PERSPECTIVE

Challenges Facing Young Investigators

Three junior researchers describe the hurdles to succeeding in the AIDS vaccine field

By Galit Alter, Jason Brenchley, and Jacques Fellay*

Since the news in September 2007 regarding the STEP trial, the HIV research community has re-introduced basic bench science as a renewed priority, with the definition of the correlates of immune protection as the primary target. At the Summit on HIV Vaccine Research and Development held by the National Institute of Allergy and Infectious Diseases last March, support for young investigators was deemed as a pivotal step toward ensuring that innovation would continue and furnish the momentum and enthusiasm to move the AIDS vaccine field forward following the recent setbacks. Here we analyze the route to success for young investigators that are pertinent to the present state of the field in the context of evolution.

Evolution of young investigators

Evolution is defined as a "change in the inherited traits of a population" that is achieved in at least three different manners: variation, reproduction, and selection. This concept is highly pertinent to the development of a young scientist. Based on the above rules for success, a young investigator must *vary* from their mentor to establish a new area of research in which they must learn to collaborate, *reproduce*, and develop their own lab in a location where they can establish their roots. They also must overcome both financial and creative *selection* imposed by the scientific community.

Step 1: Variation

Fundamental to the process of evolution is variation, upon which selective forces can act. A striving HIV research community is inherently a fast-evolving organism, and as such, it requires variation of its own kind: new ideas, creative technology, provocative experiments, and innovative concepts.

Support for young investigators is intended to build a new generation of scientists that can bring fresh and imaginative ideas to the field. Nevertheless, it is critical that we remember that youth is not—and has never been—a certificate of brightness. However, young investigators are unique in that they possess the advantage of inexperience. Being somewhat naive affords the luxury of unorthodox thinking and allows one to take unusual approaches to addressing questions. This "naive curiosity" allows young investigators to extend into novel areas, breaking down the "walls" or bridging biological sciences to other domains such as mathematics, physics, engineering, and chemistry. These extensions bring new dimensions and novel perspectives to the HIV research field which stem from the imagination of these new additions to the field.

Yet, uniqueness often can be impractical, particularly when trying to obtain funding. Novel concepts are usually not immediately accepted by the scientific community as inherently critical and therefore are difficult to fund. Funding for high-risk work is often far more difficult to acquire than money to perform work in areas that are "hot" or directly relevant to vaccine design. However, with high risk can come high reward. Some of the best scientific publications have stemmed from research projects that were, at the time of inception, very high risk. It is also true that young scientists often lack pragmatism, and, as a consequence, ideas for projects that many consider "risky" are not lacking. However, it is important to appreciate the risk. While risky projects may result in high-profile papers, they also can become exercises in futility. A lab invested too heavily in risky projects may have funding difficulties and young investigators being considered for tenure may not be favorably reviewed with multiple failed projects under their belts. Junior scientists must carefully balance risky projects, which may result in highly visible publications, with more secure, more fundable projects that can result in more guaranteed, albeit less high-profile, publications.

These days, young investigators can find unconventional support by interdigitating their novel programs in larger scientific networks to form symbiotic relationships and support their growing laboratories. One model currently employed by the field is the use of large consortia to promote collaboration and advance the science efficiently, as individual collaborators bring different types of expertise to a project. These consortia play a dominant role in scientific progress and therefore young investigators are being strongly encouraged to participate. These science consortia provide the critical mass that is indispensable to perform large-scale studies, which require both rich collaborative networks and expensive technology, and also are an integral part of many laboratories' financial backing.

Furthermore, large consortia offer support for the high-risk ideas of young scientists. Here are several examples of how our work has been influenced by these consortia. Through the Center for HIV/AIDS Vaccine Immunology (CHAVI), Galit Alter has gained visibility and been funded to perform high-risk work in the development of a new platform to quantify antibody dependent cell-mediated cytoxicity (ADCC). Jacques Fellay is also working with CHAVI on HIV host genomic projects. The Ragon Institute (formerly known as Partners AIDS Research Center or PARC) has also begun to offer innovation awards that are targeted toward young investigators interested in initiating high-risk, "out-of-the-box" collaborations to develop new technologies that may move the field forward. Through the Ragon Institute, Alter has now partnered with researchers at Massachusetts Institute of Technology to develop high-tech imaging tools to gain an in-depth appreciation for the enigmatic role of natural killer cells in HIV infection. Thus CHAVI and the Ragon Institute have taken a momentous initiative to encourage and provide small, catalyst-style grants to new investigators to support innovative ideas that pertain to vaccine design.

