Disease Models & Mechanisms 1, 90-93 (2008) doi:10.1242/dmm.001396

The future of cancer therapy: an interview with Gerard Evan

Gerard Evan is a founding editor of DMM, whose work uncovered a crucial role for the tumor suppressor Myc in cellular apoptosis. Here, he talks about the future of cancer therapy and the responsibility of academic science in tackling these complex questions.

Will there be a cure for cancer? The heterogeneity of the disease and its regulation by the signaling cascades that are fundamental components for the survival of all cells make this one of the greatest challenges in modern medicine. Gerard Evan's work helped define the role of transcription factors, such as Myc and p53, in the regulation of cell death pathways and the formation of cancer. Now, many are looking to regulation of these proteins to provide effective, new treatments for cancer.

Fifteen years after your lab demonstrated the importance of Myc as a regulator of cellular apoptosis, its altered expression and mutation are known to contribute to the genesis of cancer, but some people think that it is an 'undruggable' target. Do you agree?

I don't think that anything is undruggable. You don't have to be very old to remember when kinases were deemed undruggable because one could never get the specificity one needed. Then it turned out that you didn't need it to make a good drug after all. I remember when therapeutic antibodies were never going to be practical because no one would ever be able to manufacture them. Now, some of the top cancer drugs are kinase inhibitors or therapeutic antibodies. I think one of the problems is that we have been shoehorned for too long into thinking that there is only a very limited repertoire of druggable molecules, and Myc isn't one of them. Myc exerts its effects through protein-protein and protein-DNA interactions, as does most of biology. Such interactions are inherently difficult to drug. However, if we give up on proteins like Myc, we will only ever be able to modulate, inhibit or perturb a very small number of the information transfer machines in biology. But, I'm fairly sure that we will be able to modulate Myc interactions in a specific way. After all, there are already new drugs emerging that do interfere with protein-protein interactions. Examples of this are the inhibition of p53 and Mdm2, and the new Bcl2 inhibitors. In principle, Myc should be a really good drug target. It is expressed in very low levels, even in tumor cells its turnover is very quick and it has to form a dimer with its partner in order to work. If you can't drug that, I'm not sure what you could drug.

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What about the fundamental need for Myc in the basic survival functions of all cells?

Recently, we used a dominant negative inhibitor of Myc, which we expressed systemically in a mouse using a 'switchable' system where the inhibitor transgene is regulated by a controllable, exogenous factor. When we switch on the inhibitor, we shut down Myc in the whole animal. Tissues that would have been proliferating stop, but amazingly, the animals are fine.

This work suggests that therapeutically altering the functions of Myc, and possibly other proteins that are fundamentally important to the function of normal cells, might not produce the toxic results that were previously anticipated.

I think that is right. I have been working on Myc for a long time so it is very easy for me to preach about how Myc is different from everything else. Nonetheless, it may be that Myc is uniquely positioned for therapeutic targeting. The reason is that if you go much upstream of Myc, say to Ras and kinase signaling pathways, you encounter signaling machines that are involved in many processes in the cell in addition to proliferation. By contrast, Myc is, as far as we know, exclusively involved in coordinating the many disparate biological programs that, when coordinated, allow cells to expand within their somatic environments. This means that blocking Myc shouldn't interfere with much outside of cell proliferation. At the same time, Myc maintains all of the intracellular programs that are needed for normal and tumor cells to expand including metabolism, changes in the cytoskeleton and cell cycle progression, and extracellular programs that activate proteases that carve out space for the cell and its progeny to expand into, as well as signals for angiogenesis and so forth. This implies that blocking Myc will not merely arrest tumor cells but also pull apart the entire microenvironment that the tumor cells have created. This seems to be exactly what happens in the switchable transgenic models that we, Dean Felsher, and others have made. In tumors driven by

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Myc, pulling the plug on Myc triggers tumor collapse not only because the cells drop out of the cycle and differentiate, but also because the microenvironment and vasculature supporting the tumor collapse as well. I think Myc may be in this sweet spot. It is not involved in everything, just in proliferation and it turns out that normal tissues can sort of get by without proliferating for a rather surprisingly long time without falling to pieces.

