Dear Colleague,

Welcome to the Fall 2011 issue of *Rheumatology Connections*. I am pleased to share this collection of articles highlighting the clinical work and research by staff in Cleveland Clinic’s Department of Rheumatic and Immunologic Diseases.

In this issue, we highlight new research by Drs. Elaine Husni, Vice Chair of Rheumatology and Director of the Arthritis and Musculoskeletal Center, and Atul Khasnis, the newest member of our RJ Fasenmyer Center for Immunology and Center for Vasculitis Care and Research.

On pp. 4-5, Dr. Husni describes her team’s work, studying the increased atherosclerotic burden in patients with psoriatic diseases and whether an incremental inflammatory pathway in PsA that affects both skin and joint results in greater atherosclerotic burden compared with PsO affecting the skin alone. On p. 11, Dr. Khasnis details plans to characterize clinical and immunological features in patients with systemic autoimmune diseases using state-of-the-art immunological laboratory techniques.

You’ll also find updates on the endeavors of other department staff, including a summary of emerging therapies for osteoporosis by Dr. Chad Deal (pp. 8-9), a discussion on the challenge of assessing disease activity in vasculitis by Dr. Carol Langford (pp. 6-7) and a Q&A with Dr. Gary Hoffman on variations in disease susceptibility in autoimmune large vessel vasculitis (p. 3). Dr. Andrew Zeft also provides a snapshot of the multidisciplinary care provided at Cleveland Clinic for children with vasculitis through collaboration between our pediatric rheumatology team and the Center for Vasculitis Care and Research (p. 10).

I hope that you enjoy this issue of *Rheumatology Connections*. As always, please feel free to contact me with any questions or comments about any of our programs.

Sincerely,

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Cleveland Clinic’s Rheumatology Program is ranked No. 3 in the nation by *U.S. News & World Report*.
Q&A: Variations in Disease Susceptibility in Autoimmune Large Vessel Vasculitis

By Gary S. Hoffman, MD, MS

Q: Are vessels of the same calibre, functionally the same, regardless of their location or the organs they perfuse?

Although the answer is “no” for both small and large vessels, let’s address this issue in reference to the aorta. This tubular conduit called by one name, the aorta, is heterogeneous in regard to embryogenesis, histomorphometry, matrix components, gene expression and disease susceptibilities. The distal region is the most common site for 95 percent of atherosclerotic aneurysms, and another site, the aortic arch, is more prone to aneurysm formation due to cystic medial degenerative, other related matrix changes and aortitis. Attempts to understand differences in regional susceptibility have included evaluation of these different territories by gene expression, susceptibility to viral-induced injury, differences in inflammatory responses to the same stimuli (e.g., lipids) and canine vessel transposition research. In each case, it is clear that the proximal and distal aortas are in many ways unique.

What makes the aortic arch prone to inflammatory aneurysm formation is unknown. One possible important factor may be that the smooth muscle cells (SMCs) of the arch are derived from neuroectoderm and those from the remainder of the aorta and circulatory system are from mesoderm.

It is not known whether human forms of autoimmune aortitis can be triggered by:

1. a loss of tolerance to normal substrate antigen (Ag) or
2. an induced immune response to altered self-Ag; with alterations being due to
   a. spontaneous mutations
   b. infection and its lasting effects, even after clearance of the inciting agent
   c. age-related degenerative changes or
   d. modification of Ag due to acquisition of environmental agents, such as toxins.

The Cleveland Clinic Heart & Vascular Institute includes a Center for Aortic Diseases. Approximately 500 patients per year undergo open repair of aortic aneurysms. Of these, there are approximately 25 new cases of idiopathic aortitis. The majority of those with aortitis (69%, mean follow up > 3.5 years) have disease isolated to the surgical site and do not require systemic immunosuppressive therapies. Others have well-described forms of large vessel systemic vasculitis such as Takayasu’s arteritis (TAK) and giant cell arteritis (GCA) (1, 2).

