Invited Editorial: Current Impediments to Successful Translational Research in Stroke

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Wikipedia offers the following, quite apposite definition of translational research: “Translational research is a way of thinking about and conducting scientific research to make the results of research applicable to the population under study... In the field of medicine, for example, it is used to translate the findings in basic research more quickly and efficiently into medical practice and, thus, meaningful health outcomes ...” [1]. While the potential benefits of the translational approach are self-evident, and notwithstanding the frequent homage paid to the concept (for example, the founding of this journal), one cannot help being concerned by a variety of current structural impediments that, unless attended to and remedied, threaten to diminish future prospects for real success in translational stroke research.

In his 2005 Thomas Willis Lecture [2], Vladimir Hachinski captures the essence of the translational challenge with characteristic eloquence: “Advances in stroke are occurring at an unprecedented pace, but often in disciplinary isolation and without optimal mechanisms for systematically translating, integrating and applying the findings. *Knowledge accrues in pieces, but is understood in patterns* [italics mine]. To optimize knowledge acquisition and application, infrastructures and systems need to be set up along with appealing incentives. The approach needs to be transdisciplinary, going beyond the bounds of any given discipline, reciprocally translational, and transactional, meaning that the interchanges have to yield previously agreed benefits to the parties (The Triple T Approach). A new breed of leaders needs to be developed and nurtured to catalyze the process.... Systematically integrating what we know and

evaluating what we do could spur progress. Research is not only an activity but an attitude... No system can replace the individual initiative, creativity and insights that lead to the great discoveries, but progress is not made by breakthroughs alone. No one's work is so exalted that it cannot be improved, nor so humble that it has no value. We can all make a difference” [2].

What, then, are some remediable factors hindering translational stroke research? In my opinion, there are several:

The twilight of the NIH Program Project grant The essence of successful translational research is interdisciplinary collaboration. NIH established the Program Project funding mechanism decades ago with the express intent of (a) drawing together investigators with complementary expertise (both basic and clinical) to tackle important biomedical problems in a collaborative fashion and (b) funding a stable research “core” infrastructure to give this effort a real chance of success over time. No one is more indebted to this program than myself as my entire academic career has been shaped by this funding mechanism. My initial academic appointment at the University of Pennsylvania in the 1970s was made possible by Martin Reivich's NIH-funded Cerebrovascular Research Center. As a young clinician-investigator, I was exposed via the program–project mechanism to the research styles and ideas of many brilliant collaborators, including giants in the field of cerebral metabolism (e.g., Louis Sokoloff and Britton Chance) during a period of great intellectual ferment. To cite but one instructive example, program–project collaborations allowed the novel 2-deoxyglucose method for the quantitative mapping of local/regional cerebral metabolism [3] to be applied to animal models of stroke [4] and facilitated the development of ^{18}F -fluoro-deoxyglucose to measure local cerebral glucose utilization in humans [5],

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which in turn helped to launch the field of positron emission tomography [6]. Subsequently, I was fortunate to have led a stroke Program Project at the University of Miami for 24 years.

During the 1970s, there were an estimated 20 NINCDS-supported centers and program projects *devoted to stroke research*, and in the 1980s, this number grew to around 26 (Murray Goldstein, personal communication). In contrast, in the year 2000, the NINDS funded only 18 new and competitive-renewal P01 applications *in toto, across all of its research areas*, at a total cost of \$21 million; by way of comparison, 646 new and competitive-renewal *individual* research grant (R01) applications were awarded by NINDS in 2000, totaling \$208 million [7]. By 2009, NINDS was funding only ten new and competitive-renewal P01 applications across all fields at a cost of around \$14 million, contrasting with 463 R01 awards at \$172 million [7]. The sad reality is that the demise of any well-established Program Project or Center leads inevitably to the disbanding of its multidisciplinary core infrastructure, to the migration of former collaborators to other academic affiliations, and to an irretrievable decline in the translational mission itself, which is dependent upon *multidisciplinary collaboration*. The current NIH emphasis on funding individual research grants at the expense of collaborative programs may be an understandable response to increasingly constrained federal funds but, in the long run, will surely jeopardize the translational mission. (The NINDS P50 collaborative funding mechanism, “Specialized Programs in Translational Research in Acute Stroke” (SPOTRIAS), partially remedies this situation but emphasizes mainly *clinical* research directed toward improved stroke treatment strategies and outcomes (e.g., phase I and II clinical trials, innovative systems for delivery of clinical services, and biomarkers); preclinical research supported under SPOTRIAS must be directly related to the clinical mission rather than nurturing the basic science seeds that may (or may not) eventually bear clinical fruit [8].)

