



# ボストン留学記 実況中継

5月15日

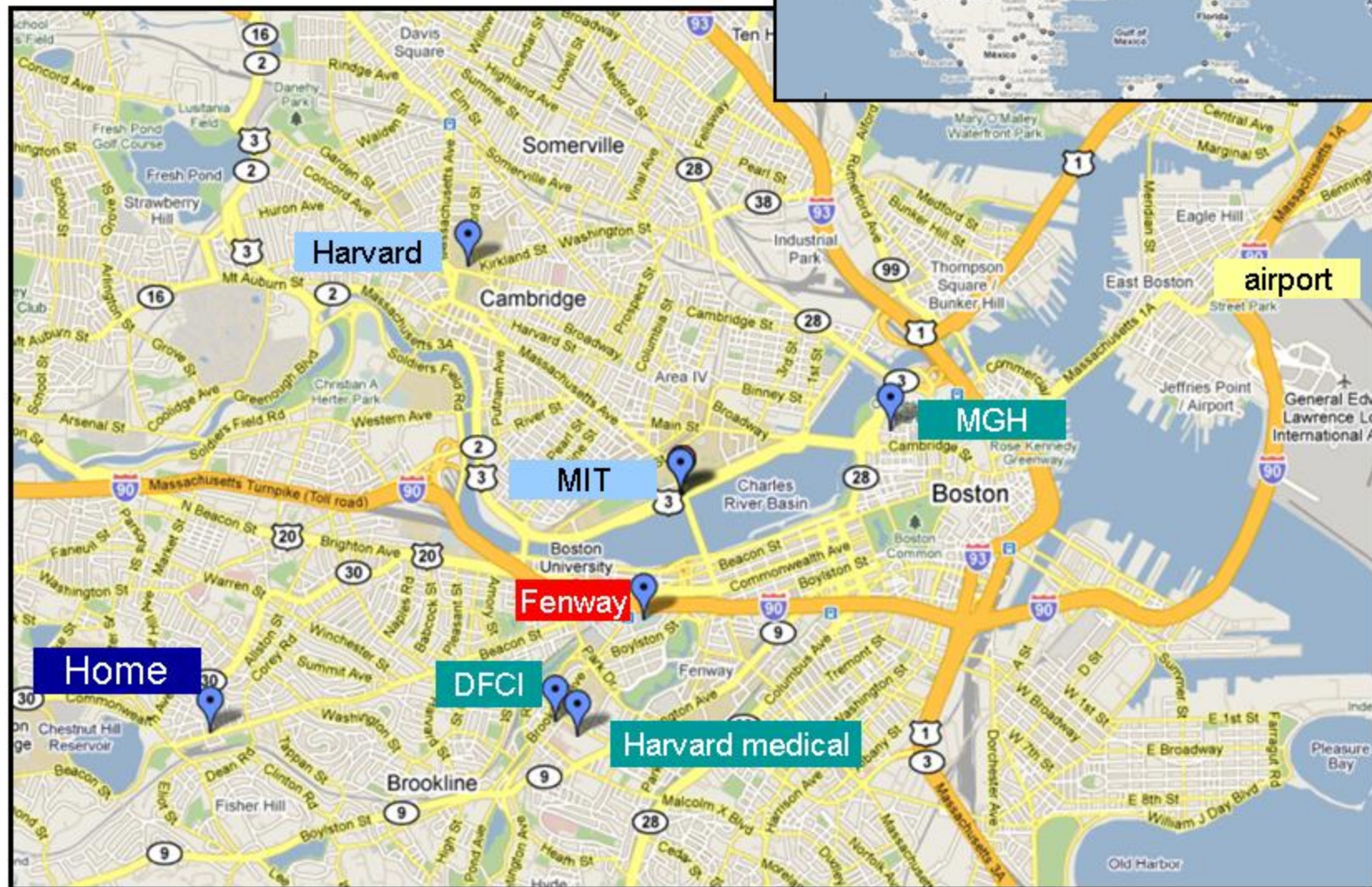
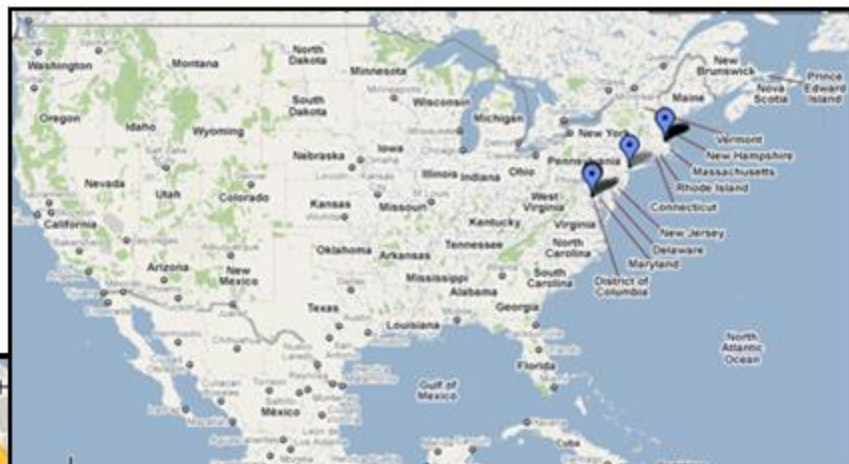
佐々木高明  
佐々木幸恵



