



# 13<sup>th</sup> International Conference for

# Behçet's Disease



Epidemiology • Pathogenesis • Clinical Findings • Management • Prognosis

May 24-27, 2008

Pörtschach / Klagenfurt (Austria)



## How to reach Pörtschach / Klagenfurt

**By plane you may reach Klagenfurt Airport directly from** Berlin, Cologne, Düsseldorf, Frankfurt, Hamburg, Hannover, Leipzig, London, and Vienna



### **Venue:**

Congress Center Würthersee  
Hauptstraße 203, 9210 Pörtschach am Würthersee, Austria



















# 13<sup>th</sup> ICBD

**May 24~27, 2008**  
**Congress Center Worthersee**  
**Pörtschach / Klagenfurt Austria**

## **\*140papers**

- \* Oral presentation-Scientific sessions (26)
- \* Poster presentation (94)
- \* Keynote lecture/ Plenary lecture (5)
- \* Update study group (15)

## **\*Meet the professor**

- dermatology, neurology, rheumatology

## **\*Controversial discussion, Open for discussion**



# Main Topic

- \* **Epidemiology (14)**
- \* **Pathophysiology and basic research (32)**
- \* **Clinical manifestations (28)**
- \* **Disease assessment, laboratory tests and imaging (14)**
- \* **Clinical studies and treatment strategies (11)**
- \* **Pediatric manifestations (5)**
- \* **Oral, genital, and skin manifestations (12)**
- \* **Ocular manifestations (13)**
- \* **Manifestations of the central nervous system (8)**
- \* **Patients' education (1)**



# Presentations

<b>Country</b>	<b>No. of abstract</b>
Turkey	31
Iran	22
Korea	13
Tunisia	13
Japan	12
Germany	9
UK	7
Moroco	7
Greece	6
USA	5
France	4
Portugal	4
Spain	3
Netherlands	3
Russia, Austria, Iraq, Israel, Egypt	2
China, Jordan	1



# Plenary Lectures

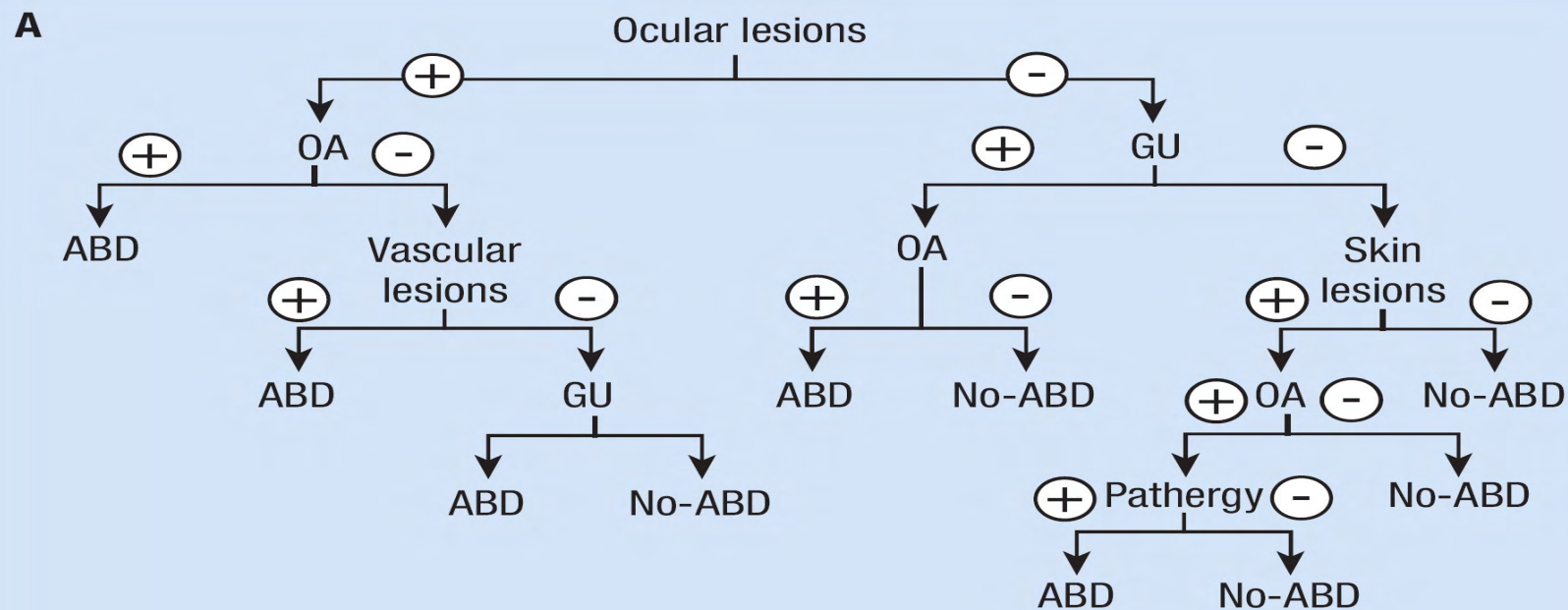
1. Infections and immunosuppression (W. Graninger)
2. BD and central nervous system (A. Al-Araji)
3. Endothelium and thrombophilia (F. Espana)
4. BD at the pediatric age (I. Kone-Paut)
5. New perspectives for BD (H. Yazici)