To date, no one has evaluated putative auto-Ag or compared immune responses from tissue specimens between these diseases in the same study. Cleveland Clinic has the resources to address the questions:

Are there unique tissue Ags in the aorta in idiopathic aortitis, TAK and GCA? Are such Ags the same in each form of aortitis? And if they differ, in what regard? What differences exist within the immune response (e.g., tissue-infiltrating cell types and cytokine profiles) for each form of aortitis?

The Center for Vasculitis Care and Research (including myself, Director Carol A. Langford, MD, MHS, and colleagues), the Center for Aortic Surgery (Director Lars Svensson, MD, PhD), investigators in Immunology (Vincent Tuohy, PhD), Immunopathology (Thomas Daly, MD), and Biochemistry (Dennis Stuehr, PhD, Ritu Chakravarti, PhD), and research support staff, ensure feasibility in regards to both case volume and methodology.

The methods employed for aortitis cases and controls (non-inflammatory aortic aneurysms) include a) immunofluorescent microscopy using autologous serum applied to cryopreserved aorta and b) Western blotting of aorta homogenates that isolate and display constituent proteins. The latter would be exposed to autologous sera to identify immune-reactive bands.

Precedent for this approach: This approach is not novel in regard to other examples of single-organ autoimmune diseases. For example, in pemphigus, similar methods have identified desmoglein 1 (dsg) 1 and dsg 3 and desmoplakin as relevant antigens that are targeted in producing blistering lesions. In neuromyelitis optica, similar approaches have identified aquaporin-4, a water channel protein in the astrocyte membrane as an important target in the pathogenesis of that disease. Recently, this approach has identified M-type phospholipase A2 receptor as the target in over 70 percent of cases of idiopathic membranous nephropathy.

Q: What would be the utility of discovering unique Ag in one or more forms of aortitis?

Knowledge of inciting Ag in any autoimmune disease holds the promise of more effective therapeutic interventions, as might be provided through peptide tolerance-induction or specific immunological or biochemical blockade of target. Such studies have been undertaken in diseases, such as Type 1 diabetes mellitus, systemic lupus and pemphigus.

Continued on pg. 11
Both psoriatic arthritis (PsA) and psoriasis (PsO) are associated with an increased cardiovascular (CV) mortality and morbidity compared to the general population. Researchers at Cleveland Clinic are studying the hypothesis that patients with psoriatic diseases may have an increased atherosclerotic burden and whether an incremental inflammatory pathway in PsA that affects both skin and joint results in greater atherosclerotic burden compared with PsO affecting the skin alone.

This concept of subclinical atherosclerosis has been well validated in large retrospective cohorts of various inflammatory joint diseases, implying that the common denominator of chronic, low-grade inflammation may be responsible. However, the exact mechanism by which inflammation causes accelerated atherosclerosis is not clear. Further detailed research is needed with more comprehensive demographic data: family history, cardiovascular history, treatment regimens and avoidance of self-reported diagnoses. Furthermore, although patients with psoriatic diseases can present with early or subclinical atherosclerosis, not all patients do and the CV risk may be different within the spectrum of psoriatic diseases.

In our analysis, the atherosclerotic burden in psoriasis patients with and without psoriatic arthritis was studied using cIMT (carotid intima medial thickness), a well-established surrogate for generalized atherosclerosis. Researchers found an incremental atherosclerotic burden in patients with both skin and joint involvement compared with patients with skin involvement alone.

