C.A.R.E. in Natural Products Research*

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Abstract
The acronym C.A.R.E. is used to explore some of the parameters in creating research awareness in the contemporary natural product sciences and to encourage graduate students, postdoctoral fellows, and junior faculty to develop good research practices and ethical awareness in developing excellence in their individual and collaborative research programs.

Keywords
natural products, research practices, collaboration, ethics, academic enterprise, publications

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Introduction
The iconic sculpture “Cloud Gate” created by Sir Anish Kapoor has resided on the lakefront in Chicago since 2004. Commissioned as a part of the Millennium Park development, it is locally known as “The Bean,” and comprises 168 highly polished, curved, welded, stainless-steel plates. What has this magnificent sculpture to do with natural product research? A lot as it turns out. It is a classic example of Chicago Art Reflecting Excellence, our first example of C.A.R.E., the topic of this article.

The Bean is fun to visit, it is playful, it does not take itself too seriously. You, the viewer, create your individual experience, and are constantly entertained in the changing shapes of your image and of the reflected background environment. Even though it is static, one’s movement makes the experience highly dynamic. At the center point underneath the sculpture one can even “disappear” to remain only as a dot. Perhaps a reminder of our transient Earthly nature. It mixes light and dark, and some say it represents the struggles and unification of the masculine and feminine, which fosters creative beauty. Being three-dimensional, any view is a partial one, and as one moves around the sculpture, the rigid and powerful Chicago skyline morphs and becomes fluid, distorting reality differently at each instant. Most of all, the sheer innovation of “The Bean” is inspirational and encourages one to think completely out of the box. Those attributes are what is experienced in the environment of research, and what is to be expected as we move the sciences and the applications of the available technologies forward into areas that are presently “out of the box” and into the fluidic unknown of the Fourth Industrial Revolution.

The welds of the plates are filled, rubbed down, and polished to create a seamless experience to sight and touch. A reminder of the extreme care necessary in conducting research, and that presenting the results, translating the bench experience and the outcomes, for the public domain is a long-term responsibility that requires careful construction and finishing. It reminds one of the “polishing” and then more polishing, to provide an error-free manuscript, or a grant proposal, or a presentation.

Professor Yoshinori Asakawa at “Cloud Nine”

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*Dedicated to a very dear friend and colleague, Professor Yoshinori Asakawa, on the auspicious occasion of his 80th birthday.

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“The Bean” reminds us also that what we may perceive as solid evidence may not be. That the interpretation of results can be fluid in time, depending on our perspective, and that the keys to success in research will always be innovation and excellence in the product, the results, and their translation into society. In the era of the Fourth Industrial Revolution (4IR) and the Quintuple Helix, where vast accumulated knowledge is available almost equally to all scientists across the world, it will be that playful essence of creativity, that risky, out-of-the-box endeavor, that will make the difference. That higher level of creativity can be referred to as a “disruptive innovation.” Something so intensely transformational and inspiring that it sets new directions, new possibilities, and most importantly enhances the human experience. One has only to look at the Second, Third, and Fourth Industrial Revolutions, and consider the innovations, and the status and activities in natural products research in those periods of time, to see the significance of disruptive innovation (Table 1). So, what is C.A.R.E.? And why is it so important, especially for the younger researchers and junior faculty, to whom this article is addressed.

Care is defined as: to have thought or regard for (verb), or to be a concern (noun). C.A.R.E. in this context is a range of expressions of caring which embrace, in a playful and concerned manner, aspects of natural products research and our respective roles in developing a productive and meaningful career in those areas of the sciences. So C.A.R.E. is an acronym, and here we will briefly look at about 100 examples of what it may mean in the research environment. Let us begin with the notion that the natural product sciences focus on a Curiosity About Responsible Experimentation and acknowledge a status update with respect to the role and expectations for society.

