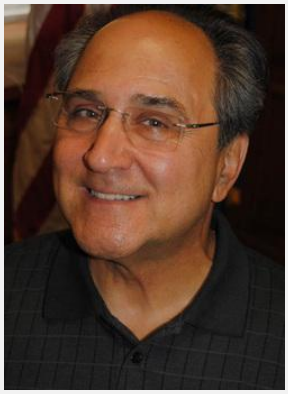
XLVIII JCET LECTURE, 08.12.2014, 9.00

Thrombopoietin Intervention in Preclinical Models of Cerebrovascular Disease: Remarkable Brain and Behavioral Protection and Restoration



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Ischemic stroke is a major cause of world-wide death and long-term and costly sensory, motor and cognitive disabilities. The only intervention for ischemic stroke is tissue plasminogen activator (tPA) thrombolysis (i.e., use approved only up to 4.5 hr post-onset). tPA-thrombolysis promotes hemorrhage which limits tPA utility and only reaches a fraction (<5%) of patients, creating an enormous gap in stroke intervention. Vascular cognitive impairment (VCI) is defined as cognitive deficits due to cerebrovascular disease (including strokes). VCI exacerbates neurodegeneration as in Alzheimers disease and contributes to most dementia. In addition to strokes, hypertension and/or forebrain hypoperfusion are major cerebrovascular disease risk factors contributing to non-stroke VCI. This presentation will describe our use of translational stroke and VCI models that mimic the pathogenesis of clinical stroke-VCI in order to better understand disease biology and intervention.

One important focus of our research has been to evaluate the utility of thrombopoietin (TPO; hematopoietic growth factor that regulates platelets) in models of cerebrovascular disease. In rodent stroke, post-stroke TPO administration can protect the brain from injury and restore its lost functioning even if administered long after injury has occurred. This presentation also will describe the therapeutic value and novel mechanism(s) involved in TPO's brain protection-restoration. TPO decreases many stroke pathological processes, including stroke-induced inflammatory cytokine expression, microvascular and brain inflammation, matrix metalloproteinase 9 (MMP-9), brain leukocyte infiltration and microgliosis, and decreases post-stroke blood-brain barrier and brain injury (i.e., infarction and edema) and neurological and cognitive deficits. Thus, TPO preserves sensory, motor and especially cognitive functioning. In addition, TPO provides a significant restoration of lost functions when administered after stroke injury has occurred. Improved functional recovery under these conditions is related to an increase in microvessels/angiogenesis and neurogenesis in the peri-infarct areas. Work in the TPO receptor knock-out mouse demonstrates that the protective effects are mediated via its TPO receptor.

Complex cognition and gait abnormalities as seen in human VCI are also exhibited in our non-stroke rodent VCI models. VCI under these conditions is induced by hypertension and/or carotid stenosis without producing brain infarctions. Reduced fiber-tract myelin staining with increased microvascular inflammation and microgliosis is observed in this non-stroke VCI, thus representing

a fiber track “disconnect condition” as observed in younger clinical VCI patients. Post-carotid stenosis administration of only one or two TPO injections provides a remarkable reduced progression of cognitive loss and gait deficits that persists for months. Therefore, TPO has significant potential to treat a variety of cerebrovascular conditions and dramatically improve outcome functioning.

Our preliminary data indicates that TPO does not significantly penetrate into the brain. Therefore, our current hypothesis is that TPO efficacy in these models is mediated by the vascular endothelium and also by changes in circulating endothelial progenitor and/or immune cells (e.g., leukocytes and T-cells). Although TPO at brain/behavioral efficacious doses does not alter platelets or hematocrit, TPO does stimulate an increase in other growth factors (e.g., PDGF-BB and TGF□□. We hope to establish collaborations with others on TPO brain protective-restorative biology and discover novel mechanisms between TPO and the endothelium, circulating progenitor/immune cells and other factors, while continuing to generate data supporting the potential clinical use of TPO in the future.

Curriculum Vitae

Personal Data:

Name: Frank C Barone

Current Titles: Professor of Neurology and Physiology & Pharmacology
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Citizenship: USA

Education:

Undergraduate: B.A., Psychology/Biopsychology (1973)

Syracuse University, Syracuse, New York

Graduate: Ph.D., Psychology/Neuroscience (1978)

Syracuse University, Syracuse, New York

Research and Mentoring/Teaching:

- 25 years in Drug Discovery functioning as research team leader in developing and executing research strategies from target discovery to drug screening and target validation in disease to marketed drug and post-market drug scientific support; History of maintained/consistent research/resource support in industrial environment for disease target research and compound progression in Discovery Research.
- 7 years doing research, teaching-mentoring students at SUNY Downstate Medical Center.
- Significant experience as consultant to Pharmaceutical Companies, and worked in both the pharmaceutical the academic environment facilitating/developing research direction, mentoring and teaching staff/students, helping in collaboarative work to secure upper management/federal research/grant support.
- Ability to Integrate Systems Pharmacology/Biology and Translational Medicine into Drug Discovery and Disease Biology Research.
- Long standing research background/experience in cardiovascular and cerebrovascular diseases.