# Boston

時差: 14時間(13時間DST)

日本時間: 午後3時----アメリカ東海岸: 午前2時



# ボストン

- アメリカの古都、歴史・文化・芸術の街

- ボストン交響楽団、ボストン美術館

- 盛んなプロスポーツ

- RedSox、Celtics、Bruinsほか

- 最先端のヘルスケア、バイオ、IT関連企業・研究機関が集積

- 世界有数のIntelligent Cosmopolitan

- Harvard, MIT, BU, BC, Tuftsなど50以上の大学



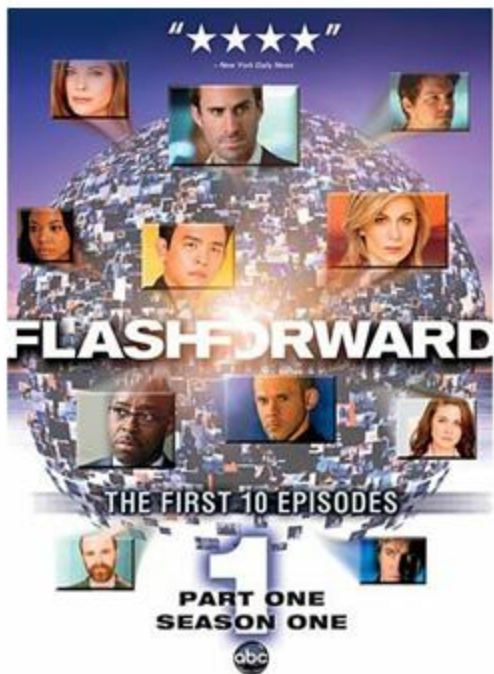
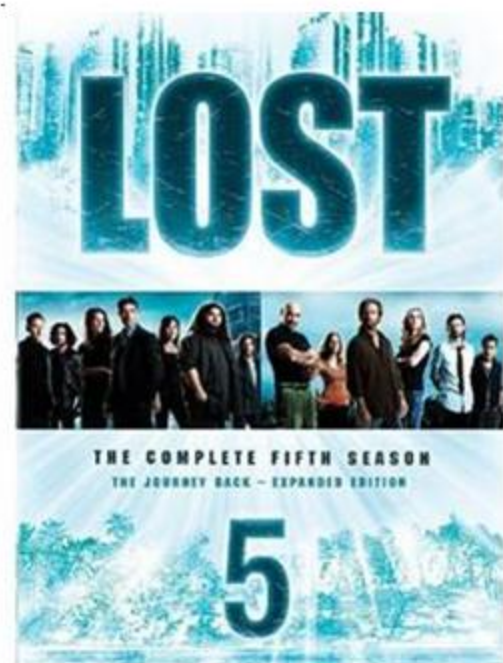
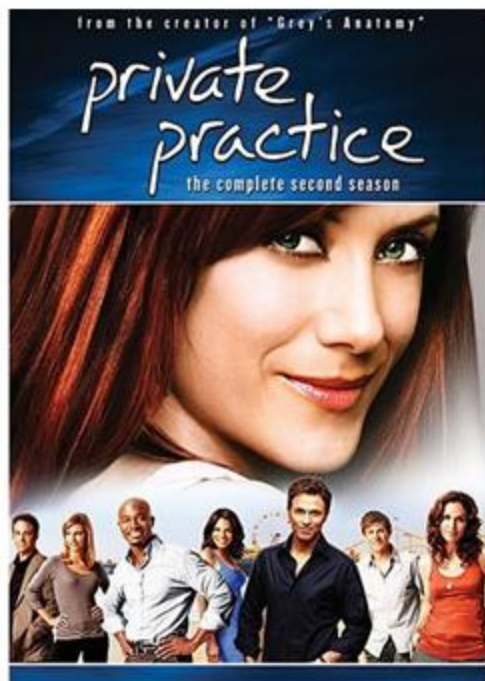
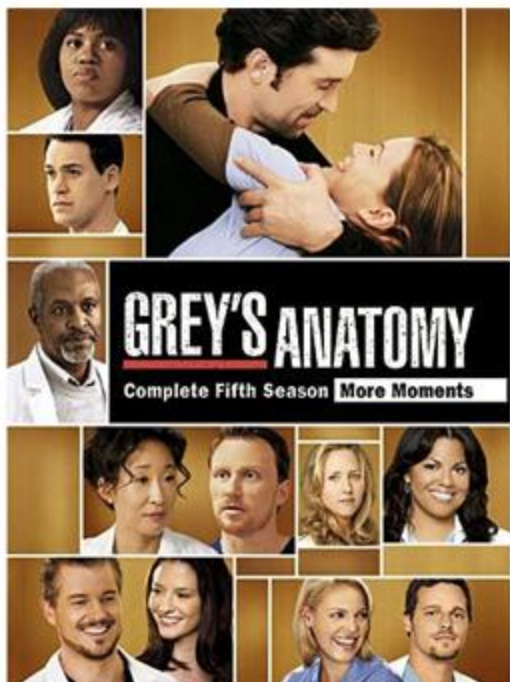


