Springer Series in Translational Stroke Research

Paul A. Lapchak
John H. Zhang *Editors*

Translational Stroke Research

From Target Selection to Clinical Trials

Springer

Springer Series in Translational Stroke Research

Series editor
John Zhang

For further volumes:
http://www.springer.com/series/10064

Paul A. Lapchak • John H. Zhang
Editors

Translational Stroke Research

From Target Selection to Clinical Trials

Springer

Editors
Paul A. Lapchak, PhD, FAHA
Department of Neurology
Cedars-Sinai Medical Center
Los Angeles, CA, USA

John H. Zhang
Loma Linda University
Loma Linda, CA, USA

ISBN 978-1-4419-9529-2 e-ISBN 978-1-4419-9530-8
DOI 10.1007/978-1-4419-9530-8
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2012934161

Stroke Progress and Promises: Going Forward (Preface)

To ancient Greeks, the hero met his nemesis or tragic ending as a direct result of his hubris or pride. Gazing over the smoking battlefield of failed clinical trials [1] one cannot help but think of the armies lost to the hubris of those who launched campaigns with terrible certainty: this plan must work because it fits everything we know. Given the spectacular stroke-trial failures of the past 2 decades, one might reasonably give the stage over to the Greek chorus, lamenting the tragic end of neuroprotection, and moving on to other therapeutic areas. Reviewing the new and novel ideas contained in this volume, as well as new twists on old ideas, one can be ensured a renewed energy and optimism.

The industry-sponsored dextrophan trial in the United States [2] brought to the forefront the "one mechanism–one drug" principle that guided drug development for decades. The trial arose from an elegant theory that a single neurotransmitter, glutamate, acting on a single channel, the NMDA receptor, injuring a single cell-type, the neuron, unlocked the secret to reversing stroke. The notion that a single drug, acting on a single receptor to activate a single, defined mechanism of action seduced trialists, basic scientists, regulators, and funding agencies. The "single mechanism" theory came to permeate translational neurology, so much so that studies of pleiotropic therapies came to a virtual standstill. Twelve years later, the spectacular demise of the free-radical scavenging agent NXY-059 [3, 4] finally and (hopefully) permanently put an end to the naïve idea that a single magic bullet therapy could overcome the plethora of pathologic processes running in parallel during ischemia.

Even worse than naiveté, however, during the 2-decade search for the "single mechanism" magic bullet, a hubritic sense permeated the field: experts knew all that anyone needed to know. Study groups designed trials—and powered them—as if there were no unknowns among human stroke victims participating in trials. For example, during the development of the steroid tirilazad, an unrecognized gender effect on drug metabolism partially influenced the outcome of the pivotal clinical trial [5]. When designing the NINDS Trial of rt-PA for Acute Ischemic Stroke [6], we were advised by very experienced and senior neurologists to exclude lacunes: it was "well known" that the mechanisms of small vessel occlusion included cystic

medial necrosis and lipohyalinosis but *not* thrombosis. Had we followed dogma and excluded lacunar stroke patients, we would have excluded the subgroup that benefited most from thrombolytic therapy [7].

Hubris of another kind affects the few companies interested in funding clinical trials in stroke. Large pharma will have little or nothing to do with stroke trials until positive results can be guaranteed; the field is left to brave start-up ventures willing to gamble on finding the next big winner in stroke. But limited funds drives these companies to design trials targeted at an idealized subgroup of patients. After retrospective review of failed trials, these businessmen conclude that we should study only the portion of the fraction of the sub-subgroup that would presumably benefit. This "threading-the-needle" principle assumes that tomorrow's treatment behaves exactly like yesterday's after we exclude patients who presumably could not have responded to therapy. The next few clinical trials will reveal whether this needle can be threaded successfully.

