FEATURE INTERVIEW

A Discussion with Keith Flaherty, M.D., Practicing Oncologist and Director of Clinical Research Trials

David Gennert

Photo of Keith Flaherty, M.D.

Dr. Keith Flaherty, M.D. is an oncologist at Massachusetts General in Boston, MA, and is a leader in the development of a new wave of cancer treatment drugs known as targeted therapy. He has been involved in clinical trials for breakthrough cancer treatment drugs for nearly ten years and has published over 15 papers that investigate the molecular mechanics of cancer development and proliferation. The New York Times ran a six-part series from February 2010-January 2011 highlighting targeted therapies and Dr. Flaherty's involvement in their clinical trials and the treatment of patients.

As a brief background, can you give an overview of the history of clinical research trials during the past 50 years?

Basically, for the past ten years and a little bit before that, too, there has been this transition point in cancer drug development from an era which was the era that produced what we term "chemotherapy," the set of drugs– there are about 40 of them– that are in practice, used in practice to varying degrees, all of which have common features, and it took about from the '50s with the earliest chemotherapy-type drug, up until even the early '90s– the little last trickle of new chemotherapy type drugs. And while chemotherapy has a famous reputation for harming normal cells, the reality is that every chemotherapy drug that ever made it in the world are ones that had some margin, not a big margin, but some margin of killing cancer cells more than they kill normal cells.

There were drugs that were thought and/or hoped that were safe that in humans turned out not to be safe. People died as a consequence of receiving those drugs. That wasn't lots and lots of drugs and/or people, but still, it happened. One of the things is that it created much of the environment in which we do clinical trials and research now for new cancer therapies. A lot of rules and regulations– and by "rules" I mean, not laws but how the process goes in hopefully an ethically sound way, and then also regulations that are federal regulations that generally the FDA sets in motion– are just statements, mandates that we all must follow because the FDA doesn't just govern the approval of drugs, they govern the whole process of drug development.

The point is, that starting in the '70s, into the '80s, and particularly by the '90s, there began to be this increase and acceleration in terms of the molecular understanding of cancer. And it wasn't until the '90s that it first began to be conceived as a way of actually developing drugs and therapies that would actually counter cancer at the molecular level.

Your area of focus when it comes to drug development is the new system of "targeted therapy." Can you describe what that is?

So that all sets the stage for this whole generation of what's happening in cancer therapies and what will continue to happen forever, which is the elaboration of so-called targeted therapies–drugs that target a specific thing. Sometimes you're targeting a specific enzyme that's mutated, and overactive, or turned on by mutation. That's been one of the big successes of the past ten years– drugs that work in that way– and there's a handful of them now that are standard FDA-approved therapies. You can't find, for every cancer, a set of key enzymes you can easily make drugs for. There are some that we wish we could make drugs for, but we still can't. The technology just doesn't exist. That doesn't mean it won't, but there is a lot of work to be done. And also, there's no cancer that is just one mutation, there is a whole complex series of events, and we think, just like with HIV [drug research], that we're going to have to counter multiple things, and we're still just in chapter one of countering individual things right now.

We can develop so-called targeted therapies, and they work, but they only work for some period of time before resistance emerges. We would love to cure it, absolutely, and we have instances where it is being cured, even with some targeted therapies used in the right setting, but the first project is just to try to build what HIV [research] did, but recognizing that HIV is one disease, cancer is a larger number than that.

The drugs we use definitely have a bigger so-called therapeutic index now– they don't have the same effects of poisoning normal tissue. It doesn't have no side effects, but they're not conventional chemotherapy drugs with a rather

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narrow window. The risk that we kill someone with these types of therapies is vanishingly small.

We're moving increasingly, as more and more targeted therapies prove themselves to be useful and get approved, to become a standard element of cancer therapy, moving gradually away from this risk profile that's inherent in the disease.

To give readers an idea of the process of drug discovery, could you describe from your end, as director of clinical research trials, the process of working with a pharmaceutical company?

All that I said about the understanding of cancer and research development happened outside [private] companies. This is a public enterprise. It is publicly funded research that generates all the knowledge we're talking about. There is not a single cancer target that's been identified by a company. All targets are identified by publicly funded research. Target identification is, which is to say understanding the biology of cancer, an incredibly inefficient process.

