Lupus, Autoimmunity, Inflammation and Immune Health Center of Excellence (LACE)

1. **Lupus, Autoimmunity, Inflammation and Immune Health Center of Excellence (LACE).** The development of a Lupus and Autoimmune Disease Center has long been proposed at Upstate. LACE would be based on strong basic and clinical research programs that have been continuously supported by the National Institutes of Health for 25 years. The research, clinical and educational programs will be widely advertised and posted on research pages and the clinical practice sites. LACE will be an attraction to students, scientists, physicians, patients, and potential donors.

2. **Population Base and Community Outreach.** Autoimmune diseases affect at least 7.6%-9.4% of the population (8) which represent a leading causes of morbidity and mortality, especially in women of child-bearing age in the United States (9). Upstate has become a major referral center for systemic autoimmune diseases, such as lupus, rheumatoid arthritis, vasculitides, spondylarthritides, inflammatory bowel disease, nephritis, and neurological diseases, such as multiple sclerosis (10,11). Patients with these conditions require integrated care and the contribution of primary care physicians and specialists. Diagnosis is often delayed and inappropriate monitoring leads to suboptimal outcomes. Upstate has a cohort of over eight hundred patients with systemic lupus erythematosus (SLE). Due to delayed or incorrect diagnosis as well as inadequate treatment, mortality is still approaching 10% over 5 years, mainly among young women. LACE would be instrumental in reaching out to the greater Central and Upstate New York Community of up to 2 million inhabitants. The Center would provide web-based information resources and live educational sessions and facilitate access to health care providers at Upstate.

3. **Health Disparities.** Autoimmune diseases preferentially affect women of child-bearing age (8,9). In the most severe form of systemic autoimmunity, SLE, a higher prevalence among African-Americans is well documented (12). The incidence and prevalence of SLE is up to 4 times higher in African-Americans compared with Caucasians (13). Due to the excessive disease burden of the African-American population, it is critical to understand and document within-group disease characteristics. This facilitates targeted consideration for early diagnosis, screening of family members, which could lead to better treatment outcomes. Increased understanding will increase minority participation in research, which has been suboptimal. The prevalence and disease burden of rheumatoid arthritis and insulin-dependent diabetes are increased among Native Americans in Central New York. Characterization and documentation of such diagnoses, disease burden, and assessment of outcome will be of primary importance.

4. **Urgency.** There have been persistent and increasingly ominous difficulties of infrastructural support. Ongoing NIH-supported programs have lost access to key metabolomic mass spectroscopy and imaging instrumentation. Such difficulties have hampered accomplishment of proposed studies and competitive renewal of grants. Flow flow cytometry capabilities have not been updated in 15 years. Since 2015, we have received three new NIH grants, two R01 and one R34, for basic and translational studies in lupus. In particular, the R34 grant is aimed to develop a multicenter trial for treatment of SLE though a UO1 Center Grant funding mechanism. This is a biomarker-driven study which requires core facilities that can monitor projected outcomes. We have secured letters of collaboration from 20 academic medical centers. Existence of the proposed Center seems essential to secure funding for the actual trial. The technical core facilities would support studies in other diseases with autoimmune and inflammatory pathogenesis. The proposed Biobank will be available for all centers at Upstate.

5. **Unmet Needs.** The current laboratory uses tools and instruments that are over 20 years old on average. The start-up will support two staff members for 3 years. One of the staff members would be study coordinator/data manager/program developer. This person will help develop study protocols and serve as liaison to the IRB. A second staff member would be a registered nurse/laboratory technician with experience in bio-banking. Funds will also be used to cover the cost of database development and information management. Beyond clinical trial participation, the staff would develop programs for continuity of care, compliance with medications and follow-up visits, coordination of care with other subspecialist, and develop patient databases for biomarker-linked assessment of outcomes. After the intra-structure has been established and protocols have been approved by the IRB, services will be advertised in gradually expanding circles. It will be important to monitor that advertisement cab be matched with services.

6. **Budget.** To start up the center, an initial investment of $1,000,000 is sought. This would provide funding for equipment and two staff members for 3 years. If possible, this account should remain open after three years to allow replenishment of funds with income from clinical trials or personal donations. I envision that one of the staff members would be study coordinator/data manager/ program developer. This person will help develop study protocols and serve as liaison to the IRB. A second person would be a registered nurse/laboratory technician with experience in bio-banking. Funds will also be used to contract with information technology/bioinformatics for development of databases and biobanks. Along with faculty members, the staff would develop programs for continuity of care, compliance with medications and follow-up visits, coordination of care with other subspecialist, develop patient database and update our infrastructure for bio-banking. After the intra-structure has been established and protocols have been approved by the IRB, our services will be advertised in gradually expanding circles. It will be important for us to monitor that we can match advertisement with services. In 3-5 years, operations of the center should be covered by new grants, such as our pending multicenter clinical trials aimed at blocked inflammation via the mechanistic target of rapamycin pathway with N-acetylcysteine (NAC) and rapamycin. These topics have been recently reviewed (1,2) (3).The center would serves as a resource for new faculty, fellows, and residents to develop pilot projects and help with initial IRB approval. The Center could be extended to other areas of rheumatology and human immunology, as new faculty can be hired and aligned with unmet needs. In summary, LACE should be a magnet for all patients seeking rheumatology and immunological care in Central and Upstate New York

Reference List

1. Perl, A. 2013. Oxidative stress in the pathology and treatment of systemic lupus erythematosus. *Nat Rev Rheumatol* 9:674-686.