# Epidemiology-1

- \* Validation of the International Criteria for BD in Germany, China, Iran, Spain (sensitivity, specificity, accuracy)



**B**

Diagnosis of Adamantiades-Behçet Disease is made with a score of 3 points:

- 1 point Oral aphthosis
- 1 point Skin manifestations (pseudo-folliculitis, skin aphthosis)
- 1 point Vascular lesions (phlebitis, superficial phlebitis, large vein thrombosis, aneurysm, arterial thrombosis)
- 1 point Positive pathergy test
- 2 points Genital aphthosis
- 2 points Ocular lesions

▲ **FIGURE 167-2** Revised International Criteria for Behçet's Disease (International Team for the Revision of ICB; coordinator: F. Davatchi) according to **(A)** the classification tree format, and **(B)** the traditional format. ABD = Adamantiades-Behçet disease; GU = genital ulcer; OA = oral aphthous ulcer. (From Zouboulis CC et al: Evaluation and revision of the International Criteria for Behçet's Disease (ICBD). Abstracts of the 21st World Congress of Dermatology, Buenos Aires, Argentina, 2007, in press, with permission.)





# Epidemiology-2

- \* Change in incidence of pathergy phenomenon in Behcet's disease over the time
- \* HLA-B5(1) and risk of Behcet's disease: A meta-analysis of genetic association studies



# Epidemiology-3

- \* **HLA-B27 in BD, 5567 patients in Iran**

- Positive: 481 patients (8.6%)

- Odds ratio compared to the normal (3.69)

- Ankylosing spondylitis, chronic diarrhea, false positive VDRL, Type III and IV WHO glomerulonephritis

- \* **HLA-B51 in BD, 1164 patients in Iran**

- Positive: 540 patients (46.4%)

- Favored some manifestations

- : Pathergy reaction, EN, joint manifestations, myocardial infarction, arterial thrombosis

- Not clinically as important to use it for any decision making





# Pathophysiology and Basic Research-1

## \* Gene

### \* HLA Class I phenotype

- \* Positive correlation: HLA-A2, B5, Bw4, Bw6
- \* Negative correlation: HLA-A1, A3, A9, A10, A28, A29
- \* HLA-B51: a prognostic indicator for a possible severe eye involvement, esp in male Behcet's disease patients

### \* HLA-A2/B51 combination related to genital lesion

- \* Significant relationship between HLA-A26 locus and ocular lesions

### \* IL-18 promoter polymorphism

- \* Susceptibility to Behcet's disease, esp to mucocutaneous form

## \* **NODs single nucleotide polymorphisms**

- \* **NOD** (nucleotide-binding oligomerization domain)

: related with the innate immunity and inflammatory control

- \* Two of three NOD2 variant alleles associated with Crohn's disease are significantly less present in BD compared to healthy controls.

-> The variant alleles might protect BD.

