As a young medical student in Colombia looking for a research project more than two decades ago, I was discouraged from working on Alzheimer disease (AD) after seeing too many classmates crowding the field. Most everyone wanted to work with the Colombian family suffering from early-onset AD caused by the PSEN1 E280A mutation, the world’s largest.1 I therefore asked my mentor, Dr. Francisco Lopera, the legendary neurologist who discovered the Colombian family with AD, to give me a more obscure project that few were interested in. He pulled out of a desk drawer the printed pedigrees of two large families suffering from adult onset of stroke. We later found with Drs. Kenneth S. Kosik and Spyros Artavanis-Tsakonas that these families had mutations in NOTCH 3 and defined a clinical and molecular diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a disease of small blood vessels.2,3 Like the family with AD, the ones with CADASIL had a similar fate, progressive cognitive decline and ultimate demise. Hence, my goal was the same: to find disease-modifying therapies to help them.

Fast forward to the present, which has seen decided advances in treatments for AD. Here, I want to discuss critical aspects that in my opinion helped the AD field achieve this milestone: i) continuity of training, fellowships, and transition to independence; ii) targeted funding; iii) scholarship, collaboration, and dissent; and iv) biomarkers. This special issue of The American Journal of Pathology includes reviews directly addressing the point of scholarship, collaboration, and dissent, whereas the other points are addressed in this editorial. It is my hope that by reflecting on what the AD field got right, we can achieve or hopefully surpass what they accomplished and deliver to our patients a safe and effective therapy for small blood vessel diseases in the brain.

Continuity of Training, Fellowships, and Transition to Independence

Developing safe and effective disease-modifying therapies for small blood vessel diseases will take a village of well-trained and highly motivated scientists and clinicians. Mechanisms to support such a goal include postdoctoral fellowships and career development grants from the American Heart Association and the K99/R00 Pathway to Independence grants from the National Institutes of Health (NIH). Continuity of funding is critical to increase the chance of landing an independent faculty position. Difficulties can arise when one works on an add-on disease with a serious recognition problem, which is the case for small blood vessel diseases in the brain. When applying to the American Heart Association, a trainee may first need to explain that small blood diseases cause stroke, because addressing stroke is within the Heart Association’s mission. The trainee may also need to explain how the rare CADASIL condition, for instance, relates to the more...
common sporadic small blood vessel disease. This issue limits access of our trainees to cardiovascular-related funding opportunities. A similar problem arises in the neurology and neurosciences universe, because small blood vessel diseases belong to the related dementias part of the Alzheimer disease and related dementias (ADRD) field. This problem of recognizing the significance of small blood vessel diseases can be alleviated with proper mentoring and craft. Effective training in the field requires a diverse pool of mentors representing relevant expertise in vascular biology, neuroscience, neurology, physiology, and cell and molecular biology. The issue will also require creative vision from faculty search committees truly committed to recruiting a diverse roster of independent scientists. Tremendous progress in the field of small blood vessel diseases in the brain will certainly be made if neurology departments recruited more vascular biologists and cardiovascular departments recruited more neuroscientists.

**Targeted Funding**

There is a likely link between the serious commitment of funding directed to AD and the recent successes in the field. In 2020 alone, NIH funding included 350 million dollars dedicated to AD and other related dementias (National Institute on Aging, [https://www.nia.nih.gov/about/naca/september-2020-directors-status-report](https://www.nia.nih.gov/about/naca/september-2020-directors-status-report), last accessed September 8, 2021). Additional funding with more lenient pay lines has propelled the field to achieve critical milestones. Partnerships between NIH and not-for-profit organizations, including the Alzheimer’s Association, Alzheimer’s Disease Discovery Foundation, UsAgainstAlzheimer’s, and BrightFocus Foundation, private donors, and industry, have provided additional support that has often diverged, more so recently, into less amyloid-centric approaches. The field of related dementias has benefited from this largesse. In particular, NIH program officers clearly understand and encourage applications addressing small blood vessel diseases to qualify for ADRD pay lines. A barrier in understanding remains within study sections, a problem that must be addressed to foster substantial progress in the field. NIH has made successful efforts in addressing the recognition issue by promoting vascular contributions to cognitive impairment and dementia (VCID) as a relevant field and by issuing requests for applications with funding commitments to directly address this condition. Patient-driven organizations specific for small blood vessel disease have grown significantly in the past few years, with some, such as cureCADASIL, awarding research grants. Worthy of note is the Fondation Leducq with its International Networks of Excellence, which have often supported small blood vessel disease research with a strong focus on training the next generation of scientists. Despite these efforts, economic analyses have argued that AD research is actually underfunded compared with other conditions, more so if one considers disease burden. By comparison, the small blood vessel disease field is severely underfunded, and significant efforts must be made to promote federal, foundation, and industry collaboration to create a critical mass of research efforts aimed at developing disease-modifying therapies.