So what companies do is they take things that have been nominated as targets, generally nominated multiple times, so it is becoming convincing that something really is a potentially important molecule to aim at, and then they will develop the drugs. How much credit they should get for that is a very viable question, in terms of how much money they should be able to make off this process or how much they should be justifiably able to charge for these drugs. They always argue that it's not the development of any given drug that they're trying to recoup the money on, but all the failed drugs that were developed in parallel.

Someone like me who takes care of patients, but got into oncology because I was interested in trying to close the gap in terms of unmet need, I do clinical trials because it is a means to that end. There is a variety of roles one can play in this process. You can be more active or more passive in the process in terms of how you deal with companies and engage companies. I am pretty active in the sense that I do a lot of work that is in the earliest phases of drug development, which is the most ethically charged. It's taking an established scientific concept created by a number of individuals, labs, and institutions, and part of what I do is follow that road and be connected with the scientific world well enough, following scientific literature and beyond that, to try to keep up with the moment in terms of what things are looking sufficiently solid that it really is something that could be a significant hope in terms of a new potential therapy. Then I will seek out companies that are developing drugs in that area. I will seek them out and try to convince them to work with me to do clinical trials from that early point of something entering human development for the first time. And then of course, if it's panning out over time, I want to stick with it, because then there are more and more questions to try to address in the context of the complexity of the cancer.

There are requirements and regulations about how you study safely and what animals species, how many of them, and how long, what doses are given. All of this is judged by the FDA before they give the green light to move into humans. I rely on that. If I'm meeting a company for the first time and getting to know the scientists and doctors who work in that area, I can't know that they think the way I do. I have my own sense of risk-rewards balance– reward being efficacy, risk being toxicity– and I can't trust that they inherently have that. The FDA is the referee of that. The companies show me their evidence and data, if I'm going to be putting anything in humans, so I very much rely on the FDA to make the call about if something is OK to move forward.

So working with companies is this building of mutual trust. Mutual in the sense that they have to trust when I get my hands on their drug, I will use it wisely and carefully and be a good and careful doctor. I won't be reckless and ignore someone who is having a serious problem that might be related to the drug and march on and ultimately have something terrible happen. They have that kind of issue about who they work with. There's this mutual dependency.

Has a pharmaceutical company ever approached you with a project to research or a clinical trial and you have just said "No," that you don't want any part of it?

Yeah, it happens all the time. I'm in the position where I'm pretty well known for this sort of early drug development piece particularly. So I get those offers all the time, where I have to say 'This just doesn't look good.' Sometimes the science is super, because it was produced by fantastic scientists and I know the data, and I know that this is an area to be interested in, but they come marching with their orders, which happens every week or two, and they'll come in the door with a drug that's meant to target that, and I'll look at their evidence, and I look at it and I say 'Thanks but no, thanks.' And they'll move on.

They're not going to give up just because I won't work with them. Can they always find somebody who will agree to participate in that trial and put that into humans? Pretty much. Worldwide? Absolutely. Even in the US, pretty much. It's created a recent ethical dilemma about the US and Europe, who are pretty much on the same standing in this regard, but Eastern Europe has become a known playground for drugs of concerning background, in terms of the level of evidence to take them forward.

You had mentioned earlier how there are some treatments that just extend a person's life maybe six months, a year, or so.

Right, we really don't know. We really never know from the individual how long they can extend their life, because we don't know how long they were supposed to live in the first place. And then we don't know for even a population of people. You can look at the results of a clinical trial that were done in thousands of people. You can say 'extended survival' with an average was four months. Some people will look at it and say 'extends survival by four months.' No, no it doesn't. In some people, it extends survival by zero. In some people, four months, in some people, 12 months, and in some people, they are still kicking four and five years later having had that

drug. But then you go into your clinic to offer that therapy that's now FDA-approved, and what do you tell someone in terms of what they're going to get, in terms of benefit? You can tell them the range; you can summarize the statistical distribution of outcomes.

There is a bell curve, people will live varying amounts of time. You can describe that bell curve in the absence of therapy, and now you can describe the bell curve for lung cancer treated with chemotherapy X and Y, or targeted therapy Z. Some people get no benefit, some people get modest benefit, some people get heroic benefit. That's not true for every therapy. There are some therapies where nobody gets heroic benefit. It's somewhere between zero and modest. It is this fundamental lack of understanding about statistics, describing distributions and the variability that is inherent in the world, in biology for sure, that people oftentimes get lost on.

People hear all the time about the "cure for cancer" being developed. But if these drugs, for example, extend a person's life one year on average, do you think the public needs to reevaluate what they're expecting from cancer research?

