

# Perspectives on Research

*jur* interviews Terry Platt, Ph.D.

*Dr. Platt is Professor of Biology, with a joint appointment in the Department of Biochemistry and Biophysics at the University of Rochester.*

*jur*: Could you tell us about your educational and professional background and experience?

Platt: I grew up in Chicago; my father was a physicist on the faculty of the University of Chicago. I went to Swarthmore College for my first two years as a physics major, but I decided to transfer to the University of Chicago. I had to change my major to mathematics, because that was the only major I could transfer to and I figured it would be good for me no matter what I did, and I enjoyed Chicago a lot. At that point, I ended up going to the Peace Corps for two years, teaching math and physics to African high school students. We were trained in New York City, and while I was there it turned out that I learned something about teaching, because their job is training teachers, so we got really good training. My father has always been on the fringes of and interested in molecular biology, and when I was in the Peace Corps he sent me a copy of Watson's book, *Molecular Biology of the Gene*. And eventually I found myself at Harvard for graduate work on the lactose repressor with Wally Gilbert and Klaus Weber. For my subsequent postdoctoral research at Stanford, I joined Charles Yanofsky's research group of around fifteen scientists, all of them initially working on different areas of the tryptophan operon: Some were doing genetics, some enzymology, some biochemistry, a few were doing gene regulation, and some were sequencing DNA or RNA. Over the three years that I was there the group made some breakthrough progress, and it was great to be part of all that. Then I joined the faculty at Yale and was there for ten years, before coming to Rochester.

*jur*: What kind of research did you do in graduate school?

Platt: I worked on the lac repressor molecule, which is a tetrameric protein that binds to a site where polymerase initiates transcription of the lactose operon, encoding the enzymes responsible for the metabolism of lactose. In the absence of lactose this repressor binding prevents that operon from initiating transcription of its messenger RNA. I worked on the structure-function relationships in the repressor and, for example, was able to show that if we treated it gently with

trypsin we cleaved off part of the molecule that turned out to be the DNA binding part, though it still bound the inducer molecule perfectly well. It was a very exciting time to be a graduate student.

*jur*: When did you first get involved in research? How have opportunities for undergraduate involvement in research changed since then?

Platt: Between my sophomore and junior years I got a summer job with the Woods Hole Oceanographic Institution. The next summer I worked at Scripps in La Jolla, where we did some hypothesis-directed research to understand diving mammals and physiology. It's hard to answer the question about changing opportunities, because I was at different schools than Rochester, but in general, all around there are huge opportunities that I didn't have. At the University of Rochester, we take pride in our undergraduate research opportunities. I would certainly say that here it's generally very easy to get involved, though you often have to start out by cleaning glassware and preparing media. If you go to lab meetings, people will know faculty members you can get involved with.

*jur*: What kind of research have you been involved in over your career?

Platt: There were two major areas that I got involved in. One stemmed directly from my post-doctoral work, and gave some interesting results that were separate from my postdoctoral involvement in the attenuation of transcription, though that gave me the tools for looking at signals at the end of the messenger RNA. I've always been interested in gene regulation and loved the idea of all the different varieties of transcriptional control at the promoter end, namely repressors or positive activators. But I thought, "Well, there are many people out there with established labs, and if I go out there and try to compete in the currently hot arena I'll get killed, unless I'm stupendously lucky or brilliant (neither seemed likely)." Then it occurred to me, "Maybe the important thing to do is to carve out my own niche that nobody's thinking about too much right now but might be really important in five years." And so, that is exactly what I did. Since I had already been working with messenger RNA sequences at the end of the tryptophan operon, it seemed natural to investigate how this molecule

(RNA polymerase, which copies DNA into RNA) knows where to stop. It's the same question as if you were studying sentence structure: how do you know where to start? You start because there's a capital letter at the beginning of the sentence. How do you know where to stop? You stop when you get to a period. At a colon or a semicolon or a comma you don't stop, you pause. The problem is one of genetic punctuation, and I chose an aspect of punctuation that was not already well-established and crowded. As I got interested in this area, I started working in yeast as well, and as a consequence of a sabbatical with Ira Herskowitz at UCSF I learned enough lore for that part of my research effort. Initially I was interested in the transcription termination of *E. coli*. The big problem there is that my earlier work was with lower eukaryotes rather than prokaryotes, and there are enough differences between the two systems that made introducing many of the same techniques that I value more difficult. That soon devolved into a really different area of the same general problem, which is that messenger RNA in eukaryotes is in fact processed. This masked anything that we could imagine to try to find out about termination, but it turned out not very much was known about the process of RNA 3' end formation, so we pursued that instead. These two big areas of transcription termination in prokaryotes and messenger RNA 3' end formation in yeast have really comprised most of my work.

