REVIEW
Immunosenescence: Immunity and Ageing

The average life expectancy of humans has nearly doubled over the past 200 years and continues to escalate. It is predicted that ~40% of the population in Europe and the United States will be more than 60 years of age in 2050. The longest human lifespan listed in verifiable records is 122 years and at present, this sets the upper limit of achievable human lifespan. Much of this gain has been a consequence of improved nutrition, medications and vaccinations protecting the human race against infectious diseases. But the quintessential query that remains unanswered is whether the fragile immune system of an elderly individual can be adapted to cope with the stress and infections of old age, thus giving him a survival advantage of an additional 40 years.

Ageing is a complex process that negatively impacts the ability of the immune system to successfully function. The mechanisms that underlie these age-related defects range from defects in the hematopoietic stem cells to defects in peripheral lymphocyte migration, maturation and function. The thymus is the central lymphoid organ responsible for production of naïve T cells, which play a vital role in mediating both cellular and humoral immunity. Chronic age-related involution of the thymus gland is thought to be one of the major contributing factors to loss of immune function with increasing age.

Immunosenescence and Inflamm-aging

The term “Immunosenescence” was introduced by Dr. Roy Walford. It denotes age associated decreased immune competence that renders elderly individuals more susceptible to chronic diseases and increases morbidity and mortality due to infectious disease compared with the young. The main observed changes in old age are a decrease in adaptive immunity and increased low-grade chronic inflammatory status, which has been referred to as “Inflamm-aging”, a process that impacts on the internal milieu of the body by changing its composition over time (change not only of the immune cells but also of their “microenvironment”). Within this perspective, chronic antigenic load and inflamm-aging are strong candidates as major driving forces of the rate of aging and of the pathogenesis of major age-related diseases. Inflamm-aging is the end result of such a process characterized by activation of macrophages and expansion of
specific clones (megaclones) of T lymphocytes directed toward antigens of common viruses such as cytomegalovirus (CMV) or Epstein-Barr virus (EBV). All these phenomena have a strong genetic component, as shown by studies in old people and centenarians, which collectively indicate that the frequency of several polymorphisms of important immune response genes involved in inflammation are present at different frequencies in long-lived people when compared with young subjects.

**Alterations in T cells**

Senescence of clonotypic immunity is mostly the result of alterations in T cells. Several studies have noted an inversion of CD4:CD8 T cell ratio in the peripheral blood of elderly with unsuccessful aging. Lifelong chronic antigen load seems to be the major driving force of immunosenescence, which impacts human lifespan, with low CD4+ and high CD8+ T cells and simultaneously fills the immunological space with expanded clones of memory and effector, *i.e.* antigen experienced, T cells. This chronic antigen load is responsible for the chronic inflammatory status that characterizes ageing. The progressive reduction of naïve T cells involving both CD4+ and CD8+ T lymphocytes and is paralleled by a concomitant increase of memory CD28 negative T cells expressing a senescent phenotype, *i.e.* progressive shortening of telomeres and reduced replicative capacity. A second fundamental aspect of immunosenescence is the progressive age-related increase of a proinflammatory status represented by an increase of inflammatory cytokines and of inflammatory markers predictive of mobility and mortality. This proinflammatory condition is referred to chronic antigenic load (bacteria, virus, fungi, toxins, mutated cells) that continuously stimulate innate immune machinery. This seems to favor the onset of typical age-related diseases (atherosclerosis, dementia, osteoporosis, neurodegeneration, diabetes and neoplasia) where immune and autoimmune factors play an important role. The Swedish OCTO immune study made a comprehensive investigation of multiple immune parameters among octogenarians and found low CD4 T cells, high CD8 T cells, poor T cell proliferation and low IL2 production as an immune risk phenotype (IRP) capable of predicting 2-year mortality in such elderly.
Immunological and Immunogenetic markers

