Program

International Academy for Advanced Oncology

IAAO

国際フォーラム 2011

Strategy for Clinical Trial in Personalized Medicine

2011年7月29日(金)・30日(土)
六本木アカデミーヒルズ 49

CHAAO Chugai Academy for Advanced Oncology

お問い合わせ先　一般社団法人中外 Oncology 学術振興会議
〒101-0032 東京都千代田区岩本町 3-9-2 PMO 岩本町ビル 8F
TEL：03-5825-2012　FAX：03-5821-2886
E-mail：chaao@chaao.or.jp　URL：http://www.chaao.or.jp/

CHAAO Chugai Academy for Advanced Oncology

IAAO 2011

Strategy for Clinical Trial in Personalized Medicine

Date » July 29 (Fri) - July 30 (Sat), 2011
Venue » Roppongi Academyhills 49
Official Language » English
Dress Code » Business Casual

Advisory Board Member

Bruce A. Chabner	MGH, Harvard Medical School, USA
Patrick G. Johnston	The Queen's University of Belfast, UK
Chikashi Ishioka	Tohoku University School of Medicine, Japan
Hiroyuki Mano	Jichi Medical University, Japan / The University of Tokyo, Japan
Yuko Kitagawa	Keio University School of Medicine, Japan
Kiyohiko Hatake	Cancer Institute Hospital, Japanese Foundation for Cancer Research, Japan
Nobuyuki Mizunuma	Cancer Institute Hospital, Japanese Foundation for Cancer Research, Japan
Masakazu Toi	Kyoto University School of Medicine, Japan

Chugai Academy for Advanced Oncology [CHAAO]
TEL: +81-3-5825-2012 / FAX: +81-3-5821-2886 / E-mail: chaao@chaao.or.jp

Time	July 29 (Fri)
12:00—	**Registration**
13:00—13:15	**Greeting** Osamu Nagayama (CHAAO Chairman) **Opening Remarks** Bruce Chabner (MGH)
13:15—18:00 Hiroyuki Mano (Jichi Univ) Nagahiro Saijo (Kinki Univ)	**Symposium-1: Personalized medicine; Targeting ALK-fusion** **1. Discovery of EML4-ALK fusion oncogene** Hiroyuki Mano (Jichi Univ) **2. Exploring for ALKoma with use of integrated diagnostic techniques** Kengo Takeuchi (JFCR) **3. Clinical trials with ALK inhibitor** Pasi Janne (Dana-Farber) **4. A large scale screening of ALK fusions** A. John Iafrate (MGH)
18:30—	**Round Table Dinner** (51F Roppongi Hills Club)

Time	July 30 (Sat)
9:00—10:00 Kiyohiko Hatake (JFCR) Yuko Kitagawa (Keio Univ)	**Symposium-2: Synthetic lethality; Theory and Practice** **Application of synthetic lethality to cancer therapy** Christopher Lord (The Institute of Cancer Res., UK)
10:30—12:00 Kiyohiko Hatake (JFCR) Nobuyuki Mizunuma (JFCR)	**Special Lecture:** **"The Methodological Challenge of delivering personalised therapy for cancer patients"** Patrick Johnston (Queen University of Belfast)
13:00—16:00 Masakazu Toi (Kyoto Univ) Chikashi Ishioka (Tohoku Univ)	**Symposium-3: Therapeutic Inhibition of oncogenic signaling** **1. PI3K pathway: Therapeutic targeting of malignancy** Jose Baselga (MGH) **2. Genetic predictors of RAF-dependence** David Solit (MSKCC) **3. Feedback and redundancy of oncogenic signaling pathways** Neal Rosen (MSKCC)
16:00	**Closing Remarks** Makoto Ogawa (Aichi Cancer Center)

Greetings

Osamu Nagayama

Chairman
Chugai Academy for Advanced Oncology (CHAAO), Incorporated Association

First of all, I would like to express my sincere appreciation for your kind support and interest in the activities of Chugai Academy for Advanced Oncology (CHAAO), which was established in October 2009 as an incorporated association. Thanks to the extensive work of the Advisory Board members, we are delighted to organize the International Academy for Advanced Oncology (IAAO) 2011 today.

Based on its mission to contribute to the development of international cancer medicines and therapies in Japan, CHAAO has engaged in various activities in the oncology field, such as establishing the "JCA-CHAAO Award" at the Japan Cancer Association to recognize achievements in basic and translational research, supporting the "Focus Symposium" to highlight cutting-edge topics in cancer research and treatment, and publishing the proceedings of the Kick-off Forum held last year, which was well appreciated by researchers and clinicians.

This time, we are focusing our discussion on Personalized Medicine, a theme which is one of the most high-profile topics in the field and has the potential to realize breakthroughs in cancer treatment. We are convinced that the sessions will be a great opportunity for all participants to share state-of-the-art research in this field.

As the Chairman, my sincere wish is that CHAAO provides an opportunity for researchers and academics from around the world and Japan to exchange valuable information, and ultimately, that our activities will lead to the realization of cancer treatments which allow patients to confront cancer proactively and with hope.

Opening Remarks

Bruce A. Chabner, M.D.

