Interview

Promoting Medical Innovation While Developing Sound Social And Business Policy: A Conversation With Thomas G. Roberts

An oncologist turned financial adviser discusses some intersections between his two chosen professions: price, profit, and continued innovation.

by Barbara J. Culliton

ABSTRACT: The development of “targeted biologics” as cancer therapy has made the field ripe for investment from the private sector and is changing the face of cancer medicine, while also raising important policy concerns about price, profit, and continued innovation. In this interview Barbara Culliton talks with Thomas Roberts, who sees this world from a unique perspective. Roberts, an oncologist, has practiced at the Massachusetts General Hospital and is currently thinking about innovation as a hedge fund manager. [Health Affairs 27, no. 1 (2008): w34–w40 (published online 27 November 2007; 10.1377/hlthaff.27.1.w34)]

Barbara Culliton: The new “targeted biologics” represent a major advance for medicine, but they come with a high price tag. Some predict that large pharmaceutical companies will be hurt as diagnostic tests that match drugs to patients result in less profitable niche markets. As an oncologist and financial adviser, what is your opinion about how things will play out?

Thomas Roberts: I think that the debate about the medical value of the new anticancer biologics versus their high price asks us, as a society, to resolve the tension between wanting to promote innovation, on the one hand, and to somehow control the costs of new therapies, on the other.

We currently find ourselves in an environment where the innovative pharmaceutical and biotechnology companies that discover and develop new so-called targeted therapies for cancer and other serious diseases have the power to charge what the market will bear, particularly in the United States. At least for now, that means that they can charge very large sums for these new products.

There are two consequences of the current situation. First, because profit margins can be very high for successful products, companies doing work in cancer have been able to attract a tremendous amount of investment capital. Cancer drugs in the pipeline now outnumber the next two most-represented therapeutic classes combined. The second consequence is...
that expenditures on cancer drugs are growing rapidly. A study by Cowen and Company, a Wall Street investment firm, estimates that growth rates for targeted cancer drugs over the next five years will be almost 20 percent per year—among the highest in all of medicine.

**Culliton:** From many perspectives, this is a good thing. Patients have really useful new options; some of these drugs have applications in intractable diseases other than cancer, such as multiple sclerosis; and some members of the pharmaceutical and biomedical industry are doing well. The downside is that even though these new agents have Food and Drug Administration (FDA) approval, they are still in what might be thought of as a “development” phase because we are not sure how well they work in which diseases; nevertheless, we are paying a high price for them. There is no doubt that new drugs are expensive to develop, but the cost to society of these particularly expensive products is steep.

**Roberts:** Yes, that’s right on both counts. I think what we’ve seen is the transformation of cancer drug development from a relatively low-budget endeavor, primarily sponsored by the federal government, to a complex, well-funded, international effort with a lot of commercial money. We are already seeing the first wave of output from that effort. And as you mentioned, the new agents can be more effective than older, traditional chemotherapy drugs, and they definitely tend to be less toxic. We are now routinely seeing four or five new agents approved each year for cancer, whereas twenty years ago we were seeing only one new agent approved each year.

There are also many different kinds of sponsors interested in cancer drug development today. In the past, only one or two big pharmaceutical companies, such as Bristol-Myers, were heavily invested in cancer research. Now every single large pharmaceutical company has a major cancer effort, as do countless smaller biotechnology companies. But the drugs that are coming on the market are now priced substantially higher than traditional chemotherapeutics have been. There is an increasing tendency in health plans to require copays from patients, so even patients who have insurance may be paying 20 percent of these costs, an amount that is not sustainable for many, many people undergoing care. Cancer-related charities and many companies offer some relief to those who cannot pay this portion, but these programs do not come close to what is needed. And then there is a larger public policy issue of how Medicare will pay for these drugs.

Cancer historically has not been a very large contributor to Medicare costs because patients tended not to live very long, and there have not been great options for truly life-prolonging therapy. What we are seeing now, however, is growth of 10, 12, 14 percent per year in Medicare costs for cancer drugs off of what was a relatively small base. These drugs are now showing up on the radar screen for Medicare, and as Congress is looking for ways to balance the budget, this is one area that seems ripe for legislative action.

**Role Of Targeted Biologics For Cancer**

**Culliton:** You’ve had experience both in policy and as an oncologist. We talk about these “targeted biologics” being “less toxic,” but they certainly have serious side effects. And although they often extend life, very few really cure patients. It’s too soon to know if they will. How do you see these drugs in the scheme of things?

**Roberts:** There has been a great leap forward, in my view. We are in a revolution in the way cancer is being treated, and, I think, as with many revolutions, it’s hard to gauge its success while you’re in it. But I think we’re absolutely seeing a difference. We get frustrated because it’s not happening quickly enough. But if we
stand back and put it into perspective, there are genuine pockets of innovation. Let me give one example.