Centenarians are equipped with gene variants that allow them to optimize the balance between pro and anti-inflammatory cytokines and other mediators involved in inflammation. Indeed, genetic markers related to a pro-inflammatory phenotype associated with the major age-related diseases have been found to be underrepresented in centenarians, whereas those associated with anti-inflammatory activity are more highly represented in centenarians, confirming that the balancing of pro- and anti-inflammatory mechanisms during aging is largely under genetic control. Thus, it can be hypothesized that genetic variations in pro- or anti-inflammatory cytokines and human leukocyte antigen (HLA) alleles that regulate type and intensity of the inflammatory immune response might influence successful ageing and longevity. An over representation of +874A allele, known to be associated with low IFN-γ production has been reported in the Italian centenarians. Possession of this allele significantly increases the possibility to achieve extended longevity, suggesting that the pro-inflammatory status characteristic of ageing may be detrimental for successful ageing. HLA studies in caucasoids suggest that longevity might be associated with positive selection of some alleles like HLA-DR11 or haplotypes like HLA-B8-DR3 that confer resistance to infectious diseases. These findings indicate that different HLA alleles as well as genes coding for pro- or anti-inflammatory cytokines might affect the individual life-span expectancy, by influencing the type and intensity of immune-inflammatory responses against environmental stressors.

It is envisaged that the coming years would witness the evolution of predictive molecular medicine. Depending on the molecular diversity of the MHC and other immunomodulatory factors like cytokine gene variants and environmental determinants, it will be possible to identify people at ‘risk’ of developing autoimmune disorders or immune deficiencies at an early stage and therefore custom-tailor their treatment profiles. Vaccine research might get skewed towards epitope immunodominance on the basis of MHC specificities of not only an individual but also at the level of the population to be vaccinated. A deeper understanding of the molecular mechanisms that determine susceptibility to infection may ultimately provide clues to the
prevention of a much wilder range of common diseases.

**Perspectives: Can we retard immunosenescence?**

The main hypothesis of ageing is that as a result of telomere erosion, memory T cells might be lost during ageing. This loss is secondary to the loss of telomerase inducibility after repeated stimulation of activated T cells. So, one possible way to retard replicative senescence in human T cells is by telomerase transfection, and this has been shown to extend the lifespan of specific clones indefinitely *in vitro*. However, it is unclear whether this would eventually lead to the development of malignancy in the transduced T cells *in vivo*. A second possibility is treatment with cytokines, such as IL-7, that have been shown to directly induce telomerase activity in T cells. However, T cells lose the ability to upregulate telomerase after repeated activation, and because these cytokines also induce T-cell proliferation, their use might eventually become counterproductive from the perspective of telomere loss. Therefore, it is clear that a better understanding of how telomerase activity is regulated in memory T cells is essential for the development of strategies to manipulate replicative senescence.

A strategy that can increase generation of naïve T cells with considerable replicative reserve, in elderly individuals, might be an alternative route in improving immunity in the elderly. For example, it has been shown that treatment of aged mice with IL-7 considerably improves the output of naïve T cells from the thymus and so enhances immunity. It remains to be determined whether this treatment, together with therapy using hematopoietic stem cells, might enable T-cell reconstitution in elderly individuals.

A third strategy to promote the persistence of T-cell memory during ageing could be to target the antigens that induce marked clonal expansions. Persistent herpes viruses, such as CMV, do not initially cause severe problems in young infected individuals and have not therefore been considered as a target for intervention. However, one way to improve the health of elderly individuals might be to vaccinate young individuals against the agents that induce the marked clonal expansions that occur later in life.

While immunosenescence is fast becoming a major area of immunology research, what remains to be resolved is the
“chicken and egg” dilemma surrounding this field. Putting it in perspective, what needs to be questioned is whether individuals live longer because of good immune function, or do they possess good immune function because other factors have enabled them to survive longer? The near future might unravel these and more secrets of successful aging.