You also work with p53, another fundamentally important protein that many people are looking at owing to its central role in cancer. Can you imagine a day when it is targeted in cancer therapy?
Yes, despite over 46,000 publications on p53 in the literature there are still so many things we don't know about it. We don't know why it is a tumor suppressor, when it acts during the evolution of the tumor, or how it suppresses tumors. Indeed, we don't even know which of its many functions are involved in tumor suppression. For example, both Manuel Serrano's and our laboratories recently provided evidence suggesting that p53-induced cell death, in response to DNA damage, is not involved in tumor suppression. It may well be that p53 originally evolved as a mediator of DNA damage and that it brings that legacy with it, even though it has recently been re-tasked to the job of tumor suppression.

We do know that p53 is activated by stress, and in response to being activated by stress it does lots of tumor suppressive things such as killing cells, arresting them, putting them into an autophagic state where, at least for a limited amount of time, they can hide without many nutrients, and activating their repair machinery. It is clear that the p53 pathway, either p53 itself or its upstream or downstream signals, are inactivated in the vast majority of human tumors. One problem is that we don't know if that is because p53 senses a small number of common elements that are peculiar to the tumor state – some sort of common conduit of oncogenic signals that p53 is sensing – or, if p53 recognizes many different signals that, between them, cover each of the different tumor types. We don't know, and because of that we really can't predict the consequences of restoring p53 function in an established tumor. Although we know that p53 is selected against during tumorigenesis, we don't really know whether there is a transient period during which the evolving tumor has to do without p53, or whether the absence of p53 is continuously required. For example, if you take the common idea that p53 is a tumor suppressor by being the guardian of the genome, its principal tumor suppressor function is to prevent cells from surviving after they have acquired mutations. Once a cell has acquired all of the mutations it needs to become a tumor cell, it couldn't care less whether p53 is there or not and restoring p53 in those tumor cells is not going to make much difference. However, Scott Lowe's lab, Tyler Jack's lab and our lab have shown that, at least in experimental mouse model systems, tumor cells of varying types remain dependent on the absence of p53 throughout their pathological history, which means that restoring p53 would be good news for cancer treatment. All of the upstream signals to activate p53 are there in cancer cells, as is all of the downstream machinery for p53 to execute destruction of the tumor.

How one would restore p53 is a different issue. There are already some potential experimental drugs that are able to 'bend' mutant p53 back into a native configuration so that it becomes active again. Once in that state, it can execute its tumor suppressor function. In some tumors, p53 remains functional but it doesn't 'know' that it is in a tumor cell because the oncogenic signals coming to it are blocked in some way, for example by amplification of the intrinsic p53 regulator Mdm2, which keeps p53 activity low. Nonetheless, p53 can still be activated therapeutically in these tumor cells by other triggers such as DNA damage. In tumors where p53 itself is lost, where even mutant p53 is absent, restoring its function is a more intractable problem. Maybe you could re-introduce p53 using gene therapy, although I suspect that is unlikely to be a particularly effective way forward.

One completely outrageous idea for cancer therapy is to reprogram and rebuild the tumor suppressor mechanisms in human beings. There is already evidence that if you equip a mouse with extra copies of p53, rather than the two that we are graced with by evolution, it takes longer for those extra copies to be eroded by inactivating mutations, and tumor suppression is much more robust. To do this in humans would involve the ethical nightmare of modifying the human germline. It's going to happen one day. We can do it in mice and it suppresses tumorigenesis in those animals. As far as we can tell, there is no reason, apart from ethical concerns, not to do it in humans. At the moment it doesn't seem that it would be particularly dangerous or cause problems, but of course until you do the experiment you don't know. The thing we always have to remember about tumor suppression is that it is not optimized by evolution for a long and healthy life. It comes at a cost to the organism, so evolution selects for tumor suppression mechanisms that are good enough to maintain the organism, or the majority of organisms, up to reproductive age. Beyond that, evolution has no part to play. Tumor suppression has to be good enough to get us to reproductive age and, because it is good enough to do that, it usually gets us quite a bit further to 60, 70 or 80 years of age. However, our anti-cancer mechanisms don't need to be that good – it's just lucky that they are and that we live so long. This means that it is not beyond the ability of human beings, with intellect and science, to augment the tumor suppressor mechanisms that we have, such as p53. I believe that we can do this and that we should do it, even if it means modifying the germline.

A move such as making germline changes in humans makes us very dependent on mice recapitulating human disease appropriately and responding similarly to genetic modifications. What do you think of the mouse models for cancer?
[*Laughing*] I have said on several occasions that the problem with the mouse is that human cancer doesn't recapitulate cancer in the mouse.

