

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

© Springer Science+Business Media, LLC 2012

All rights reserved. This work may not be translated or copied in whole or in part without the written permission of the publisher (Springer Science+Business Media, LLC, 233 Spring Street, New York, NY 10013, USA), except for brief excerpts in connection with reviews or scholarly analysis. Use in connection with any form of information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed is forbidden.

The use in this publication of trade names, trademarks, service marks, and similar terms, even if they are not identified as such, is not to be taken as an expression of opinion as to whether or not they are subject to proprietary rights.

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

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

Part I Theoretical Overview

1 Vascular Targets for Ischemic Stroke Treatment.....	3
Sara Morales Palomares and Marilyn J. Cipolla	
2 Identifying Vascular Targets to Treat Hemorrhagic Stroke.....	37
Paul A. Lapchak	
3 Experimental Platforms for Assessing White Matter Pathophysiology in Stroke.....	57
Ken Arai, Loc-Duyen D. Pham, and Eng H. Lo	
4 Neuroprotection in Stroke.....	79
Aarti Sarwal, Muhammad Shazam Hussain, and Ashfaq Shuaib	

Part II Mechanisms and Targets

5 Protein Aggregation and Multiple Organelle Damage After Brain Ischemia	101
Chunli H. Liu, Fan Zhang, Tibor Krisrian, Brian Polster, Gary M. Fiskum, and Bingren Hu	
6 Antioxidants and Stroke: Success and Pitfalls	117
Fernanda M.F. Roleira, Elisiário J. Tavares-da-Silva, Jorge Garrido, and Fernanda Borges	
7 Caspase-Independent Stroke Targets.....	145
Ruoyang Shi, Jiequn Weng, Paul Szelemej, and Jiming Kong	
8 Hypoxia-Inducible Factor: A New Hope to Counteract Stroke.....	175
Chunhua Chen and Changman Zhou	

9	Thrombin in Ischemic Stroke Targeting	189
	Bo Chen	
10	Toll-Like Receptor Agonists as Antecedent Therapy for Ischemic Brain Injury: Advancing Preclinical Studies to the Nonhuman Primate	205
	Frances Rena Bahjat, Keri B. Vartanian, G. Alexander West, and Mary P. Stenzel-Poore	
11	Angiogenesis and Arteriogenesis as Stroke Targets	231
	Jieli Chen and Michael Chopp	
12	Hematopoietic Growth Factor Family for Stroke Drug Development	251
	Ihsan Solaroglu and Murat Digicaylioglu	
13	Soluble Epoxide Hydrolase as a Stroke Target	277
	Jonathan W. Nelson and Nabil J. Alkayed	
14	Membrane Potential as Stroke Target	295
	Jens P. Dreier, Maren Winkler, Dirk Wiesenthal, Michael Scheel, and Clemens Reiffurth	
15	Hypothermia to Identify Therapeutic Targets for Stroke Treatment	305
	Masaaki Hokari and Midori A. Yenari	
16	Stroke Preconditioning to Identify Endogenous Protective or Regenerative Mechanisms	321
	Liren Qian, Prativa Sherchan, and Xuejun Sun	
17	microRNAs in Ischemic Brain: The Fine-Tuning Specialists and Novel Therapeutic Targets	335
	Ashutosh Dharap, Venkata P. Nakka, and Raghu Vemuganti	
18	Neuroglobin: A Novel Target for Endogenous Neuroprotection	353
	Zhanyang Yu, Ning Liu, and Xiaoying Wang	
19	Characterization of Novel Neuroprotective Lipid Analogues for the Treatment of Stroke	373
	Pamela Maher, Alain César Biraboneye, and Jean-Louis Kraus	
20	Na⁺/H⁺ Exchangers as Therapeutic Targets for Cerebral Ischemia	387
	Yejie Shi and Dandan Sun	
21	Iron as a Therapeutic Target in Intracerebral Hemorrhage: Preclinical Testing of Deferoxamine	403
	Ya Hua, Richard F. Keep, Yuxiang Gu, and Guohua Xi	