2. Joseph, N., Y. Zhang-James, A. Perl, and S. V. Faraone. 2015. Oxidative Stress and ADHD: A Meta-Analysis. *J. Atten. Disord.* 19:915-924.

3. Perl, A. 2016. Mechanistic Target of Rapamycin Pathway Activation in Rheumatic Diseases. *Nat. Rev. Rheumatol.* 12:169-182.

4. Vas, Gy., K. Conkrite, W. Amidon, Y. Qian, K. Banki, and A. Perl. 2005. Study of transaldolase deficiency in urine samples by capillary LC-MS/MS. *J. Mass. Spec.* 41:463-469.

5. Perl, A., Y. Qian, K. R. Chohan, C. R. Shirley, W. Amidon, S. Banerjee, F. A. Middleton, K. L. Conkrite, M. Barcza, N. Gonchoroff, S. S. Suarez, and K. Banki. 2006. Transaldolase is essential for maintenance of the mitochondrial transmembrane potential and fertility of spermatozoa. *Proc. Natl. Acad. Sci. USA* 103:14813-14818.

6. Hanczko, R., D. Fernandez, E. Doherty, Y. Qian, Gy. Vas, B. Niland, T. Telarico, A. Garba, S. Banerjee, F. A. Middleton, D. Barrett, M. Barcza, K. Banki, S. K. Landas, and A. Perl. 2009. Prevention of hepatocarcinogenesis and acetaminophen-induced liver failure in transaldolase-deficient mice by N-acetylcysteine. *J. Clin. Invest.* 119:1546-1557.

7. Perl, A., R. Hanczko, Z.-W. Lai, Z. Oaks, R. Kelly, R. Borsuk, J. M. Asara, and P. E. Phillips. 2015. Comprehensive metabolome analyses reveal N-acetylcysteine-responsive accumulation of kynurenine in systemic lupus erythematosus: implications for activation of the mechanistic target of rapamycin. *Metabolomics* 11:1157-1174.

8. Cooper, G. S., M. L. Bynum, and E. C. Somers. 2009. Recent Insights in the Epidemiology of Autoimmune Diseases: Improved Prevalence Estimates and Understanding of Clustering of Diseases. *Journal of Autoimmunity* 33:197-207.

9. Walsh, S. J., and L. M. Rau. 2000. Autoimmune diseases: a leading cause of death among young and middle-aged women in the United States. *Am J Public Health* 90:1463-1466.

10. Perl, A. 2004. Pathogenesis and Spectrum of Autoimmunity. In *Autoimmunity. Methods and Protocols*. A. Perl, ed. Humana Press, Totowa, N.J., pp. 1.

11. Perl, A. 2009. Editorial: Overview of signal processing by the immune system in systemic lupus erythematosus. *Autoimmun. Rev.* 8:177-178.

12. Fessel, W. 1974. Systemic lupus erythematosus in the community: Incidence, prevalence, outcome, and first symptoms; the high prevalence in black women. *Arch. Int. Med.* 134:1027-1035.

13. Somers, E. C., W. Marder, P. Cagnoli, E. E. Lewis, P. DeGuire, C. Gordon, C. G. Helmick, L. Wang, J. J. Wing, J. P. Dhar, J. Leisen, D. Shaltis, and W. J. McCune. 2014. Population-Based Incidence and Prevalence of Systemic Lupus Erythematosus: The Michigan Lupus Epidemiology and Surveillance Program. *Arthritis Rheumatol* 66:369-378.

14. Lai, Z.-W., R. Hanczko, E. Bonilla, T. N. Caza, B. Clair, A. Bartos, G. Miklossy, J. Jimah, E. Doherty, H. Tily, L. Francis, R. Garcia, M. Dawood, J. Yu, I. Ramos, I. Coman, S. V. Faraone, P. E. Phillips, and A. Perl. 2012. N-acetylcysteine reduces disease activity by blocking mTOR in T cells of lupus patients. *Arthritis Rheum.* 64:2937-2946.

15. Garcia, R. J., L. Francis, M. Dawood, Z.-W. Lai, S. V. Faraone, and A. Perl. 2013. Attention Deficit and Hyperactivity Disorder Scores are Elevated and Respond to NAC treatment in patients with SLE. *Arthritis Rheum.* 65:1313-1318.

16. Lai, Z.-W., R. Borsuk, A. Shadakshari, J. Yu, M. Dawood, R. Garcia, L. Francis, H. Tily, A. Bartos, S. V. Faraone, P. E. Phillips, and A. Perl. 2013. mTOR activation triggers IL-4 production and necrotic death of double-negative T cells in patients with systemic lupus eryhthematosus. *J. Immunol.* 191:2236-2246.

17. Meszaros-Szombathyne, Z., A. Perl, and S. V. Faraone. 2012. Psychiatric symptoms in systemic lupus erythematosus: a systematic review. *J. Clin. Psychiatry* 73:993-1001.