

KENT J. JOHNSON, M.D.
PROFESSOR OF PATHOLOGY
DEPARTMENT OF PATHOLOGY

ANNUAL DEPARTMENTAL REPORT
1 JULY 2000 - 30 JUNE 2001

I. CLINICAL ACTIVITIES:

- A. Immunopathological evaluation of skin and renal biopsies.
- B. Director, Morphology Core.
- C. Renal pathology.
- D. Autopsy coverage.

II. TEACHING ACTIVITIES:

- A. Lecturer Genitourinary Pathology - Second Year Pathology Course.
- B. Lectures on Renal Pathology - Nephrology Fellows.
- C. Lectures on Renal and Skin Immunopathology - Pathology Residents.
- D. Lectures on Genitourinary Pathology - Dental Pathology Course.
- E. Laboratory Instructor - Second year Pathology Course.
- F. Lecturer Genitourinary Pathology – Second Year Pathology Course, Michigan State University Medical School

III. RESEARCH ACTIVITIES:

SPONSORED SUPPORT:

- A. Co-Principal Investigator, "Pathophysiology of Aspiration Pneumonitis", with Paul Knight, Anesthesia , R01, National Institutes of Health - Budget - \$720,866; \$187,518 annual, 08/96 - 07/04.
- B. Principal Investigator, "Inflammatory Cells and Lung Injury", Core C, National Institutes of Health, \$291,025.
- C. Co-Investigator, "Nanomolecule-Based Agents for Pathogen Countermeasure", with James Baker, Allergy, 03/01/97 – 02/28/01, Dept of Defense.
- D. Co-Investigator, "A New Approach to Treat Lupus Nephritis", with Gary Glick, Chemistry. National Institutes of Health, 02/22/00 – 02/21/04.

PENDING SUPPORT:

- A. Co-Principal Investigator, "MMPs in Prostate Cancer" NIH
- B. Co-Principal Investigator, "Mechanisms of MMP Involvement in Acute Lung Injury" NIH
- C. Principal Investigator, "Mechanisms of Vasculitis", Pfizer

PROJECTS UNDER STUDY:

- A. Pathogenesis of IgG and IgA immune complex lung injury.
 - 1. Role of oxygen radicals.
 - 2. Role of proteases.
 - 3. Role of terminal components of the complement system.
- B. Oxidant and protease interaction in inflammation.
- C. Pathogenesis of aspiration pneumonitis.
- D. Pathogenesis of viral pneumonitis.
- E. Pathogenesis of pancreatitis and pancreatitis induced ARDS.
- F. Adhesion molecules and cytokines in inflammation.
- G. Cyclosporin-induced nephrotoxicity.
- H. Role of heme oxygenase in renal injury.

IV. ADMINISTRATIVE ACTIVITIES:

DEPARTMENTAL:

- A. Director, Immunopathology Fellowship Program.
- B. Renal Pathology Conference - Biweekly.
- C. Space Utilization Committee.
- D. Stobbe Funds Committee.

REGIONAL AND NATIONAL:

- A. Associate Editor - Laboratory Investigation.
- B. Reviewer for the following journals:
 - 1. American Journal of Pathology.
 - 2. American Review of Respiratory Diseases.
 - 3. American Journal of Respiratory Cell and Molecular Biology
- C. Consultant/Grant reviewer for the Veteran's Administration.
- D. NIH NHLBI Study Section.

V. INVITED LECTURES AND SEMINARS:

- 1. Invited Main Speaker – 5 Ali Conference, Tokyo, Japan.
- 2. Invited Speaker- Mechanisms of Human Vasculitis, Milan, Italy.

VI. PUBLICATIONS:

ARTICLES PUBLISHED OR ACCEPTED FOR PUBLICATION IN REFEREED JOURNALS:

- 1. Warner, R.L., Bless, N.M., Lewis, C.S., Younkin, E., Beltran, L., Guo, R.F., Johnson, K.J., and Varani, J.: Time-dependent inhibition of immune complex lung injury by catalase: Relationship to alterations in macrophage and neutrophil matrix metalloproteinase elaboration. Free Rad. Biol. Med., 2000; 29:8-16.
- 2. Shanley, T.P., Davidson, B.A., Nader, N.D., Bless, N., Vasi, N., Ward, P.A., Johnson, K.J., and Knight, P.R.: Role of macrophage inflammatory protein-2 in aspiration-induced lung injury. Critical Care Medicine. 2000;28(7):2437-2444.

3. Rich, P.B., Reickert, C.A., Sawada, S., Awad, S.S., Lynch, W.R., Johnson, K.J., Hirschl, R.B.: Effect of rate and inspiratory flow on ventilator-induced lung injury. *J Trauma*. 2000;49:903-11.
4. Yung, R., Ray, D., Eisenbraun, J., Deng, C., Attwood, J., Eisenbraun, M., Johnson, K., Miller, R., Hanash, S., and Richardson, B.: Unexpected effects of a heterozygous DNMT1 null mutation on age-dependent DNA hypomethylation and autoimmunity. *J. Gerontology:Biological Sciences*. 2001;56(6)B268-B276.
5. Warner, R.L., Beltran, L., Younkin, E.M., Lewis, C.S., Weiss, S.J., Varani, J., and Johnson, K.J.: Role of stromelysin 1 and gelatinase B in experimental acute lung injury. *Am J of Respir Cell and Mol Biol*, 2001;24:537-544.
6. Warner, R.L., Lewis, C.S., Beltran, L., Younkin, E.M., Varani, J., and Johnson, K.J.: The role of metalloelastase in immune complex-induced acute lung injury. *Am J of Pathol*. 2001;158:2139-2144.
7. Varani, J., Hattori, Y., Dame, M.K., Schmidt, T., Murphy, H.S., Johnson, K.J., Wojno, K.J.: Matrix metalloproteinases (MMPs) in fresh human prostate tumour tissue and organ-cultured prostate tissue: levels of collagenolytic and gelatinolytic MMPs are low, variable and different in fresh tissue versus organ-cultured tissue. *Br J Cancer*. 2001;84:1076-83.
8. O'Shea, S., Johnson, K., Clark, R., Sliwkowski, M.X., Erickson, S.L.: Effects of in vivo heregulin beta1 treatment in wild-type and ErbB gene-targeted mice depend on receptor levels and pregnancy. *Am J Pathol*. 2001;158:1871-80.

