XXIV JCET LECTURE, 18.10.2013, 9.00

NOX, a Retrospective on the Challenges & Triumphs of Targeted Therapy

Prof. Patrick J. Pagano,

Department of Pharmacology & Chemical Biology,

Vascular Medicine Institute, Pittsburgh, USA

This seminar will focus on the evolution of the reactive oxygen species and NADPH oxidase (Nox) fields with particular emphasis on the decade-long quest for isoform-specific inhibitors of Nox.

New discoveries with respect to the mechanisms of Nox signaling in vascular dysfunction will also be explored.

Curriculum Vitae: Prof. Patrick J. Pagano

POSITION TITLE:
Professor, Department of Pharmacology & Chemical Biology,Vascular Medicine Institute, University of Pittsburgh, USA.

EDUCATION/TRAINING:

- Binghamton University-Harpur College: B.A. degree on May 1985 (chemistry)
- New York Medical College: M.Sc. degree on May 1988 (Pharmacology)
- New York Medical College: Ph.D. on May 1991 (Pharmacology)
- Boston University Medical Center, Vascular Biology Unit: Postdoc. On May 1994 (Vascular Biology).

A. Personal Statement

A vascular biologist by training, my laboratory explores multiple aspects of cardiovascular cell biology as they relate to tissue dysfunction. The laboratory's primary focus has been the vascular effects of reactive oxygen species. Among the first to identify NADPH oxidase (Nox) in the vasculature, we subsequently cloned phagocyte-like p67-*phox* in cells from the vascular adventitia and demonstrated robust upregulation of this and catalytic subunits of this complex enzyme in response to the pro-hypertensive hormone angiotensin II. Our major research interests include paracrine effects of adventitial Nox-derived reactive oxygen species (ROS) on cell hypertrophy, proliferation and vascular tone dysfunction. We have many years of experience in *in vivo* models of oxidative stress-induced disease as well as detection of tissue ROS. To elucidate the role of Nox signaling in cardiovascular disease, major emphasis has been placed on the development of novel cell-targeted peptidic inhibitors and small molecule inhibitors which may also serve as potential Nox-targeted therapies in disease.

B. Positions and Honors

Positions and Employment

1996-1998 Assistant Professor of Medicine (tenure track), Boston University School of Medicine

1998-2008 Senior Staff investigator, Hypertension & Vasc. Res. Division, Henry Ford Hospital

2003-2008 Director, Vascular Biology Research, Hypertension & Vasc. Res. Division, Henry Ford Hospital

2004-2008 Assistant Professor of Medicine (tenure track), Case Western Reserve University

2004-2008 Associate Professor of Physiology, Wayne State University

2008- Professor, Dept. of Pharmacology & Chemical Biology, Univ. of Pittsburgh, School of Medicine

2010- Director, Graduate Program, Molecular Pharmacology. Univ. of Pittsburgh, School of Medicine

2013- Vice-Chair for Graduate Education, Dept. of Pharmacology & Chemical Biology, Univ. of Pittsburgh

Other Experience and Professional Memberships

American Heart Association

American Physiological Society

American Association for the Advancement of Science

Society for Free Radical Biology and Medicine (formerly The Oxygen Society)

Inter-American Society of Hypertension (Conference Organizing Committee)

Honors

1985	Academic honors, Harpur College, Binghamton University
1987, 1988	National Science Foundation Honorable Mention
1990	Pharmaceutical Manufacturers' Foundation, Advanced Pre-doctoral Fellowship
1991-94	Cardiovascular Training Fellowship, Boston University
1996-2001	NIH F.I.R.S.T. Award
2001-	Fellow, American Heart Association
2002	Invited International Participant, Cold Spring Harbor Laboratory, First International Nox Symposium, "Oxidases in Inflammation and Cellular Signaling" symposium
2006-	Editorial Board, Cardiovascular Research
2006-	Editorial Board, American Journal of Physiology
2005-2010	Established Investigator Award, American Heart Association
2011-	Standing Member, Hypertension & Microcirculation Study Section, NIH NHLBI
2012-	Associate Editor, *Clinical Science*

B. Selected Peer-reviewed Publications of a Total of 88.

Most relevant to the current application

1. **Pagano, P.J**., Clark, J.K., Cifuentes-Pagano, M.E., Clark, S.M., Callis, G.M., and Quinn, M.T. (1997) Localization of a constitutively active, phagocyte-like NADPH oxidase in rabbit aortic adventitia: enhancement by angiotensin II. *Proc. Natl. Acad. Sci., USA*. 94:14483-14488. PMID: 9405639, PMCID: PMC25029

2. Rey FE, Cifuentes ME, Kiarash A, Quinn MT, **Pagano PJ**. (2001) Novel competitive inhibitor of NAD(P)H oxidase assembly attenuates vascular O_2^- and systolic blood pressure in mice. *Circ Res.* 89(5):408-14. PMID: 11532901.