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REVIEW

Th17: a brief note

CD4+ T cells, after antigenic stimulation, proliferate and differentiate into various effector subsets with different cytokine profiles and distinct effector function. Until recently, T cells were divided into two distinct subsets: T helper type 1 (TH1) and TH2, based on their cytokines. TH1 cells produce large quantities of interferon-γ (IFN-γ), whereas TH2 cells produce interleukin 4 (IL-4), interleukin-5 (IL-5) and interleukin-13 (IL-13). A third subset of interleukin-17 (IL-17) producing effector T helper cells, called Th17 cells, has now been discovered and characterized. TH17 cells have been identified as a unique subset of T helper cells and are producing IL-17A (IL-17A), IL-17F and IL-22 and, to a lesser extent, tumor necrosis factor (TNF) and interleukin - 6 (IL-6). IL-17 is the founding member of the IL-17 family of cytokines, which includes IL-17A (also called IL-17), IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25), and IL-17F. IL-17E (or IL-25) is not produced by Th17 cells, but it is produced by Th2 cells. IL-25 induces the expression of Th2- type cytokines and chemokines such as CCL5 (RANTES) and CCL11 (Eotaxin) and might be involved in Th2-type allergic responses.

Besides being produced by Th17 cells, both IL-17A and IL-17F are also produced by a variety of cell types, including T cells, NKT cells, NK cells, neutrophils, and eosinophils. Thus, IL-17 and IL-17F are effector cytokines that are produced by cells of both the innate and the adaptive immune systems, suggesting a bridging function of this type of immunity between innate and adaptive immune responses. Both IL-17A and IL-17F have proinflammatory properties and act on a broad range of cell types to induce the expression of cytokines (TNF, IL-1, IL-6, GM-CSF, G-CSF), chemokines (CXCL1, CXCL8, CXCL10), and metalloproteinases. Th17 cells also secrete IL-21 to communicate with the cells of the immune system. The development of Th17 cells depends on the various differentiation factors (TGF-β, IL-6 or IL-21), the growth and stabilization factor (IL-23), and the transcription factors: signal transducer and activator of transcription 3 (STAT3), retinoic-acid-receptor-related orphan receptors alpha (RORα), and gamma (RORγ). In humans, a combination of TGF-β, interleukin-1 (IL-1) and interleukin-23 (IL-23) induces Th17 differentiation from naive T cells. Both interferon gamma (IFN-γ) and IL-4, the main stimulators of Th1 and Th2 differentiation respectively, have been shown to negatively regulate Th17 differentiation.

IL-17 acts in vitro and in vivo as a potent inflammatory cytokine. It has pleiotropic activities, one of which is to coordinate tissue inflammation by inducing the expression of proinflammatory cytokines (IL-6 and TNF), chemokines (MCP-1 and MIP-2) and matrix metalloproteinases, which mediate tissue infiltration and tissue
destruction. IL-17 is also involved in the proliferation, maturation and chemotaxis of neutrophils. In addition to its involvement in the induction of proinflammatory cytokines, chemokines and matrix metalloproteases, IL-17 is directly involved in the destruction of cartilage and bone, as noted in patients with rheumatoid arthritis. They are considered developmentally distinct from Th1 and Th2 cells and excessive amounts of the cell are thought to play a key role in autoimmune disease such as multiple sclerosis, psoriasis, autoimmune uveitis, juvenile diabetes, rheumatoid arthritis.

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VIEW POINT:

Current Scientific Research status in India

India’s research productivity will be on par with most G8 nations within 7-8 years and we could overtake them between 2015-2020. The study, *Global Research Report: India*, informs policymakers about the research and collaboration potential of India and its current place in world science. “India’s current rise in science is as impressive as its economic surge of recent years and clearly has immense potential to become the home for world-class research,” said Mike Boswood, CEO, Healthcare & Science business, Thomson Reuters.

The study draws on data found in *Web of Science*, available on the *ISI Web of Knowledge* platform — the world’s largest citation environment of the highest quality scholarly literature. Key findings include:

- In the last decade, India has seen a substantial growth in its annual output of scientific publications — from roughly 16,500 in 1998 to nearly 30,000 in 2007, an increase of 80 percent.

- India’s annual growth rate has vaulted in recent years to rival comparable figures from such well-established European and Asian nations as Japan, France, German, and the United Kingdom.

- India’s research portfolio is markedly balanced between the life sciences and physical sciences.

- India has established stable and growing research partnerships with a variety of nations —notably, the United States, Germany, the United Kingdom, and Japan.

- South Korea has hugely increased its percentage of papers collaboratively with Indian authors in what is generally a doubling in volume of Indian collaborative output with Asian partners, possibly signaling the emergence of a clearer regional research network.