To further investigate the possibility that well-known CV risk factors in the general population may influence atherosclerotic burden (such as metabolic syndrome, family history, adverse drug treatments, and certain novel biomarkers), Cleveland Clinic researchers studied more than 250 psoriatic disease patients of the COMPASS cohort (Cardiometabolic Outcome Measures in Psoriatic Arthritis Study). These results, reported at the 2011 American College of Rheumatology national meeting, demonstrated that the presence of inflammatory joint disease in patients with psoriasis is a significant risk factor for metabolic syndrome. PsA patients were also found to have a significantly higher prevalence of conventional CV risk factors and higher Framingham risk scores as compared to PsO patients. However, there was no significant difference once patients were on active disease-modifying antirheumatic drugs (DMARDs) for psoriatic diseases. After adjusting for significant associations with metabolic syndrome
Table 1: Adjusted ORs for Metabolic Syndrome Risk Factors

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Adjusted ORs (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PsA vs. PsO</td>
<td>3.423 (1.431, 8.189)</td>
<td>0.006</td>
</tr>
<tr>
<td>Age</td>
<td>1.033 (1.005, 1.061)</td>
<td>0.020</td>
</tr>
<tr>
<td>Family history of CV risk</td>
<td>3.568 (1.368, 9.305)</td>
<td>0.009</td>
</tr>
<tr>
<td>CRP</td>
<td>1.590 (1.169, 2.164)</td>
<td>0.003</td>
</tr>
<tr>
<td>Biologics/DMARDs</td>
<td>2.336 (1.049, 5.200)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Table 2. QoL Outcomes in Patients with Psoriasis and Psoriatic Arthritis

<table>
<thead>
<tr>
<th>Quality of Life Outcome</th>
<th>Psoriatic Arthritis (N = 107)</th>
<th>Psoriasis (N = 145)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) PCS (Mean ± SD)</td>
<td>41.7 ± 11.6</td>
<td>49.3 ± 10.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(b) MCS (Mean ± SD)</td>
<td>49.6 ± 9.6</td>
<td>46.6 ± 12.2</td>
<td>0.043</td>
</tr>
<tr>
<td>HAQ (Median [Q1, Q3])</td>
<td>0.4 (0.0, 0.9)</td>
<td>0.0 (0.0, 0.1)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>DLQI (Median [Q1, Q3])</td>
<td>3.0 (1.0, 9.0)</td>
<td>6.0 (3.0, 10.0)</td>
<td>0.009*</td>
</tr>
</tbody>
</table>

* non-parametric analysis

This research was funded in part by the National Psoriasis Foundation, Arthritis National Research Foundation, and RJ Fasenmyer Center for Clinical Immunology. Physician investigators included Chang Lin, MD, and Deepan Dalal, MD (Rheumatology); Stephen Nicholls, MD, PhD, and Kiyoko Uno, MD (Cardiology); Esther Kim, MD (Vascular Medicine); and Kevin Cooper, MD, Neil Korman, MD, and Neil Borkar, MD (Dermatology).

Dr. Husni, Vice Chair of Rheumatology and Director of the Arthritis and Musculoskeletal Treatment Center, and Director of Clinical Outcomes Research, can be reached at 216.445.1853. She is the principal investigator of the Psoriatic Disease project at Cleveland Clinic.

Recommended Reading

(Abstrats available at rheumatology.org)

1. Cardio-Metabolic Risk Profile of Patients with Psoriatic Arthritis and Psoriasis: The COMPASS-1 Study.
3. Quantifying the Harmful Effects of Psoriatic Diseases on Quality of Life Outcomes – The COMPASS 3 Study
Question:
Do these patients have active granulomatosis with polyangiitis (Wegener’s) (GPA)?

Case 1:
A 55-year-old man was diagnosed with GPA three months ago. He presented with sinus disease, pulmonary involvement with bilateral nodules, glomerulonephritis with a peak creatinine 3.5mg/dL, peripheral neuropathy with left foot drop and right peroneal sensory loss, and a (+) PR3-cANCA. For this, he was treated with glucocorticoids and cyclophosphamide. At today’s visit, he is still having nasal crusting, paresthesias and left foot immobility, unchanged from previously. On examination, the nasal membranes do not appear inflamed. Urinalysis is negative for blood but shows 3+ protein and casts containing round structures (Figure 1), creatinine 2.0 mg/dL, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are normal and PR3-cANCA remains positive. Chest imaging shows resolution in all but one nodule that has decreased from 3.1 cm to 1.0 cm.