## \* **P Selectin glycoprotein ligand-1 (PSGL-1) variable number of tandem repeats (VNTR) polymorphism**

- \* **PSGL-1**: important adhesion molecule involved in lymphocyte recruitment

- \* Increased risk of thrombosis in patients with anti-phospholipid antibody syndrome

- \* Contribute to the thrombotic tendency observed in patients with BD



- \* **IFNAR1 and IFNAR2 polymorphisms in patients with BD**
  - \* IFNAR1, IFNAR2 polymorphisms were disclosed to confer susceptibility to multiple sclerosis characterized by **Th1 polarization**
  - \* BD patients had a significantly higher frequencies of the genotypic combinations of IFNAR1 and IFNAR2 polymorphisms  
-> **jointly but not individually**, may confer susceptibility to BD
  
- \* **CTLA-4 gene polymorphisms**
  - \* **CTLA4**
    - Co-stimulatory molecule expressed on activated T cells
    - Plays a key role of inhibitory regulator of the T lymphocyte activation
  - \* **SNPs of promoter region on CTLA4 gene** have a candidate predisposing to BD
  - \* **The CTLA4-1722T>C** polymorphism may contribute to the clinical useful marker of BD with **ocular lesion**



# Pathophysiology and Basic Research-2

## \* Cell

### \* **Endothelial progenitor cells (EPCs)**

- \* A subtype of BM-derived progenitor cells expressing surface antigens of both hematopoietic stem cells and endothelial cells: maintenance of vascular integrity and neoangiogenesis
- \* **Severe reduction of circulating EPCs** in BD -> **impaired endothelial recovery** -> vascular damage

### \* **RBCs**

- \* EM changes in RBCs of BD patients
  - : increased proportions of non-discocytic erythrocytes
  - > reduced deformability -> impair blood flow, endothelial dysfunction, tissue hypoxia

### \* **PMN cells**

- \* Elevated serum MPO in BD -> increased activation of PMN, increased production of free radicals, LDL oxidation-> oxidative stress
- \* Decreased serum lactoferrin -> impaired antioxidant defense





# Pathophysiology and Basic Research-3

## \* Cytokine

- \* IL-12, IL-6, IL-8, IL-17
- \* IL-6 siRNA injected symptomatic BD mice
  - \* Downregulate IL-6, decreased severity score, upregulated Foxp3+ Treg cells
- \* Impaired interferon-beta production from plasmacytoid dendritic cells in patients with BD after CPG-ODN stimulation

## \* Infections

- \* **Oral streptococci**
  - \* Bes-1 DNA and HSP-65 derived from *S. sanguinis* (previously called as *S.sanguis*) in mucocutaneous lesions of BD patients
  - \* Bes-1 gene: highly homologous with the peptides of human HSP-60
  - \* HSP-65 and HSP-60: high homologies to T cell epitope
    - > proinflammatory Th1 type cytokine production



# Pathophysiology and Basic Research-4

## \* Antimicrobial peptides

### \* CSA-13

- \* Antimicrobial cationic steroid mimic
  - : functions against harmful bacterial infections
  - : suppressive effect to vascular morphogenesis
  - > treatment of hyper-progressive ocular vasculitis

### \* Human neutrophilic peptide (HNP) 1-3, LL37, S100

- \* Salivary HNP 1-3 levels were significantly higher in patients with BD
  - : associated with severe organ involvement
- \* Salivary LL37 and S100 levels seemed to be higher in BD
  - : correlated with the frequency of oral ulcers and plaque index score reflecting microbial plaque accumulation
- \* Salivary levels of **HNP 1-3, LL-37 and S100** might be related to **disease severity, oral ulcer activity and oral infection focuses** in BD.



# Pathophysiology and Basic Research-5

## \* Toll-like receptor (TLR)

- \* TLR expression (TLR 1, TLR2, TLR3, TLR4, TLR9) at rest and after stimulation, in T cells and monocytes from patients with BD **did not differ** from that of healthy individuals
- \* TLR signaling is **not impaired** in patients with BD

## \* TLR and VitD

- \* Higher expression of TLR2 and TLR4 in the monocytes of active BD
- \* Serum 25(OH)VitD was lower in active BD.
- \* VitD3 dose-dependently suppressed the expressions of TLR2 and TLR4.  
-> VitD: may be a therapeutic option in BD

## \* TLR and Heme oxygenase (HO)-1

- \* Reduced expression of HO-1 in PBMC from active BD
- \* Increased expression of TLR4 in PBMC from BD  
-> Microbial pathogen stimulate the innate immune system through TLR4 in PBMC  
-> **Defective HO-1 expression contribute to augmentation of inflammation**





# Pathophysiology and Basic Research-6

## \* **EGFR and its ligands in buccal swabs**

- \* Not increased secretion of EGF and TGF- $\alpha$  in BD patients with active oral ulcers
- \* High expression of EGFR during remission
- \* Downregulated expression of EGFR during active ulcerations