Kidney cancer has been treated by surgery for 100 years, and not very successfully at that. Then, the FDA approved a biological agent for kidney cancer in the 1990s. It was very toxic and had little impact on survival for most patients, but it was at least a start. (Approximately 30,000 Americans die of kidney cancer each year.) There were theoretical reasons to think that it would be useful even though it was not particularly helpful in practice. In the past eighteen months or so, the FDA has approved three molecularly targeted agents for kidney cancer, and within the next twelve months we expect to have at least one additional approval. 

**Culliton:** Which drugs are these?

**Roberts:** The three approved agents are Sutent (sunitinib) from Pfizer; Nexavar (sorafenib) from Bayer/Onyx; and Torisel (temsirolimus) from Wyeth. The forth agent is a Genentech drug called Avastin (bevacizumab), already on the market for other tumors, which the FDA is likely to approve for kidney cancer in combination with interferon. Two of the new approvals, Sutent and Nexavar, are both pills, therefore convenient to take. Both have relatively few side effects: minimal hair loss, no nausea, and little in the way of lowered blood counts, especially when compared to traditional chemotherapy. They are fairly well tolerated, and in both cases appear to double the time patients survive without progression of their kidney cancer. That is real progress.

Liver cancer is also important in this discussion. Although not a predominant cancer in the United States, it ranks among the top five cancer killers worldwide. Particularly in Southeast Asia and sub-Saharan Africa, where hepatitis is a big problem, we see huge rates of liver cancer. And again, there have not been really significant improvements in treatment of liver cancer since the time of Hippocrates. Then again, just within the last few months we’ve heard that Nexavar, one of the drugs I mentioned for treating kidney cancer, can significantly extend survival time for patients with liver cancer.

So one by one we’re seeing these seemingly intractable tumors give way to new therapies. We obviously have to temper enthusiasm somewhat, but I do think we’re seeing the first wave of successes from the molecularly targeted therapies.

**Culliton:** Do you think that the price of these new drugs may eventually go down if the indications for the drugs or the populations of patients who can be treated successfully increases? Will supply and demand work to lower prices?

**Roberts:** Yes; I think that if the cancer pipeline turns out to be as promising as we hope it will, prices will come down as new drugs hit the market. But I also think that falling prices may also have the impact of diminishing venture capital investment in this area.

It is not just supply and demand, though. Prices will come down for several other reasons. One is public outcry, from patients and insurers alike. There’s been a public relations problem with some of the larger biotech firms in particular. Biotech firms have traditionally avoided a lot of the public scrutiny aimed at the broader pharmaceutical industry, but that may be changing. Although large biotech companies rightly point to the high cost of research and development, they have been less than skillful about explaining their prices. Now, in the face of backlash, Amgen and Genentech, two of the biggest biotech companies, have instituted financial caps on what patients will pay per year for some of their drugs. For example, Genentech put a cap of $55,000 per year on the cost of Avastin for patients below a certain income level, as long as the drug is used for any of the three tumors for which it has FDA approval. Amgen recently instituted an annual cap for patient copays on its colon can-
cer drug Vectibix (panitumumab), which now competes with the Bristol-Myers/Imclone drug Erbitux (cetuximab). Under the Amgen plan, patient copays will be limited to 5 percent of gross income. Amgen has also priced its drug at a 20 percent discount to the price of Erbitux, obviously hoping to gain a competitive advantage and generate good will.

Culliton: You noted earlier that the number of drugs in the pipeline is increasing. Competition is clearly coming to this area of cancer therapeutics. How will payers react to the additional drugs as they come to market?

Roberts: As I discussed, public relations and competition will play important roles. I think we’re also going to see increasing pressure from Medicare and insurance payers to either reduce prices or impose strict limits on who is eligible for certain drugs. As Lee Newcomer of UnitedHealthcare has pointed out, insurers may start requiring physicians to enter patients into a data registry to collect information on a drugs’ long-term usefulness. There may be increasing limits on reimbursement for off-label reimbursement. These drugs, despite FDA approval, are in one sense still very experimental. We know that they can shrink tumors; we do not know how long they will prolong high-quality life in many instances.

Culliton: Do you think that this is a reasonable policy? Or do you think that it will stifle innovation? It’s a tricky issue, obviously, because a lot has been learned from off-label use of drugs.

Roberts: That’s right.

Culliton: But not off-label use of drugs at these prices.

Roberts: Exactly. But I think, from a historical perspective, we have learned a lot from well-considered off-label prescribing. So I would hate to see it end altogether. I also think that we have reached a real inflexion point regarding returns on investment for the new molecularly targeted therapies. At least in my opinion, returns will be much greater per dollar spent today than they were in the in the past. I’d worry that any decrease in capital influx into this research would have a nonlinear, negative impact to the number of agents ultimately approved.

