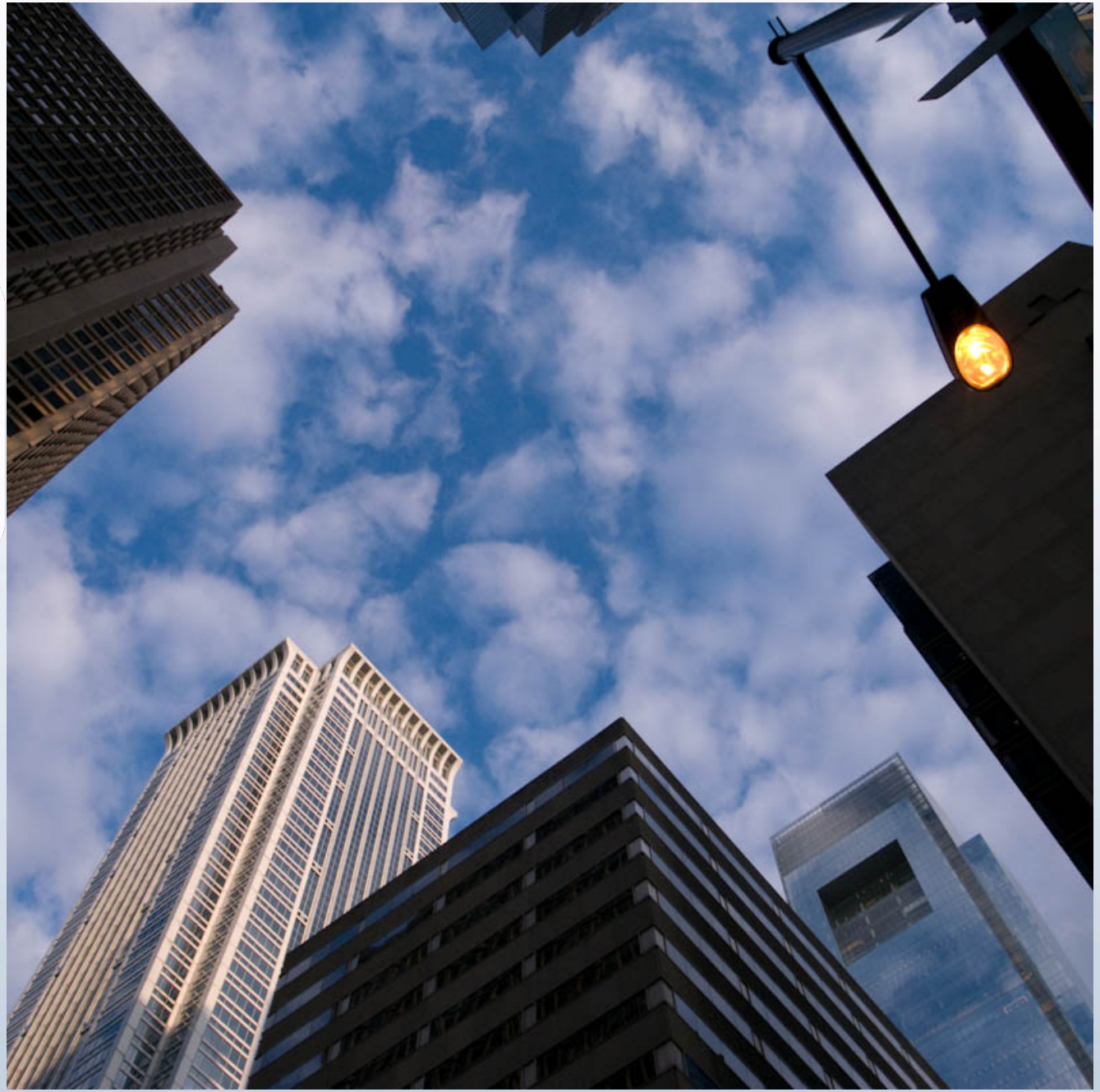
ACR Report

October 17-21, 2009
Philadelphia



Fumihide Ogawa

Department of Dermatology
Nagasaki University

2009年の演題数

- Plenary session: 2題
- Concurrent abstract session:　18演題
- Poster session: 127演題 （日本の施設から10演題）
    - Keyword;
        - Scleroderma　　61 演題
        - Systemic sclerosis　　88 演題
        - 合計: 147 演題