Case 2:
A 30-year-old woman was diagnosed with GPA eight weeks ago. At presentation, she had alveolar hemorrhage, palpable purpura, and glomerulonephritis with a peak creatinine 2.1 mg/dL. For this, she was treated with glucocorticoids and rituximab. Current medications are prednisone 35mg/d and trimethoprim 160mg/sulfamethoxazole 800mg three times a week. She now has a cough and dyspnea that feels similar to when she first presented. Examination is notable for temperature 37.4, pulse 102, blood pressure 130/76, respirations 20. Laboratories creatinine 1.3 mg/dL, urine shows trace blood and one red blood cell (RBC) cast, ESR 65 mm/hr, CRP 7.5 (normal range 0-1.0). Chest imaging reveals a new focal infiltrate (Figure 2A,B).

Discussion: So does either of these patients have active GPA? The answer in both is no.

Assessing disease activity is one of the greatest challenges faced by physicians in caring for patients with vasculitis. There is no absolute indicator and the determination of active disease is based upon evidence from symptoms, physical examination, laboratories, and imaging. Features that could suggest active disease can also occur from damage, infection, medication toxicity or other causes.

For Case 1, the issues that could raise the question of active disease are nasal crusting, ongoing neuropathic symptoms, abnormal creatinine, and persistence of a pulmonary nodule. However, all of these features can result from damage,
as was the case for this patient. The casts seen on urine microscopy are fatty casts that are not indicative of active disease but reflect lipiduria. Under polarized light, fatty casts reveal a characteristic “Maltese cross” appearance that allows differentiation of lipid droplets from red blood cells (Figure 2B). The finding of a persistent (+) PR3-cANCA is not helpful in assessing this patient’s disease status. Unfortunately, large-scale studies have demonstrated that ANCA does not accurately measure disease activity, and changes in ANCA should not be used to guide treatment decisions.

For Case 2, the issues that could raise the question of active disease would be the increased acute phase reactants, pulmonary infiltrate, and the RBC cast on urinalysis. However, this patient was found to have a bacterial pneumonia as the cause of the infiltrate and ESR/CRP. In an immunosuppressed patient, the finding of a new pulmonary infiltrate should be considered an infection until proven otherwise. What about the RBC cast? Hematuria and even RBC casts may take time to clear and can persist in some patients, particularly given how recently her diagnosis was made.

Although not present in either of these patients, medication toxicity warrants special mention. Examples include the potential for non-glomerular hematuria due to bladder injury or neoplasm in cyclophosphamide treated patients, pneumonitis in patients receiving methotrexate, or azathioprine hypersensitivity – all of which can mimic active vasculitis.

The assessment of disease activity can be even more difficult in other forms of vasculitis, such as giant cell arteritis or Takayasu’s arteritis. While the assessment of disease activity is again based on symptoms, acute phase reactants and imaging, these similarly remain imperfect in that they can be influenced by other causes and can reflect damage rather than activity.

So what lies ahead? The challenges with disease activity assessment are well appreciated by vasculitis investigators and it remains a priority to identify better strategies to detect active disease. Such strategies may come from blood, imaging or other techniques. Biomarker investigation remains a top priority of the Center for Vasculitis Care and Research and the Vasculitis Clinical Research Consortium that is funded by the National Institutes of Health and in which Cleveland Clinic is an active participating site. It is the ultimate hope that the search for biomarkers will not only assist in assessing disease activity, but will also lead to a better understanding of disease pathogenesis since it is through such understanding that novel treatments may emerge.