Apartment

2BL; rent \$1800 (16.6万円!!)

築130年





Napa Valley/SF



SF/IASLC



Annapolis/Washington DC/AACR



Lexington/Concord







Bruce E Johnson  
Lung cancer  
Program director  
Prof. Harvard  
Medical school



Pasi A Jänne  
Assoc Prof.  
Harvard Medical  
school  
TRL director



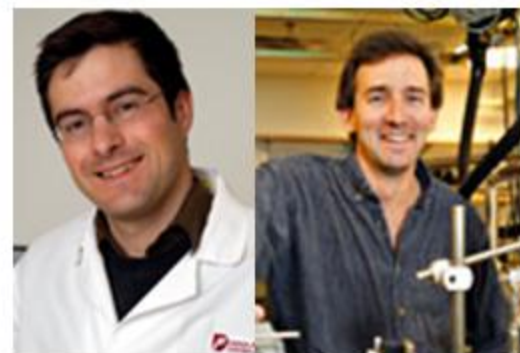
Matthew Mayerson  
Prof. Harvard  
Medical school  
Cancer genomics  
Broad Institute



Kwok Kin-Wong  
Assist. Prof.  
Harvard Medical  
school  
Genetic engineering  
animal model



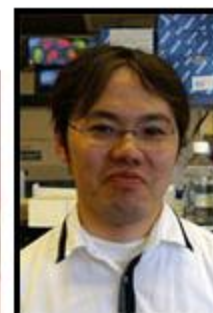
Geoffery Shapiro  
Assoc. Prof.  
Harvard Medical  
school  
Phase I center