### Coming of Age is Relatively Easy

For natural products it has been a long period of growth. Natural products research is coming “of age” only now, and it has taken over 200 years to reach this point. “Of age” in this context meaning fully integrated scientifically into society, and in doing so fulfilling an anticipated and important contributing role in the health and welfare of society. We are not fully “there” yet. There are still many aspects in society where we are not contributing to our technical capacity. For example, in assuring the quality control of a traditional medicine, a dietary supplement, or a phytotherapeutic preparation for the unequivocal benefit of the patient, contemporary science and technology vastly exceeds current societal impact; any issue of the leading journals in the field will affirm that. The capacity is available to develop a much-needed third class of medicinal agents for the majority of the world which assures that a quality, safe, effective, consistent, and accessible (QSECA) product\(^1\)\(^-\)\(^5\) can be formally approved for human use based on a phalanx of scientific evidence, thereby dispelling the myths of traditional medicine.\(^4\)\(^-\)\(^10\) We are not fulfilling our potential to address the needs of a world where many antibiotics and antiparasitic drugs simply do not work anymore, or where there are so many rare and neglected diseases which require new, safer, and more effective drugs, as well as finding treatments for those diseases for which there is no drug available at all.\(^11\) As we delve further into the discussion, we will Contemplate Areas of Research for Envisioning more intense applications of the sciences and technologies of 4IR in relation to the development of natural products.\(^5\)

### Environment

Assuming a long-term role in global health care, and a population in 2050 of about 9.74 billion (7.87 billion in June 2021), the demands on the environment for resources, including those for medicines, as well as for foods, spices, and essential oils will steadily and inevitably increase.\(^12\)\(^-\)\(^13\) That scenario requires two considerations and responses: Critical Actions to Respect the Environment and Concerns About Restoring the Environment. What are the natural resources being used in vast quantities in health care and in personal care? What are the anticipated needs for natural products in the future and how will those be met? Surely more Cultivation And Responsible Environmentalism will be required. Respecting the Current Applications of the Resources of Earth and challenging the volume being used based on scientific explorations of safety and efficacy and requiring an answer to the question “What is the dose of a traditional medicine?” will be paramount as efforts toward higher levels of sustainability are required. Conservation And Replenishment of the Environment, marine and terrestrial, must become a global activity, for climate, as well as health care and other resource requirements. These evolve into ethical issues of the sustainability of medicinal resources.
Agricultural yields for food crops will change in the next 20 to 30 years as periods of drought, Concerns About Raining Excessively, and salinity from rising sea levels impinge environments differentially throughout the world.14-18 Metabolite profiles of medicinal plants and their essential oils, critical for the thriving health and personal care industries, will also be modified in an unpredictable manner. The research outcome is that Climate Alterations Require Experimentation. For the key medicinal and essential oil plants, more experimentation is needed now to be able to respond as local weather patterns change, when warming access to water (too little or too much) modifies the life cycle experience of plants, or when the salinity of the soil changes.

The introduction of the concepts of Green Chemistry,19 which were summarized as philosophies and practices for natural products research in the term “ecopharmacognosy,”20-4 brought consciousness to the impact that day-to-day research activities can have on the environment. The challenge now is to Consider Always Reducing Energy, whether that involves reducing temperatures for chemical reactions, performing extractions at room temperature, or more energy-efficient storage facilities for chemical and biological samples, or even working from home when possible, rather than commuting. As a corollary, for the laboratory, there is a new prospective question: Can we Achieve the Recycling of Everything? Are there better ways to conserve the solvents used for extraction of natural resources, the heavy-metal catalysts, the broken glassware, the pipettes, the plasticware, etc. For synthetic purposes, recall that Carrots (and Coconuts) Are Reagents for Enantiomers, and are high yielding, highly enantioselective, Cheap, Available, Reusable, and Environmental systems for certain synthetic organic reactions.20 It is still the beginning of the application of intact natural resources for performing specific chemical processes, as well as the Careful Assembly of Reactive Enzymes for the total synthesis of natural products.21

