Drug Design and Development

Part II: Reflections from an Academic-based Center

*by Paul Erhardt*

As a follow-up to a previous issue of *Chemistry International*, which conveyed a feature article about the University of Toledo’s Center for Drug Design and Development (UT’s CD3) accompanied by a conference report on its special anniversary celebration [C/I 2014, Vol 36, No 6, p. 8 and 27, respectively], I am delighted to share a few insights that I have gained while serving as the CD3’s Director during the last 20 years. Intended for IUPAC readers and the medicinal chemistry community at large, my comments may be particularly useful for the numerous academic-based drug discovery centers bursting upon the scene of today’s pharmaceutical enterprise. I will focus upon just three topics: people, people, and people. As I have emphasized repeatedly within the CD3’s newsletters, it is our active participants who constitute the true heart-beat of our academic-based, core resource center. And I submit that it is only the enthusiasm of these active participants that can make an R&D center successful over time, regardless of a given technology’s promising utility or a parent institution’s array of physical resources and prestigious reputation. In this regard the CD3 is extremely fortunate to have been blessed with a long list of talented people who have always been committed to selflessly working together as a team to accomplish common goals in a collaborative manner.

My first ‘people comment’ is directed to a drug discovery center’s need for a range of highly interdisciplinary scientists. A critical mass of five or more individuals is key to establishing the core expertise required to seriously undertake drug discovery and development. The range of disciplines should encompass: molecular pharmacology/biology/bioinformatics; computational chemistry/molecular modeling/docking; synthetic medicinal/process chemistry; intellectual property (IP) management and patenting; analytical/bioanalytical chemistry with competency in devising validated Good Laboratory Practice (GLP)-compliant methods; pharmacology/pharmacokinetics/toxicology; and physical pharmacy/formulation. While the need for this breadth of expertise quickly becomes apparent to anyone reading about the overall process of drug design and development [1-3], I would like to share two subtle additional insights that may be useful in allowing a cohesive team to flourish within the distinct environment of an academic setting. First, despite frequently outstanding individual qualifications, it is generally very difficult for faculty within U.S. institutions to serve as members of a team dedicated toward providing core resources for others. These same faculty are typically obliged to operate in a tenure system that places high priority on teaching and personal scholarly activity, while service duties are finally recognized at a distant third. Despite even the highest levels of willingness and sincere collegiality, it remains difficult for faculty to devote serious time toward advancing someone else’s technology when they are obliged to develop their own scholarly works and research activities. Thus, the cadre of experts needed for a drug discovery center is better assembled as non-traditional, non-teaching faculty, i.e. as ‘research faculty’, which typically means that these people will be on non-tenure track lines. Working along this type of strategy the CD3 was able to assemble a critical interdisciplinary mass by bringing in extramural dollars at an annual rate of $1M or more in direct funds for several years. This, in turn, supported more than 20 staff members and participating graduate students at its peak. Seemingly a remarkable success, this strategy has been repeatedly acknowledged quite favorably by UT’s administrators, who also become the beneficiaries of the very hefty indirect dollars that accompany such high levels of extramural research funding. But in an insider’s closer analysis, is this really such a success? Here’s the quandary which then constitutes the second, more subtle insight to conclude my first ‘people comment’: we were so busy during this funding heyday trying to accomplish the numerous milestones associated with the aims of the CD3 grants, sponsored research agreements, and contracts, that we had very little time to help anyone else. While ‘successful’ within the context of our own lab, we could not even begin to fulfill the CD3’s broader mission to truly assist others. On the positive side we were able to serve as a source of equipment/instrumentation, offer a wide range of considerable expert consultation, and importantly to join collaborative grant submissions on behalf of others. However, actual preliminary data is often needed for grant submissions by those that need core assistance the most, and our free time to help generate this real data in any major, hands-on capacity was extremely limited. So what is the key insight I might offer to address this dilemma? Any administration assembling a drug discovery center as a core resource should be prepared to fund the salaries of several research staff whose paid mission is to serve the organization at large. Most U.S. institutions can already do this in some ways,
such as by aligning the IP/patenting component (generally staffed by non-tenure track positions within a university’s typical technology transfer office) as a collaborative operation with the center. The suggested new positions might be funded only in part—ideally at some level just above 50% so as to allow the incumbents to be fully entitled to the organization’s standard benefits packages, providing a strong base for longevity rather than continual turn-over. The remainder of these salaries could then be funded by grant or contract applications to extramural sources that the research staff would be expected to submit in collaboration with regular faculty across the campus. The staff’s partial rather than fully funded base would thereby act as further incentive for establishing these highly desirable modes of collaborative initiatives. Having finally come to appreciate this specialized arrangement myself, I will admit that, although it is quite easy to convey as advice, in practice the CD3 is still striving to adopt such an ‘ideal’ arrangement—we rely on a very mixed version at this time. As will be indicated below, the Director is a full-time tenured faculty who can buy himself out of didactic teaching with extramural funds that are then used by his academic department to hire a visiting professor to cover the teaching gap. This, however, has been working exceptionally well in our case because it also affords the Director a formal academic advisor/mentoring relationship with a constant flow of truly inspiring graduate students. In line with the recommendation, the CD3 has formed a strong collaborative relationship with UT’s technology transfer office/staff that goes even beyond just IP strategies and patenting matters. This is synergistic in our case because the Director happens to be a U.S. Patent & Trademark Office (PTO) certified Patent Agent. The CD3’s synthetic medicinal chemistry staff and students likewise remain strongly supported, but in this case largely by several collaborative, extramural grants wherein the demand for this particular component appears to be highly needed by several ‘Project Teams.’ Alternatively, the bioanalytical core is only minimally funded in a similar manner, while the computational and biology cores remain struggling during these tough financial times to gain funding from any/all sources so as to just be able to sustain their presence within the CD3’s overall structure.