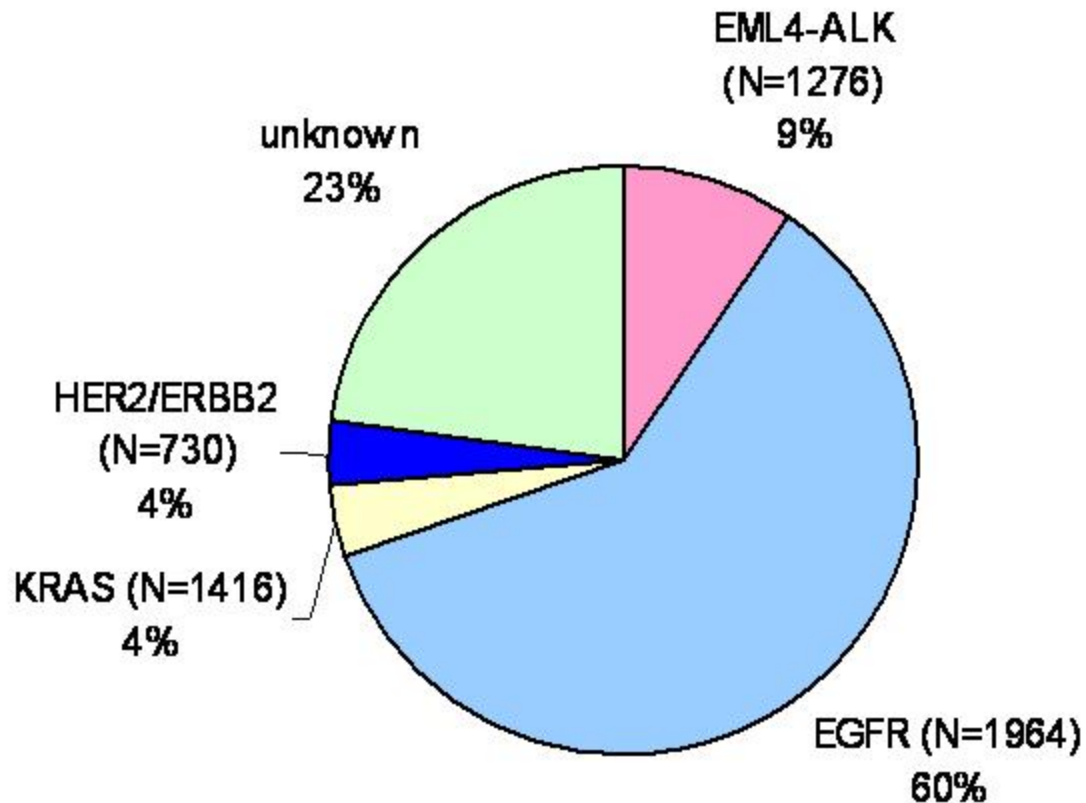
Nathanel Gray  
Chemist

Michel Eck  
Crystal structure

# Pasi Jänne Lab



# Genetic alterations in non-smoker NSCLC



# 肺癌の分子標的治療

## EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paez,<sup>1,2\*</sup> Pasi A. Jänne,<sup>1,2\*</sup> Jeffrey C. Lee,<sup>1,3\*</sup>  
Sean Tracy,<sup>1</sup> Heidi Greulich,<sup>1,2</sup> Stacey Gabriel,<sup>4</sup> Paula Herman,<sup>1</sup>  
Frederic J. Kaye,<sup>5</sup> Neal Lindeman,<sup>6</sup> Titus J. Boggon,<sup>1,3</sup>  
Katsuhiko Naoki,<sup>1</sup> Hidefumi Sasaki,<sup>7</sup> Yoshitaka Fujii,<sup>7</sup>  
Michael J. Eck,<sup>1,3</sup> William R. Sellers,<sup>1,2,4</sup>  
Bruce E. Johnson,<sup>1,2</sup> Matthew Meyerson<sup>1,3,4</sup>

IN NEW ENGLAND JOURNAL OF MEDICINE

BRIEF REPORT

## EGFR Mutation and Resistance of Non-Small-Cell Lung Cancer to Gefitinib

Susumu Kobayashi, M.D., Ph.D., Titus J. Boggon, Ph.D., Tajhal Dayaram, B.A.,  
Pasi A. Jänne, M.D., Ph.D., Olivier Kochef, M.D., Ph.D.,  
Matthew Meyerson, M.D., Ph.D., Bruce E. Johnson, M.D.,  
Michael J. Eck, M.D., Ph.D., Daniel G. Tenen, M.D., and Balázs Halmos, M.D.

NATURE

Vol 442/7147/28 December 2009/4420-4426/nature08642

## LETTERS

## Novel mutant-selective EGFR kinase inhibitors against EGFR T790M

Wenjun Zhou<sup>1,2\*</sup>, Dalia Ercan<sup>1,3\*</sup>, Liang Chen<sup>1,4\*</sup>, Cai-Hong Yun<sup>1,2\*</sup>, Danan Li<sup>1,4</sup>, Marzia Capelletti<sup>1,5</sup>,  
Alexis B. Cortot<sup>1,6</sup>, Lucian Chiriac<sup>2</sup>, Roxana E. Iacob<sup>2,7</sup>, Robert Padera<sup>2</sup>, John R. Engon<sup>2,8</sup>, Kwok-Kin Wong<sup>1,9,10</sup>,  
Michael J. Eck<sup>1,11</sup>, Nathanael S. Gray<sup>1,2</sup> & Pasi A. Jänne<sup>1,4,12</sup>