Sure. Yes is the bottom-line answer, but to go back to the problem with the distribution of outcomes, it turns out that Herceptin, which is a targeted therapy that was one of the earliest approved, extends survival by a range of times, but doesn't cure anybody in the metastatic breast cancer setting. So, in breast cancer, it can make a difference, but it doesn't cure people.

Understand, and this is where much of society focuses and I understand why, on metastatic full-blown cancer that's all over the place That's where people think about the issue and challenges of dealing with cancer in that situation. Remember, even metastatic testicular cancer can be cured– wiped out, even in the big-tumors-all-over-the-place situation– but there are others that can't be touched with available therapies. There are metastatic diseases you can't do a damned thing about with available therapies, so there is a spectrum, to be sure.

But the point is, that none of us, myself included, are interested in sitting back and waiting for cancer to show up in the full-blown metastatic state and then trying to wrestle with it then. We're interested in trying to cure it. That's the way cancer drug development works. It's a societal agreement. It's the whole operation. It's everybody involved– doctors, patients, their overseers. When I say 'society's agreement,' there are probably some people in Des Moines who aren't aware of what rules and regulations govern this process. Maybe more people need to be informed about it. We try to inform people, like patients, who walk in the door. I have yet to meet a patient who is savvy about this entire process we've been talking about So when someone walks in the door, and we're serving their options with them, and if there's this available option that's good and they have done that and it didn't work, and now they're out of those options, I have to explain to them what I just explained to you, this testing era for it because here's what's known or not know about it so far.

If you're focusing a trial on a drug that has been projected to extend life six months or a year, or that's what the estimate was, is your approach in the trial different than if it were a drug that was projected to be more efficient?

We can't project that. [Let's say] the drug's been in trials up to a certain point for melanoma, and we're getting the sense that people are living longer that we thought they would. By 'getting the sense,' I mean we haven't tested that yet, just this group of people received this drug, and [by calculating] their survival distribution, they seem to be doing better than the average. We could be getting lucky. We could just have happened to pick 30 people unintentionally who happened to live longer from their melonoma. Sometimes you have this sense that the projection is based on what you've observed. But you have a certain amount of confidence or non-confidence based on the number of people you treated, the characteristics of them in terms of how bad the disease was.

Then if you're going to try to test it, the issue is 'Are there are instances in which you need to test it or not test it?' Meaning that it looks so good, it looks so much better than available therapies, then you don't need to test that. The answer is yes. In the area of targeted therapy, the FDA has approved drugs on the basis of phase 2 trials, meaning non-randomized trials. B-RAF drugs likewise get that kind of treatment. Because it looks too much better. You can't do a phase 3, unless you believe at the outset that there is so-called equipoise, which is to say that you think the outcome is most likely the same between the two groups. You're randomizing them between treatment A and treatment B, and you can't do that if you know that treatment A is better than treatment B.

You can't know that one is going to be better and do that. That's not a problem. That's a problem solved. If the FDA doesn't agree, then you yell at them a bit. This came up with the B-RAF story, and it's been coming up. A new drug comes along, it's quite safe, we know that early on, and it's looking pretty damn effective. The drug just gets approved on the basis of phase two. It's happened multiple times. More often than not in the era of targeted therapy.

One of the things that the Times article didn't delve into is that this is quite a global issue. Would it be appropriate for a drug, a new kickstart, to get approved in the US and not anywhere else? Is that ethical? In a grand society way, to have privately approved drugs? Because we have different levels of proof needed here than elsewhere. Whether its ethical or not, it happens. It absolutely happens, that some drugs don't get approved elsewhere because the regulatory authorities in that place value a therapeutic index differently. They want more efficacy or less toxicity, or they want some bigger separation than what is available with a given therapy.

It was becoming clear in discussions between the company and the regulatory bodies– [in] the US and Europe and Australia – of 'What do we need to show? What evidence do you need to see?' in advance of doing it. Basically, the US had its answer, different European countries had their answers, and Australia had its own. And so they got different answers, which creates a situation of maybe you have to do a phase three randomized trial to satisfy some people or countries

and not others. Because I was centrally involved in the development of this drug, I got asked about this many times along the way, and my answer would be 'For what I need to know about a therapy, we're good. We know what we need to know. We don't need a randomized trial. This is a terrible disease, available therapies are terrible, and this is an advance, period. And, I think, I don't know, that the FDA would agree with that and it would become an available therapy for me and my patients here.' But I couldn't say, and as I was hearing feedback coming from other corners of the world, that that would be true elsewhere. Would I have a problem going to bed at night with the idea of endorsing a development plan that wouldn't get the drug the same chance of being made available because the trials weren't done? Yeah, I would have a problem with that. Why are Americans somehow more deserving than other people in other parts of the world? This gets complicated pretty quickly in terms of trying to come with a single way of judging [a new therapy].