Dr. Langford is the Director of the Center for Vasculitis Care and Research. She can be contacted at 216.445.6056 or langfoc@ccf.org.
Emerging Therapies for Osteoporosis

By Chad Deal, MD

Antiresorptive agents work by decreasing bone resorption but they also decrease bone formation. New antiresorptive agents may have less effect on bone formation and thus increase their efficacy. New anabolic agents affecting Wnt signaling offer promise for the treatment of low bone mass. We review these emerging therapies and how they differ from current treatments for low bone mass.

ANTIRESORPTIVE AGENTS

Cathepsin K inhibitors

Osteoclasts are specialized cells that affect bone resorption. Bone resorption requires dissolution of the mineral components and removal of organic bone matrix. Demineralization requires acid secretion by osteoclasts into resorption lacunae, while matrix degradation is accomplished by cysteine proteases including cathepsins. Drugs that do not result in osteoclast apoptosis (as bisphosphonates do) and therefore inhibit cathepsin K may allow osteoclast-osteoblast cross talk to continue and not result in decreased osteoblast function.

Odanacatib given as a weekly oral dose in postmenopausal women showed increases in bone density of the spine (+5.7%), total hip (+4.1%), femoral neck (+4.7%) and radius (+2.9%). While urine N-telopeptide of type I collagen, a marker of bone resorption, declined 52 percent, bone-specific alkaline phosphatase, a marker of bone formation, declined only 13 percent (decline with placebo was 3%). This finding suggests less inhibition of bone formation than found with current antiresorptive therapies.

After discontinuation of odanacatib, bone density declined and appeared to be more rapid than what occurs after discontinuation of bisphosphonate therapy. Markers of bone resorption increased to more than 50 percent above baseline after discontinuation of odanacatib. This drug, like the recently released denosumab, has what could be termed a rapid resolution-of-effect while bisphosphonates have a more prolonged resolution-of-effect. Rapid resolution of effect might be preferable in some clinical settings, as a well-known effect of bisphosphonate therapy is blunting the effect of subsequent teriparatide; this may not occur with drugs that have rapid resolution of effect. These drugs may also be preferable if long-term side effects are a concern, or in women of childbearing potential. However, interruptions in therapy and poor compliance will result in rapid loss of bone and fracture effect. The fracture trial results for odanacatib are expected in 2012.

Glucagon-like peptide 2 (GLP-2)

Glucagon-like peptide is an intestinal hormone released in response to food intake. Bone remodeling has a circadian rhythm with a nocturnal rise in bone resorption. The circadian variation seen in humans, high in the morning and low in the evening, may not be an inherent mechanism, but may be the result of fasting or food intake. GLP-2 is a polypeptide released from the intestinal mucosa after food intake. Treatment with GLP-2 at bedtime results in a significant reduction in bone resorption that normally occurs overnight. GLP-2 does not reduce bone formation as evidenced by osteocalcin levels. A 120-day phase 2 trial in 160 postmenopausal women given GLP-2 resulted in an increase in hip bone density, a reduction in the nocturnal rise in CTX with no effect on osteocalcin. If this pattern were sustained, GLP-2 would have the advantage over available antiresorptive agents that decrease bone formation.

Nitrates

Both the Study of Osteoporotic Fractures (SOF) and the Canadian Multicenter Osteoporosis Study (CaMOS) demonstrated small increases in bone mass and reduction in fractures in nitrate users. A case control study in Denmark reported a 15 percent reduction in hip fractures in patients on nitrates. In this 24-month RCT trial of once-daily NTG ointment, 15mg/day given at night, subjects on NTG had increases in BMD in the lumbar spine (+6.7%), femoral neck (+7.0%), and total hip (+6.2%) at 24 months (p=0.001). Markers of bone resorption (NTX) declined while a marker of bone formation (bone-specific alkaline phosphatase) increased. This uncoupling of bone remodeling is unlike typical antiresorptive agents and may make TNG more efficacious. Headache was the most common side effect. This drug is inexpensive and further evaluations are ongoing.
ANABOLIC AGENTS

