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GRANTS

New blood: Creative funding of disease-specific research

IN HIS BOOK *THE ACT OF CREATION*, ARTHUR KOESTLER MAKES THE CASE THAT “ALL decisive advances in the history of scientific thought can be described in terms of mental cross-fertilization between different disciplines” (1). However, current requirements for successful research-grant applications make it difficult for a scientist with expertise and accomplishments in one field of study to gain support for work in another. The typical path for a biomedical scientist is one of success by virtue of focus: develop expertise in a given research area and then stick to it, authoring a collection of impactful papers and attracting research funding in one’s chosen field. An applicant for a research grant from the U.S. National Institutes of Health (NIH) is expected to have a proven track record in the scientific area of their grant proposal and, often, extensive preliminary data to support the proposed research project. But is this the most effective way to support ground-breaking science? Here, we describe a grant program designed by the American Asthma Foundation (AAF) that taps talent from diverse pools of investigators—a model that might spur innovation in other research realms.

At the start of the 21st century, Herb and Marion Sandler, a philanthropic couple with a personal interest in asthma, conceived a creative funding approach that focused on recruiting outstanding investigators from scientific disciplines outside of the asthma field. A series of discussions with scientists led the couple to conclude that progress in asthma research had been sluggish and benefited too little from the vast biological knowledge acquired in the previous several decades. During the same period, the prevalence of asthma rose such that, today, ~1 in 13 adults and ~1 in 11 children suffer from asthma (www.cdc.gov/nchs/fastats/asthma.htm). The work of Julius Comroe, who had linked basic research to clinical advances in diagnosis and therapy (years before the term “translational medicine” was coined) (2), influenced the Sandlers, who went on to found AAF in order to focus their support on fundamental research into the causes of asthma, with the ultimate hope of finding new targets for therapy. Since 2000, the AAF has provided more than \$100M of research support (www.americanasthmafoundation.org).

NO ASTHMA? NO PROBLEM

The key distinguishing feature of AAF is that nearly all of its support has gone to investigators who had not previously studied asthma, with the goal of ushering in new research perspectives. This untried approach was risky. AAF’s scientific review board (SRB) was tasked with selecting promising ideas in the absence of preliminary evidence that predicted success. In general, investigators from other fields know little about the biology of asthma and the tools used to dissect the disease process. At best, there would be a steep learning curve for the new investigators. At worst, researchers would waste considerable time and money on flawed approaches because they lacked an understanding of the current state of asthma research. In the face of these risks, there was real concern at the start that the program would fail miserably.

The AAF uses several approaches to attract diverse investigators and to help them conduct investigations that would have an impact on asthma research and development:

- **Marketing.** The program is marketed broadly, not only across all biomedical sciences but also in engineering, imaging, and chemistry.
- **Substantial unfettered funding.** Initially, the AAF provided awards at two levels. Senior investigator awards provided \$250,000 per year for 3 years, an amount chosen to compete with NIH grants. Junior investigator awards provided \$125,000 for 3 years (raised to \$150,000 per year in 2004). In 2011, the AAF limited funding to junior investigators, seeing a particular need for funding at this career stage. There are relatively few restrictions on the use of funds and few obstacles to changing research direction. Certain limited indirect expenses are included in the award amount.
- **Easy to apply.** Limited to seven pages, the grant application requires no preliminary re-

sults and no budget (unless the grant is funded). The turn around time from application to funding is less than 5 months.