## \* **Killer immunoglobulin-like receptor (KIR)**

- \* HLA-B51 express the Bw4 epitope that can bind to a group of polymorphic receptors (KIR) expressed on NK cells and cytotoxic T cells.
- \* KIR3DL1/S1 allelic association with BD  
-> **HLA-KIR interaction is involved in the development of BD.**

## \* **Soluble endothelial protein C receptor (EPCR)**

- \* EPCR was discovered at the surface of endothelial cells, binds protein C, and enhances its activation.
- \* Soluble EPCR was also detected in plasma.
- \* Plasma sEPCR was significantly higher in patients with BD



# Pathophysiology and Basic Research-7

## \* Disease activity marker

### \* Adiponectin

- \* Adiponectin from adipose tissue: **antiinflammatory effect**
  - Decreases expression of adhesion molecules
  - Inhibits attachment of active macrophage to endothelial surface
- \* Serum adiponecin levels **were high during both active and inactive stage** in patients with BD.

### \* B-cell activating factor of the TNF family (BAFF)

- \* Polarization of T lymphocytes toward the Th1-type
- \* Serum BAFF was associated with increased disease activity in BD.
  - > useful marker for the disease activity and potential therapeutic target

### \* Homocysteine

- \* Independent risk factor for venous or arterial thrombosis in Iranian patients with BD
- \* Negative correlation between HLA-B51 and serum homocysteine



# Treatment Strategies-1

- \* **Rebamipide (Mucosta<sup>®</sup>)**
  - \* Improve the efficacy of colchicine for the herpes simplex virus-induced inflammation in a BD mouse model
- \* **Rituximab (anti-CD20 monoclonal antibody)**
  - \* Reduce macular edema on fluorescein angiography and optical coherence tomography
- \* **N-acetyl cysteine** as an adjuvant therapy
  - \* No additional benefit on disease activity
- \* **The effect of immunosuppressive treatment on skin pathergy reaction**
  - \* Colchicine, azathioprine, cyclosporine, or interferon-alpha 2b does not affect the skin pathergy reaction.





## Treatment Strategies-2

- \* **Treatment of sight-threatening panuveitis**
  - \* Single infliximab infusion has a faster beneficial effect than intravitreal triamcinolone or high dose intravenous methylprednisolone.
- \* **Combination therapy** of pulse cyclophosphamide, azathioprine, and prednisolone is **the best choice in ocular BD**
  - \* 1000mg cyclophosphamide in 500 ml serum saline 5% once monthly, 2-3mg/kg azathioprine daily orally, 0.5mg/kg prednisolone daily orally
- \* **Mycophenolate sodium (case report)**
  - \* A good therapy before using biologicals or chemotherapeutics in therapy-refractory BD patients with severe ileo-colitis.



# Oral, Genital and Skin manifestations

## \* Clinical feature

- \* **Pemphigus vulgaris misdiagnosed as aphthae**
- \* **BD mimickers**  
: recurrent aphthous stomatitis, pemphigus vulgaris, erosive lichen planus, bullous pemphigoid, herpes simplex, erythema multiforme, fixed drug eruption, drug eruption, candidiasis, mechanical ulceration, psoriasis, SLE, vasculitic ulceration
- \* **Index for oral ulcer activity** : VAS pain score
- \* **Oral ulcer activation after dental and periodontal treatment**
- \* **Case report**: EM, Cutaneous PAN

## \* Therapy

- \* **Sublingual IFN-a tablet**: effective
- \* **Topical tacrolimus** for mucosal lesion: effective
- \* **Tropical Nigella sativa 100% oil**: safe and effective for RAS
- \* **Zinc sulphate 5% mouthwash**: effective, prophylactic for RAS
- \* **Bifidobacterim lactis DN-173 010 strain**: effective



# Eye involvement and treatment-1

## \* Clinical feature

- \* **Pathergy reaction on conjunctiva after intravitreal TA injection**
- \* **A specific finding of Behcet's uveitis:** inferior peripheral pearl-like precipitates
- \* **The risk factors of blindness in Behcet's disease:** higher frequency of uveitis, longer duration of uveitis, retinal vasculitis, initial low vision