Anabolic agents increase bone mass to a greater degree than antiresorptive agents. These agents also improve bone quality and increase bone strength, in part by affecting micro-architectural features (such as connectivity density) and geometric features (such as diameter). Recombinant human PTH1–34, teriparatide, is the only anabolic agent currently available in the United States. Recombinant human PTH1-84 is available in Europe for the treatment of patients with low bone mass. In patients treated with PTH therapy, bone density changes are underestimated by dual X-ray absorptiometry (DXA). When quantitative CT, a volumetric measure of bone mass, is used to measure change in bone density during PTH treatment, increases are significantly greater than with DXA, an areal measure of bone mass. Since the use of PTH is limited to two years in the U.S. and 18 months in Europe, there is an unmet need for additional anabolic agents.

Wnt signaling: sclerostin and Dickkopf-1

The discovery and elucidation of the underlying causes of high bone mass (HBM) and low bone mass (LBM) phenotypes in humans have resulted in many potential drug targets for osteoporosis therapy. Wnt proteins are a large family of glycoproteins that help regulate bone remodeling. Wnt proteins bind to two membrane receptors, LRP5 and frizzled, resulting in activation of an intracellular pathway that results in accumulation of B-catenin. B-catenin accumulates, translocates to the cell nucleus and binds to transcription factors that affect gene transcription, which are important in osteoblast function and bone formation.

Inhibitors of Wnt signaling, including sclerostin and Dickkopf-1, bind to frizzled or LRP5 (sclerostin and Dickkopf-1) and prevent the Wnt signaling pathway, leading to a decrease in bone formation. By contrast, deficiencies in these inhibitors or antibodies to the inhibitors result in increased Wnt signaling and, therefore, increased bone formation.

A human disease of high bone mass, sclerosteosis, is the result of a homozygous mutation in the SOST gene, which encodes sclerostin. A deficiency of sclerostin results in increased Wnt signaling and high bone mass, with numerous complications such as entrapment of cranial nerves and increased intracranial pressure leading to stroke. Heterozygous mutations in the SOST gene result in moderate increases in bone mass and fewer skeletal complications. Since sclerostin is a protein that is almost exclusively a product of osteocytes, antibodies offer a way to specifically target bone formation. Antibodies to sclerostin increase bone formation in osteopenic estrogen-deficient rats. A single subcutaneous dose of an antibody to sclerostin in postmenopausal women resulted in an increase in N-terminal propeptide of type I collagen levels (60-100%) at day 84 of treatment, with no increase in serum C-telopeptides, and a 6 percent increase in lumbar spine bone density. The increase in markers of bone formation without an increase in markers of resorption is unlike the effect of teriparatide, our current anabolic agent. Further trials in postmenopausal women and for fracture healing are in progress.

Dr. Deal is Head of the Center for Osteoporosis and Metabolic Bone Disease. Physicians may contact him at 216.444.6575 or dealc@ccf.org.
Unfortunately, children may be affected by rare and potentially organ- or life-threatening forms of vasculitis. The rarity of these childhood conditions has limited our understanding of the most efficacious approaches to treating childhood vasculitis. However, at Cleveland Clinic our pediatric rheumatology team works within the Center for Vasculitis Care and Research. This onsite collaboration provides a breadth of expertise within the center, and allows for the delivery of expert care to children with vasculitis.

Cases of childhood vasculitis are complex, and they require a specialized team approach. At Cleveland Clinic, the most advanced therapies are available to evaluate and treat children with vasculitis:

- Otolaryngologists specialize in the treatment of subglottic stenosis resulting from granulomatosis with polyangiitis (GPA, aka Wegener’s granulomatosis).

- Vascular surgeons are experienced in managing stenotic or aneurismatic changes in vessels affected by medium (polyarteritis nodosum) and large vessel vasculitis (Takayasu arteritis).

- Neurologists are specialized in the diagnosis and treatment of primary brain vasculitis.