Current Positions: Director of Clinical Research
Cancer Center
Massachusetts General Hospital, Boston Massachusetts

Office Address: General Hospital Cancer Center
10 North Grove Street, LRH 214
Boston MA 02114-2617

Work Phone: (617) 724-3200

Work Email: bchabner@partners.org

Work FAX: (617) 643-2683

EDUCATION

1961	BA *Summa cum laude*	Biology	Yale College
1965	MD *Cum laude*	Medicine	Harvard Medical School

FACULTY ACADEMIC APPOINTMENTS

1995-	Professor of Medicine	Medicine	Harvard Medical School
1999-2002	Adjunct Professor	Institute of Health Professions	Massachusetts General Hospital, Boston

APPOINTMENTS AT HOSPITALS/AFFILIATED INSTITUTIONS

1995-	Physician	Department of Medicine	Massachusetts General Hospital, Boston
1996-2001	Chief Medical Officer		Dana Farber/Partners Cancer Care, Boston
2010-	Director of Clinical Research	Cancer Center	Massachusetts General Hospital, Boston

MAJOR ADMINISTRATIVE LEADERSHIP POSITIONS

Local (Current)

1999-	Associate Director	Clinical Science	Dana-Farber/Harvard Cancer Center, Boston
2010-	Director of Clinical Research	Cancer Center	Massachusetts General Hospital, Boston

National and International (Latest)

1982-1995	Director	Division of Cancer Treatment	National Cancer Institute

COMMITTEE SERVICE (Current)

Local

1995-	Chairman, Executive Committee of the Clinical Operations Team	Massachusetts General Hospital

NATIONAL AND INTERNATIONAL (Current)

1997-	Advisory Board	Al Amal Cancer Center, Amman, Jordan
2006-	Member, USA-Japanese Foundation for Cancer Research Collaboration	MGHCC/JFCR
2006-2012	Member, National Cancer Advisory Board	National Cancer Institute
2010-	Acting Chair, National Cancer Advisory Board	National Cancer Institute
2010-	Co-Chair, working Group, National Cancer Institute Review, National Cancer Advisory Board	National Cancer Institute

PROFESSIONAL SOCIETIES (Current)

1971-	American Association for Cancer Research	Board of Directors
1982-	American Society for Clinical Investigation	Member
1985-	American Society of Hematology	Member
1985-	Association of American Physicians	Member
1990-	American Clinical and Climatological Association	Member
1991-	American Society of Clinical Oncology	Board of Directors
1995-	Massachusetts Society of Clinical Oncology	Member
2003-	Society for Translational Oncology	Member

EDITORIAL ACTIVITIES (Current)

1994-	Editor-in-Chief	The Oncologist
2001-2006	Senior Editor	Clinical Cancer Research

HONORS AND PRIZES

1961	Phi Beta Kappa		Yale College
1965	Alpha Omega Alpha		Harvard Medical School
1976	Commendation Medal		Public Health Service
1983	Outstanding Service Medal		Public Health Service
1984	Unit Citation		Public Health Service
1986	Melville Jacobs Award		The American Radium Society
1986	Distinguished Oncologist for 1986		Dayton Oncology Society
1987	Meritorious Service Medal		Public Health Service
1990	Equal Employment Opportunity Special Achievement		National Cancer Institute
1990	Equal Opportunity Officer's Recognition Award		National Cancer Institute
1991	Awarded the flag rank of Rear Admiral		Public Health Service
1993	The Steven Beering Award	Indiana University	Awarded for Advancement of Biomedical Science
1994	Distinguished Medal		Public Health Service
1996	Kantor Family Prize		For Cancer Research Excellence
1998	Bruce F. Cain Memorial Award		
2005	Paul Calabresi Award		
2005	Timothy Gee Humanity in Medicine Award		The Lauri Strauss Leukemia Foundation
2006	Bob Pinedo Award		The Society for Translational Oncology
			For Contributions to Improvement in the Care of Cancer Patients (First recipient)
2009	George S. Mitchell Award	Queens University, Belfast	For Distinguished Contributions to Cancer Research
2010	Bloch Award	Ohio Sate University Cancer Center	For Distinguished Contributions to Cancer Research

REPORT OF SCHOLARSHIP

>180 Peer-reviewed publications in print or other media
> 280 Reviews, Chapters, Monographs, and Editorials