## \* Therapy

- \* **Intravitreal TA injection:** effective for the suppression of recurrent ocular inflammation, but high frequency of complications
- \* **Interferon-alfa vs cyclosporine in ocular BD:** long-term remission and better final visual acuity in IFNa compared to CyA
- \* **Cyclophosphamide pulse therapy:** effective for treatment of severe ocular involvement like posterior segment uveitis or panuveitis in BD
- \* **N-acetyl cysteine as anti-oxidant therapy:** effective as alternative therapy, but not conclusive



# Eye involvement and treatment-2

- \* **Chemokine environment of intraocular lymphocytes in BD uveitis**
  - \* **Aqueous humor of non-BD:** CD4+ cells-> high expression of CXCR3
  - \* **Aqueous humor of BD:** CD8+ cells, high expression of IL-8, IP-10
- \* **TNF-alpha level in BD patients with and without ocular involvement**
  - \* Serum TNF-alpha level is higher in BD patients with ocular involvement
- \* **Osteopontin (OPN)**
  - \* Acidic phosphoglycoprotein, contains arginine-glycine-aspartic acid cell-binding sequence in extracellular matrix
  - \* Act as a cytokine contributing to the development of Th1 immunity
  - \* Experimental autoimmune uveoretinitis (EAU): a model for human intraocular inflammation such as BD
    - > EAU was ameliorated in OPN-deficient mice and wild type mice treated with OPN neutralizing antibody or OPN-siRNA





# Neurologic involvement and treatment

## \* Clinical feature

- \* **Recurrent meningitis, pseudotumor cerebri**
- \* **Neurologic manifestation of BD** in USA, Japan, Turkey
- \* **Symptom Check List 90-Revised in BD:** SCL 90-R was unable to detect major psychological symptoms in BD.

## \* Therapy

- \* **Infliximab for chronic progressive neuro-BD:** effective treatment by reducing CSF IL-6 levels, smoking might be one of resistance factors to treatment.
- \* **Interferon-alpha 2a:** effective in refractory juvenile BD with CNS involvement



# Vascular involvement

- \* **Large vessel involvement**

- Aortic and peripheral arterial involvement at an older age compared to pulmonary artery aneurysm and venous involvement, not associated with venous lesions

- \* **Intracardiac thrombosis**

- \* **Pulmonary artery aneurysm**

- \* **Coronary artery aneurysm**

- \* **Vascular involvement of the intra-abdominal organs**

- SVC obstruction, IVC obstruction, Budd-Chiari syndrome, mesenteric artery aneurysm, splenic artery thrombosis, mesenteric artery occlusion, pulmonary embolism



# Other involvement

- \* **Sacroilitis and HLA B27**
  - not increased in BD
- \* **Thyroid disorders**
  - Graves' disease, Hashimoto's thyroiditis, thyroid nodule, diffuse goiter
- \* **Renal involvement**
  - Renal lithiasis, amyloidosis, CRF, hematuria, arterial hypertension, renal TB
- \* **Chylothorax and chylopericardium**
- \* **Sjogren's syndrome**
- \* **Comorbidities in BD**
  - diabetes mellitus, renal disorder, malignancy
- \* **Malignancy**
  - BCC, rectal adenocarcinoma, lung cancer