**Scholarship, Collaboration, and Dissent**

The AD field got quite a few items right with regard to scholarship, collaboration, and dissent. Relevant examples include establishing networks for coordinated clinical and scientific research, such as the NIH-funded Alzheimer’s Disease Research Centers (ADRC) for late-onset disease, and the Dominantly Inherited Alzheimer’s Network (DIAN) for early-onset disease. As yet, we do not have anything nearly as well organized for small blood vessel disease. Notwithstanding, the Alzheimer’s Disease Neuroimaging Initiative (ADNI) has given us tremendous information about the role of white matter abnormalities, lacunes, and microhemorrhages in VCID. Also, it is noteworthy what our European colleagues have been able to accomplish in terms of clinical and imaging characterization of CADASIL in European families in efforts led by Drs. Martin Dichgans and Hughes Chabriat. A desirable approach, considering that we are objectively behind in this area in the US, would be to leverage the infrastructure provided by the ADRC and DIAN networks to piggyback efforts for sporadic and familial small blood vessel disease in the brain.

Even more remarkable is what AD researchers were able to achieve with the AlzForum website ([https://www.alzforum.org](https://www.alzforum.org), last accessed September 30, 2021), where relevant scientific advances are systematically discussed with active contributions by prominent leaders in the field. Many individuals in different biomedical fields have attempted this type of open discussion of manuscripts with little to no success. I look at the collective achievements of AD researchers with awe and optimism because they have much to show for their efforts, including blood and cerebrospinal fluid biomarkers, some of which possess striking predictive properties; quantitative measures of pathology for both tau and amyloid, the telltales of Alzheimer brain pathology, via positron emission tomography; and dozens of clinical trials completed and ongoing, with at least one drug, Aduhelm, recently approved by the FDA. Papers focusing on small blood vessel disease are often discussed in the AlzForum website, though it is fair to ask if a dedicated website is needed and can be sustained to directly address the field.

The amyloid cascade hypothesis has become a highly controversial issue among AD researchers. There is nothing as galvanizing in the area of small blood vessel diseases, though it is worth keeping in mind the potential issues that could arise. Competing views of small blood vessel disease pathophysiology have been proposed, and in some aspects may resemble discussion in the AD field. An example is the
Notch 3 accumulation cascade hypothesis, which has been assumed to be in opposition to the Notch 3 signaling deficiency hypothesis in CADASIL. A review on this subject that Dr. Dorothee Schoemaker and I wrote addresses these issues in a comprehensive manner. The review also explores if new terminologies that are more encompassing to the diversity of NOTCH3 mutations recently associated to small blood vessel disease are in order by introducing the notion of NOTCH3-associated small vessel disease. A similar revision may be helpful of cerebral autosomal recessive arteriopathy with subcortical infarcts and leukencephalopathy (CARASIL) due to mutations in HTRA1. How good is the term CARASIL, which enshrines a recessive nature, after reports of patients suffering from cerebral small blood vessel disease due to autosomal dominant heterozygous HTRA1 mutations? Some disease boundaries in small blood vessel disease may be only artificial, as suggested by findings discussed by Wang et al supporting major commonalities between CADASIL and cerebral amyloid arteriopathy. These conditions were thought of as completely different from each other, at least mechanistically. Consistent with the subtheme of breaking artificial disease boundaries, Sepulveda-Falla and Kalaria’s contribution discusses existing evidence for small blood vessel disease in sporadic and familial AD, proposing the need of incorporating relevant vascular biomarkers in the biological definition of AD. Eikermann-Haerter and Huang discuss the mechanisms underlying the differences and similarities between migraine-related deep white matter hyperintensities and small blood vessel disease. The review by Ashby and Mack addresses multiple modes of endothelium-derived blood flow regulation and how they may contribute to the pathophysiology of small blood vessel disease, whereas Montagne et al consider the extent to which loss of pericytes and the resulting loss of endothelial-pericyte crosstalk contributes to dementia pathology. Access to better animal models of small blood vessel disease will tremendously enhance our understanding of mechanism and enable preclinical testing of new therapies. To that end, Fang-Liao et al contribution discusses the endothelial nitric oxide synthase (eNOS)-deficient mice as a model of age-dependent, spontaneous small blood vessel disease. I would argue that another underestimated and very relevant mouse model is the viable and fertile Notch3 knockout mouse, which also develops age-dependent cerebral small blood vessel disease. Finally, the contribution of Kim and Whitmore reviews the rapidly evolving field of vascular consequences of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As noted in this article, the next few years will tell us more about intriguing neurovascular effects of SARS-CoV-2 and how they impact cognition.

Biomarkers, Biomarkers, Biomarkers

Though biomarkers in AD have had a tortuous path through validation and approval, it is clear by now that they accurately measure pathology. It is tempting to consider that a first disease-modifying therapy for small blood vessel in the brain may also be supported by robust biomarker data as a surrogate predictor of future clinical benefit. A conceptual and technological framework to identify such biomarkers has been established by consortia like ADNI in the US and by the remarkable work done in Europe to characterize imaging and clinical features of CADASIL as discussed earlier. Another success story is the launch of the MarkVCID consortium, charged with developing biomarkers for small vessel disease with support from NIH and BrightFocus. One can dream of a predictive and highly sensitive biomarker of small blood vessel disease to support approval of safe and effective disease-modifying therapies. For CADASIL, that could be a way to measure granular osmiophilic deposits in brain vessels or the levels of Notch3 activity. Broader spectrum markers may target basement rarefaction or mural cell loss. It is clear, though, that the next frontier can only be crossed when and if we get such biomarkers developed and properly validated for use in enabling clinical trials.

References