Plenary Session I

(549) dsRNA Drives Type I and Type II Interferon-Mediated Inflammation, Fibroblast Activation and Dermal Fibrosis through TLR3-Dependent and Independent Signaling

- Skin biopsy
  - Lesional SSc, Non-lesional SSc, and healthy control skin
- Dermal fibroblast
  - SSc and normal fibroblast

Plenary Session I

(548) Genome-Wide Association Study of Systemic Sclerosis in a Large US Cohort of Over 1,500 Cases

- Caucasian SSc case: 1534 (182 men and 1352 women) Caucasian control: 3597 (464 men and 3133 women)

- Result
  - **7 MHC Genes**
    - HLA DQB1, HLA DQA2, MICA, PSORS1, HLA DRA, MICB, HLA DQA2)
  - **3 non-MHC Genes**
    - TNPO3 (=transportin 3; linkage disequilibrium with IRF5)
      - Important in HIV infection
      - IRF5 polymorphism in SSc (Japanese and French) and in SLE and DM
    - XKR4
    - TSSC1 (=tumor suppressing subtransferable candidate gene1)
      - Rlevance to SSc is unclear
      - Less significant in combined US/EU cohort

ACR Concurrent Abstract Sessions

Scleroderma and Fibrosing Diseases: Clinical Trials and Outcomes

(606) Imatinib Mesylate (Gleevec) in the Treatment of Systemic Sclerosis: Interim Results of a Phase IIa, One Year, Open Label Clinical Trial

- Severe dcSSc: imatinib 400mg/day
  - 毎月ごと1年間のfollow、中止後3ヶ月のfollow
- Endpoints:
  - 安全性の確認
  - Modified Rodnan Skin Score (MRSS)、FVC、DLcoの変化
  - HAQ-DI、SF-36、心エコー、皮膚病理の変化
- 30 SSc patients
  - African American 13.3%
  - Caucasian 86.7%
  - 罹病期間: 4年以下 20人、4年以上10人
  - 脱落 : 6人

- 副作用:
  - 24例の重大な副作用(死亡 1例、IPに伴う市中肺炎)
  - その他の副作用 (浮腫 80%、嘔気 73%、倦怠感 53%、CK ↑ 37%)
- 16人の患者が1年間の投薬が可能であった
  - Mean MRSS 30.8 ± 9.7 vs. 23.5 ± 11.1 (p< 0.001)
    - MRSSの改善は3ヶ月では認められなかったが、6ヶ月以降で改善
  - Mean FVC 84 ± 22 vs 90 ± 23 (p< 0.039)
  - Mean %DLco 80 ± 21 vs 88 ± 27 (p< 0.037)
  - 皮膚所見でも改善が認められていた
- 結論: ImatinibはdcSScの治療に安全かつ効果がある

ACR Concurrent Abstract Sessions

Scleroderma and Fibrosing Diseases: Clinical Trials and Outcomes

(608) A Proof of Concept Trial of Gleevec (Imatinib) in Active Diffuse Scleroderma (DSSc)

- Imatinibの二重盲検試験 (6ヶ月)
  - 10 active dSSc (9: active, 1:placebo)
    - 7 female: 3 male
    - Mean age: 51, diseas duration: 3.1
    - mRSS skin score: 32 ± 8
- 6ヶ月間投与できたのは、4人
  - 浮腫、嘔気、胸痛、脱毛などで脱落
  - 最後まで投与できた場合でも同様の副作用が認められた
- ITT解析により
  - Skin score, CRP, ESR, QOLスコア, skin sample, plasma cytokine などいずれにも有意な変化は認められなかった。