- Radiologists are expert in both noninvasive and invasive vascular imaging techniques required to carefully evaluate the extent of vasculitic disease.

Pediatric rheumatologists Drs. Zeft and Steven Spalding both maintain active roles as primary investigators in research protocols aimed at better understanding the causes and pathogenesis of childhood onset vasculitis\(^1\)\(^3\). Dr. Zeft was recently awarded a three-year grant from the U.S. Environmental Protection Agency to study the effect of pollution exposures on childhood vasculitis. He is investigating potential associations of environmental particulate matter (pollution) with both the clinical onset of Kawasaki disease and the clinical flare of Henoch-Schönlein pupura. Dr. Spalding recently partnered with our pediatric otolaryngology colleagues, authoring a paper examining the occurrence and treatment of upper airway involvement in children with GPA\(^4\). In addition, there are other studies with enrollment currently open to children, including a North American Pediatric Vasculitis registry\(^5\), a longitudinal biomarker study in which clinical data are collected and blood and urine samples are studied in collaboration with Vasculitis Clinical Research Consortium members, and an NIH-funded clinical trial in the safety, efficacy and immunological outcomes of the medication abatacept in Takayasu arteritis.

**Suggested Reading**


Dr. Andrew Zeft specializes in pediatric rheumatology with a clinical and research focus in children with vasculitic diseases. He can be reached at 216.444.5801 or zefta@ccf.org.
Clinical and Immunological Characterization of Patients with Systemic Autoimmune Diseases

By Atul Khasnis, MD

The Department of Rheumatic and Immunologic Diseases at Cleveland Clinic is a tertiary referral center for a wide variety of systemic autoimmune diseases ranging from inflammatory arthritis to systemic vasculitides. It is well accepted that myriad immunologic alterations underlie the expression of these diseases; over the past decade, there has been a growing number of biologic therapies entered into the clinic to treat them. There is, therefore, a growing need to carefully characterize in detail the patients’ immunologic profiles during various stages of their illnesses as well as the effects of intervention with targeted immunologic therapies. Although these therapies are typically “targeted” to one molecule or cell of the immune system, their effects on the entire immunologic network cannot be overemphasized. Owing to the rarity of these systemic autoimmune diseases in the general population, the numbers of patients with these diseases referred to the Department of Rheumatic and Immunologic Diseases provides an important opportunity to study the clinical profile and immunologic underpinnings of these diseases.

The RJ Fasenmyer Center for Clinical Immunology has been a pioneer in promoting research in the field of HIV medicine owing to the longstanding collaboration between Leonard Calabrese, DO, and Michael Lederman, MD, at the Cleveland Clinic and Case Western Reserve University respectively. The Special Immunology Unit under Dr. Lederman’s direction is a world leader in HIV immunopathogenesis and in recent years has focused on the role of inflammation and immune dysregulation in HIV pathogenesis. Drs. Calabrese and Lederman have been well aware of the seemingly shared pathways of immunodysregulation in autoimmunity and HIV and have been planning to jointly study this seam between the diseases. Now, thanks to a $3 million grant from the RJ Fasenmyer Foundation and the resources of the RJ Fasenmyer Center for Clinical Immunology, we plan to build an infrastructure for detailed clinical and immunological characterization of patients with systemic autoimmune diseases using state-of-the-art immunological laboratory techniques.

Atul Khasnis, MD, the newest member of the RJ Fasenmyer Center for Immunology and Center for Vasculitis Care and Research, will coordinate the project. Dr. Khasnis plans to start by establishing and characterizing a longitudinal cohort of patients with granulomatosis with polyangiitis (Wegener’s), and then extend this network to other systemic autoimmune diseases. The information gained from these serial immunologic studies coupled with detailed clinical characterization of patients will provide invaluable insight into alterations of their immune system. In addition, we also plan to store samples in a Bio-bank at Cleveland Clinic for future immunologic analyses. This project will be a dynamic process and as we make progress, we expect that we will be able to ask further relevant questions regarding the pathogenesis of these diseases and the effects of newer treatments.