Relationships and Collaborations

Only fools climb mountains on their own. Almost no one in the field of natural products does research on their own anymore. The days of seeing a single author research paper are almost gone. The concept and practice of “multidisciplinary research” is epitomized in the world of natural products research, and the types of expertise required for an effective program are highly diverse. The integration of new technologies, whether analytical, computational, robotic, chemical, biological, or within those fields, one of the “-omics,” has brought us to a point where Collaborations Are Really Essential, and Exciting. A lot is learned, sometimes in a “black-box” mode, about these technologies. Knowledge of the capacity of the instrumentation and the supporting data systems fosters new research directions; it is how Creativity Advances Research and Experimentation. In the process of developing these collaborative scientific relationships, teams are created to address program strategies and protocols, and standards of practice. For leaders to be effective there are important facets of responsibility to the team and the research program. The leader must be Collecting the Assets for Research Excellence, the people and the places, the scientific infrastructure, and the intellectual, informational, physical, and fiscal needs, anticipated for the conduct of the research.

The supervisor, team leader, or research manager has a wide range of responsibilities to various audiences. He or she has the ultimate Command and Authority of the Research Essentials, including the personnel, the collaborators, the research program, reports, publications, further grants, training, meeting presentations, the funders, local administrators, etc. Overall, they provide the Care and Attention for Research Execution, keeping the whole operation on track for a long-term, meaningful, and responsive program.

The assembly and functioning of the team leads us to Consider, Appreciate, and Respect Everyone, for who they are as an individual, and what expertise they contribute to solving the issues at hand as a team member. Collaboration is an Amazing and Rewarding Experience for all participants, especially if the Colleagues Are Really Excellent, thinking at their best level of creativity for the benefit of the team, and fully participating toward solving the challenges at hand, with egos set aside. Plans are made through regular meetings, and the team develops Commonly Agreed Research Experiments for the next steps in program development. Of course, there are often negotiations required so that everyone feels comfortable with their role in the research.

Particularly when several institutions or companies are involved, there is the legal necessity to Create Agreements for Research Explorations, memoranda which embrace financial issues, publications, authorship, training opportunities, technology transfer, functional responsibilities, timeframes, performance deadlines, confidentiality, patents, communication channels, site visits, meeting schedules, etc. Research that involves the possibility of patenting or specific licensing agreements requires systems in place for establishing security, including authenticity, confidentiality, and timeliness. Authenticity is assured through Certification of All Research Experiments by a supervisor or a coworker and Cybersecurity Attest to the Relevant Evidence of an invention. The result is that Controlling Access Requires Enterprise for the investment in a dedicated information framework, which has the capacity to store in the blockchain mode the various research inputs into an immutable system of records based on limited access, so that the transfer of Collaborative Assets is Robustly Encrypted.

Ethics

Day-to-day research demands ethical practices, and thus Considering Aspects of Research Ethics must be an essential beginning to any graduate education program. The aspects of falsification, fraud, and plagiarism (FFP) are well established as practices to be avoided when recording, interpreting, and reporting data. Those who do plagiarize are not respected, and some would say those Copycats Are Rotten Eggs, bringing
the stench of disrepute to a program. It is essential to indicate the sources of pertinent statements and giving appropriate credit to those who have gone before is regarded as Completely attributing Related Experiences. Assessing in a fair and consistent manner the contributions of colleagues who provided experimental expertise and/or made intellectual Contributions to Actual Research Efforts are critical aspects of maintaining group cohesiveness and esprit de corps when authorships of presentations, publications, and patents are being considered. Creating And Retaining the Equilibrium in the team requires leadership at an early stage in the program to reach agreements regarding authorship on various types of papers and reviews originating from the group. This will assure that any Conflicts in Authorship are Resolved Equitably. The ethical issues in authorship are significant here also. In preparing manuscripts, Contributions Are Really Essential to justify authorship. There should be neither guest authors, nor ghost authors, those who do not contribute and are listed, and those who do contribute but are not included, respectively. For every publication or presentation, the leader must have the significant Concern that Authorship is Really Earned through intellectual engagement.