3. Liu J, Ormsby A, Oja-Tebbe N, **Pagano PJ.** (2004) Gene transfer of NAD(P)H oxidase inhibitor to the vascular adventitia attenuates medial smooth muscle hypertrophy. *Circ Res.* 95(6):587-94. PMID: 15308582.
4. Csanyi G, Cifuentes-Pagano E, Al Ghouleh I, Ranayhossaini DJ, Egana L, Lopes LR, Jackson HM, Kelley EE, **Pagano PJ**. (2011) Nox2 B-loop peptide, Nox2ds, specifically inhibits the NADPH oxidase Nox2. *Free Radic Biol Med.* 51(6):1116-25. PMID: 21586323. PMCID: PMC3204933. NIHMSID: NIHMS310918.
5. Frazziano, G., Champion, H.C., and **Pagano, P.J.** (2012) NADPH oxidase-derived ROS and the regulation of pulmonary vascular tone. *Am. J. Physiol., Heart & Circ*., 302:H2166-2177 PMC3378288
6. Cifuentes-Pagano, E., Saha, J., Csányi ,G., Al Ghouleh, I., Sahoo, S., Rodríguez, A., Wipf, P., **Pagano, P.J**., and Skoda, E.M. (2013) Bridged tetrahydroisoquinolines as selective NADPH oxidase 2 (Nox2) inhibitors. *Med. Chem. Comm.* 4: 1085 – 1092.
7. Csányi, G., Yao, M., Rodriguez, A.I., Al Ghouleh, I., Sharifi-Sanjani, M., Frazziano, G., Huang, X., Kelley, E.E., Isenberg, J.S., and **Pagano, P.J.** (2012) Thrombospondin-1 impairs blood flow via NADPH oxidase 1. *Arterioscler Thromb Vasc Biol*. 32:2966-2973.

Additional publications of importance to the field

1. Rey FE, Li XC, Carretero OA, Garvin JL, **Pagano PJ**. (2002) Perivascular superoxide anion contributes to impairment of endothelium-dependent relaxation: role of $gp91^{phox}$. *Circulation.* 106(19):2497-502. PMID: 12417549.
2. Liu J, Yang F, Yang XP, Jankowski M, **Pagano PJ**. (2003) NAD(P)H oxidase mediates angiotensin II-induced vascular macrophage infiltration and medial hypertrophy. *Arterioscler Thromb Vasc Biol.* 23(5):776-82. PMID: 12637340.
3. Jacobson, G.M., Dourron, H.M., Liu, J., Carretero, O.A., Reddy, D.J., Andrzejewski, T., and **Pagano, P.J**. (2003) Novel NAD(P)H oxidase inhibitor suppresses angioplasty-induced superoxide and neointimal hyperplasia of rat carotid artery. *Circ. Res*. 92:637-643 PMID: 12609967
4. Haurani MJ, Cifuentes ME, Shepard AD, **Pagano PJ**. (2008) Nox4 oxidase overexpression specifically decreases endogenous Nox4 mRNA and inhibits angiotensin II-induced adventitial myofibroblast migration. *Hypertension*. 52(1):143-9. PMID: 18474828. PMC Journal – In Process.
5. Cascino T, Csanyi G, Al Ghouleh I, Montezano AC, Touyz RM, Haurani MJ, **Pagano PJ**. (2011) Adventitia-Derived Hydrogen Peroxide Impairs Relaxation of the Rat Carotid Artery via Smooth Muscle Cell p38 Mitogen-Activated Protein Kinase. *Antioxid Redox Signal*. 15(6):1507-15. PMID: 21126185. PMCID: PMC3151421.
6. Al Ghouleh, I, Khoo, N.K., Knaus, U.G., Griendling, K.K., Touyz, R.M., Thannickal, V.J., Barchowsky, A., Nauseef, W.M., Kelley, E.E., Bauer, P.M., Darley-Usmar, V., Shiva, S., Cifuentes-Pagano, E., Freeman, B.A., Gladwin, M.T., and **Pagano, P.J**. Oxidases and peroxidases in cardiovascular and lung disease: new concepts in reactive oxygen species signaling. *Free Rad Biol Med.* 51:1271-1288 (2011) PMC3205968
7. Al Ghouleh, I., Frazziano, G., Rodriguez, A.I., Csanyi, G., Maniar, S., St. Croix, C.M., Kelley, E.E., Ega?a, L.A., Song, G.J., Bisello, A., Lee, Y.J., and **Pagano, P.J**. Aquaporin 1, Nox1 and Ask1 mediate oxidant-induced smooth muscle cell hypertrophy. *Cardiovasc. Res.* 97:134-142 (2013). PMID: 22997161 PMC3527765
8. Cifuentes-Pagano, M.E., Csányi, G., and **Pagano, P.J**. NADPH oxidase inhibitors: A decade of discovery from Nox2ds to HTS. *Cell Mol. Life Sci*., 69:2315-2325 (2012). PMID: 22585059