Declining numbers of M.D. clinician/investigators Medical students graduating from private medical schools in 2006 had a total average indebtedness of \$160,000; for those graduating from public medical schools, total debt was \$120,000. These figures appear to be rising at 6–7% per year [9]. Not surprisingly, economic factors, including the prospect of higher earnings, strongly influence medical residents' choice of specialty [10]. In this economic climate, it becomes more difficult to attract medical students and residents to relatively modest-paying postdoctoral research fellowships and to academic careers that may be far less remunerative than private practice opportunities. Nonetheless, in my view, successful translational research *requires* the collaborative expertise of medically trained physician-

investigators, who by virtue of their training are *instinctively aware of the clinical context and implications* of the topic under investigation and, as a consequence, are better suited to tailor their research strategies toward the translational goal. PhDs lacking a medical degree may be conceptually brilliant and technically adept researchers but, in the absence of input from medical colleagues, often have limited or misguided insight into the clinical applicability (or lack thereof) of their chosen research endeavor. The cadre of physician-investigators could be amplified by a federally guaranteed waiver of medical school indebtedness in return for a commitment to an academic research career. However, this is unlikely to happen in the near future.

The cult of the individual According to the pioneering sociologist Emile Durkheim, modern society is held together by a division of labor in which individuals specialize in different types of work and are therefore dependent upon each other [11]. Indeed, this interdependence is at the crux of the interdisciplinary collaborations needed to foster translational research. In contrast, present-day institutions of higher learning tend to foster a “cult of the individual” by conferring academic and monetary rewards (e.g., promotion, tenure, and higher salary) upon those individuals who distinguish *themselves* by virtue of attracting *individual* research grant funding, publishing *first-authored* peer-reviewed manuscripts, and the like. In point of fact, however, not everyone is well suited to that role; many gifted scientists are content to function within collaborative research groups in which they contribute their crucial expertise with minimal fanfare and without the obligation to attain individual distinction. To the extent to which this type of person is selected against in the academic setting or in the competition for federal funding of collaborative research programs, the more is translational research likely to suffer.

The ambivalent role of the pharmaceutical industry The pharmaceutical industry already brings an impressive armamentarium to bear on translational research: very large research budgets and resources sufficient to span the entire “bench to bedside” research spectrum, from large-scale screening of promising agents to the execution of extensive animal studies to establish proof-of-principle of efficacy, define toxicity, establish dose–response, and characterize the therapeutic window; to the conduct of the very expensive toxicity and carcinogenicity studies required for FDA approval; and to the funding, organization, and execution of large-scale randomized multicenter clinical trials. Nonetheless, pharma often falls short owing to a misguided selection of “promising” agents for clinical trials and suboptimal trial design (often influenced by market-driven

factors such as perceived return-on-investment), a failure to heed the advice of academia, a failure to publish their negative preclinical and clinical trial findings, etc. In this regard, Giora Feuerstein (himself a superb exemplar of industrial-plus-academic wisdom) is precisely on-target in calling for a consortium approach designed around partnerships among academia, government (FDA/NIH), and the pharmaceutical industry [12].

In conclusion, translational research remains a laudable goal with bright prospects for research in stroke and other disorders, but to succeed, it requires more than wishful thinking on the part of individual researchers. Wisely conceived and constructively implemented collective efforts at the level of individual academic institutions, federal funding agencies and the pharmaceutical sector are urgently needed.

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