldmann is using these two techniques together. At a recent Bristol-Myers Squibb symposium on cancer research, he reported his results with an yttrium 90 labeled monoclonal antibody that targets the interleukin-2 receptor on T-cell leukemic cells. Interleukin-2 is a critical growth factor for these tumor cells.

Waldmann treated 14 patients, 10 of whom responded well to the therapy. These patients had at least a 95% reduction in tumor cells, a loss of skin tumors, and some had a return of normal immune function. Three of the responders went into complete remission, one of which has lasted more than 15 months. Many patients experienced a modest depletion of blood cells.

In other studies, some types of lymphoma patients also have responded to radiolabeled monoclonals. But most of the phase I clinical trials of radiolabeled monoclonals used to treat solid tumors have not had promising results. Many of these treatments failed, presumably because not enough radioactivity penetrated tumor tissues. Those patients who did respond usually had small tumor burdens at the onset of the study.

"Solid tumors are a difficult target to address," said Waldmann. "We will have to treat them over and over again to peel them like an onion from the outside. We may not be able to get to the center of such tumors in our first course of treatment."

Humanized MoAbs

Repetitive treatments with monoclonal antibodies are only feasible, however, if investigators can prevent their patients from making antibodies to them. Newly "humanized" monoclonal anti-

bodies, which substitute a human constant portion of the antibody for the mouse arm, may prevent anti-antibodies from developing.

The circulation time of such a monoclonal was six times that of its mouse counterpart in colon cancer patients, one study showed. When Levy used a humanized monoclonal to treat T-cell lymphoma patients, he found it did not prompt the production of anti-antibodies as much as mouse monoclonals did.

Researchers are also arming monoclonals targeted to tumor cells with lethal toxins. Favorable responses were seen when these monoclonal conjugates were used to treat lymphoma patients in phase I trials, according to NCI's Ira Pastan, M.D. But when the conjugates were tested on patients with breast, colon, or ovarian cancers, little or no response occurred.

Cross Reactions

The therapy has severe side effects when used to treat patients with solid tumors, mainly because of cross reactions of the antibodies to normal tissues. Patients have developed neuropathy, encephalopathy, bone marrow toxicity, and edema. Many of the patients also developed anti-antibodies.

Screening the conjugates on various tissue types for cross reactions prior to treatment might prevent some of these severe side effects, according to Arthur Frankel, M.D., of the Florida Hospital Cancer and Leukemia Research Center in Altamonte Springs. Shorter treatment schedules and the use of steroids, he added, might prevent edema.

Levy is still getting good results with his custom-made monoclonal antibodies, which target the distinguishing antigen (idiotype) found on an individual's cancer cells. He's tested the monoclonals on 14 B-cell lymphoma patients.

Eight of these patients responded to the monoclonal therapy, including two who went into complete remission that lasted at least 5 years. Minor "flu-like" side effects were associated with the therapy. Few patients made antibodies to the monoclonals, probably because their immune systems were suppressed by their cancer or previous chemotherapy.

Those patients who didn't respond to the monoclonal antibody therapy or whose responses were temporary had additional tumor antigens that were not targeted by the monoclonal used, Levy's studies suggested. He "rescued" the responsiveness of one of these patients by treating him with an additional monoclonal antibody. Cocktails of monoclonal antibodies for each patient may increase their effectiveness, he noted.

Try Them Earlier

Another way to get better results from all the different monoclonal antibodies and their attached weapons might be to use them early on in cancer therapy, Mulshine speculated. For the

Stat Bite

Cigarette Ads and Smoking Risk: Coverage in Magazines

Tobacco companies spent $355 million on magazine cigarette ads in 1988. A study of 99 U.S. magazines over 25 years provides statistical evidence that the tobacco advertising policies of a magazine influence its news coverage of smoking risks. Women's magazines in particular appeared more likely to restrict their coverage of smoking health risks if they accepted cigarette ads.

Magazines	Magazine-Years*	Probability of Coverage (% per Magazine-Year)
All Magazines		
No Cigarette Ads	403	11.9%
Any Cigarette Ads	900	8.3%
Women's Magazines		
No Cigarette Ads	104	11.7%
Any Cigarette Ads	212	5.0%

*A Magazine-Year represents all the issues of a given magazine in one calendar year.

Source: *NEJM* 326:305, 1992

— *By Tom Reynolds*

Dr. James L. Mulshine

most part, monoclonals are currently used as a last resort on patients with metastatic disease that doesn't respond to standard radiation or chemotherapy. But monoclonals are more likely to be effective earlier when tumors are smaller and have a simpler metabolism that is easier to target.

Interferon

Monoclonals might also be aided in finding their targets if they are administered with interferon. This cytokine can boost the amount of antigen sported on the surface of tumor cells. Clinical researchers are starting to test the possibility that such combination therapy might be more effective than monoclonal antibody therapy by itself.

However they are used, monoclonal antibodies are evolving at a rapid pace, thanks to clinical and laboratory studies. "There's been a learning curve from the failures," said Waldmann. "And what we've learned is just beginning to have an impact."

—By Margie Patlak

Abeloff Ends ASCO Tour; Assesses Issues Faced

Martin Abeloff, M.D., professor of oncology and medicine at The Johns Hopkins School of Medicine and clinical director of The Johns Hopkins Oncology Center, ends this week his year-long term as president of the 9,000-member American Society of Clinical Oncology. A *Journal* correspondent met with Abeloff in his office at Johns Hopkins, where he shared his thoughts on issues he faced during his presidency.

Question: *This past year the National Cancer Institute won a significant increase in its budget for the first time in over a decade, amounting to $276 million over the previous budget. How can the cancer community, and ASCO, make sure this trend continues?*

Answer: That's got to be an ongoing concern of ASCO, that we continue to support funding for cancer research, that we continue to support funding for the National Cancer Institute. That's of critical import.

I'd like to say I had some tremendously unique strategy that would solve the problem, but I think the overall strategy is to be as helpful as we can as part of coalitions, such as the National Coalition for Cancer Research. We also want to make sure we're as educated as we can be about the details of the budget for the National Cancer Institute.

Q.: *How will ASCO deal with competition for scarce research dollars?*

A.: The way we've tried to function is to make sure we do not position ourselves in a competitive way with other worthwhile areas. We've been very sensitive to that. We are not going to advocate funding for things that are important to us at the expense of colleagues in other important areas. We are going to be sensitive to the funding environment and fiscal problems that the Congress face

Q.: *Oncologists, like other physicia must answer to many masters, from government agencies to third-party payers. While judging what is the bes treatment for the patient, oncologists must take into consideration the trend toward cost containment; further, the must find a way for patients to partici pate in studies or receive experimenta procedures, many of which are not covered by insurers. What is your po tion, and ASCO's on this tangle?*

A.: The enthusiasm for saving hea care dollars is not even counterprodu tive, it's worse than counterproductiv it's destructive. It has impact across t medical community. The position we tried to take is that we can't really th of a better expenditure of the health dollar than for properly peer-reviewe clinical research.

We have spent a lot of time this y working with third-party carriers, w parties such as Blue Cross/Blue Shie with the American Medical Associa with other physician groups, trying make reasonable recommendations, obviously it's unsolved.

The term that's being used is the "hassle factor." What we need is fo tors to be able to effectively, efficie and passionately take care of patien without all this bureaucratic red tap

Q.: *One of the questions that AS faces is whether to get involved in nology assessment. Why would t organization do this?*

A.: The AMA has called ASCO many occasions for advice regardi whole issue of reimbursement for search areas such as high-dose che