22 Potential Therapeutic Targets for Cerebral Resuscitation After Global Ischemia.....	417
Yan Xu	
23 The Splenic Response to Ischemic Stroke: Neuroinflammation, Immune Cell Migration, and Experimental Approaches to Defining Cellular Mechanisms	451
Christopher C. Leonardo, Hilary Seifert, and Keith R. Pennypacker	

Part III Translational Models

24 Overcoming Barriers to Translation from Experimental Stroke Models.....	471
Ludmila Belayev	
25 Animal Models of Stroke for Preclinical Drug Development: A Comparative Study of Flavonols for Cytoprotection.....	493
Carli L. Roulston, Sarah McCann, Robert M. Weston, and Bevyn Jarrott	
26 Clinical Relevance in a Translational Rodent Model of Acute Ischemic Stroke: Incorporating the Biological Variability of Spontaneous Recanalization.....	525
Kama Guluma	
27 A Clinically Relevant Rabbit Embolic Stroke Model for Acute Ischemic Stroke Therapy Development: Mechanisms and Targets	541
Paul A. Lapchak	
28 Animal Models of Intracranial Aneurysms	585
Elena I. Liang, Hiroshi Makino, Yoshiteru Tada, Kosuke Wada, and Tomoki Hashimoto	
29 Animal Models of SAH and Their Translation to Clinical SAH.....	595
Tommaso Zoerle and R. Loch Macdonald	

Part IV De-Risking of Drug Candidates

30 ADME (Absorption, Distribution, Metabolism, Excretion): The Real Meaning—Avoiding Disaster and Maintaining Efficacy for Preclinical Candidates	617
Katya Tsaioun and Steven A. Kates	

- 31 CeeTox Analysis to De-risk Drug Development:
The Three Antioxidants (NXY-059, Radicut, and STAZN)..... 639**
Paul A. Lapchak

Part V Therapy Delivery

- 32 Site-Specific, Sustained-Release Drug Delivery
for Subarachnoid Hemorrhage..... 659**
R. Loch Macdonald
- 33 Therapeutic Potential of Intranasal Delivery of Drugs
and Cells for Stroke and Other Neurological Diseases..... 681**
Heyu Chen, Caibin Sheng, Weiliang Xia, and Weihai Ying

Part VI Therapy Development

- 34 High-Dose Albumin for Neuroprotection in Acute
Ischemic Stroke: From Basic Investigations
to Multicenter Clinical Trial 691**
Myron D. Ginsberg
- 35 The Translation Procedure of Low-Level Laser Therapy
in Acute Ischemic Stroke: A Nonpharmaceutics
Noninvasive Method 721**
Yair Lampl
- 36 Use of Microbubbles in Acute Stroke..... 745**
Marta Rubiera and Carlos A. Molina
- 37 Transcranial High-Intensity Focused Ultrasound
for Sonothrombolysis in Stroke 753**
Thilo Hölscher, Golnaz Ahadi, Daniel Lotz,
Ceryl Schendel, David Fisher, and Arne Voie
- 38 Cellular Therapy for Ischemic Stroke..... 777**
Todd Deveau, Shan Ping Yu, and Ling Wei

Part VII Clinical Trial Design

- 39 Repair-Based Therapies After Stroke 817**
Steven C. Cramer
- 40 A Critical Review of Stroke Trial Analytical Methodology:
Outcome Measures, Study Design, and Correction
for Imbalances 833**
Pitchaiah Mandava, Chase S. Krumpelman,
Santosh B. Murthy, and Thomas A. Kent

41 Metabolic Imaging in Translational Stroke Research	863
Krishna A. Dani and Keith W. Muir	
42 Computational Analysis: A Bridge to Translational Stroke Treatment.....	881
Nirmalya Ghosh, Yu Sun, Christine Turenius, Bir Bhanu, Andre Obenaus, and Stephen Ashwal	
43 Innovations in Stroke Clinical Trial Design.....	911
Karen L. Furie and Michael K. Parides	
Index.....	917

