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Chemical Biology in a Time of Transition

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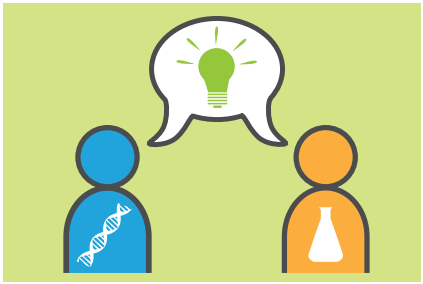
Known as the Chinese curse, the old saying "may you live in interesting times" will, I am sure, bring a wry smile to many as we contemplate the turbulent period in which we now live. Nonetheless, troubled times do bring opportunities. We have the chance to do vital things that would be a hard sell in more settled periods; hence the Obama administration's advice to "never let a serious crisis go to waste". Thus, in the spirit of change, I would like to take this occasion to outline my views on the state of the union between chemistry and biology and highlight one path to the continued growth of this field.

There is no question that the field of chemical biology is now firmly established. There are multiple journals dedicated to the subject; chemical biology meetings are being held around the world and are attracting ever increasing numbers of people; and several departments have changed their name, or have been created, to reflect this new spirit of "bipartisanship" between the chemical and biological communities. Perhaps most tellingly, a large number of graduate programs in chemical biology have been established in the U.S. and overseas: if we are branding our students chemical biologists, then presumably we think the field is no fad! While the foregoing affirmation of chemical biology is a classic case of "taking coals to Newcastle" given the eponymous title of this journal, it is nonetheless important to recall the extraordinary speed with which all this has come about. Chemical biology did not formally exist when I was a postdoc back in the mid-1990s. What did exist was a growing feeling among many, myself included, that the kind of science we were doing did not fit neatly into one of the established disciplines such as biochemistry or bioorganic chemistry. Thus, I think "chemical biology" quickly became a rallying point for a slightly disenfranchised group of mostly chemists. Of course, we all struggled to define what "chemical biology" really was and what it was not, but hey, that was a mere detail.

So here we are over a decade on, and as I have already noted, the field has gained considerable traction. Nonetheless, it seems to me that chemical biology is entering a transition period, and necessarily so if it is to remain vibrant and continue to grow. To a great extent, the field has been driven by the development of new methods, not surprising given the natural proclivities of the chemist for inventiveness—this is what we bring to the table. For the most part, these methods have been developed in the context of proof-of-principle-type studies that do not penetrate too far into biology. I would be the first to concede that some of the work from my group on the use of inteins illustrates this point. There are many reasons for this initial emphasis on model systems. First, it is sensible to develop a method in the context of a well-behaved test system, because one can presumably apply the analytical tools needed for optimization of the approach. Of course, an added virtue of this strategy is that it leads to quick publications, thus relieving the pressure that all investigators feel to maintain a certain pub-



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lication rate in order to achieve tenure or obtain/retain grants (that could be the subject of another essay). Those who have gone on to apply their methods to *bone fide* biological problems (*i.e.*, defined as such by a biologist) know that nature tends to give up her secrets reluctantly; this takes its toll on publication rates but does put your method through its paces. The third "benefit" of using a model system is that it usually obviates the need to collaborate. Many young investigators are aware of an unwritten law against excessive collaboration. Hence, they may feel pressured into abstinence. I have seen a great many tenure packages over the years and have been saddened by the number of times candidates emphasize (I think because they feel they have to) in their dossiers that their research output was achieved *sans la collaboration*. I am saddened because I see collaboration as the life-blood of chemical biology. Let me be absolutely clear here, by collaboration I refer to investigator-initiated "artisanal" research involving at most two or three groups and not big science initiatives. I think some of the best work in our field has been the result of small teams of chemists and biologists (broadly defined herein) working together on a problem—often one that the former was not aware of and that the latter had no idea how to tackle. Certainly, I believe the best work from my own group has been fueled by collaboration. Indeed, I have gotten to the point now that I begin to fret when my group undertakes something with a biological component to it *without* a biological collaborator—I worry that maybe we are deluding ourselves over the importance of the problem.