## MET Amplification Leads to Gefitinib Resistance in Lung Cancer by Activating ERBB3 Signaling

Jeffrey A. Engelman,<sup>1,2,3</sup> Kreshnik Zejnullahu,<sup>4,5</sup> Tetsuya Mitsudomi,<sup>6</sup> Youngchul Song,<sup>2,3</sup>  
Courtney Hyland,<sup>7</sup> Joon Oh Park,<sup>4,5</sup> Neal Lindeman,<sup>7</sup> Christopher-Michael Gale,<sup>3</sup>  
Xiaojun Zhao,<sup>5</sup> James Christensen,<sup>8</sup> Takayuki Kosaka,<sup>9</sup> Allison J. Holmes,<sup>4,5</sup>  
Andrew M. Rogers,<sup>5</sup> Federico Cappuzzo,<sup>9</sup> Tony Mok,<sup>10</sup> Charles Lee,<sup>7</sup> Bruce E. Johnson,<sup>4,5</sup>  
Lewis C. Cantley,<sup>2,3</sup> Pasi A. Jänne<sup>4,5\*</sup>

- EGFR標的治療 (Iressa, Tarceva)
  - Sensitizing mutation; 奏効率70%
    - ほぼ全例で獲得耐性
    - ~50%; Gatekeeper mutation (T790M)
      - Irreversible EGFR-TKI, WZ4002
    - ~20%; MET遺伝子増幅
      - MET inhibitorとの併用療法
    - ~30%; 不明
- ALK標的療法 (PF-02341066)
  - ALK遺伝子転座; 奏効率70%
    - 獲得耐性が報告されてきている
    - 耐性機序は今のところ不明

## Cancer Therapy: Preclinical

## EML4-ALK Fusion Gene and Efficacy of an ALK Kinase Inhibitor in Lung Cancer

Jussi P. Koivunen,<sup>1,2</sup> Craig Mermel,<sup>2,9</sup> Kreshnik Zejnullahu,<sup>1,2</sup> Carly Murphy,<sup>4</sup> Eugene Lifshits,<sup>6</sup>  
Alison J. Holmes,<sup>1,2</sup> Hwan Geun Choi,<sup>3,7</sup> Jhingook Kim,<sup>10,11</sup> Derek Chiang,<sup>2,9</sup> Roman Thomas,<sup>12</sup>  
Jinseon Lee,<sup>10,11</sup> William G. Richards,<sup>8</sup> David J. Sugarbaker,<sup>8</sup> Christopher Ducko,<sup>8</sup>  
Neal Lindeman,<sup>4</sup> J. Paul Marcoux,<sup>1,2,4</sup> Jeffrey A. Engelman,<sup>6</sup> Nathanael S. Gray,<sup>3,7</sup>  
Charles Lee,<sup>4</sup> Matthew Meyerson,<sup>1,2,3,4</sup> and Pasi A. Jänne<sup>1,2,5</sup>