# Disease assessment

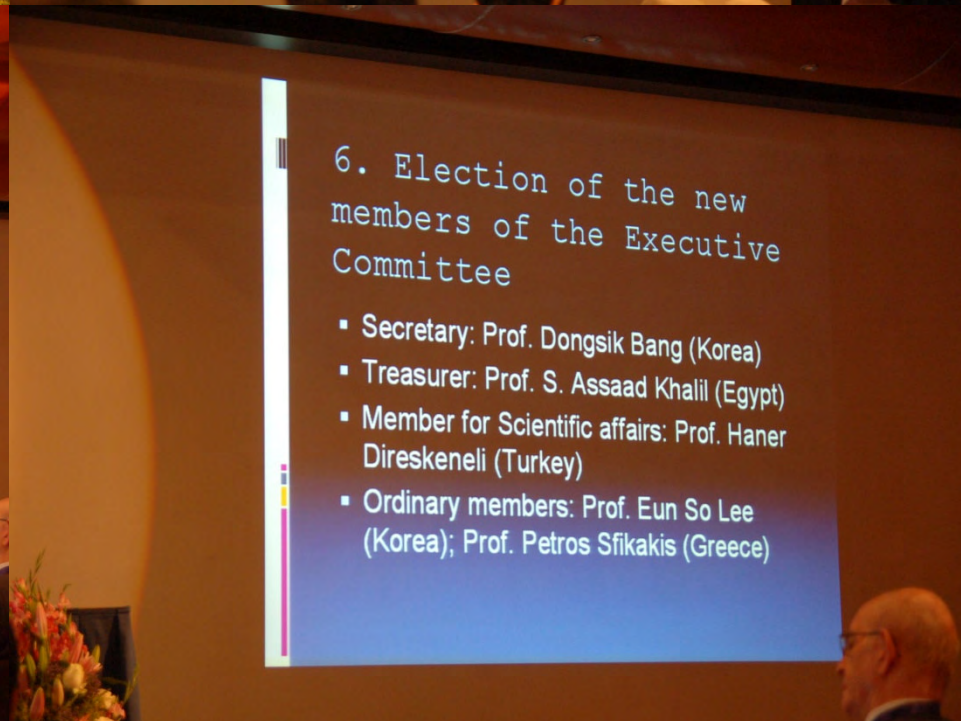
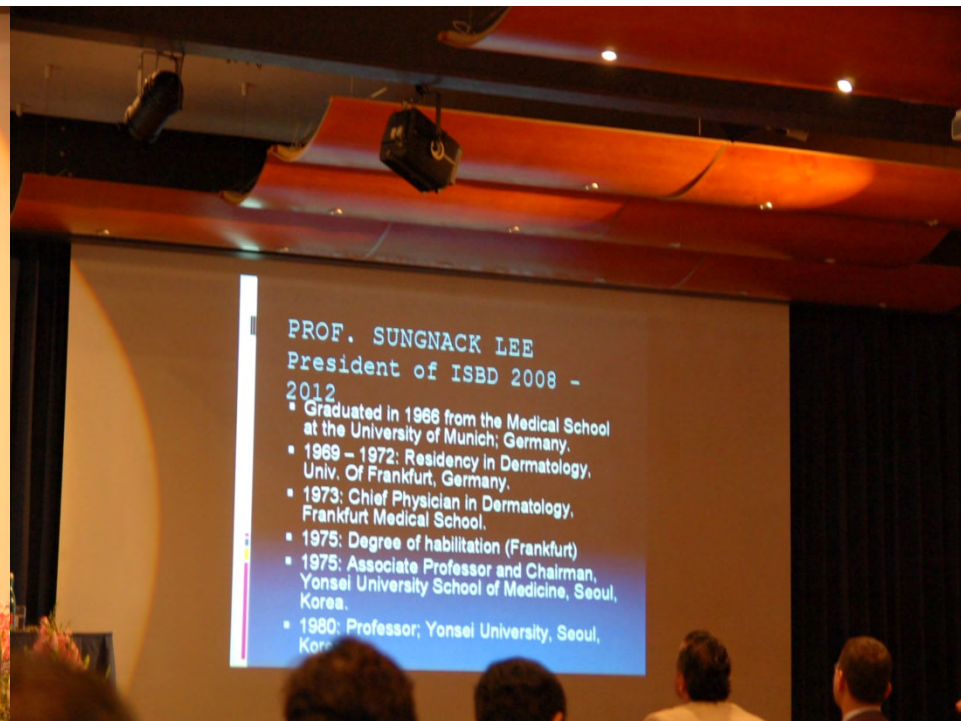
- \* **Intima-media thickness (IMT) of carotid artery in BD**
  - Thinning of IMT: risk factor of aneurysm formation
- \* **Increased carotid arterial stiffness (augmentation index: AI) and thickness (IMT) in BD**
  - Independent predictors of elevated cardiovascular risk
- \* **Reduced pressure wave reflections (low AI) in active BD**
- \* **PPD reaction is not augmented in BD**
  - not affected by the pathergy reaction
- \* **Nailfold capillaroscopy In BD**
  - Nail fold abnormality, mainly enlarged capillaries are frequent in BD. These may be related to superficial phlebitis or high blood pressure.



# HULUSI BEHCET AWARD









- \* **The 14<sup>th</sup> ICBD**
  - \* United Kingdom (London)
  - \* July 7-10, 2010
  - \* President : Prof. Dorian O Haskard F



*Thank You!!*