Publications in 2011

1. **Chabner BA**. General Principles of Cancer Chemotherapy. In: Brunton L, Chabner BA, Knollmann, BC, eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 12e. New York: McGraw-Hill; 2011, 1667-1676.
2. **Chabner BA**, Bertino J, Cleary J, Ortiz T, Lane A, Supko JG, Ryan D. Cytotoxic Agents. In: Brunton L, Chabner BA, Knollmann, BC, eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 12e. New York: McGraw-Hill; 2011, 1677-1730.
3. **Chabner BA**, Barnes J, Neal J, Olson E, Mujagic H, Sequist L, Wilson W, Longo DL, Mitsiades C, Richardson P, Targeted Therapies: Tyrosine Kinase Inhibitors, Monoclonal Antibodies, and Cytokines. In: Brunton L, Chabner BA, Knollmann, BC, eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 12e. New York: McGraw-Hill; 2011, 1731-1754.
4. Chong CR, Zirkelbach JF, Diasio RB, **Chabner BA**, Pharmacogenetics. In: Chabner BA, Longo DL, eds. Cancer Chemotherapy and Biotherapy: Principles and Practice. 5e. Philadelphia: Lippincott Williams & Wilkins; 2011, 80-95.
5. **Chabner BA**, Allegra CJ, Antifolates. In: Chabner BA, Longo DL, eds. Cancer Chemotherapy and Biotherapy: Principles and Practice. 5e. Philadelphia: Lippincott Williams & Wilkins; 2011, 109-138.
6. Grem JL, **Chabner BA**, Ryan DP, Wadlow RC, 5-Fluoropyrimidines. In: Chabner BA, Longo DL, eds. Cancer Chemotherapy and Biotherapy: Principles and Practice. 5e. Philadelphia: Lippincott Williams & Wilkins; 2011, 139-170.
7. **Chabner BA**, Glass J, Cytidine Analogues. In: Chabner BA, Longo DL, eds. Cancer Chemotherapy and Biotherapy: Principles and Practice. 5e. Philadelphia: Lippincott Williams & Wilkins; 2011, 171-191.
8. **Chabner BA**, Hydroxyurea. In: Chabner BA, Longo DL, eds. Cancer Chemotherapy and Biotherapy: Principles and Practice. 5e. Philadelphia: Lippincott Williams & Wilkins; 2011, 210-215.
9. Gerson SL, Bulgar AD, Weeks LD, **Chabner BA,** Alkylating Agents Part A: Classical Alkylating Agents. In: Chabner BA, Longo DL, eds. Cancer Chemotherapy and Biotherapy: Principles and Practice. 5e. Philadelphia: Lippincott Williams & Wilkins; 2011, 267-292.
10. Reed E, **Chabner BA**, Platinum Analogues. In: Chabner BA, Longo DL, eds. Cancer Chemotherapy and Biotherapy: Principles and Practice. 5e. Philadelphia: Lippincott Williams & Wilkins; 2011, 310-322.
11. **Chabner BA**, Bleomycin and Other Antitumor Antibiotics. In: Chabner BA, Longo DL, eds. Bleomycin and Other Antitumor Antibiotics. 5e. Philadelphia: Lippincott Williams & Wilkins; 2011, 323-341
12. **Chabner BA**, Friedmann AM, Asparaginase. In: Chabner BA, Longo DL, eds. Bleomycin and Other Antitumor Antibiotics. 5e. Philadelphia: Lippincott Williams & Wilkins; 2011, 411-420.
13. **Chabner BA**, Differentiating Agents. In: Chabner BA, Longo DL, eds. Cancer Chemotherapy and Biotherapy: Principles and Practice. 5e. Philadelphia: Lippincott Williams & Wilkins; 2011, 459-461.
14. **Chabner BA**, Arsenic Trioxide. In: Chabner BA, Longo DL, eds. Cancer Chemotherapy and Biotherapy: Principles and Practice. 5e. Philadelphia: Lippincott Williams & Wilkins; 2011, 462-464.
15. **Chabner BA**, Arsenic Trioxide. In: Chabner BA, Longo DL, eds. Cancer Chemotherapy and Biotherapy: Principles and Practice. 5e. Philadelphia: Lippincott Williams & Wilkins; 2011, 462-464.
16. Murphy JP, **Chabner BA**. Reflections on the Knife Edge. The Oncologist 2011;16(2): 257-259.
17. **Chabner BA**. Early Accelerated Approval for Highly Targeted Cancer Drugs. N Engl J Med. 2011 Mar 24;364(12):1087-9.
18. La Vecchia C, Giordano SH, Horobagyi GN, **Chabner BA**. Weight, body mass index, diabetes and risk of breast cancer: interlocking pieces of the puzzle. The Oncologist 2011, in press.

>20 Books/Textbooks for the Medical or Scientific Community

1. **Chabner BA**, Longo DL, Lynch TJ. Harrison's Handbook of Oncology. 1st ed. New York: McGraw-Hill; 2008.
2. **Chabner BA**, Longo DL, editors. Cancer chemotherapy and biotherapy: principles and practice. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.

NARRATIVE REPORT ON CAREER AND RESEARCH INTERESTS

Dr. Bruce Chabner is a Professor of Medicine at Harvard Medical School and Director of Clinical Research at the Massachusetts General Hospital Cancer Center.

Dr. Chabner graduated *summa cum laude* from Yale College in 1961. He received his M.D. from Harvard University *cum laude* in 1965 following which he completed an internship and junior residency in internal medicine at Peter Bent Brigham Hospital in Boston and a senior residency in internal medicine at Yale-New Haven Medical Center.

Dr. Chabner has had extensive experience in the field of cancer drug discovery and development. After joining the National Cancer Institute (NCI) as a Senior Investigator in the Laboratory of Chemical Pharmacology in 1971, he participated in the training of clinical and research fellows there for the following 24 years, including three years (1976-1979) as Chief of the Clinical Pharmacology Branch; two years (1979-1981) as Director of the Clinical Oncology Program and its fellowship programs in medical, pediatric, radiation, and surgical oncology; and, in 1981, one year as Acting Director, and for 13 years as permanent Director of the Division of Cancer Treatment, NCI.