Current Perspective

## The biology and treatment of EML4-ALK non-small cell lung cancer

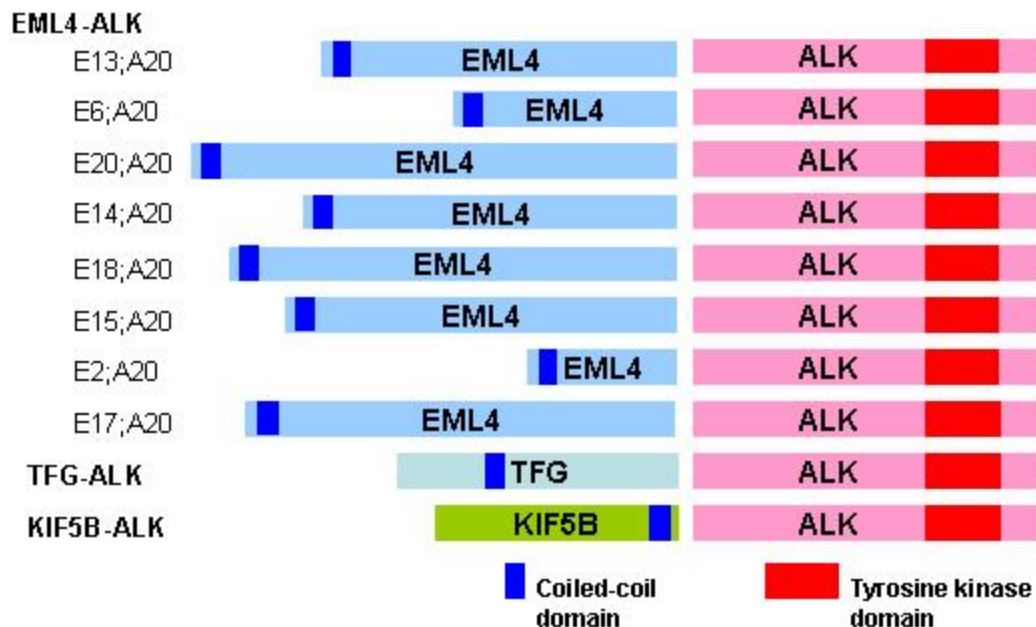
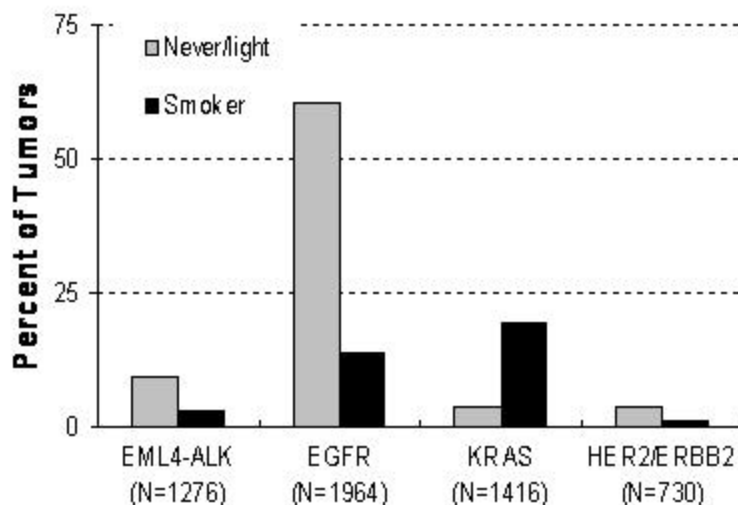
Takaaki Sasaki <sup>a,b</sup>, Scott J. Rodig <sup>c</sup>, Lucian R. Chirieac <sup>c</sup>, Pasi A. Jänne <sup>a,b,d,\*</sup>