Animal research and human subject research require prior approval by a local team of experts. Certain types of biological experiments may also require prior approval; different countries will have different regulations which apply. What is important is to recognize that international journals and granting agencies will typically request assurances (and details) with respect to the local approval of the research being discussed. Sometimes, when issues are not clear, Consulting About Research Ethics with experts may be necessary to resolve a challenging issue.

Another ethical issue seen frequently in the literature is the hyperbolic case that is made by comparing apples and oranges (or sometimes even apples and apples!). Let us be clear: that does not represent an ethical interpretation of results. For example, a test of a compound at 10 μg/mL shows better inhibition (90% vs 74%) of an enzyme than the standard drug, and the statement is made that the compound has superior activity and is a candidate for development as a drug. Hyperbole!! When one looks at the control standard, the dose was only 0.01 μg/mL. It is therefore important when assessing the significance of the results obtained that you Compare All Related Examples, including similar tests that may be in the literature. By the way, a single in vitro test does not a drug make!

Since the Convention on Biological Diversity and the subsequent Nagoya Protocol, permissions to access the biome, whether marine or terrestrial, whether a higher plant, a fungus, or soil organisms, are required from local authorities, as well as a formal negotiated agreement, and an accompanying local scientist during resource acquisition. These are a part of the Considerations for Access to the Research Environment. Some professional societies ask their members to commit to upholding these ethical standards of practice. Once again, journals typically require certification, and possibly proof, that these steps to be granted access have been taken as a prelude to the research, for locally, as well as internationally, collected organism samples.

In most chemical and biological research facilities, the days of walking into a laboratory and starting work at the bench are long gone. As a result, and possibly Contrary to Anticipation, Rules are Everywhere. They are an integral and necessary aspect of establishing an experimentally safe and a harassment-free environment in which to perform research, and it is the openness of the supervisor and the confidence of the bench researcher that action will be taken when there are personal or experimental emergency situations requiring attention. The work environment must be one in which there is high-level support to Continue to Always Report Exigencies, where corrective actions will be taken.

It is quite easy as a researcher to fall into an appearance, or even the reality, of a conflict of interest. It can be described sometimes as Continuing Alternative Research Enterprises. The concept strikes at the very core of societal trust in research results through the ability to Consider All Research Equally and without bias. As an example, a company funds research on one of its products (a drug, a new instrument, or device) in your laboratory. As a prior investor, you already have shares in the company. What do you do? Divest or hold? Transfer to a family member? When the results are to be published and the journal asks if you have a conflict of interest what is your honest response? How does future funding for your laboratory relate to the results of the initial research? Doing the research with a personal view that it enhances the public good to know whether a product is safe and effective, does not overcome the real appearance of Confusing Altruism with Responsible Ethics, when you have a personal and financial stake in the outcome, directly or indirectly. Policies typically exist at academic institutions and at journals when submitting an article, for the management of conflicts of interest.

Annual statements of potential conflicts and of financial interests are required by many institutions as a requirement for employment.

In developing protocols for agreements for research collaboration, it is important to be alert for limitations proposed by companies or institutions on the review and publication of research results from the testing of their products; read the proposed Memorandum of Understanding carefully for such restrictions. Confluence of Acceptance in Research Experimentation by the researcher and the sponsor should lead to full disclosure of the results, not a limitation if the drug, product, device, etc, does not work as claimed. Make sure the research can be published in a timely manner, irrespective of a positive or negative outcome; that is Communicating Appropriately the Research Evidence and serves to maintain societal trust in science. Failure to do so results in “reporting bias.” Hiding untoward results from public awareness to maintain a perception of effectiveness can be a very detrimental action scientifically and financially. Concealing Adverse Results of Evidence will typically fail and lead to a culture of
diminished overall honesty and creativity in a team or organization. In the direst of circumstances, it may even be a Criminal Act that Risks Expiration of the patient.