So, the problem is the human?
There are many differences between mice and humans. There are differences in lifespan, metabolic rate and in the architecture of many tissues. Still, we are quite close evolutionary cousins. I think primates and rodents are only about 75 million years apart and there are many more commonalities than differences. One issue is that we don't really know why mice are so much more susceptible to cancer per cell per unit time than humans. A mouse has 100 times fewer cells than a human being, so you might think that it has 100 times less chance of one of those cells acquiring oncogenic mutations, in which case it should be 100

times less likely to get cancer than the human. By the same logic, whales should not exist, because by the time they are born they should just be tumors floating around in the ocean and that is clearly not true. In some way, the risk of cancer is clearly scaled to the size and longevity of the organism by evolution, and we really don't know how that works. So, we don't know if there are really qualitative dramatic differences between the mouse and human or whether this is something that will not be biologically important. I suppose it will be a mixture of both. The point is that many of the aspects of tumor biology that we are interested in now entail understanding tumors, not as clonal monocultures of cells like a cell line, but as a deranged tissue with many different types of cells interacting with one another. The things that make tumors are hijacked programs that are part of normal cellular development, repair and regeneration. There is not much that is new in a tumor, it is just how processes are regulated or, in the case of cancer, not regulated properly that makes it a tumor rather than normal tissue. The problem is that we don't know how to do experiments on tumor cells, surrounded by all of the other cell types they need for support, in a culture dish. We can only do this type of complex research inside an animal. The only animal that we can really do it inside of is the mouse, because of their tractable genetics and because they are easy to keep, maintain and manipulate. Nobody likes doing experiments in animals, but unfortunately we cannot think of tumor cells existing in isolation. We have to study them in intact tissues and the mouse is the best model we've got. We have to do as much as we can in the mouse and then do the more difficult experiments that map those findings onto the equivalent process in human beings to see how good our mouse model is.

There seems to be a difference in the roles of academia and industry in the quest for cancer therapy. Are these just different business paradigms in the cancer field or are there different contributions to be made by each?

I think you touch on an important question. Academia works on the basis that academics have the security, which means salary support and resources, to do clever things that they think are interesting and important without having to deliver 50 hamburgers an hour all day every day. Security, time and freedom are the whole point of the academic setting. One of the problems I think you see in some scientific systems is that academics are now being forced to generate more and more of their personal income from their grants. This sets up, what must be the ultimate conflict of interest. 'You have to believe my data even though it is paying my mortgage.' It also sets up this very visceral urgency and sometimes panic in academics, because if academics don't keep continuously generating tangible results, then they won't get their grants renewed and if they don't get their grants renewed then they won't be able to get their kids through school or keep their house. This problem is particularly acute in the USA, where almost everybody in academia gets the bulk of their salary from grant income. In a situation like that, I don't think that academia is that different from industry. It should be, but it is not because they both need to generate products all of the time and stick to timelines. It's a shame because I think it is the responsibility of academia to not function like a small business but to serve as the arena for more imaginative, risk-taking enterprises.

I think the most undervalued quality in a good scientist is courage. After all, we're all smart and everyone works incredibly hard and has a lot of focus. But courage needs to be nurtured by encouraging people to take risks. It feels like we are moving into a phase of society that is very risk adverse. People want to know 'look, you made one really important discovery in the past 5 years, so every year you should make 0.2 discoveries and we want to see it written up and we want a progress report.' No imaginative, creative human endeavor ever works like that. Creativity can't be shoehorned into that paradigm, and if you try to do so, you generate an academic environment that is basically like a rather impoverished business environment without the venture capital and other things that make the business environment work.

The great strength of the commercial environment is in getting people together as teams to work together on things that need a lot of sorting out. The way that academic labs work, and the only way that they should work, is that people come into the lab of the principal investigator and spend a few years there, and in that time they want to show that they are capable of creating their own discoveries, so that they can then go off and do their own thing. I think that one of the most difficult things in any lab is to get people to collaborate and to breed a constant sense of collaboration and collegiality in their lab. When push comes to shove, only one person will go as first author and only one person will go as the last author. We just haven't yet found a civilized and fair way of dealing with all the authors in between. We need to change what we are trying to do in academia because science has become almost like the Olympics. You see the same 'top' people at meetings again and again and again. It's like a club, a nice club, but it shouldn't be like that.