By examining India’s scientific focus and how its areas of concentration map to the rest of the world, policymakers and institutions who are interested in engaging with India’s growing research base will be provided with useful information and insights, that will help them leverage opportunities for innovation.

Sathyapriya,
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VIEW POINT:
First Real-Life Frankenstein"

Artificial life created by totally manmade DNA injected in to a lifeless cell…

This is first time when scientists have created a new life by injection of a totally synthetic DNA in to a lifeless cell. The world-renowned scientist Dr. J. Craig Venter announced that he and his team at the J. Craig Venter Institute (JCVI) became the first in history to synthetically create a living, self-replicating cell. This news has a groundbreaking potential in the field of medical science, environmental biology, food-processing industry, bio-fuel, biotechnology field and many more. This research marks a responsible milestone in the synthesis and implantation of artificial DNA.

What is synthetic life? Synthetic life is artificial life created from non-living (abiotic) substances. It belongs to the discipline of synthetic biology. It is usually distinguished from mechanical life that usually belongs to the discipline of robotics. It is created in vitro from bio-chemicals and their component materials as opposed to normally implied in silico using the broader term "alife". (From Wikipedia).

Science Behind The Achievement:
In the current research Venter and his colleagues first synthesized Mycoplasma's full genome. Then they added hundreds of thousands of additional base pairs to the DNA to distinguish it from a natural one. The completed DNA sequence was more than one million base pairs long. However no machine can turn out a single piece of DNA anywhere close to that long. Instead, Venter and his colleagues started with many relatively small pieces of DNA. Then the scientists transferred DNA pieces back and forth between a yeast cell and E. coli bacteria, turning the many short pieces into fewer but longer DNA segments. By using simplified organism instead of using vast complex organism we can design more simplified experiments and can produced more elegant results. Needless to say, the process of assembling such a lengthy piece of synthetic DNA was complicated. For the case of the expression several of the synthetic genes did not work properly, but the most important from them got work, i.e. the gene responsible for the growth and reproduction worked out so, the mycoplasma cells has grown up and divided.
Future Aspects: This work could lead to staggering findings in two major ways. First, cells with synthetic genomes could allow scientists to essentially snip out the complexities of living cells leaving only the simpler parts. This would give researchers a better way to untangle the enormously complicated interactions that occur in natural cells, and could help unravel the secrets of diseases like cancer (greater potential to unlock the mysteries of the signal transduction mechanisms).

Second, while cells with synthetic genomes couldn't be used to recreate extinct creatures, they could be used to create organisms that have the genes of extinct organisms, possibly even those of earth's earliest life forms. This could lead to a better understanding of the very nature of life and how life began.

This new invention gives a vast idea about the chemical and biological pathways and their interrelation. This could also reveal that how the interaction of two or more pathways involves in the disease formation. By using simplified organisms instead of using vast complex organism can produce more elegant results and more simplified experiment.

So this could be a novel invention, the effect of this could be seen in the near future.

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JUMBLE WORDS

BYMLTOSLPHA
TPLCEOMNEM
ETGR
P3OFX
TIHROUDAEMSHITAIHRR
LNCRLTIIUEI
SPAOTIOSP
TACSALEA

Clues
Immune system
Regulation
Autoimmunity
Elimination
Filaria

Scramble the highlighted letters to fill the following blanks:

[Blank spaces for scrambling]
Here is the Clue..

Kirthika Sreenivas,  
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PARTICIPATION REPORT:
2nd European Congress of Immunology, Berlin, Germany

The 2nd European Congress of Immunology under the motto ‘Immunity for Life – Immunology for Health’ was organized under the auspices of EFIS (European Federation of Immunological Societies) from September 13 – 16, 2009 at the International Convention Centre in Berlin, Germany. The congress is held every 3 years with the first one being held in Paris, France.

More than 3500 abstracts were received for the conference from 75 countries across the globe, with 220 late breaking abstracts as well. The conference organizers, under the presidency of Prof. R. E. Schmidt (Director, Clinic for Immunology & Rheumatology, Hannover Medical School, Germany), had put together a great scientific programme in four tracks covering the most recent developments in basic and clinical immunology.