Language

English is now the universal language of science, in print, in lecture presentations, and on the web, even though for only about 5% of the global population is English their native language. A single language provides an effective global means of communication, while at the same time providing distinct challenges for nonnative English speakers. Publishers typically offer (for a fee) access to native English speakers to edit manuscripts prior to submission. However, for a productive group that will become expensive rapidly. Therefore, alternative Considerations for Acquiring Readable English should be contemplated, including specific online course opportunities.

The reality is that if you want your research to be read, quality English language in the Abstract and in the first few sentences of the text, is Critical to Attract the Readers’ Engrossment (Engagement). In this regard, it helps greatly to be reading the studies published in the same journal to become familiar with the style of writing and the contemporary phraseology in the field, especially as the technical terms in the natural product sciences are evolving rapidly. These are some of the Challenges About Relatable English that need to be addressed by authors so that the arguments and points being made are presented Concisely, and Appropriately in Readable English. However, Considerations for Accuracy by Reviewers and Editors are also important so that the imperfect English in a manuscript does not dominate the initial consideration and review of the science itself.

Different reviewers of manuscripts or grants have different styles of presenting their comments; constructive and detailed critiques are to be valued. Copy editors at the publisher are usually the final arbiters of language and style. Prior to either of these external processes there is the internal team effort to turn a draft document (manuscript or grant proposal) into a memorable experience for the reader (that’s the way citing others and funding research goes!). The whole group will take what is written and be aggressively Critiquing Aspects of the Resplendent English, as well as the data interpretation and presentation. Accepting changes can be a challenge!! You will need to Curb the Activity of a Raging Ego and realize that all that is written is discussable by the team.

Experimentation

Reproducibility is a fundamental aspect of science, and the trust that is placed in science by society. It is one of the principal issues for the development of natural products in academia and in industry, where plants or other organisms may not be recollected in the same location as the original sample, and as a result may or may not have the same chemical profile. In addition, Creating A Reproducible Experiment in the laboratory is a nontrivial activity. That issue may be evident in the extraction and processing of an extract, the details in the description of chemical methods, the evaluation of the biological tests that are conducted with the necessary positive and negative controls, and the subtle changes occurring in spectral data between instrument configurations (for mass spectra) and for different concentrations and solvents (for nuclear magnetic resonance). All of which makes the use of large datasets Challenging As Reliable Entities when seeking comparative data for the identification of metabolites between datasets. Human intervention for final assessment is still required.

In conducting natural product research there is a need for Concern About Reality in Experiments, and whether factors other than those inherent in the material being examined are involved in the generation and the interpretation of the results. That requires the experimenter to Create A Realistic Expectation for an observed, not anticipated, outcome of the experiments, and not either overanalyze or overinterpret the results based on a desired outcome. One sees this in the studies of a traditional medicine, where the term “validation” is often used in describing the biological experiments on a material from a traditional medicine. To accomplish objectivity and remove the perception of inherent bias in this instance, the neutral terms “assessment” or “examination” should be used, with the appropriate neutral experiment being conducted.

To achieve the absence of bias it is necessary to Consider All of the Relevant Experiments that might address a particular issue, whether biological, chemical, or taxonomic. Examining all the possibilities for alternative experiments to be conducted is vital. There is a tendency sometimes to use a sledgehammer of advanced technology when a small hammer will suffice. Simplicity in experimental design, through Conserving And Reducing Experimentation represents an elegant approach. Once all the experiments are run, it is necessary to Collect and Analyze the Relevant Evidence, and have Careful Afterthoughts Relating to the Experiments. Although that may sound trivial, it rarely is. It is at this point where dramatic innovative discoveries are sometimes made. A positive (anticipated?) outcome brings delight. A failed experiment brings disappointment. Does it also bring analysis and inquisitiveness? What went wrong? Was it me, or the experiment? What is that new product? Why did those cells die? Why is that reaction so slow? What happened that the field-test crop failed to produce? One has only to think of the discoveries of penicillin, of vinblastine, of Nylan, of lysergic acid diethylamide (LSD), of sildenafil, and of aspartame to see the importance of persistent inquisitiveness and creativity; the list in natural products research is long. These are sometimes referred to as serendipitous events, when truly they are being made through acute scientific observation, seeking an interpretation, and then acting, not dismissing the result as “another failed experiment.” Indeed, serendipity is described as sagacity transformed into opportunity. An open mind, willing to explore further the unanticipated outcome, is essential. It is important to be Critically
Analytical of the Real Experiences, and at the same time to Consider All Relevant Explanations for the observation in question. Are there precedents? Alternatives? A missed earlier report? An ill-prepared ingredient? The team comes together and ponders the outcome. Repeated disappointment from failed experiments Compromises Acuity and Resistance Ensues to move on to the next series of experiments.