During the period from 1971 to 1989, he maintained an active laboratory program in cancer pharmacology, focusing on the mechanism of action, and resistance of antifolates and other antimetabolites, and led the development of Taxol. His research contributed significantly to the development of high dose chemotherapy regimens, and to standard therapies for lymphoma.

In 1995, he joined the Massachusetts General Hospital as Clinical Director of its cancer center and Chief of Hematology/Oncology. With the formation of the Dana-Farber/Harvard Cancer Center, he assumed responsibilities as Associate Director for Clinical Sciences of that consortium, which includes the Massachusetts General Hospital, Brigham & Women's Hospital, Dana-Farber Cancer Institute and Beath Israel Deaconess Medical Center.

He has authored and edited the standard text, Principles and Practice of Cancer Chemotherapy and Biological Response Modifiers, now in its fourth edition, has contributed the chapter on Antineoplastics in Goodman and Gilman's textbook of Pharmacology and has authored chapters for numerous other textbooks of internal medicine, hematology, oncology and pharmacology.

Over the years, Dr. Chabner has received numerous awards, including Phi Beta Kappa, Alpha Omega Alpha, the Public Health Service's Distinguished Service Medal, the Karnofsky Award of the American Society for Clinical Oncology and the Bruce F. Cain Award for Drug Development of the American Association for Cancer Research. In 2006, he was the first recipient of the Bob Pinedo Award for Contributions to Improvement in the Care of Cancer Patients.

Dr. Chabner is a senior editor for the Oncologist and serves on the executive advisory boards for some of the industry's leading innovators in drug development. In 2006, Dr. Chabner received a presidential appointment to the National Cancer Advisory Board at the National Cancer Institute.

Opening Remarks of IAAO2011

Reference: About the Cancer Education Consortium

Dear Colleague,

The Cancer Education Consortium is a not-for-profit organization dedicated to providing unique and innovative educational programming for physicians who are actively pursuing a career in the field of oncology. It offers yearly courses designed to enhance and expand fellowship training in clinical and translational research related to cancer. Attendees come from all of the subspecialties of cancer medicine, including surgical, medical, pediatric, and radiation oncology. They may apply for more than one workshop, as the individual curricula provide in-depth training and mentorship in specific complementary areas of clinical research. The two primary areas of emphasis include Clinical Pharmacology and drug development, and Molecular Oncology.

The Consortium is supported by unrestricted grants from a group of funders who have recognized the need and importance of expanded educational experiences that will update the knowledge base, foster mentoring and peer relationships, provide networking opportunities, and enhance the research skills of physicians entering the field.

The CEC is administered by an independent Board of Trustees composed of distinguished educators, clinicians and researchers who are leaders in their respective disciplines. Board members represent the subspecialties of medical oncology, hematology, gynecologic oncology, medical education, pediatric oncology, surgical oncology and radiation oncology. They are constantly monitoring developments in the field to ensure that programming is timely and immediately relevant.

These pages describe the programs offered by the CEC. Workshop attendance is limited to no more than 25 attendees to ensure a highly interactive experience with the faculty. Candidates are selected from a national pool of applicants. Selection criteria include demonstrated interest in research related to the workshop topic and the recommendation of program directors. We urge you to take advantage of these unique training opportunities.

Bruce A. Chabner

CHAAO expresses deep condolences for victims of the earthquake and sincerely hope for the recovery of the people affected by the disaster on March 11, 2011.

Symposium 1

Personalized medicine; Targeting ALK-fusion

Chairperson:
Hiroyuki Mano
Jichi Medical University /
Graduate School of Medicine,
The University of Tokyo, Japan

Chairperson:
Nagahiro Saijo
Kinki University
School of Medicine, Japan

Hiroyuki Mano, M.D. & Ph.D.

Current Positions:
1. Professor of Medicine, Department of Medical Genomics, Graduate School of Medicine, The University of Tokyo, Tokyo
2. Professor of Medicine, Division of Functional Genomics, Jichi Medical University, Tochigi

Office Addresses:
1. Department of Medical Genomics, Graduate School of Medicine, The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
Tel: +81-3-5841-0633
Fax: +81-3-5841-0634
E-mail: hmano@m.u-tokyo.ac.jp
2. Division of Functional Genomics, Jichi Medical University,
3311-1 Yakushiji, Shimotsukeshi, Tochigi 329-0498, Japan
Tel: +81-285-58-7449
Fax: +81-285-44-7322
E-mail: hmano@jichi.ac.jp

PERSONAL HISTORY

Mar. 1984. I graduated from School of Medicine, Faculty of Medicine, University of Tokyo.
May. 1984. I passed National Examination of Medical Doctor, Japan.
Jun. 1984. I became a member of medical staff at Tokyo University Hospital.
Jun. 1986. I became a member of The Third Department of Internal Medicine, Faculty of Medicine, University of Tokyo.
May. 1989. I became a postdoctoral researcher at Department of Biochemistry, St. Jude Children's Research Hospital, TN, USA.
Aug, 1991. I became an Assistant Professor of The Third Department of Internal Medicine, Faculty of Medicine, University of Tokyo.
Aug, 1993. I became the Associate Professor of Department of Molecular Biology, Jichi Medical University.
Apr. 2000. I became the Associate Professor of Division of Functional Genomics, Jichi Medical University.
Jun. 2001. I became the Professor of Division of Functional Genomics, Jichi Medical University.
Sep, 2009. I became the Professor of Department of Medical Genomics, Graduate School of Medicine, The University of Tokyo.