Track A: Innate Immunity
Track B: Adaptive Immunity
Track C: Diseases of the Immune System
Track D: Immune Interventions

The opening ceremony included some talks by eminent scientists in immunology including Michael Reth and a special lecture ‘Cancer Causation by Infections’ delivered by Noble laureate Harald zur Hausen. An exhibition on ‘The History of the Birth of Immunology’ was also put up on display in the main lobby of the convention centre.

There were educational courses for Ph.D. students and post docs during each of the main tracks in the meeting. Here highly competent lecturers from all over Europe were presented and given an overview on fundamental and applied aspects of immunology. In addition, young scientists also had the chance to meet symposia speakers in an interactive discussion.

Thirteen ‘Progress in Technology’ Sessions were also organized, which confronted the delegates with the newest developments in modern laboratory methods or systems biology and even software programmes. Furthermore the progress in translational immunology was also represented in a number of outstanding satellite symposia organised by various global companies. Altogether these exciting scientific results were presented in more than 55 symposia and 112 workshops which covered both the physiology and pathology of the immune system.
And at the end of the day the sights and scenes of the beautiful city of Berlin provided the refreshing change needed to recharge the scientific enthusiasm among the delegates.

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(The author presented two posters on the 3rd and 4th day of the conference. One of the posters was presented in ‘Track C PC05 – Deficiencies of the Innate Immune System’ while the other was presented in ‘Track C PC19 – Reproductive Immunology’. Both the posters were critically appreciated by several experts in the field)

Mouse had no discernible phenotype.. till the cat jumped on him!
PARTICIPATION REPORT:
14th International Immunology Congress, 22nd -27th August 2010, Kobe, Japan

The 14th International Immunology Congress (14th ICI 2010) under the theme ‘Immunology in the 21st century: Defeating infection, Autoimmunity, Allergy and Cancer’ was organised under the auspices of “The Japanese Society for Immunology, The Japanese Society for Clinical Immunology, Science Council of Japan and the IUIS (International union of Immunological Societies) from August 22nd -27th 2010 at the Kobe International Convention Centre in Kobe, Japan. This congress is held once in 3 years. More than 3800 abstracts were received for the conference across the globe, with 6000 delegates. The conference organizers, under the presidentship of Prof. Tadamitsu Kishimoto University of Osaka, had put together a great scientific programme spanning for 6 days with the most recent developments in basic and clinical immunology.

I was privileged to have attended the International Union of Immunological Society (IUIS) meeting also. This provided me with the chance to meet immunologists from almost all the immunological Societies around the world.

The evening sessions began with the keynote lecture by Novel laureate Dr David Baltimore. Dr. Baltimore spoke on miRNA and its implications on the immune system. He discussed its role in the immunology of T and B cells and how they work individually and with other. He talked on how to enrich specific miRNA in mouse. This was followed by a live Osaka Philharmonic orchestra performance and a Japanese Taiko Drum live performance at the opening ceremony.

The congress spanning for 6 days was packed with two master lectures per day and six simultaneous symposiums in the morning. The lunchtime was also kept busy with six simultaneous lunchtime lectures that required prior booking. The afternoons were packed with seven workshop lectures sessions running simultaneously. This was followed by the poster discussions. The participants had ample time to see the posters.

There were some special lectures like "progress of cancer immunotherapy” “Present state and future of biologics in autoimmune disease Cytokines” “Present state and future of biology in autoimmune disease and Immune Cells” Few other brainstorming lectures were on “Il-6- Back to the future” by
Dr. T Kishimoto, “New paradigm in TB sero-detection Computational analysis to classify profiles of anti TB antibodies by multiplex micro bead arrays”

The sessions on Th17/Tregs, Human Th17 cells and Th1/2, Innate immunity and viral infections were very informative with lectures like “Communication between innate and adaptive immune response to viral infections by CA Biron from Brown University, “Immune evasion of innate and adaptive immunity by Dr W.M Yokoyama from Washington School of Medicine, “Anti cytokine Biologicals- prospects for the future: by Dr M Feldman from Kennedy Institute of Rheumatology,

The session on HIV pathogenesis and immunity and Immunity to retrovirus infection which was of direct importance of my research work included talks like “The quality and quantity of gag specific responses directed against conserved and variable epitopes in association with disease progression by CL Perez from Karolinska Institute, “HIV disease progression is associated with disruption of lymphopoisis driven by immune activation" by Dr D Sauce from INSERM, France, “Defiance IL-21 production leads to decreased survival and function of CD4+ and CD8+ T cell in HIV infected individuals by Dr A Lannello from University of Montreal. All the talks could be found on the website of ICI2010.