Culliton: So a decrease in investment could lead to decreased innovation.

Roberts: Precisely. And I worry that because we’re in this inflexion point where for years we spent, spent, and spent and haven’t gotten that much output, we have to be careful to remember that we’re just starting to get the needed output now. And only historians will know this, but I worry that we would look back and discover that we had stifled innovation at exactly the wrong moment.

Other Important Medical Innovations

Culliton: Can you compare this surge in biologics to any other really important innovations in medicine? I think, for example, of heart transplantation, which was very expensive and difficult and controversial when it began and now has become relatively routine. It remains an expensive medical procedure, but it works, and we pay for it.

Roberts: Right. I think that’s a good example. I was trying to think of other examples around medications.

Culliton: Or dialysis—not a medication, but it’s innovative technology.

Roberts: Right. As you mentioned, there are a great number of examples in the history of medicine where we learned how to apply these technologies in a more rational way after the fact. This makes me think about biomarkers—the signals that tell us which drugs might be most useful for which tumor. It’s a classic win-win if we are successful in developing large numbers of biomarkers that accurately match drug to patient in a cost-efficient way. Bruce Chabner of the Massachusetts General Hospital got me excited about this approach six or seven years ago. This effort will take more research, but it is better than turning off the spigot of new drugs because of worries about high prices. Limiting reimbursement is a pretty blunt instrument and may have the unintended consequence of stifling innovation and denying access. It would be smarter for us to actually concentrate on using these drugs for those patients who are most likely to re-
ceive a benefit and to spend money learning how to use the agents in a more rational way. After all, the thing that makes molecularly targeted agents different from the traditional chemotherapy is that they do offer some hope that we will be able to use them in a more rational way. So I think that’s where I would like to see more of the effort being spent.

Industry And Academic Involvement

Culliton: Is a lot of that effort coming from industry now?
Roberts: Yes.
Culliton: Is there a way to distinguish how much of it is coming from industry from how much of it is coming from academic research?
Roberts: It is my view that ten years ago, industry was reluctant to get into the biomarker world because they were worried that if you reduce the patient population for a new drug, you might reduce market size. But there are highly logical reasons why industry has embraced biomarker research more recently. For example, as competition among drugs for various cancers has increased, companies developing new agents must now try to differentiate their agents by being better than other drugs for a defined subset of patients. The company may have a smaller patient population, but they would have all of it. Diagnostics companies have also moved in the direction of linking proprietary biomarkers to a drug’s use.

Ten years ago, there was not a lot of competition in cancer, the field was too new, and companies didn’t need to differentiate themselves. Now they know that the playing field is changing. Niches within the broader market have become more valuable. The need to develop niches within larger indications will continue to grow. This effort will require more basic and translational research on how drugs behave in cellular pathways. This is clearly an evolutionary period and will need to be an iterative process.

The problem is that a lot of the science has lagged the clinical development, which is somewhat paradoxical. We’d like to think that it’s the science which leads and the clinical development which follows; but what we’ve found is that we can get these drugs approved relatively quickly, and it’s only been after the fact that we see in whom they really work. Iressa, which was initially approved for the treatment of non–small cell lung cancer, is a classic example. Only after it was on the market did clinical investigators discover that it is most effective in tumors that harbor certain activating mutations within receptors for epidermal growth factor. Researchers could then identify which patients had the mutation. Up to 80 percent of patients with the mutation will experience a response to Iressa, compared to less than 20 percent for an unselected lung cancer population. More than ever, industry now sees the value of collaborating with academic clinicians and scientists.

It is also clear that pharmaceutical companies are changing. They are performing biomarker research and clinical development in parallel. I developed an economic model where I examined whether a company would try to stratify patients early on to identify those patients most likely to receive a benefit, even in instances where it cuts market share by up to two-thirds. The model demonstrated that embracing a stratified development plan based on biomarkers can produce greater economic benefit for pharmaceutical companies under certain assumptions. As long as the stratified approach increases the probability of success for a given agent under development from 10 percent to 15 percent and allows for greater average duration of therapy, it can actually be rational to embrace a stratified approach where companies target only a subset of the overall market. The stratified approach may also allow companies to rationalize continued high prices for their drugs, as the clinical benefit afforded to each patient is also likely to be higher under a stratified approach.
There are a couple of good examples where we have been able to pursue a stratified approach. One is gastrointestinal stromal tumors [GIST], a type of sarcoma that can be characterized on a molecular level. Until ten years ago, these gastrointestinal tumors were essentially untreatable except with surgery, which did not provide a cure for most patients. Some astute clinical researchers realized that the drug imatinib (Gleevec), initially developed for chronic myeloid leukemia [CML], could also inhibit a growth factor receptor called c-kit. An activated form of c-kit was known to be important in the onset of these tumors. In 2001, researchers from Finland and the United States reported that Gleevec had impressive activity against these gastrointestinal tumors. So, suddenly, Gleevec had a new use.