SELECTED AWARDS

Oct. 2008 JCA-Mauvernay Award from The Japanese Cancer Association
Nov. 2008 The Medical Award from The Japan Medical Association
Apr. 2009 The Gold Medal Award from Tokyo Techno-forum 21
Nov. 2009 The Science Award for Special Scientific Research by The Sagawa Foundation for Promotion of Cancer Research
Feb. 2010 The Princess Takamatsu Cancer Research Fund Prize
Oct. 2010 The Academic Award of The Mochida Memorial Foundation
Nov. 2010 The Takeda Prize for Medical Science from The Takeda Science Foundation
Jan. 2011 The Brilliant Scientist Award from The National Institute of Science and Technology Policy, Japan
Mar. 2011 The Uehara Prize from The Uehara Memorial Foundation
Apr. 2011 The Prize for Science and Technology from the Ministry of Education, Culture, Sports, Science and Technology, Japan
Jul. 2011 The Takamine Memorial Daiichi Sankyo Prize from The Daiichi-Sankyo Foundation of Life Science

PUBLICATIONS RELATED TO THE *EML4-ALK* ONCOGENE

1) Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, Fujiwara S, Watanabe H, Kurashina K, Hatanaka H, Bando M, Ohno S, Ishikawa Y, Aburatani H, Niki T, Sohara Y, Sugiyama Y & Mano H. "Identification of the transforming *EML4-ALK* fusion gene in non-small-cell lung cancer" ***Nature*** 448: 561-566, 2007.
2) Choi YL, Takeuchi K, Soda M, Inamura K, Togashi Y, Hatano S, Enomoto M, Hamada T, Haruta H, Watanabe H, Kurashina K, Hatanaka H, Ueno T, Takada S, Yamashita Y, Sugiyama Y, Ishikawa Y & Mano H. "Identification of novel isoforms of the *EML4-ALK* transforming gene in non-small cell lung cancer" ***Cancer Res*** 68: 4971-4976, 2008.
3) Chen Y, Takita J, Choi YL, Kato M, Ohira M, Sanada M, Wang L, Soda M, Kikuchi A, Igarashi T, Nakagawara A, Hayashi Y, Mano H & Ogawa S. "Oncogenic mutations of ALK kinase in neuroblastoma" ***Nature*** 455: 971-974, 2008.
4) Soda M, Takada S, Takeuchi K, Choi YL, Enomoto M, Ueno T, Haruta H, Hamada T, Yamashita Y, Ishikawa Y, Sugiyama Y & Mano H. "A mouse model for *EML4-ALK*-positive lung cancer" ***Proc Natl Acad Sci U S A*** 105: 19893-19897, 2008.

5) Takeuchi K, Choi YL, Togashi Y, Soda M, Hatano S, Inamura K, Takada S, Ueno T, Yamashita Y, Satoh Y, Okumura S, Nakagawa K, Ishikawa Y & Mano H. "KIF5B-ALK, a novel fusion oncokinase identified by an immunohistochemistry-based diagnostic system for ALK-positive lung cancer" ***Clin Cancer Res*** 15: 3143-3149, 2009.
6) Choi YL, Soda M, Yamashita Y, Ueno T, Takashima J, Nakajima T, Yatabe Y, Takeuchi K, Hamada T, Haruta H, Ishikawa Y, Kimura H, Mitsudomi T, Tanio Y & Mano H. "EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors" ***N Engl J Med*** 363: 1734-1739, 2010.

Talk at IAAO2011

Session: Personalized medicine; Targeting ALK-fusion

Title: Discovery of EML4-ALK fusion oncogene

Selected References

1. Soda M, ChoiYL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-smallcell lung cancer. Nature 2007; 448:561-6.

Improvement in the clinical outcome of lung cancer is likely to be achieved by identification of the molecular events that underlie its pathogenesis. Here we show that a small inversion within chromosome 2p results in the formation of a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 (EML4) gene and the anaplastic lymphoma kinase (ALK) gene in non-small-cell lung cancer (NSCLC) cells. Mouse 3T3 fibroblasts forced to express this human fusion tyrosine kinase generated transformed foci in culture and subcutaneous tumours in nude mice. The EML4–ALK fusion transcript was detected in 6.7% (5 out of 75) of NSCLC patients examined; these individuals were distinct from those harbouring mutations in the epidermal growth factor receptor gene. Our data demonstrate that a subset of NSCLC patients may express a transforming fusion kinase that is a promising candidate for a therapeutic target as well as for a diagnostic molecular marker in NSCLC. Lung cancer remains the leading cause of cancer deaths in western countries1. Patients with NSCLC, which accounts for ,80% of lung cancer cases, are often diagnosed at advanced stages of the disease. Given that conventional chemotherapeutic regimens only marginally improve the outcome of such individuals, their median survival time is less than one year after diagnosis (ref. 2). A subset of NSCLCs was recently shown to harbour activating mutations in the epidermal growth factor receptor gene (EGFR)3,4; such cancers are responsive to gefitinib, a specific inhibitor of the tyrosine kinase activity of EGFR. The efficacy of targeting key 'growth drivers' in cancer treatment is further exemplified by chronic myeloid leukaemia, for which another tyrosine kinase inhibitor, STI571, is highly effective in reducing the number of cancer cells5. However, EGFR mutations are associated preferentially with NSCLC of non-smokers and Asians4,6. Few oncogenes have thus been identified for NSCLC in individuals with a smoking habit, who constitute most cases of the disease. Retrovirus-mediated complementary DNA expression systems allow expression of the encoded proteins in most of the targeted cells. Through modification of the method used in ref. 7, we have achieved reliable amplification of cDNAs from small quantities of clinical specimens as well as the generation of retroviral libraries for expression of these cDNAs8–10. Application of such a cDNA expression library prepared from an NSCLC specimen to a focus formation assay with mouse 3T3 fibroblasts has now led to the identification of a fusion oncogene.