*jur*: What makes the rho utilization (*rut*) site what it is?

Platt: We simply don't know. My laboratory group and many other laboratories have tried for years to figure out what it is about this particular region in bacteria that confers the ability to terminate transcription. Every hypothesis that we've thought to test has failed. There are some ideas in the literature, and we know that cytidine residues are important; but if I had to guess, I would say that we don't know enough to ask the right question. It's lurking there, but I would guess that we haven't yet asked the right questions. It's like self-splicing RNA molecules, before that was accepted as "real" – researchers spent a decade trying to purify the protein factors that they were sure had to be in there to carry out the splicing. So thoroughly was everyone imbued that RNA can't be an enzyme that they kept trying to purify their RNA more and more and it still kept doing the splicing reaction, albeit very slowly, and that kind of fit in with their prejudice that there had to be a really tiny contaminant there doing it. And, so, back to your question, the answer to the *rut* site is that we don't know, and if I had to guess I'd say there's some kind of sequence or structure there that is being formed, possibly in conjunction with one or more other proteins, and that it doesn't happen until the right circumstances are present. We've tried all the sequence bashing that we can do, and it hasn't given us an answer. So the point is that we need to know more information before we can do an experiment that tests this hypothesis. The concepts don't exist. We're just missing one critical piece of the puzzle, and as I say, if I had to guess, it would be in the realm of RNA structure.

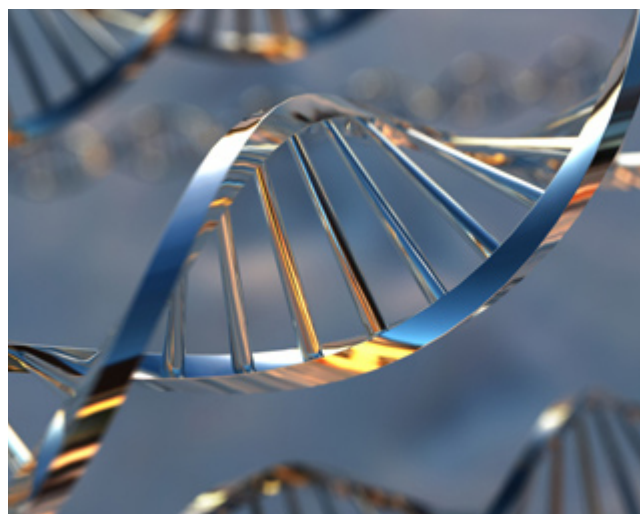
*jur*: What is the role of rho protein and what experiments are you performing to discover more about it?

Platt: Rho protein acts at these mysterious sites, and we don't know how it acts. Let me tell you a true story; this is one of the big breakthroughs we had in my lab. It had been

known for some time that rho factor has an RNA-dependent ATPase activity. Our idea was somehow that the hydrolysis of ATP would help it catalyze transcription termination by the bacterial polymerase. I remember very clearly our breakthrough on its function with this site. I was at a Gordon Conference; these are summer scientific conferences with between 100 and 200 scientists. A lot of the great moments at the Gordon conferences happen outside the lecture halls, where people go for hikes in the woods or sit around the bar in the evening and talk science or go sailing and talk science. One day at lunch I was sitting with Howard Nash from the NIH and he said, "Hi Terry, how are things going? What's new with rho factor?" So I said, "Well, we're trying to figure out how it works. The puzzle is that that we know it can hydrolyze ATP, and we think that we know there is an elongation bubble, where the DNA is separated and the RNA is base-paired with part of the bubble and somehow the rho factor bound to the RNA has to be able to separate this bit of RNA, the last 10-12 base pairs that's duplexed to the DNA, which is about one turn of the helix." And as I said "helix", I thought to myself, "That's it! Rho has to be a helicase, because its job must be to unwind that helix and separate it from the DNA strand!" So I went back to my lab, very excited. We did the first experiment in a week to test the hypothesis by making an artificial duplex with a piece of RNA that we know would be a substrate for rho, and annealing it to some single stranded DNA, to form a duplex region, of some 20-30 base pairs. It is amazing to be able to come up with a hypothesis in the middle of a sentence and to go back to your laboratory and test it; and we found out that in this case it was right, based on the control. That happened a long time ago, and a big difficulty in the interim has been that we haven't learned a lot more about rho factor in the intervening years. Another question is how the system I just described, which is independent of RNA polymerase, actually coordinates its action with RNA polymerase to get it to terminate.