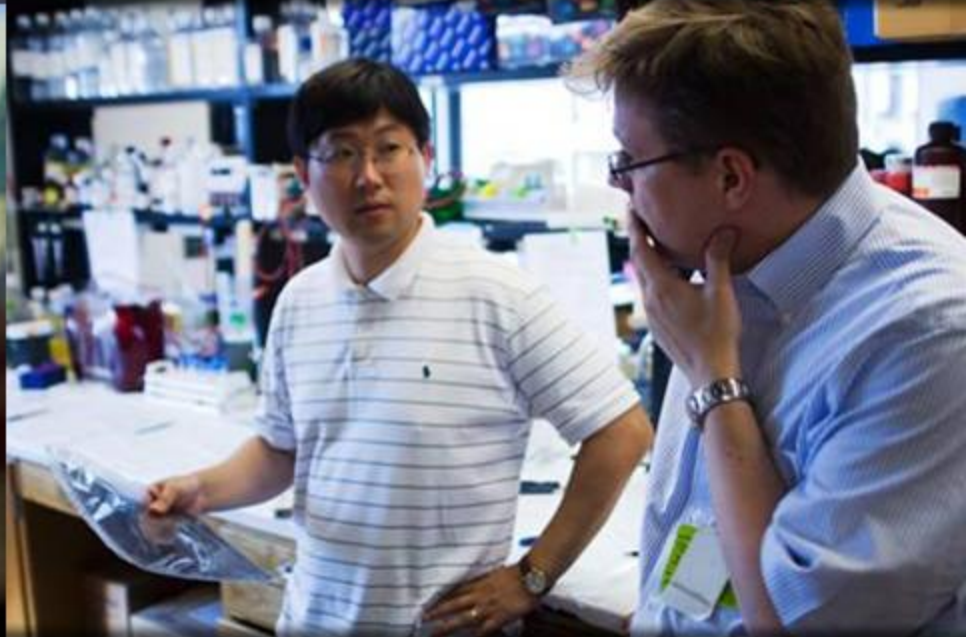
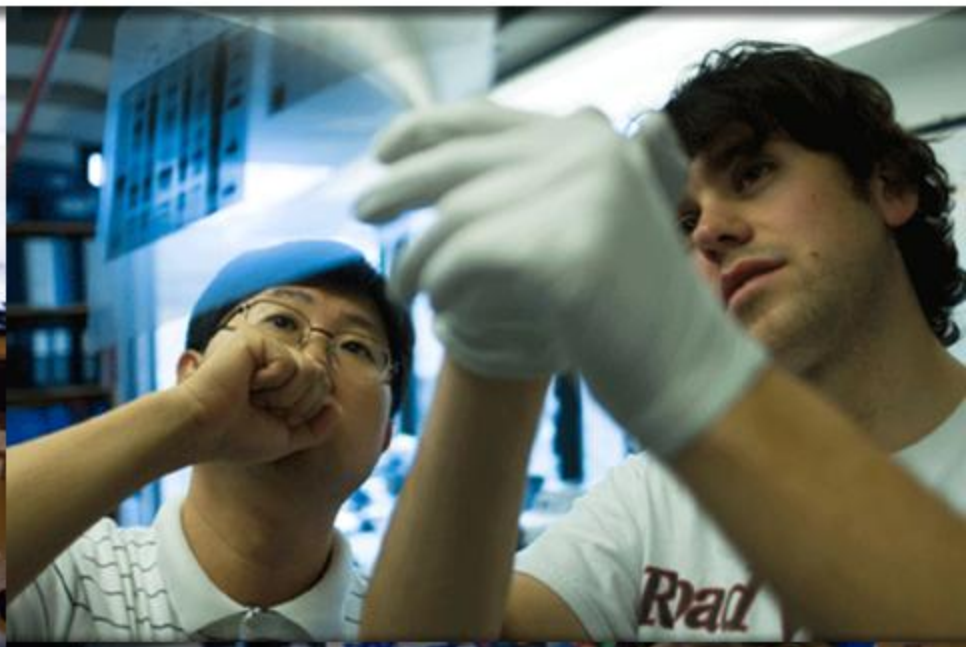
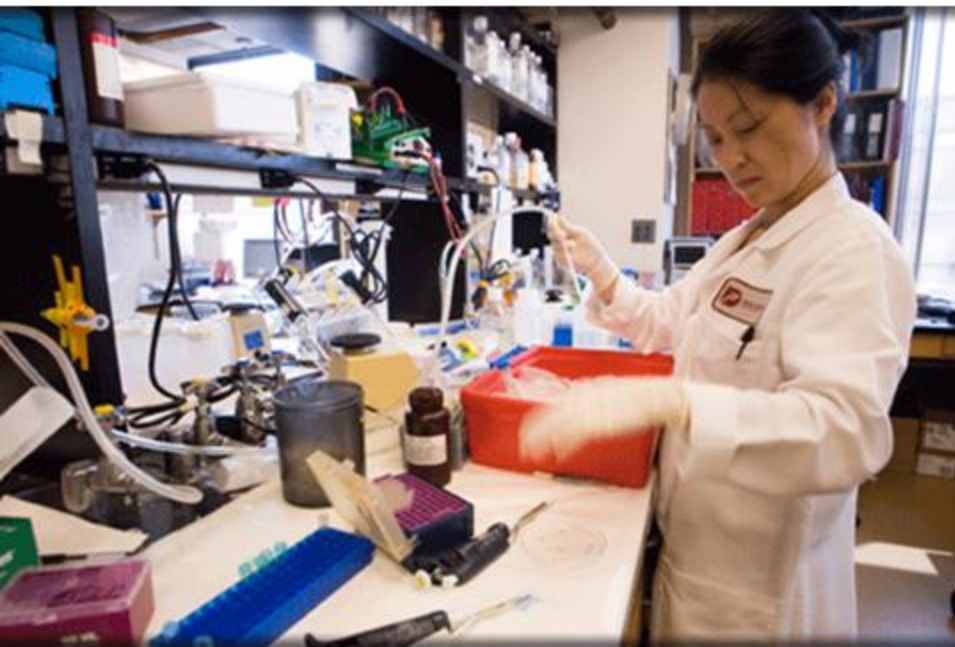
<sup>a</sup> Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

<sup>b</sup> Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

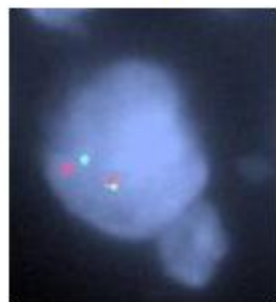
<sup>c</sup> Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA

<sup>d</sup> Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

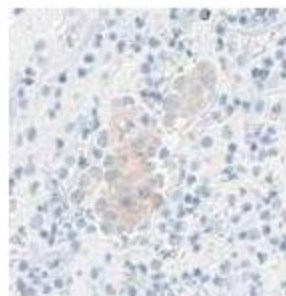




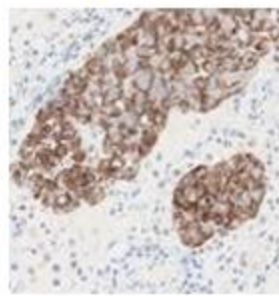
## Diagnosis / screening



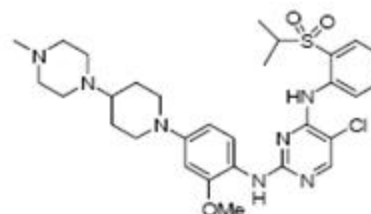
FISH



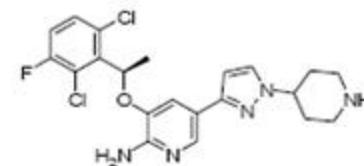
IHC



## Drug development



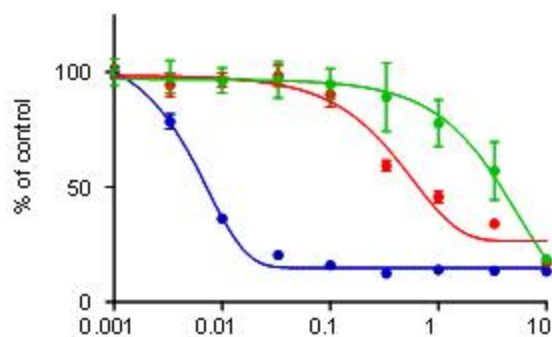
TAE684



PF2341066

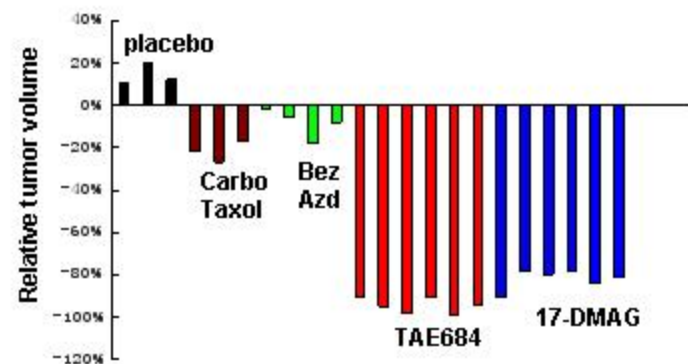
## Mechanism(s) of acquired resistance

H3122TR (TAE684 resistance)



- Gatekeeper mutations
- ENU mutagenesis
- Patients sample

## Alternative treatment



## Clinical trial

## Molecular Biology

- Cell/Tissue Culture / cell line generation from patients samples
- Cell-Based Assays (Transformation, invasion, migration assay)
- Immunoassays (western blot, immunoprecipitation)
- ELISA
- Luminex assay (DFCI)
  
- Cloning / Vector Construction / Transformation
- PCR / Genotyping
- DNA Sequence Analysis (Molecular Biology Core Facilities)
- Mutagenesis
- Transduction (retro, lenti viral)
- RNAi (siRNA, shRNA)
- RT-PCR / qRT-PCR
- Protein Expression / Protein Purification / Protein-Protein Interaction
- Protein Sequence Analysis / Mass Spectrometry (J Maro Lab, DFCI)
  
- Microarray Analysis (Microarray Core Facility, M Mayerson Lab, DFCI / Broad Institute)
  - SNP analysis (500K chip)
  - Gene Expression Analysis
  
- Antibody Generation (Monoclonal antibody core facility)
- Flow Cytometry (Flow Cytometry Core facility)
- Immunohistochemistry (Brigham and Women's hospital pathology)
- FISH / high-throughput FISH (DF/HCC Research Pathology Cores)
- Drug synthesis (N Gray lab, DFCI)
- Transgenic mice / Xenografts (K Wong lab, DFCI)
- Molecule structure (M Eck lab, DFCI)

Whole-genome sequence

ChIP-seq

RNA-seq

# Conclusion

- 充実した海外生活
- 刺激的な研究生活
- 異文化交流→広がる視野
- 離れてわかる日本の良いところ悪いところ