- Member of journal editorial boards and NIH study groups; Scientific reviewer to many journals, granting organizations and study groups/sections; Member of numerous scientific societies; Four faculty appointments; Published over 200 scientific manuscripts, reviews and chapters; Mentored many students; E.g., undergraduate (>25), graduate (>30), post-docs (9), Medical (>15), visiting/sabbatical researchers (9).
- Courses taught: Drug Discovery for Graduate Students: Leader of GSK course entitled "In Vivo Pharmacology: Animal Research, Disease Models and Drug Discovery" (Thomas Jefferson University Graduate School); SUNY Downstate Graduate Biochemistry (Enzymes Kinetics and Basic Pharmacology); SUNY Downstate Medical PBL Facilitator (Unit 5; Cardiovascular and Pulmonay).

Academic Appointments:

SUNY Downstate Medical Center, Brooklyn, New York 2008 - Present

Professor of Neurology and Director, Basic Research, Cerebrovascular Division

Primary Appointment in the Department of Neurology

Professor of Physiology & Pharmacology

Joint Appointment in Neural and Behavioral Science Program (School of Graduate

Studies, Department of Physiology & Pharmacology)

Graduate Mentor to SUNY Downstate Medical and Graduate Programs

Medical Student Research Advisor

Member, Faculty Committee, Alumni Fund Summer Research Program

Member, Executive Committee for the Robert F. Furchgott Society

Member, Institutional Setting Subcommittee, LCME Research Workgroup

Thomas Jefferson University, Philadelphia, Pennsylvania 1997 - 2007

Associate Professor, Adjunct Graduate School Faculty

Department of Biochemical and Molecular Pharmacology

Temple University School of Medicine, Philadelphia, Pennsylvania 1987 - 2007

Professor, Adjunct Graduate School Faculty

Department of Physiology

Syracuse University, Syracuse, New York 1978 - 1982

Research Assistant Professor; Brain Research Laboratory

Industrial Appointments:

WYETH PHARMACEUTICALS, Collegeville, Pennsylvania 2007 - 2008

Consultant, Department of Translational Medicine

VITAE PHARMACEUTICALS, Fort Washington, Pennsylvania 2007 - 2008

Consultant, Department of Discovery Biology

GLAXOSMITHKLINE (GSK), King of Prussia, Pennsylvania 1982 – 2007

Left as ***GSK Director, Discovery Research, High Throughput Biology***

Publications (selected from over 200):

1. **Barone, F.C.**, Clark, R.K., Feuerstein, G., Lenkinski, R.E. and Sarkar, S.K.: Quantitative comparison of magnetic resonance imagining (MRI) and histologic analyses of focal ischemic damage in the rat. Brain Res. Bull., 26:285-291, 1991.

2. **Barone, F.C.**, Hillegass, L.M., Price, W.J., White, R.F., Feuerstein, G.Z., Sarau, H.M., Clark, R.K. and Griswold, D.E.: Polymorphonuclear leukocyte infiltration into cerebral focal ischemic tissue: Myeloperoxidase activity assay and histologic verification. J. Neurosci. Res. 29:336-348, 1991.

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4. **Barone, F.C.**, Schmidt, D.B., Hillegass, L.M., Price, W.J., White, R.F., Feuerstein, G.Z., Clark, R.K., Griswold, D.E. and Sarau, H.M.: Reperfusion increases neutrophil and LTB4 receptor binding in focal ischemia. Stroke 23:1337-1348, 1992.

5. Cheng, H.-Y., Liu, T., Feuerstein, G. and **Barone, F.C.**: Distribution of spin-trapping compounds in rat blood and brain: In vivo microdialysis determination. Free Rad. Biol. Med. 14:243-250, 1993.

6. Clark, R.K., Lee, E.V., Fish, C.J., White, R.F., Price, W.J., Jonak, Z.L., Feuerstein, G.Z. and **Barone, F.C.**: Progression of cerebral changes following middle cerebral artery occlusion in the rat: A quantitative planimetric, histologic and immunohistochemical study. Brain Res. Bull. 31:565-572, 1993.