The next phase—and hopefully a more mature phase—of stroke clinical trials seems to be emerging and this volume seeks to illustrate two critical points relevant to this renaissance. First, the need for pleiotropic and combinatorial therapies is obvious. The search for the "magic bullet" is over and therapies like hypothermia, with multiple mechanisms, should receive priority [8]. Second, while a "thread-the-needle" approach to finding magic subgroups may succeed, such is doubtful. A viable alternative strategy includes a confession of humility: we do not know everything and we should power our trials to include the unforeseen responsive or nonresponsive populations. Larger trials may cost more, but new approaches can reduce risk by including stronger futility analyses, adaptive and sequential designs, and frequent interim analyses. Larger trials that can be pooled with other large trials allow for *rational* subgroup analysis and the rigorous confirmation of trends. Obviously, larger trials demand simplified designs and the collection of only the most salient data. Regulatory reform must arise on multiple continents.

The time is ripe for many of the ideas presented in this volume and the Editors have done a good job attracting new talent bringing novel, perhaps radical, ideas. In Part I, the neurovascular unit comes to the forefront, as it should. What were we thinking when we designed therapies targeted only at neurons, as if there were no other cells in the nervous system? Conceptually, the neurovascular unit seems obvious and simple—as do all major advances in science—but the implications may be complex and protean. The second part of this book offers the reader a potpourri of new therapeutic possibilities. Few, or perhaps none, of these proposals will pan out, but in investigating these and other new targets, we should stumble our way into a significant advance like thrombolysis. Some—like laser therapy—are far-fetched and hard to accept given our current understanding of ischemia. Others—like hypothermia—are very old ideas newly reformulated thanks to technical delivery advances. While we cannot predict which of these ideas will prove successful, we can assert that at least something here will move our field forward significantly. Parts III and IV tackle the very real but arcane details of modeling. No small part of our collective failure lies with the preclinical models, and a critical review will inform the reader on limitations of past and present animal stroke models.

Part V offers updates on therapies currently on the "hot list" and illustrates some of the pitfalls inherent in clinical trials. Part VI offers criticism and proposals for improving clinical trial design; these revisions are sorely needed.

Stroke research is not for the faint of heart. We fight a common, devastating disease and lose more often than we win. But every year around the world, more patients receive intravenous rt-PA, more stroke centers open up, and more Fellows are trained as Vascular Neurologists. Undoubtedly, a multi-mechanistic neuroprotective treatment—and likely something first glimpsed in this book—will emerge to compliment recanalization, but only if we humbly learn the lessons of the last 2 decades and thoughtfully plan for the unknown.

Patrick D. Lyden

References

1. O'Collins VE, Macleod MR, Donnan GA, Horky LL, van der Worp BH, Howells DW. 1,026 experimental treatments in acute stroke. Ann Neurol. 2006;59(3):467–77.
2. Albers GW, Atkinson RP, Kelley RE, Rosenbaum DM. Safety, tolerability, and pharmacokinetics of the *N*-menthyl-D-aspartate antagonist dextrorphan in patients with acute stroke. Stroke. 1995;26:254.
3. Shuaib A, Lees KR, Lyden P, et al. NXY-059 for the treatment of acute ischemic stroke. N Engl J Med. 2007;357(6):562–71.
4. Lyden PD, Shuaib A, Lees KR, et al. Safety and tolerability of NXY-059 for acute intracerebral hemorrhage: the CHANT Trial. Stroke. 2007;38(8):2262–9.
5. Haley EC, Jr. High-dose tirilazad for acute stroke (RANTTAS II). RANTTAS II Investigators. Stroke. 1998;29(6):1256–7.
6. NINDS rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333(24):1581–7.
7. NINDS rt-PA Stroke Study Group. Generalized efficacy of t-PA for acute stroke. Stroke. 1997;28:2119.
8. Hemmen TM, Lyden PD. Multimodal neuroprotective therapy with induced hypothermia after ischemic stroke. Stroke. 2008;40(3 Suppl):S126–8.
9. Lyden P. The future of basic science research and stroke: hubris and translational stroke research. Int J Stroke. 2011;6(5):412–3. DOI:10.1111/j.1747-4949.2011.00657.x.

Contents