After all, the great thing about academia is the freedom of exchange, tempered with a healthy lack of respect for titles and prestige. But to create such an environment, without any hierarchy or patronage, requires a solid sense of job security. The institutions that look after the careers of academics have to understand that science is above all a social enterprise. It is about shared ideas, shared discoveries and people working together because they enjoy doing so.

All career paths have bottlenecks. In this model of academia, what do you use as criteria to determine who gets to play on the team?

Anybody should be able to play on the team if they have the ideas and are prepared to really think about them.

Does that mean endless support for science?

No. I think there are periods in the world where doers are dominant and there are periods in the world where thinkers are dominant. We are moving, in biology in particular, into a period where the doers are pre-eminent. There are just so many clever things that we can do. Sequencing this, that and the other genome, high-throughput analysis of this, that and the other process. I'm sure that all of it will one day be useful data. But what interests me is the thought process of science – testing novel hypotheses through experimentation to understand a process, rather than describing it in ever greater detail. A lot of people go into science in the first place because they believe they are going to have time to think, and then take intriguing ideas and hy-

potheses and test them out. For that to happen, they need to have space, freedom and the trust of the people around them to allow them to do it.

Sadly, in this age of accountability and counting beans, it seems that few people trust scientists. We have to be constantly accountable for what we did yesterday and what we are going to do tomorrow. This is strange because nobody asks that of composers or artists and yet scientific creativity comes from the same place as the idea for a new musical composition or painting. Science is a creative, almost artistic, endeavor and constraining it with time points and milestones perverts it into something that is driven by process, not innovation.

It doesn't need saying that most of the great discoveries in biology and science were fortuitous and came from people who were not trying to solve a particular practical problem. Obvious examples include monoclonal antibodies, interferon, organ transplantation, and tumor viruses. All of these discoveries came from people who were just interested in a basic scientific problem, and while the fruits of their discoveries were fantastic and they were doubtless very happy about it, it wasn't what they set out to do. Of course, I'm not saying that everybody should be like that. However, it is important that we continue to allow a sizable proportion of the scientific community to be able to think and be creative, with the space, trust and security they need to do the brave thing.

You are being interviewed, not for the first time, as a cancer expert. You are someone who understands what causes cancer and what the possibilities are for curing it. Did you ever picture that for yourself when you were growing up?

I always thought I'd be a scientist, long before I even really knew what that was. I went through the typical pattern. First, I was interested in dinosaurs. I went on from that to reading books on relativity that I never understood. I was an avid science fiction reader, which I credit with helping me think outside the box. The influence of science fiction may seem rather trivial, but for me I think it is actually very important. I got interested in biology because when I was 10 years old I went to see a crazy B movie called Fantastic Voyage, in which people were miniaturized in a submarine and injected into someone's bloodstream. I thought 'Wow, this is really cool'. The rest is my history.

Encouraging the imagination of kids is the most important thing. You have to let them think what they want and show them how interesting things are. Nowadays, it is chillingly clear that we have to do more to show kids and young adults how interesting science is. We have to show them that it's not dry and boring, but fascinating and fun. After all, being a scientist means that, at an incredibly early stage in your life, people support you to do whatever you want. You can do things that nobody else in the world is doing and, sometimes, things that nobody else has even thought about doing.

My own focus on cancer came quite by chance. My mom died when I was young, my father remarried and my step mom at the time was a secretary in the London hospital at the Cancer Research Institute. I would go up there and look at all the laboratories and see sick patients and think 'Wow, that would be so amazing to do something about cancer.' I didn't know what cancer was! But I knew it was a big problem that concerned everyone.

Now, of course, I realize that cancer is such a fascinating piece of biology because it deals with mutations in genes that regulate processes in cells and tissues, and deals with fundamentals such as how cells seem to know who they are, where they are and how to behave, even though they are presumably only aware of their local, and more diffusely, their general, surrounding environment. It offers glimpses into levels of order and structure that are fascinating to behold.

Gerard Evan was interviewed by Kristin Kain, Associate Reviews Editor. We greatly appreciate his time and willingness to share his personal opinions about cancer biology and the paradigms in which scientists work to bring better health to human patients.

Is there someone whose work in model organisms and approach to research practice that you find particularly inspiring? If there is someone you would like to recommend as a subject for 'A Model for Life' piece, or if you have a suggestion for someone you would like to interview, please email us at dmmreviews@biologists.com.