- **Cores.** To facilitate redirection of research toward asthma, the University of California, San Francisco, makes available to AAF investigators core facilities to assess asthma in mouse models, perform next-generation sequencing, and study genes in large cohorts of well-phenotyped patients with asthma (including African-American, Latino, and Caucasian patients). The University of California, Davis, performs studies of primates (http://www.americanasthmafoundation.org/sites/all/files/sabre_cores.pdf).
- **Meet and exchange.** In addition to seminars by the grant awardees, AAF annual meetings include presentations by prominent asthma researchers to help educate awardees about the field; ample unscheduled time to foster interactions among the investigators; space for scientists to bring a trainee or colleague along as a way to attract new investigators to the field; and an opportunity for the SRB to connect grantees with other asthma researchers and to identify mechanisms by which to further their research.
- **Inventions.** To facilitate the translation of discoveries toward clinical application, AAF makes no claim on intellectual property stemming from its sponsored research.
- **Extension awards.** To help move fundamental biological knowledge toward the clinic, the AAF provides some grantees with extension awards—up to \$150,000 for 1 or 2 additional years—for situations in which an AAF study has revealed a potential new therapy that requires additional preclinical testing. Extension awards can be given at any time after completion of the original AAF award. As an example, an extension award was given in 2013 to Daniele Piomelli, whose original AAF award in 2002 was to study lipid mediators in asthma. In the years since, he developed a lead compound to block the metabolism of anti-inflammatory fatty acid ethanolamides, and his AAF extension award allowed him to examine the pharmacokinetics of the drug and test it in a mouse asthma model.
- **Super SRB.** The AAF relies heavily on its SRB for continuous evaluation not only of investigators but also of the program itself. The SRB consists of nine prominent basic scientists, most of whose research is unrelated to asthma. This collection of expertise gives credence to the stated goal of sponsoring multidisciplinary science and applying it to the study of asthma biology. Because the SRB, rather than outside reviewers, evaluates all grant applications, the proposed projects are judged by the same criteria and are compared with each other for merit. This process, however, places a substantial burden on the SRB. To make the task manageable, written reviews are not provided to applicants. Each successful applicant is assigned a member of the SRB to help guide them in their studies, and the SRB meets yearly to discuss the program and to participate in the 2.5-day annual meeting, reviewing the progress of each of the current awardees. For their efforts, SRB members are compensated at a level comparable to corporate consultation rather than following the common practice of paying scientific reviewers little if anything for their work.

TRACK RECORD

The national grants program began in 1999, with initial awards granted in 2000. As of 2014, AAF has supported 169 grants, almost all of which were to investigators outside the field of asthma. From the first year, the breadth of the science funded has been notable, and the number and quality of applications have remained high, making the program highly competitive. Among the awardees, 115 were Ph.D.s (three of whom also had veterinary degrees), 28 were M.D.-Ph.D.s, and 26 were M.D.s. The relatively high number of Ph.D. awardees speaks to AAF's commitment to basic science.

The ultimate success of the AAF will be measured by its effect on the lives of people with asthma. This goal has not yet been reached, but other indicators provide evidence for early success.

- **Sticking with it.** Two-thirds of past awardees continue to pursue studies related to asthma. In addition, AAF grants have brought 428 trainees to the field, 56 of whom have since become independent researchers.

- **Publications.** AAF-supported work has yielded 527 publications in peer-reviewed journals from 124 awardees over 14 years.
- **Growing support.** AAF awardees have obtained 135 new grants from external sources totaling more than \$107 million in direct costs, exceeding the cost of the AAF awards.
- **Potential therapies.** Wholly, or in part, on the basis of research sponsored by the AAF, 5 drugs have entered phase I or II clinical trials; several potentially useful leads are in the preclinical segment of the development pipeline; and more than two dozen potential new therapeutic targets have been identified. The studies that led to the five clinical trials are (i) interruption of the immune response in asthma by blockade of OX40 interactions with OX40 ligand (3); (ii) blockade of receptors for adenosine, which promotes inflammation and airway remodeling (4); (iii) the use of beta-blockers in asthma (Used acutely, beta-blockers worsen asthma, but AAF-sponsored studies indicate that low doses might improve the condition.) (5); (iv) simultaneous blockade of two phosphokinases that promote inflammation, PI3K δ and PI3K γ (6); and (v) blockade of S-nitrosogluthathione (GSNO) reductase, an enzyme that is overactive in asthma, reducing levels of the small molecule GSNO in the lung (7).

The study that examined the blockade of OX40 has been stopped because it did not meet primary end points in phase II trials (8). The AAF appreciates that the great majority of new drugs brought to clinical trials on the basis of sound preclinical studies will not prove effective in treating patients. In fact, both in clinical and preclinical studies, the AAF considers failures to be a natural outcome of funding high-risk research. If most of the grants were successful, this result would indicate that the AAF was too conservative, choosing only applications with safe projects.

No single factor has been predictive of the success of an AAF award. Notably, early-career investigators did as well as senior investigators in bringing new drugs to clinical trials. The SRB has made the subjective observation that risky ideas have more often proved successful than risky investigators—those whose past achievements leave uncertain their ability to pursue the work.

The AAF remains atypical among supporters of bench science in its broad embrace of investigators from fields beyond asthma R&D. There are other approaches that also seek to promote innovation and to support high-risk research, and we do not claim that the AAF's approach is superior. We suggest, however, that for many other kinds of disease-related research, fresh perspectives brought by established investigators with alternate expertise would be as beneficial as they have been for asthma.

– William E. Seaman, Richard M. Locksley, Michael J. Welsh

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