A new experiment is frequently an emotionally exciting experience. To assure that the experiment is conducted appropriately, a Calm Apprehension Releases Endorphins and brings concentration and presence to the moment. The successful experiment which provides the anticipated chemical or biological outcome requires summation as the initial aspect in translation to the broader audience, to scientific colleagues in the team, at a meeting, in a presentation or publication, or perhaps in a blog or other electronic venue; research Communication Access is Rapidly Evolving. Those are the Conclusions After Real Experiments and must be considered in the context of other local successful experiments, and in the context of the field in general. That cycles back to the comparison of apples and oranges and the hyperbole that may result. Perspective of the field is critically important. Isolating another cytotoxic sesquiterpene lactone is not a breakthrough in the treatment of cancer; it joins throngs of sesquiterpenes with similar activity. Similarly, finding a catechol derivative with antioxidant activity is typically no longer even a publishable event. Unjustified Conclusions will be Astutely Rejected by an Editor. In summary, make Claims Appropriate to the Research Experiment, not to experiments yet to be conducted.

In some instances, the success is sufficiently profound for there to be patent and licensing considerations, which is Certifying Aspects as Really Enthralling for the future. Although, depending on the circumstances, such acts of protectionism should be balanced with other considerations of purpose and local and global needs. In the broader context, after a series of successful results, the translational aspects may Culminate in the Associated Reputation Enhancement of the team. It will be an example of Championing the Achievements of Research Efforts, bringing a wider appreciation of the creative success of the group and the institution into the scientific and public domains.

Safety in laboratory and field experimentation, whether botanical, chemical, or biological must be a constant consideration. The goal is to Circumvent Accidental Risky Exposures and to Curtail All Research Explosions. Is the plant or marine organism, or other biological sample known, or suspected, to be toxic in some manner? Are there specific biosafety precautions needed because of real or suspected pathogenicity of an organism? What are the chemical hazards associated with a particular reaction that involve the use or generation of certain gases or the use of flammable solvents? Are those chemical and biological materials, when not in use, being stored appropriately? Are the personnel using those biological and chemical hazards appropriately Cautioned And Ready to Experiment?

Recording of Research

When you move from a laboratory to take another position, your research records, electronic or paper, will remain in some form at the original site. The research records that you have maintained should reflect success and failure honestly, including answers to questions such as why did the experiment work (or fail)? What will be done in the case of a failure to rectify and change conditions? The data reflect the scientists’ ability to Conduct Appropriate and Rigorous Experiments and fully interpret and present the results. Reaction yields, sources of biological materials and responses, chromatographic and spectral data, purity assessments, etc. should represent reality. Fundamental in the recording of the information for others to review is to Commit to Accurate Report as an Experimentalist. Those reports are at the core of reproducibility. If the laboratory has switched to electronic notebooks, it is Computerization Assuring the Research Evidence can be found and remains authentic. Good records will enhance the full experimental disclosure and reproducibility at a time of publication or patenting. After all, without good research records it will require Considerable Ability to Repeat Experiments, and to prepare reports and research manuscripts that do reflect authenticity. In addition, organization of data from individual scientists must be subject to facile Curation And be Recoverable Evidence. Otherwise, report and manuscript writing, as well as materials in support of chemical and biological claims, may become challenging to trace. With experience, the supervisor will be able to transmit to the bench scientist that Consideration and Awareness of Research Experimentation, i.e., what works, what does not, and keeping track of the difference, is an important facet of success as reports are made and future plans are established by the team.