However, after about fourteen months of therapy many patients with these stomach cancers become resistant to Gleevec because genes in the tumor itself are able to mutate. Researchers were able to find secondary mutations within the c-kit protein that caused resistance to develop. They quickly screened for molecules that could inhibit the new, secondary mutations. It turned out that Sutent, the drug I mentioned for kidney cancer, was among the first agents identified and developed as a therapy for patients whose gastrointestinal tumors progressed while they were on Gleevec. Sutent was approved as a follow-on therapy within two or three years of trial initiation. The same pattern is seen with targeted therapies for chronic myeloid leukemia. Follow-on products have emerged very quickly.

Culliton: You have talked a lot about changes in the research arm of the pharmaceutical industry. What do you think the academic world’s role is now? Do you think that its role is to go back to a more basic level and to look at the kinds of problems that made this revolution possible in the first place, or do you think that it has a different role?

Roberts: If I had $100 in research funding to give, I would donate $70 to clinical or translational science and $30 to very basic research. Why do I say that? There are some very talented, sophisticated research physicians who are seeing patients; they and their academic colleagues have the ability to correlate clinical findings with insight into what’s actually happening at the molecular level. I’ll give an example.

Initially, it seemed that Iressa would only be effective in 10–15 percent of patients with lung cancer, which is similar to or even slightly worse than what is seen with traditional chemotherapy. However, some of my former colleagues at Harvard, along with others, started to notice strikingly positive responses in certain types of patients. Some Asian women and non-smoking patients in particular appeared to have almost “Lazarus-like” responses to the agent, but other patients with this same profile did not respond. Then the “Lazarus-like” response was seen in other groups of patients. It was certainly confusing. Then, two teams at Harvard figured it out. The teams, which included clinical, translational, and basic researchers, each sequenced tumor epidermal growth factor receptor genes from patients who either responded or failed to respond to the drug. Within a very short time they had their answer. Iressa is particularly effective in killing tumors that have a particular mutation in the epidermal growth factor receptor. I think that if members of those teams had not been treating patients with this agent, they might not have been able to make the intuitive leap as quickly or might not have had access to appropriate tissues from patients. So I do think that academics need to be central to this process. They contribute ideas and observations that pharmaceutical researchers don’t have a chance to see, and when that happens, they push industry to pursue products that
might otherwise be abandoned. There can be enormous synergy there.

**Interaction Of Policy And Research Worlds**

*Culliton:* Let me ask you one last question, about the dialogue among biomedical researchers and policy scholars and insurers that *Health Affairs* has been thinking about and working to foster. Is it important for the health care policy community to be talking to people in academic research as they go about doing very basic studies, or is it more important to create or expand the dialogue that already exists among industry and insurers and policy people? Should basic researchers think about public policy as they do their science, or should they focus on research and innovation rather than policy and economics?

*Roberts:* I think that this gets to the whole issue of the value of information in public policy debates. We're talking about a very complex problem, and we need input from a lot of different sources. President Nixon signed the National Cancer Act into law in 1971, but we are just starting to see real declines in cancer mortality in the United States.

As you noted earlier, right now I spend my time investing in life science companies. Whenever an investor is evaluating a complex situation, they need to assess the variables that will drive the outcome. Many investors will assign distributions around all those variables and run simulation models to try to determine the most likely outcomes. What this process usually shows is that two or three of the variables are the most critical to the ultimate outcome. Many investors will then ask how much effort it would take to provide better estimates of the key input variables, such as the probability that an experimental agent will succeed in a pivotal trial. The investor tries to gauge how much would it take to narrow that estimate and how much an improved estimate would help make a decision whether to invest. This is a long-winded way of saying that a similar process should probably be undertaken by policymakers, who are—after all—investing society's money.

Basic scientists should undoubtedly play a role in helping to inform any debate involving the public's investment in cancer. It would be wonderful, for example, to know when we will be able to identify the most important genes responsible for putting women at risk for breast cancer. That knowledge may help policymakers in their funding decisions. The problem is that it is very difficult—if not impossible—to predict real fundamental breakthroughs. Eminent scientists may be able to offer some probabilities, but it's very difficult to actually place parameters around the likelihood of discovery. While I think it's great to get the basic scientists involved in the debates, I think that we're going to have to assign pretty wide confidence intervals around their predictions. In fact, I would just as well hope that they pursue the most interesting scientific questions without too much concern for the immediate policy implications of their work. In the long run, that's how they will do the most good.

This interview on the interface between biomedical research and health policy, along with two additional interviews published simultaneously as *Health Affairs* Web Exclusives, arose out of several projects on that topic that are supported in part by the Merck Company Foundation and the Pew Charitable Trusts.