*jur*: What kind of research is going on in your field at the University of Rochester, and how can undergraduates get involved?

Platt: There is a great deal of research going on at UR; in immunology, microbiology, biochemistry, genetics, and so on, an enormous variety of projects. The best way to get involved with any of those is to talk to a faculty member who has gotten



you interested in something. Also, talk to any of your friends who are working in laboratories and find out what they like and don't like. You can also check the departmental or faculty websites and rosters to find out who is doing research in various areas. At that point, you just start knocking on doors, looking for possible jobs in the labs.

*jur:* The workshop approach to education at the University of Rochester is well-known to students here. Could you tell us about its history, particularly with your own biochemistry classes?

Platt: There's a problem in high school because you're encouraged to be your own study person, and you're often not supposed to work together – students are taught that they must answer problems on their own. And so many people were pointing out that this is not a great way to work. Indeed, if you think about the real world after college, in what arena does anyone have a job where you're not supposed to talk to anyone else about what you're doing, or get other people's advice, or brainstorm? That's basically the origin of this. And at the University of Rochester, Vicki Roth, the director of Learning Assistance Services, came here around 1990 and did some pilot studies. Then in 1995 she and Jack Kampmeier came up with a grant proposal and got money from the NSF that helped actually set up and implement the workshop model here. When I was starting to teach the junior level biochemistry course I thought workshops could be very beneficial. So I asked Vicki Roth about setting up workshops in biochemistry. And so we talked about it, and she gave a lot of advice and then helped get it started. I think it's a great complement to a lecture course because it really gets students involved and working together. The value of workshop is that there are three things you are going to be asked by future employers once you leave college: Are you a critical thinker? Do you know your subject matter? Do you work well with other people? They want to know whether you have engaged in synergetic activities where the work that comes out of the group is greater than the sum of the abilities or skills of the individual members.

*jur:* How does the workshop system help students make their way through difficult subject matter and better understand the material?

Platt: I think the workshop helps in a number of different ways. One way is that it shows everybody that they're not alone in their difficulty mastering the subject. But the other side is that it generally helps people in showing them the material from a variety of viewpoints; it helps them in organizing the material as well. I want to add that one of the areas of research that is going on at the University of Rochester is research on education. This is a study that I just passed out based on my workshop experience in biochemistry, after I'd been teaching the course for three years, in which we actually asked whether workshops are working at all, and how we know. And the answer is that yes, they are helping. Students who attend workshops do better than those who do not. That's the area of research I am currently involved with now. I study the effects in variation in workshop design that will be beneficial to students. And I certainly think that the University of Rochester is in the forefront of institutions with respect to this area of research. I think the answer to the last part of is that medical schools, in

particular that of the University of Rochester, have Problem Based Learning (PBL) as an integral part of the curriculum. In fact, this is the way that real physicians and real scientists work. You get together once a week and you talk about the problems – research or medical – that you are working on. As a University of Rochester undergraduate it is very useful to have this sort of thing available.

*jur:* What direction do you see the domain of research going? Do you feel that some of the ethical debates raging between the political and scientific communities are impeding medical research?

Platt: I think the major impediment is a lack of understanding of what science really is, and the idea that hypotheses are there to be tested. Faith-based initiatives are fine, but they cannot be confused with science. People can believe what they want but if you want to prove that something is true or not true, you should always be prepared to propose and conduct experiments to test your hypothesis. And for sure, politics is always going to impinge on various aspects of science; sometimes it will end progress, but there are checks and balances imposed, but sometimes they can be a good thing.

*jur:* How does research develop a student, as opposed to rote memorization and reading?

Platt: I think there are two or three parts to that. One is, getting back to the idea of hypothesis testing and the methods of strong inference, that if you start applying those ideas to critically finding out the truth rather than being persuaded by an idea and then trying to fit the facts into what you're looking at, it's certainly a benefit – most research you get involved in will force you to do that. But I think more importantly, the moment you start doing research of your own, you create interest because of the ownership component that is really exciting and attractive. And part of the excitement, which goes hand and hand with frustration, is that when you're doing research you're trying to do something that nobody in the history of the world has ever looked at before, and if the answers were to emerge easily then you wouldn't be doing it because somebody else would have done it long ago. The cutting edge of research is at the same time a very exciting area and a very frustrating area – you have to be prepared for that, and you have to like the process of research and get away from the idea that you're only in it for the answers, because the answers are often a long time coming. Finally, it's healthier overall if you can be satisfied with small but steady incremental advances rather than always striving for the big scientific coup. You can't push the river, but you can steer the canoe...