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My second ‘people comment’ pertains to hiring the director for a newly forming drug discovery center. A regular faculty member is again unlikely to have the time and appropriate effort priorities to accommodate this service role. However, this may be less important if the director functions more as a scientific administrator and consultant than as a hands-on, lab-based practitioner trying to directly assist others’ technologies in a manner analogous to the center’s core technical staff. In my case I was hired as a tenured Full Professor, but I am also allowed to use extramural funding to ‘buy out’ my teaching load. This has worked very well for me personally and is the only way that I can do the homework needed to become even adequately informed about the wide variety of projects in our center’s portfolio. The director must advocate appropriate strategic options and offer the best advice to progress a given technology, while optimally deploying center and network resources in conjunction with addi-
tional resources from Federal or contract research organizations (CROs)—all while trying to move forward as fast as possible with the least expenditure of precious funding. The sheer number of CD3 team and project-specific group meetings that accompany the different projects takes a huge toll on one’s time. Alternately, a regular faculty role affords an opportunity to mentor PhD and MS graduate students who, in my experience, have continued to be a wonderful gain in the overall personnel. In a ‘win/win’ synergism these students can engage in projects as a complementary part of their own lab-based thesis work. This key relationship is further described in the last ‘people comment.’ Finally, in terms of structural arrangements it should be noted that while operating as team in all regards, the CD3 strives to minimize administrative activities and instead practices a reductionist approach toward bureaucratic paperwork when entertaining new projects as well as ultimate bean-counting upon completing them. Thus, for any given project our goal is to determine what’s needed for its advancement and what might best be done by us, immediately followed by ‘getting the latter done.’