I believe that the continued growth of our field requires that we move away from a focus on tool development in the context of model systems, to tool application to important biological problems. Such a transition, which I sense is well underway, is helped by *more* collaboration, not less. As I see it, there are two approaches to collaborative science of the type defined earlier. In the first, a chemist with the right tool and a biologist with the right question somehow team up and make hay. There are plenty of splendid examples of this, and it is a model that improves with age. The better known a technology becomes, the more successes it has had, and then the more people will come to you with interesting problems. This has been my experience. The shortcoming of this model is that the chemist is in some sense gambling from the outset that his or her tool will be broadly applicable to biology. Of course, some bets are better than others; for example, if you come up with a bullet-proof way of controlling the activity of designated members of a large family of proteins, say, kinases, then you will probably do just fine. Nonetheless, I suspect that plenty of really clever chemistry-driven techniques are out there that either have too many moving parts to be palatable to biologists or for whatever reason fail to make it onto their radar screens. I have also seen this first-hand. Indeed, I offer the following piece of advice to any chemist who wants to develop a new technology platform with presumptive applications to biology: run it by as many biologists as possible before investing a lot of time and effort.

This then brings me to the second collaborative model in which a chemist and a biologist are drawn together by mutual interest in a problem. In this case, the resulting chemical biology tool may be useful only in this specific area. An example of this would be a small molecule discovered using a phenotypic screen. This collaborative approach has the big advantage that the problem has been vetted from the outset; thus if a tool can be developed, at the very least it will have an impact in one area. Implicit in this model is that the chemist has chosen to focus his or her efforts on a particular area of biology rather than developing a technology platform *per se*. For chemists to make such a commitment, it almost follows that they must have spent time in a biological laboratory at some point in their training. Thus, I consider it a very good thing that more and more chemists are choosing to carry out their postdoctoral work in biology or biochemistry laboratories. For the budding chemical biologist, this is a terrific investment in the future; it provides broad exposure to the big problems in contemporary biology and, importantly, provides networking opportunities that may enable collaboration down the line.

Beyond the different routes one can take to investigator-initiated collaborative science, a critical variable in the equation is the environment in which one works. We are all, to a degree, shaped by the environments in which we find ourselves. I have the very good fortune to work at an institute that truly encourages collaborative science. The physical proximity of the laboratories and the lack of a departmental structure at Rockefeller are a catalyst to be sure, but more importantly, junior faculty are not penalized for working as part of a team. A number of places share these favorable characteristics, and it is not surprising to me that they have become centers of chemical biology with a capital "b". Of course, there are some places where collaboration between the life and physical sciences is a little bit more difficult, either because the chemistry department is distant form the biology department or medical school and/or because there is a lingering cultural bias against this type of science. Things are rapidly improving to be sure, but it is nonetheless advisible for a fledgling chemical biologist to perform the necessary due diligence before accepting a position in a traditional chemistry (or biology) department. It is not a good sign if the chairperson of a chemistry department cannot point to the biology department or medical school on a campus map, or if the chairperson of the biology department views chemical biology as small-molecule screening only! Seriously though, faculty candidates should ask themselves to what degree would collaborative science be pos-

sible (or embraced) if they worked in a particular department.

Chemical biology has always been difficult to define. In thinking about the broad sweep of work that is published under the chemical biology banner, it seems to me that some stratification at the level of technology emerges. As I see it, chemical biology strategies have been developed that allow one to interrogate biology either at the level of entire systems, specific biological pathways, or a single biochemical step within that pathway. The first of these, the systems stratum, encompasses all the "omics" techniques that allow one to catalogue the levels, activities, and modification status of primary and secondary metabolites *in vivo*. The second grouping comprises the more focused chemical biology tools that allow a particular biochemical pathway to be manipulated, usually in cells, in order to elucidate its precise role in a fundamental process or in disease. The last set of tools is geared toward understanding the molecular mechanisms underlying a given biochemical step; typically, these methods bring the resolving power of chemistry to the analysis of reconstituted systems *in vitro* and are used in conjunction with traditional methods of biochemistry such as structural analysis and enzymology. A number of powerful approaches have emerged in each of these areas, approaches that have proven their worth by contributing to our understanding of various biological phenomena. In the best examples, investigators are able to move through the aforementioned strata as dictated by the problem they are studying. For example, a proteomics tool might generate a hypothesis that is then verified using a more focused methodology, or the physiological relevance of a mechanistic insight from *in vitro* work might be explored using a cell-based tool. In this regard, chemical biologists should not be resistant to the idea of using techniques developed in other chemical biology laboratories. There is no need to reinvent the wheel; if a good method already exists, use it. Better still, collaborate with a group that is expert in its use.

In this essay, I have tried to make the case for increasing the amount of collaborative science practiced by chemical biologists. The strength of chemistry as applied to biology is the ability to ask precise and quantitative questions about how the molecules of life work. Often, we need to develop new methods to do this. However, we should always ask ourselves whether a new method really offers an improvement over an existing approach. I believe that the answer to this critical question only comes into focus when we attempt to apply the approach to a real biological problem. Thus, the sooner one takes this step the better, and more often than not, the quickest way for a chemist to do so is to collaborate with a biologist.