ARTICLES SUBMITTED FOR PUBLICATION:

1. Kershaw, D.B., Bunchman, T.E., Johnson, K.J., Sedman, A.B., Kelsch, R.C.: Crescentic glomerulonephritis with subsequent hemolytic uremic syndrome in a child. Submitted for publication.
2. Varani, J., Hirschl, R., Dame, M. and Johnson, K.: Neutrophil infiltration is reduced during liquid ventilation: II. In Vitro analysis. Submitted for publication to *Amer. J. Respiratory & Critical Care Medicine*.
3. Sawyer, R.G., Chenault, R.H., Merion, R.M., Johnson, K.J., Kuta, E.G., and Hebert, C.A.: Antibody to interleukin-8 decreases systemic and pulmonary sequelae of sepsis: evidence for early chemokine regulation of cytokine activity in a porcine model of bacteremia. Submitted for publication.
4. O'Shea, S., Johnson, K.J., Gordon, D., Pisacane, P., Clark, R., Sliwkowski, M.X. and Erickson, S.L.: Effects of heregulin on adult breast and other epithelial tissues: an in vivo study of wildtype, heregulin, ErbB2 and ErbB3 heterozygous null mice. Submitted for publication.
5. Reuter, J.D., Myc, A., Cao, Z., Johnson, K.J., Wright D.C., Brisker, J., and Baker, J.R.: Prevention of influenza A virus infection by non-ionic surfactant nanoemulsions in a murine model. Submitted for publication.
6. Heard, P.L., Bleavins, M.R., Johnson, K.J., Shi, M. and de la Iglesia, F.A.: Induction of Alanine Aminotransferase Gene Expression by Tacrine in Hep G2 Cells. Submitted for publication.
7. Yung, R., Kaplan, M., Ray, D., Schneider, K., Ru-Ran, M., Johnson, K.J., and Richardson, B.: Common Effector functions of autoreactive Th1 and Th2 cells suggest a mechanism for tolerance abrogation and autoantibody induction. Submitted for publication.
8. Yung, R., Kaplan, M., Ray, D., Schneider, K., Ru-Ran, M., Johnson, K.J. and Richardson, B.: Autoreactive murine Th1 and Th2 cells kill syngeneic macrophages and induce autoantibodies. Submitted for publication.

BOOKS AND CHAPTERS IN BOOKS:

1. Warren, J.S., Johnson, K.J. and Ward, P.A.: Phagocytes and reactive oxygen substances as mediators of acute lung injury, in, Hyers, T. (ed), Diffuse Alveolar Damage and Respiratory Failure, Futura Press, New York, In Press.
2. Till, G.O., Johnson, K.J. and Ward, P.A.: Oxygen free radicals in inflammation, in, Messmer, K. and Hammersen, F. (eds), Prog. Appl. Microcirc., Volume 9, Karger, Basel, In Press.
3. Ward, P.A., Warren, J.S. and Johnson, K.J.: Oxygen radicals, inflammation and tissue injury, in, Pryor, W. and Godber, S.L. (eds), Free Radical Biology and Medicine, In Press.
4. Varani, J. and Johnson, K.J.: Modulation of endothelial cell injury by all-trans retinoic acid: Role of the anti-inflammatory effects of RA, in, Jesaitis, A. (ed), Molecular basis of oxidative damage by leukocytes. CRC Press, In Press.

ABSTRACTS, BOOK REVIEWS, PUBLISHED LETTERS TO THE EDITOR, MISCELLANEOUS PUBLICATIONS IN UNREFEREED JOURNALS:

1. Gough, A., Walsh, K., Johnson, K., Kennedy, J., Pegg, D., and de la Iglesia, F.: Nephrotoxicity of HIV protease inhibitor, CI-1029, in humans and monkeys. Submitted to ACVP Meeting, 2000.
2. Okechukwu, C.N., Meier-Kriesche, H.U., Killen, P.D., Johnson, K.J., Armstrong, D., and Kaplan, B.: Histologic evolution of acute rejection by era. Submitted to AST Meeting, 2000.
3. Varani, J., Dame, M., Johnson, K.J., and Wojno, K.J.: Elaboration of matrix metalloproteinases by fresh human prostate tissue and by prostate tissue in organ culture. Experimental Biology 15(4):475.12, 2001.
4. Warner, R.L., Lukacs, N.W., Lewis, C.S., Varani, J., and Johnson, K.J.: Role of matrix metalloproteinases in a model of allergic inflammation in mice. Experimental Biology 15(4):50.1, 2001.
5. Burmeister, W., Varani, J., Bleavins, M., Dame, M., and Johnson, K.J.: Effects of three matrix metalloproteinase inhibitors (PD-159879, PD-166793 and marimastat) on proliferation of fibroblasts from human, marmoset, cynomolgus monkey, and rat. Experimental Biology, 15(4):131.11, 2001.
6. Johnson, K.J., Warner, R.L., Beltran, L., Younkin, E.M., Lewis, C.S., and Varani, J.: Role of stromelysin-1 and gelatinase B in experimental acute lung injury. Experimental Biology, 15(4):71.5, 2001.