We've been hearing a lot about end-of-life care and options lately. As an oncologist, I'm sure these scenarios arise all the time. What are your thoughts on what should be legal, encouraged, or even prohibited, as it relates to end-of-life care? How far do you feel ethically comfortable to go, in terms of leaving a morphine drip on or some other measure to all but kill a patient?

I go that far routinely Which is to say that my stance, and I think it's a common one, is to have no limit in terms of stopping suffering. By that, I mean if there is a symptom that I can improve, I improve it. Some people then say 'If someone's suffering, ending their life could be a way to stop that suffering.' I've never done that, and I can't envision doing that, but you absolutely can raise the issue that a morphine drip is somewhere in between that. It's good for pain, it's good for shortness of breath, and that if someone's got excruciating, terrible pain, and a little bit of morphine won't do the job, and a fair amount of morphine won't do the job, you keep going to try to get the pain to reasonable level. And in doing so, someone is now comatose. I would say that's OK, completely OK, because the alternative is that they be in excruciating pain, and I feel as though I would not be serving my purpose as a physician in my view if I let that state of affairs be.

Does that ever result in someone not living as long? We talked before about not knowing how long a [cancer patient] will live. Well we don't know that when people are actively dying, right then and there, meaning they will be dead in hours to days. Do I know that I shorten someone's lifespan by six hours? I don't know that. Might I have? Absolutely. Am I OK with that? Absolutely. The standard I have to serve is my own internal standard. There is no standard. There is no law about this. That is, that I will not hold myself back, I will not stop giving narcotics, I will not give less narcotics in the face of cancer pain because I would be concerned that it would shorten someone's life by a day or a few days.

I have discussions with patients about what my stance is, as it becomes reality. It's hard to have these conversations, to be honest. How much of this discussion can you and I get into now? But having a discussion with cancer patients who have a finite lifespan– which is to say a 95% likelihood that they're going to die of this cancer; maybe they will respond to therapy so well that they're cured, which happens 5% of the time– when do you have the discussion about how we are going to manage, as you get increments closer to, dying. This whole distribution of potential survival for that one individual sitting in front of you. I've done this, and those conversations have very little staying power for those patients. They will feel differently about things as they march eventually, at different paces, towards a confrontation with end of life. That's when it becomes quite real, when someone's sitting in the office having this conversation when they're feeling perfectly well and then when the circle of events comes around. None of us are that bright. This is not an entirely intellectual conversation; it's an emotional one, and it's a combination of the two. It starts hitting chords that don't get hit in life until one is in that situation. It comes up with cancer patients all the time. It's not so simple. It's a murky area.

Do you and you colleagues tend to engage in social media or other internet-based communication or collaboration?

Scientifically, yes. On topics of our understanding of disease and the like, yeah, it happens all the time. That comes up increasingly now, trying to come up with ways that aren't just emailing about individuals, but more systematically, [and it] has become a much more common way of communicating. There are other ways to create ongoing dialogue in various wikis, posting comments, but not in the blogging kind of way. And sometimes we have scientific collaborations or communications that are password protected on sites of that nature.

That has been multiplying from what I've seen, but in my own field and my national/international community of colleagues and those who I collaborate or communicate, it's become fairly standard practice. It used to be medical conferences where it would be in-person [dialogue], but those conferences would happen every so often, and you would have to travel there, and so this is a much more fluid way. It hasn't supplanted the conference world, partly because my children will have an easier time doing this, but for many of us, there's a different type of communication that happens face-to-face.

Compared to where we are now, in terms of the flow of information, I would say it's a totally different game. There's this acceleration in terms of how we evolve hypotheses, test them, then recycle and modulate our model of how we think about, in this case, melanoma. How do we subdivide the disease into meaningful, discreet, biologic entities in cancer? In cancer, you can make the statement that it's not all one beast. That's much of what my career is– getting lab-based investigators back and forth so that they understand what's happening or not happening in the clinical trial, and likewise so that I'm informed by what they're doing.