Collaborations are also important for young investigators because they increase their visibility within their respective fields. For example, while working as a post-doctoral fellow Jason Brenchley became involved in a consortium led by Michael Lederman of Case Western Reserve University in Ohio called "The Bad Boys of Cleveland" (BBC). This consortium began as a small group of researchers interested in the role and causes of immune activation in the chronic phase of HIV infection. These researchers would meet every nine months to discuss current data and plan future experiments. These meetings significantly increased the visibility of Jason Brenchley, generated many active collaborations, led to five co-authored papers (one as a first author and one as last author), and introduced him to several premier researchers in the field. These introductions ultimately led to his being able to recruit a very talented post-doctoral fellow into his own lab. The BBC is now funded by an US National Institutes of Health (NIH) P01 grant and the productive collaborations continue.

The NIH also recently launched larger grants that are directly aimed at supporting young scientists as they transition from their mentored to their independent phases, the K99/R00. These young investigator grants are a vital resource in the tenuous period during the early career transition to independence. The K99/R00 has played a pivotal role in the early career development of Galit Alter and afforded her with the financial support to tran-

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sition to independence and build her laboratory. With this grant, she was able to recruit a post-doctoral fellow and begin to engage in the development of a novel technological approach to defining the role of innate immune receptors on the evolution of the T-cell synapse. Similarly, CHAVI and the HIV Vaccine Trials Network will also offer a "track to independence award" targeted at young investigators interested in simian immunodeficiency virus (SIV) research, and will hopefully catalyze a renewed movement in the area of primate research, which is imperative. These types of awards are absolutely vital in providing the financial stability to upcoming young investigators to engage in independent research programs that will likely flourish in their future lab interests.

Step 2: Reproduction

While the role of reproduction in the evolution of a young investigator may not be evident, academia forms an everlasting ecosystem due to the cyclical processes that sustain it. Thus through apprenticeship, young investigators learn from their mentors during graduate and post-graduate work, after which they themselves must provide the support to grow their own generations of mentees. The struggle in reproduction is therefore three-fold: separation and survival from the mentor, finding young mentees to build a lab, and finding a nurturing environment in which to build a lab.

It is impossible to argue that training is not the most critical catalyst for success. The skills one learns from a mentor mold the young investigator. We have all been privileged to work with exceptionally talented mentors that have certainly had an immeasurable impact on our development as investigators. Our greatest obstacle is then to diversify ourselves from these remarkable role models and to generate independent areas that are equally successful. The pressure is on, but similar to our mentors who rose to the occasion when they left their impressive mentors, it is clear that those that overcome this obstacle are the ones that have a chance to make it in this ultra-competitive world.

One of the most critical resources in the scientific community is the mentee, both in the form of students and post-doctoral candidates. These individuals form both the labor and the neural network that are responsible for the rapid evolution of the career of a young investigator. The hurdle is attracting these young mentees away from the established investigators that offer some security of success. However, there are certainly advantages for mentees who choose to conduct their training with young mentors, as these mentors at this early phase in their careers are highly involved and intensely invested in the success of their mentees. At this early stage in the career of a young investigator, the generation of high-quality manuscripts is absolutely vital. Whilst a highly invested young mentor may be attractive to some trainees, this problem is both a cultural hurdle for the academic community as well as a problem with advertising for young mentors who have available positions in their laboratories.

Geography is also at play in the reproduction process. At the crossroad between scientific expectations and life experiences, every young researcher will be confronted, often repeatedly, with the daunting task of deciding where to conduct research. Indeed, a scientist early on in their career has the opportunity to experience both the freedom and the loneliness of a migratory bird, free to roam where the grass is always greener. However, with independence comes the necessary decision of where to set roots.