2. ChenY,TakitaJ, ChoiYL, et al. Oncogenicmutations of ALK kinase in neuroblastoma. Nature 2008;455: 971- 4.

Neuroblastoma in advanced stages is one of the most intractable paediatric cancers, even with recent therapeutic advances1. Neuroblastoma harbours a variety of genetic changes, including a high frequency of MYCN amplification, loss of heterozygosity at 1p36 and 11q, and gain of genetic material from 17q, all of which have been implicated in the pathogenesis of neuroblastoma2–5. However, the scarcity of reliable molecular targets has hampered the development of effective therapeutic agents targeting neuroblastoma. Here we show that the anaplastic lymphoma kinase (ALK), originally identified as a fusion kinase in a subtype of non-Hodgkin's lymphoma (NPM–ALK)6–8 and more recently in adenocarcinoma of lung (EML4–ALK)9,10, is also a frequent target of genetic alteration in advanced neuroblastoma. According to our genome-wide scans of genetic lesions in 215 primary neuroblastoma samples using high-density single-nucleotide polymorphism genotyping microarrays11–14, the ALK locus, centromeric to the MYCN locus, was identified as a recurrent target of copy number gain and gene amplification. Furthermore, DNA sequencing of ALK revealed eight novel missense mutations in 13 out of 215 (6.1%) fresh tumours and 8 out of 24 (33%)neuroblastoma-derived cell lines. All but one mutation in the primary samples (12 out of 13) were found in stages 3–4 of the disease and were harboured in the kinase domain. The mutated kinases were autophosphorylated and displayed increased kinase activity compared with the wild-type kinase. They were able to transform NIH3T3 fibroblasts as shown by their colony formation ability in soft agar and their capacity to form tumours in nude mice. Furthermore, we demonstrate that downregulation of ALK through RNA interference suppresses proliferation of neuroblastoma cells harbouring mutated ALK. We anticipate that our findings will provide new insights into the pathogenesis of advanced neuroblastoma and that ALK-specific kinase inhibitors might improve its clinical outcome.

3. Choi YL,Takeuchi K, Soda M, et al. Identification of novel isoforms of the EML4-ALK transforming gene in

non-small cell lung cancer. Cancer Res 2008;68: 4971- 6.

The genome of a subset of non–small-cell lung cancers (NSCLC) harbors a small inversion within chromosome 2 that gives rise to a transforming fusion gene, EML4-ALK, which encodes an activated protein tyrosine kinase. Although breakpoints within EML4 have been identified in introns 13 and 20, giving rise to variants 1 and 2, respectively, of EML4-ALK, it has remained unclear whether other isoforms of the fusion gene are present in NSCLC cells. We have now screened NSCLC specimens for other in-frame fusion cDNAs that contain both EML4 and ALK sequences. Two slightlydif ferent fusion cDNAs in which exon 6 of EML4 was joined to exon 20 of ALK were each identified in two individuals of the cohort. Whereas one cDNA contained onlyexons 1 to 6 of EML4 (variant 3a), the other also contained an additional 33-bp sequence derived from intron 6 of EML4 (variant 3b). The protein encoded byt he latter cDNA thus contained an insertion of 11 amino acids between the EML4 and ALK sequences of that encoded bythe former. Both variants 3a and 3b of EML4-ALK exhibited marked transforming activity in vitro as well as oncogenic activity in vivo. A lung cancer cell line expressing endogenous variant 3 of EML4-ALK underwent cell death on exposure to a specific inhibitor of ALK catalytic activity. These data increase the frequency of EML4-ALK–positive NSCLC tumors and bolster the clinical relevance of this oncogenic kinase.