- 結論
  - 以上の結果より、比較的早期例のdSScに対しては、皮膚硬化や炎症という観点からは、imatinibは有用な治療とはならないのではないか

ACR Concurrent Abstract Sessions

Scleroderma and Fibrosing Diseases: Clinical Trials and Outcomes

(1263) Tyrosine Kinase Inhibitors (TKI) Are Promising Therapeutic Agents for the Proliferative Vasculopathy in SSc

- TKI (nilotinib)をvascular SScマウスに投与した
  - Fra-2 tg mice:
    - PAHに類似する肺の増殖性血管障害
    - Fibrosis (skin, lung)
    - TKIのターゲットであるp-c-ablやp-PDGFRβの発現が肺血管で増加
- 結果:
  - 肺血管の増殖を抑制
  - 肺の線維化には効果がなかった
  - Skin fibrosisを抑制 (fibroblastや血管にp-c-abl, p-PDGFRβ発現)
  - SSc human skinでは、TKIのターゲットは、血管に限局

Summary of the effects of TKI

- **Fra-2 tg mouse model**
  - Nilotinib improves proliferative pulmonary vasculopathy
  - No effects on lung or skin fibrosis
- **Bleomycin model**
  - Imatinib, nilotinib, dasatinib effective in the prevention and treatment of skin and lung fibrosis
- **Tight skin mouse (TSK1) model**
  - Imatinib reduces skin fibrosis
- **Human SSc**
  - Preliminary data for imatinib indicate rather moderate effects in skin/lung fibrosis, but potentially effective in PAH

Conclusion

- **Expression of activated TKI targets in human SSC**
  - Lower than expected
  - Similar to that of non-responsive animal models
  - Predominant in vascular structures
- **Tyrosine kinase inhibitors (TKI)**
  - Potentially promising drugs to treat proliferative vasculopathies such as SSc-PAH

ACR Concurrent Abstract Sessions

Scleroderma and Fibrosing Diseases: Epidemiology and Prognotic Considerations

(1199) Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS): Two-Year Outcomes for Pre-Pulmonary Arterial Hypertension (PAH)

- **Scleroderma-related PH**
  - Group 1 PAH
  - Group2 Pulmonary hypertension secondary to left heart – diastolic left heart dysfunction + systolic heart failure
  - Group3 PH secondary to interstitial lung disease

  Right heart catheterization is performed to confirm the diagnosis of PH and to accurately classify its etiology to determine appropriate tereatment

- **PHAROS Pre-PAH Entry Criteria**
  - SSc patients with one of the following entry criteria:
    - DLCO ≤ 55% predicted
    - FVC%/ DLCO% ratio > 1.6
    - Echocardiographic (echo) PASP ≥ 40mmHg
- **PHAROS Methods**
  - Biannual patients generated data
  - Yearly objective data
    - Clinical information, WHO functional class
    - PFT, echo/doppler, 6 minutes walk test
    - Lboratory, including NT-pro BNP
  - Right-heart catheterization (RHC) performed in patients clinically suspected to have PH

- **Pre-PAH Patients**
  - 206 pre-PAH subjects have enrolled
- **Follow up Data**
  - 152 patients had follow up visits and 110 had repeat studies
  - 19 patients were clinically suspected and confirmed by RHC to have PH 0.5 to 2 years after entry
    - 14 patients with PAH
    - 5 patients with diastolic dysfunction
- **Comparison between pre-PAH and New PAH**

Race %C / %A-A	76/18	64/**29**
Antibody (%) Nucleolar	12	**26***
DLCO % (at base line)	**50.5**	**40.1***

- **Conclusion**
  - There was a 22% cumulative development of high risk pre-PAH patients evolving to definite PAH at 2 years.
  - A very low DLCO was the best predictor for evaluation to PAH.
  - Echo sPAPs were variable over time and did not correlate with the sPAP on RHC.

ACR Concurrent Abstract Sessions

Scleroderma and Fibrosing Diseases: Epidemiology and Prognotic Considerations

(1200) Point Prevalence of Pulmonary Hypertensions in Systemic Sclerosis: Results From Two Large Cohorts (of European Caucasian patients) and Meta-Analysis

- Prevalence of PH in large European Cohorts
- Associations between presence of PH and subset at risk