The responsibility falls more heavily on young investigators from developing countries. The pressure to return to their homeland is much greater, due to the need in their nations for capacity building. Despite the luxuries in science these individuals may experience in developed countries, they face especially tough personal and societal demands when making the decision to stay or go back. The differences are innumerable, starting with scarcer financial support systems, less intellectual capacity, difficulties in obtaining reagents, less chance of up-to-date technological equipment, etc. Despite the HIV research community's clear appreciation for these hurdles faced by young investigators in the developing world, a dearth of grants are available for those brave enough to make the journey home. However, the next generation of AIDS researchers should not only replenish the existing army of experienced investigators, significantly expand the number of successful scientists working in developing countries.

Step 3: Selection

Selection pressures in the world of HIV research are not driven by chance or circumstance. They are clearly determined by the scientific agenda of the community. Thus grant review panels and journal reviewers are profoundly involved in determining the fate of a young investigator. The conundrum lies in the fact that a virtual agenda is defined annually through conferences, publications, and brainstorming sessions that help shape the path forward.

Naturally, due to their exemplary track records, the allocation of funds to experienced investigators is "safe" and is believed to have a greater likelihood to generate high-impact publications. However, young investigators must compete fiercely, and as mentioned above, risky propositions are not always favored for the fledglings. Therefore new investigators must be mindful to develop programs that are relevant to the current interests of the community, and yet sufficiently novel to appeal to their peers.

The idea that chance might play a part in the success of a young scientist is definitely a debatable topic. Timeliness seems to be a recurrent success tip: should investigators that develop exciting new topics at a time when the scientific climate favors that subject be construed as lucky, or just clever? Fundamentally, the flexibility to maneuver through the scientifically relevant and novel areas of research with stealth and success is definitely the trait that has served the most successful scientists well. Timing might be due to luck, but the art of flexibility might also lend itself to being able to stay at the leading edge of the field.

As stated above, some of the best scientific publications stem from research projects that are derived from ideas that arose outside the domains of the proverbial box. Often young researchers have not been in their respective fields long enough to actually know the confines of such a box, and many of their ideas therefore represent novelties in nature that, if successful, aid in scientific evolution. For example, one of the hallmarks of chronic HIV infection is pleiotropic activation of the immune system. While a post-doctoral fellow, Jason Brenchley led a project with the hypothesis that the damage to the gastrointestinal (GI) tract that occurs during acute HIV infection would allow microbial products to translocate from the lumen of the GI tract into peripheral circulation. These microbial products would then be a cause of the immune activation. This hypothesis was met with some pessimism in the field, but the data supported the hypothesis and was ultimately published in a high-profile journal. This "novelty in nature" has subsequently been confirmed by several other groups and has been shown to have a role in AIDS dementia, failure to reconstitute $CD4^+$ T cells after initiation of antiretroviral therapy, and perhaps atherosclerosis. Moreover, several novel therapeutic interventions that aim to reduce microbial product-mediated immune activation are currently in trial.

Future considerations

HIV research requires both long-term commitment as well as a sense of urgency. Scientific and political leaders have made it a priority to build a solid "next generation" of scientists that can quickly contribute to the vitality of HIV research by bringing fresh and imaginative ideas. In direct response to this pressing need, the Global HIV Vaccine Enterprise has launched the Young and Early Career Investigators (YECI) Initiative to contribute to the development of the Enterprise's 2009 Scientific Strategic Plan by articulating the importance of young investigators as drivers of innovation and by proposing the structural and cultural changes required to engage and retain new scientific talent and to integrate innovative ideas and new technologies into HIV vaccine research. Co-chaired by Dan Barouch and Thumbi Ndung'u, the YECI Committee is comprised of scientific investigators from around the world who are age 40 or younger, or who are within 10 years of receiving their terminal degree or related clinical training. The Enterprise's YECI Committee will increase dialogue between young and established researchers and provide innovative and constructive recommendations that address the challenges young investigators face in both developed and developing countries.

The main question that this committee and the field have to address is how do we best attract young researchers to the field? And what type of support, both financial and otherwise, is needed to keep young investigators involved in HIV vaccine research? When trying to support the next generation of scientists, we have to ask ourselves the following questions: How can we increase the visibility of the next generation of thinkers, provide new opportunities to support high-risk initiatives of these new minds, revolutionize the mechanism used to evaluate success in light of the new scientific climate, and provide a support system to help recruit mentees for young investigators? Appropriate answers to these challenges should offer benefits well beyond the newest generation of HIV scientists to the whole HIV research community. ■

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