4. **Soda M,Takada S,Takeuchi K, et al. A mouse model for EML4-ALK -positive lung cancer. Proc Natl Acad Sci US A 2008;105:19893- 7.**

EML4-ALK is a fusion-type protein tyrosine kinase that is generated in human non-small-cell lung cancer (NSCLC) as a result of a recurrent chromosome inversion, inv (2)(p21p23). Although mouse 3T3 fibroblasts expressing human EML4-ALK form transformed foci in culture and s.c. tumors in nude mice, it has remained unclear whether this fusion protein plays an essential role in the carcinogenesis of NSCLC. To address this issue, we have now established transgenic mouse lines that express EML4-ALK specifically in lung alveolar epithelial cells. All of the transgenic mice examined developed hundreds of adenocarcinoma nodules in both lungs within a few weeks after birth, confirming the potent oncogenic activity of the fusion kinase. Although such tumors underwent progressive enlargement in control animals, oral administration of a smallmolecule inhibitor of the kinase activity of ALK resulted in their rapid disappearance. Similarly, whereas i.v. injection of 3T3 cells expressing EML4-ALK induced lethal respiratory failure in recipient nude mice, administration of the ALK inhibitor effectively cleared the tumor burden and improved the survival of such animals. These data together reinforce the pivotal role of EML4-ALK in the pathogenesis of NSCLC in humans, and they provide experimental support for the treatment of this intractable cancer with ALK inhibitors.

5. **KIF5B-ALK, a Novel Fusion Oncokinase Identified by an Immuno-histochemistry-based Diagnostic Systemfor ALK-positive Lung Cancer (Clin Cancer Res 15, 3143-3149 (2009))**

Abstract Purpose: EML4-ALK is a transforming fusion tyrosine kinase, several isoforms of which have been identified inlung cancer. Immunohistochemical detection of EML4-ALK has proved difficult, however, likely as a result of low transcriptional activity conferred by the promoter-enhancer region of EML4. The sensitivity of EML4-ALK detection by immunohistochemistry should be increased adequately.

Experimental Design: We developed an intercalated antibody-enhanced polymer (iAEP) method that incorporates an intercalating antibody between the primary antibody to ALK and the dextran polymer-based detection reagents.

Results: Our iAEP method discriminated between tumors positive or negative for EML4-ALK in a test set of specimens. Four tumors were also found to be positive forALK in an archive of lung adenocarcinoma (n = 130) and another 4 among fresh cases analyzed in a diagnostic laboratory. These 8 tumorswere found to include1with EML4-ALK variant1,1with variant 2, 3with variant 3, and 2 with previously unidentified variants (designated variants 6 and 7). Inverse reverse transcription-PCR analysis revealed that the remaining tumor harbored a novel fusion in which intron 24 of KIF5B was ligated to intron 19 of ALK. Multiplex reverse transcription-PCR analysis of additional archival tumor specimens identified another case of lung adenocarcinoma positive for KIF5B-ALK.

Conclusions: The iAEP method should prove suitable for immunohistochemical screening of tumors positive for ALK or ALK fusion proteins among pathologic archives. Coupling of PCR-based detection to the iAEP method should further facilitate the rapid identification of novel ALK fusion genes such as KIF5B-ALK.

6. **EML4-ALK Mutations in Lung Cancer That Confer Resistance to ALK Inhibitors (N Engl J Med 2010;363:1734-9 (2010))**

The EML4 (echinoderm microtubule-associated protein-like 4)–ALK (anaplastic lymphoma kinase) fusion-type tyrosine kinase is an oncoprotein found in 4 to 5% of non–small-cell lung cancers, and clinical trials of specific inhibitors of ALK for the treatment of such tumors are currently under way. Here, we report the iscovery of two secondary mutations within the kinase domain of EML4-ALK in tumor cells isolated from a patient during the relapse phase of treatment with an ALK inhibitor. Each mutation developed independently in subclones of the tumor and conferred marked resistance to two different ALK inhibitors.

Kengo TAKEUCHI, M.D., Ph.D.

Current Position: Project leader / Senior staff scientist

Office Address: Pathology Project for Molecular Targets / Division of Pathology,
The Cancer Institute
Japanese Foundation for Cancer Research
3-8-31 Ariake, Koto, Tokyo 135-8550,
Japan

Office Phone: +81-3-3520-0111 ext. 7149
Office Fax: +81-3-3570-0230
E-mail: kentakeuchi-tky@umin.net

EDUCATION

1996 M.D. The University of Tokyo

2000 Ph.D. (Medical Science) The University of Tokyo

FACULTY APPOINTMENTS

2000 Assistant Professor. Department of Pathology, the University of Tokyo

2004 Staff scientist. Division of Pathology, The Cancer Institute

2011 Project leader / Senior staff scientist. Pathology Project for Molecular Targets /Division of Pathology, The Cancer Institute

PROFESSIONAL MEMBERSHIP

- The Japanese Society of Pathology
- The Japanese Society of Lymphoreticuloendothelial System
- The Japanese Society of Hematology
- The Japanese Cancer Association
- Tokyo Lymphoma Study Group

AWARDS

- 2010 Young Investigator Award. The Japanese Society of Pathology
- 2010 Young Investigator Award. The International Academy of Pathology

PUBLICATIONS

>100 publications in peer-reviewed journals.

Publications in 2011

1. Watanabe T, Tobinai K, Shibata T, Tsukasaki K, Morishima Y, Maseki N, Kinoshita T, Suzuki T, Yamaguchi M, Ando K, Ogura M, Taniwaki M, Uike N, Takeuchi K, Nawano S, Terauchi T, Hotta T. Phase II/III Study of Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone (R-CHOP-21) Versus Two-Week R-CHOP (R-CHOP-14) for Untreated Indolent B-Cell Non-Hodgkin Lymphoma: Japan Clinical Oncology Group (JCOG) 0203 Trial. ***J Clin Oncol***. in press.