The strengths of the envisioned project is centered around the clinical expertise and patient resources of the staff in the Center for Vasculitis Care and Research led by Director Carol A. Langford, MD, MHS, who will also serve as a lead investigator, and the basic science expertise of the laboratory of seasoned investigators, such as Dr. Lederman. In many ways, we are strategically positioned to make this happen, and considering these strengths, we feel that we owe it to our patients to undertake this exciting research.

Dr. Khasnis is a member of the Center for Vasculitis Care and Research at Cleveland Clinic. He can be reached at 216.444.5632 or khasnia2@ccf.org.

Suggested reading:

Dr. Hoffman is a member of the Department of Rheumatic and Immunologic Diseases, Center for Vasculitis Care and Research, and Professor of Medicine at Cleveland Clinic Lerner College of Medicine. He can be reached at hoffmag@ccf.org or 216.445.6996.
Global Joint Ventures:
Cleveland Clinic and the Peking Union Medical College Hospital Join Forces for Medical Education

How Cleveland Clinic is working with one of the world’s fastest-growing rheumatology markets

On Aug. 16, 2011, a delegation from the Department of Rheumatic and Immunologic Diseases was hosted at the Peking Union Medical College Hospital (PUMCH) in Beijing, China, by Feng-chun Zhang, MD, Chief of the Department of Rheumatology, Chair of the Department of Medicine and President of the Chinese Rheumatologists Society. The Cleveland Clinic delegation was led by Leonard Calabrese, MD, and included Elaine Husni, MD, MPH, and Qinping Yao, MD, PhD. The goal of the meeting was to create a framework for a partnership whereby the two institutions will build a bilingual web site designed to bring high-quality western “CME style” education to the rapidly growing Chinese Rheumatology community. The meeting ended with great enthusiasm on behalf of both parties and an informal commitment to design and implement such a plan.

The concept of a joint web-based educational venture has two major stimuli. First, there is a growing need for novel forms of education among the rapidly expanding Chinese rheumatology community. At the present time, there are only 2,200 rheumatologists in China caring for more than an estimated 400 million people with rheumatoid arthritis, while there are over 5,000 rheumatologists in the U.S. caring for a much smaller population. The Chinese rheumatology community, however, is growing rapidly and they target an expansion to 6,000 practitioners by 2015 and 10,000 by 2020. There are currently numerous obstacles to providing high-quality postgraduate education in China: a language barrier to medical-scientific English especially outside the large Western-style medical centers, the cost of travel to international meetings and the lack of familiarity of the array of educational offerings in the West. Cleveland Clinic’s educational website (ccfcme.org) is an award-winning site; the rheumatology section under the direction of Dr. Calabrese of the RJ Fasenmyer Center for Clinical Immunology has been the most rapidly growing portion of the site. The rheumatology web presence started in 2005 and now posts more than 100 online offerings. The U.S. and Chinese physicians discussed how offering audio and graphic content both in Chinese and English could, in addition to providing state-of-the-art medical content, also provide an opportunity for learning medical-scientific English. Dr. Zhang expressed that the expertise and experience of Cleveland Clinic’s CME department and the international reputation and broad-based content of the Fasenmyer website could help ensure ongoing and accessible education throughout the country.

The RJ Fasenmyer Center offers a highly acclaimed series, Rheumatology Highlights Report, which attempts to summarize important developments presented at meetings such as the annual meetings of the American College of Rheumatology, EULAR and other disease-specific forums by breaking each down into multiple brief learning opportunities delivered through the perspective of international authorities. The bilingual version would be similar, but the faculty would include equal numbers of Chinese and US/European academic leaders. The initiative would be the first of its kind and hopefully will springboard other bilingual educational initiatives in other areas between PUMC and Cleveland Clinic.