In terms of the director’s expertise, the CD3 has tapped the pharmaceutical industry on both of its new-hire occasions, first for my predecessor and then for me about twenty years ago. In large part this strategy is also being practiced by today’s newly forming centers. However, the importance of hiring a medicinal chemist with pharmaceutical industry experience to direct the early stages of drug discovery may not be nearly as important today compared to a few years back. Having traversed an era of heavy reliance on high-throughput screening (HTS) of random compound libraries by the private sector, it is now questionable how much additional savvy individuals from industry may be able to bring to early-stage, rational ligand design compared to an academician who has also been well trained in classical medicinal chemistry principles. For example, today the average ‘customer’ knocking on the door of a U.S. academic-based drug discovery center will typically be a molecular biologist who has uncovered a novel feature of a signal transduction pathway for which they have screened either an NIH library or a commercial vendor’s ‘drug like’ library. A hits compound already in-hand, the expertise needed at that point (after a highly recommended confirmation, by the way, of the hit’s supposed chemical structure) will be ‘hit follow-up’ testing based upon the methodical elaboration of structure–activity relationship (SAR) details gained in a collaborative manner between chemist and biologist. Even when the quality of such initial hits as adequate leads for progression of the technology becomes debatable (as is so very often the case), this still represents a good point to embark on intelligence-driven ‘directed library’ exploration (perhaps accompanied by earlier rather than later scaffold-hopping if there is indeed skepticism about the initial hit’s quality), rather than continuing in yet another excursion across large, structurally diverse libraries using ultra-HTS that relies upon a random search to address perceived shortcomings in the hit. Alternately, there appears to be considerable value in the special knowledge uniquely gleaned from industry experience associated with the practical development of a preclinical candidate compound. Still requiring considerable research but now in more of an applied mode, the drug development process is also governed by strict analytical procedures and standard compound comparisons at every step of the way, and in the U.S., a considerable amount of protocol-driven experiments mandated by the FDA, particularly with regard to drug safety. Thus, depending upon which end of the drug design and development spectrum a given center wants to emphasize, the nature of the credentials and background needed by the director can be somewhat different. Ideally for a comprehensive center, a director should have the complete gamut of rational (efficient) ligand design / hit follow-up credentials, plus actual drug development experience. He/she must also be willing to accommodate an academician’s pay scale after having come to fully appreciate the unique attributes that an academic environment has to offer within this overall enterprise.

My third and final ‘people comment’ is simple but is perhaps the most important: cherish the academic base and be prepared to nurture the students. On behalf of the latter, encourage collaborative arrangements with third parties able to recognize the students’ inherent potential, if not their immediately applicable technical attributes, and discourage arrangements that are exclusive of your center’s academic ties via strict contract specifications. In almost all cases, clear win/win scenarios can be devised for the benefit of both the student and the center’s collaborative partners. It is from the academic arrangement that an unending flow of bright and eager new participants will flow into the center. I have learned that whatever their level, these students can often be a tremendous source of creative ideas because of the questions they seemingly cannot help but ask, as well as always being a source of unwinding energy generally coupled to unbridled enthusiasm. The camaraderie that can be nourished among interdisciplinary scientists when coupled across generations, rich international cultural backgrounds, and widely differing levels of professional maturity can itself lead to distinct synergisms. These apply to accomplishing serious research and educational
initiatives, and also for simply deriving some important fun while doing so.

The accompanying three pictures provide glimpses of some of our CD3 people across the last 10 years, the first two while ‘at work’ in the lab or out in the field, and the third while taking a break to share in some ‘fun.’ The first picture also attempts to capture the pride that the CD3 takes in its educational activities. Having stepped into one of our synthesis labs, I am surrounded in this picture by several students all of who have now gone on to become accomplished medicinal chemists. The second picture is one of our ‘Soybean Harvest Teams’ gearing up for a field trip to collect infected plants as a source for a unique family of phytoalexin natural product compounds that demonstrate high potential to treat breast and prostate cancers [4]. The last and most recent picture shows the CD3 staff and students gathered to celebrate the U.S. New Year (Chinese New Year and Diwali celebrations followed) while enjoying one of the CD3’s periodic ‘Friday lunch outings’ at a local restaurant. These three pictures serve as a perfect closing to my overall remarks and again emphasize the importance of a center’s “people, people and people.”

References