7. Liu, T., McDonnell, P.C., Young, P.R., White, R.F., Siren, A.L., **Barone, F.C**. and Feuerstein, G.Z.: Interleukin-1¤ expression in ischemic rat cortex. Stroke 24:1746-1751, 1993.

8. **Barone, F.C**., Knudsen, D.J., Nelson, A.H., Feuerstein, G.Z. and Willette, R.N.: Mouse strain differences in susceptibility to cerebral ischemia are related to cerebral vascular anatomy. J. Cereb. Blood Flow Metab. 13:683-692, 1993.

9. Liu, T., Young, P.R., McDonnell, P.C., White, R.F., **Barone, F.C**. and Feuerstein, G.Z.: Cytokine-induced neutrophil chemoattractant mRNA expressed in cerebral ischemia. Neurosci. Lett. 164:125-128, 1993.

10. **Barone, F.C**., Clark, R.K., Price, W.J., White, R.F., Storer, B.L., Feuerstein G.Z., and Ohlstein, E.H.: Neuron specific enolase increases in cerebral and systemic circulation following focal ischemia. Brain Res. 623:77-82, 1993.

11. Siren, A.-L., McCarron, R.M., Liu, Y., **Barone, F.C**., Spatz, M., Feuerstein, G. and Hallenbeck, J.M.: Perivascular monocyte/macrophage within endothelium as a mechanism through which stroke-risk factors operate to increase stroke likelihood. J. Vascul. Surg., 18:125-126, 1994.

12. **Barone, F.C**., Globus, M.Y.-T., Price, W.J., White, R.F., Storer, B.L., Feuerstein, G.Z., Busto, R. and Ohlstein, E.H.: Endothelin levels increase in rat focal and global ischemia. J. Cereb. Blood Flow Metab. 14:337-342, 1994.

13. **Barone, F.C**., Price, W.J., Jakobsen, P., Sheardown, M.J. and Feuerstein G.Z.: Pharmacological profile of a novel neuronal calcium channel blocker includes reduced cerebral damage and neurological deficits in rat focal ischemia. Pharmacol. Biochem. Behav. 48:77-85, 1994.

14. Liu, T., Clark, R.K., McDonnell, P.C., Young, P.R., White, R.F., **Barone, F.C**. and Feuerstein, G.Z.: Tumor necrosis factor-¤ expression in ischemic neurons. Stroke 25:1481-1488, 1994.

15. Clark, R.K., Lee, E.V., White, R.F., Jonak, Z.L., Feuerstein, G.Z. and **Barone, F.C**.: Reperfusion following focal stroke hastens inflammation and resolution of ischemic injured tissue. Brain Res. Bull., 35:387-391, 1994.

16. Wang, X.K., Siren, A-L., Yue, T-L., **Barone, F.C**. and Feuerstein, G.Z.: Upregulation of intracellular adhesion molecule-1 (ICAM-1) on brain microvascular endothelial cells in rat ischemic cortex. Mol. Brain Res., 26:61-68, 1994.

17. Wang, X.K., Yue, T-L., **Barone, F.C**., White, R.F., Young, P.R., McDonnell, P.C. and Feuerstein, G.Z.: Concommitant cortical expression of TNF-¤ and IL-1¤ mRNA following transient focal ischemia. Mol. Chem. Neuropathol, 23:103-114, 1994.

18. Wang, X.K., Yue, T-L., Young, P.R., **Barone, F.C.** and Feuerstein, G.Z.: Expression of interleukin 6, c-fos and zif268 mRNA in rat ischemic cortex. J. Cereb. Blood Flow Metab.,15:166-171, 1995.

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22. **Barone, F.C**., Lysko, P.G., Price, W.J., Feuerstein, G.Z., Hunter, A.J., Bailey, S. and Benham, C.D.: SB 201823-A antagonizes calcium currents in central neurons and reduces the effects of focal ischemia in rats and mice. Stroke 26:1683-1690, 1995.

23. Fan K., Young, P.R., **Barone, F.C**., Feuerstein, G.Z., Smith, D.H. and Macintosh, T.K.: Experimental brain injury induces expression of interleukin-1 beta messenger RNA in the rat brain. Mol. Brain Res. 30:125-130, 1995.

24. Wang, X.K., Yue, T.L., **Barone, F.C**. and Feuerstein, G.Z.: Monocyte chemoattractant protein-1 (MCP-1) mRNA expression in rat ischemic cortex. Stroke, 26:661-665, 1995.

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53. Wang, X.K., Li, X., Yaish-Chad, S., Sarau, H.M., **Barone, F.C.** and Feuerstein, G.Z.: Molecular cloning and expression of the rat monocyte chemotactic protein-3 gene: A possible role in stroke. Mol. Brain Res., 71: 304-312, 1999.

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