We had lot of science in informal sessions, which gave me an opportunity to talk to people about my work and my institute. This would act as a foundation for future collaborations.

My poster entitled “Novel HIV-1 gag CTL epitopes recognized by south Indians” was scheduled on the 4th day during the HIV-TB sessions. The poster was well read and criticized. My poster talked about three HIV gag epitopic regions found among the south Indians that have not been recognized previously. These epitopic regions are restricted by HLA-B*40 the most common HLA allele. This has future implication for vaccine studies.

I take this opportunity to thank Dr. V Kumaraswami, Director-In-charge, TRC, whose constant guidance prepared me to present my work at an international event. I am grateful to my mentors Dr PR Narayanan, Dr. Soumya Swaminathan, Dr Sudha Subramanyam, Dr Luke Elizabeth Hanna at Tuberculosis Research Centre for their support.

I was privileged to have received a grant from GL Talwar Immunology foundation, The
Department of Science and Technology Government of India and the Organisers of ICI 2010. I take this opportunity to thank them all.

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PARTICIPATION REPORT:
Keystone Symposia “HIV Vaccines” and “Viral Immunity”

I am writing this about my recent participation in Joint Keystone Symposia “HIV Vaccines” and “Viral Immunity”, held at Banff, Alberta, Canada (21st to 27th March, 2010). It is my pleasure to share my best scientific experience so far with budding scientists and the experts here. It is worth to mention that this time I was fortunate enough to be the only Indian selected for the prestigious Global Health Travel Award for the same. This award covered all my expenses towards accommodation, return airfare and in addition allowance of 200 USD for out of pocket expenses. The application for this award involved my statement of purpose and various questions related to my ongoing work, future goals, and contribution to the developing world after participation and in addition a recommendation from guide, thanks to Prof. N K Mehra, who always motivates me for such bright opportunities.

In this scientific event, my abstract was selected for poster session entitled “HIV Epidemic in India: Deciding the Decisive Immunogenetic Correlates for Developing Vaccine Strategies”. My focus was to emphasize the influence of HLA, chemokine receptors and cytokine gene polymorphism in relation to HIV epidemic in India and how our findings are different from western world and what ultimately this means in term of future vaccination approaches and therapeutic and prognostic options. I won’t go into details and would refer to our group’s recent reviews in international journals like Vaccines and Tissue Antigens.

Overall, it was a great experience; there were more than eight hundred participants from different regions all over the world. The organizers put all the efforts to make it convenient for participants to reach the venue with all the required valuable information and assistance. Scientists of international repute like Peter Doherty, Bruce Walker, Guido Silvestri and many others were very much involved with the participants with their novel ideas and upcoming technologies. The impact of abstracts was very good, abstract book was supplemented with long poster sessions in the evenings with plethora of unpublished data and saturating information in continuation with lite bites. Lectures were well organized with strict adherence to the time schedule. Further, there were special sessions for learning Los Alamos sequence database for HIV research. One interesting thing to share with you is the strict prohibition of photography or video recording in conference halls during all the scientific and poster sessions.

All the scientific sessions were well supplemented with social functions and interactive sessions. Also, participants got many options for sightseeing as Banff is a souvenir town and a place meant for tourists, the natural beauty in a true sense, cool
and calm. People all over the world visit this place as it is famous in the world for skiing, so it was fun to do some extra curricular activities in addition to science. With this brief outline, I would suggest you all to participate in future versions of this highly prestigious keystone symposium.

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You are the Postdoc. You should know how to make ends meet!
Answers: Puzzle

Lymphoblast
Complement
Treg
Foxp3
Rheumatoid Arthritis
Citrulline
Apoptosis
Catalase
Wolbachia
Setaria digitata
Vasculitis
Lymphangitis

LEAPS PEPTIDE VACCINE