Everybody makes unintentional mistakes in research, and sincere effort is made to see that the mistakes do not appear in the literature before they are found. From a laboratory perspective, Correcting Avertible Research Errors, whatever the experimental source, requires vigilance. That may involve repeating an experiment, correcting a structure, reinterpreting biological data with a different applied statistic, etc. This leads to a deeper Concern About a Responsible Environment, and how failures due to experimental error are handled by the individual, by the supervisor, and by the team. The supervisor has the responsibility to have Compassion Always for Real Emotions. Researchers who do err should not be shamed and blamed, either individually or especially in front of the team. They will already be feeling as though they let the team down. The supervisor and the team should show support; it may be their turn next!

Research Funding is an Investment

In one form or another it is society that invests in research with the expectation that discoveries will lead to benefits. In health
care research, the patient expectations are for better quality, standardized, safer, consistent, and more effective drugs, irrespective of the source, prescription, over the counter, dietary supplement, or traditional medicine. Those programs typically represent extended research efforts. They are not short-term projects which answer a question, get a publication, and for which there is no follow-up for society. In the obverse, society expects their investment to be productive and the money not wasted in inappropriate experiments, unnecessary duplication of research, or personnel or collaborators who are not performing to the expectations of the group, etc. As well as the science, the team is also responsible for Critically Accessing Research Expenditures, especially when budgets are limited and priorities and their funding must be carefully established for personnel, instrumentation, supplies, publications, travel, etc.

Natural product research program development should be dynamic, not static, and certainly not dead-end. If a research program is operating in the same way it was 5 years ago, something is probably incongruous at the fundamental level, and the “program” goals will never be met. Collaboration requires ongoing analysis of effectiveness by the team. Successful programs have long-term goals for expansion beyond current funding, so that additional students, technical staff, and postdoctoral researchers can be hired, and more advanced research goals accomplished. That is what happens when Continuity Accrues in a Reputable Environment. Grant funding is not curtailed, and when programs are successful, grant funders invest for a longer term, for 5 or 7 years, not 2 or 3. The emphasis is on quality results and their short- and long-term significance, not the numbers of publications in a year. Stability returns to research, and the focus shifts to doing research from writing about doing research. There is deep Caring About the Research Environment in a group or at a Center Advocating Research Excellence. There are status and benchmark performance reviews, resulting in the Continuous Assessment of Research Endeavors of the program, including by external assessors, to maintain the highest program standards. At some point, the team reaches an important milestone, a place to go no further, either due to lack of success, or not having the expertise in the group and the funding necessary, or that other priorities have arisen. This is an example of Curtailing Avertible Research Efforts; knowing when to stop wasting resources on research that does not add to the whole program in a meaningful manner. Industry researchers are typically better at saying “Stop” than academics. Even though switching from an unsuccessful project can be enlivening experience for all concerned.

Excellence

External and internal peer reviews are important to Create an Atmosphere for Research Excellence and to maintain a Critically Acclaimed Research Experience. In addition to these reviews there are two other important aspects to achieving and maintaining the excellence which subsequently merits a continuing funding stream: (i) the quality, consistency, and effectiveness of the collaborations and (ii) competition, internally to maintain standards, facilities, quality of personnel, meet deadlines and complete phases of the program, etc, and with outside groups who may be seeking the same funds in a future granting opportunity. In fact, it is a case where Competition Accelerates the Regard for Excellence, where competitors will themselves be inspired, and their activities will be stimulated and improved, by the prospect of a future competition. Top-quality Collaborations Are Really Essential for program success. These relationships are frequently independent of the main program and are located at a secondary site and chosen for what they have to offer to the main program, and for the quality of their programs. A third factor in meaningful and productive collaborative research programs is Continually Applying Research Energy. The individuals and the collective must be dedicated to the research program (and their other programs). No weak links in the experimental Chain are Allowable for Research Excellence.

Enterprise

It was already noted how initiating a research program that has long-term objectives in responding to a significant scientific need is likely to lead to Creating A Research Enterprise which can flourish. This will not happen overnight, it may take 5 to 10 years of successful research efforts within the larger program, as well as the associated publicity of oral presentations at meetings, research manuscripts, and related review articles. Locally, the completion of PhD students and the job successes of postdoctoral fellows will add to the program’s reputation. Branching out to related, or new areas, may depend on initiatives from collaborators, groups seeking collaboration, or the parent group taking on new long-term challenges. It is easy to become stretched and to lose focus requiring Centering And Research Evaluation to restore long-term objectives and priorities.

Success in enterprise also requires good mentoring on a regular basis. Mentoring does not stop after a PhD or a postdoctoral experience. It continues throughout a research, teaching, and administrative career, and may involve not one, but several, experienced scientists who may or may not be in your area of research, probably not at your institution, possibly not even in the same country. The key is for the mentor to be passionate about the success of the mentee. So it is “Calling All Research Executives.” Use your experience and find a mentee who you can work with long term. Volunteer through a university or a professional society to make the connection. And remember to make sure that the goal is for the mentee to be more successful than you have been!!

Invitations

Invitations indicate you have been recognized as a scientist. Or do they? Be careful!! The predators are out there! Suddenly, the
invitations (“With great pride and pleasure we would like to invite you as an Honorable speaker ...) appear in your SPAM (Sleazy People After Money) folder or in your main mailbox, those inevitable flattering invitations to write an article, be the editor of a special issue of a journal, present a lecture at a meeting, organize a symposium, etc. As the wise man said, if you cannot explain something, track the money. These solicitations are only about money … getting access to yours. Science, beyond a name, “Nanomedicine” for example, is not a factor. That whole aspect of Charging for Articles is Really Exceptional (up to 2000 CHF) when the purpose is to publish your invited article, and then offering a 10% discount, if you are lucky. All because you published another article with a title that can be replayed to lure you in. Check All Relevant Erudition by searching the names, the phone numbers, the address given (if any), and the website of the meeting/journal. In a recent example, the cited corporate address was in a tiny village in England (pop. 2626) with 3545 companies listed at the same address!! Do not Compromise Any Realistic Expectations, only those that money-makers try to create for you. They can be Callous And Rather Evil as far as your interests are concerned. Do the research and Consider Acting Really Excessively …. Ignore, completely. Do not let the perpetrators Capitalize Always on Research Exploitation.

Self-care
Graduate students are typically quite financially challenged and must budget their fellowship or stipend support carefully. At the same time, their work is demanding and, as we have seen, requires a high level of Care, Attention, Resiliency, and Effort on a consistent basis. Self-care becomes even more important at times of intense experimentation (especially when failures are being encountered), report or thesis writing, and preparing for meetings. That is when it is important to try to Consume, Always, Real Eats, and not junk food. Easier said than done on a budget …, think in terms of brain fodder. It is vital not to make the laboratory your only life. Each day, and certainly for one day over the weekends, look after other aspects of life and Create an Abundance of Relaxation and Exercise to maintain and restore physical and mental health. Your research outcomes may depend on that.

Conclusions
In this tongue-in-cheek presentation, the topics of C.A.R.E. in natural product research are discussed. Most of the comments are quite general in application, and not specific to the field of natural products research. Two concepts stand out as important for success in developing good qualities as a researcher: (i) being Committed Always to Research Excellence and (ii) establishing high standards for the inclusion of Communication, Accuracy, Reproducibility, and Enterprise in program development. In summary, the many diverse facets described here for Creating an Appropriate Research Environment are fundamental for individual and collective success.

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