2. Kijima T, Takeuchi K, Tetsumoto S, Shimada K, Takahashi R, Hirata H, Hoshino S, Nagatomo I, Takeda Y, Kida H, Goya S, Tachibana I, Kawase I. Favorable Response to Crizotinib in Three Patients with EML4-ALK Fusion-type Oncogene-positive Non-Small Cell Lung Cancer. ***Cancer Sci***. in press.

3. Kimura H, Nakajima T, Takeuchi K, Soda M, Mano H, Iizasa T, Matsui Y, Yoshino M, Shingyoji M, Itakura M, Itami M, Ikebe D, Yokoi S, Kageyama H, Ohira M, Nakagawara A. ALK fusion gene positive lung cancer and 3 cases treated with an inhibitor for ALK kinase activity. ***Lung Cancer***. 2011.

4. Tanimoto T, Matayoshi T, Yagasaki F, Takeuchi K, Kami M. Safety and efficacy of zoledronic acid in multiple myeloma. ***Lancet***. 2011;377:2178.

5. Yao R, Natsume Y, Saiki Y, Shioya H, Takeuchi K, Yamori T, Toki H, Aoki I, Saga T, Noda T. Disruption of Tacc3 function leads to in vivo tumor regression. ***Oncogene***. 2011.

6. Takeuchi K, Soda M, Togashi Y, Sugawara E, Hatano S, Asaka R, Okumura S, Nakagawa K, Mano H, Ishikawa Y. Pulmonary Inflammatory Myofibroblastic Tumor Expressing a Novel Fusion, PPFIBP1-ALK: Reappraisal of Anti-ALK Immunohistochemistry as a Tool for Novel ALK Fusion Identification. ***Clin Cancer Res***. 2011;17:3341-3348.

7. Tachibana T, Tomita N, Furuya M, Yamanaka S, Takeuchi K, Nakamura N, Fujita H, Ishigatsubo Y. Aberrant CD20 Expression in Angioimmunoblastic T-cell Lymphoma. ***Intern Med***. 2011;50:495-499.

8. Watanabe N, Noh JY, Narimatsu H, Takeuchi K, Yamaguchi T, Kameyama K, Kobayashi K, Kami M, Kubo A, Kunii Y, Shimizu T, Mukasa K, Otsuka F, Miyara A, Minagawa A, Ito K. Clinicopathological features of 171 cases of primary thyroid lymphoma: a long-term study involving 24 553 patients with Hashimoto's disease. ***Br J Haematol***. 2011;153:236-243.

9. Okuda C, Kim YH, Takeuchi K, Togashi Y, Masago K, Sakamori Y, Mio T, Mishima M. Successful treatment with pemetrexed in a patient with mucinous bronchioloalveolar carcinoma: long-term response duration with mild toxicity. ***J Thorac Oncol***. 2011;6:641-642.

10. Takeuchi K, Soda M, Togashi Y, Ota Y, Sekiguchi Y, Hatano S, Asaka R, Noguchi M, Mano H. Identification of a novel fusion, SQSTM1-ALK, in ALK-positive large B-cell lymphoma. ***Haematologica***. 2011;96:464-467.

Talk at IAAO 2011

Session: Personalized medicine; Targeting ALK-fusion

Title: Exploring for ALKoma with use of integrated diagnostic techniques

Abstract

For molecular targeted therapy, an accurate selection of patients who benefit from therapy, i.e., a precise detection of the target molecule in tumor tissues, is most important. The following 3 methods are useful for analysis of EML4-ALK: FISH, RT-PCR, and immunohistochemistry (IHC). However, each method has its own analytical difficulties, which arise because of the unique features of this fusion. *EML4-ALK* has many fusion points; therefore, RT-PCR primer settings need to be well refined. We developed a multiplex RT-PCR technique for detecting all theoretically possible fusion variants and identified 5 unknown variants. Conventional anti-ALK IHC for EML4-ALK is unreliable probably because of its low expression level. To overcome this, we developed a sensitive anti-ALK IHC method, the iAEP method. This method has enabled efficient and sensitive detection of EML4-ALK and has helped in identifying novel ALK fusions: KIF5B-ALK, SQSTM1-ALK, PPFIBP1-ALK and others. We recently developed a 5′-RACE-based system optimized for formalin-fixed paraffin-embedded (FFPE) tissues and identified a novel ALK fusion in lung cancer tissues. To the best of our knowledge, it is the first oncogenic fusion identified using FFPE tissues only. This will broaden the potential value of archival FFPE tissues. Studies employing an integrated diagnostic technique for identifying ALK fusions in various types of sample from various cancers are providing further biological and clinical insights in ALKoma.

SELECTED REFERENCES RELATED TO THE TALK

1. Takeuchi K, et al. Pulmonary Inflammatory Myofibroblastic Tumor Expressing a Novel Fusion, PPFIBP1-ALK: Reappraisal of Anti-ALK Immunohistochemistry as a Tool for Novel ALK Fusion Identification. ***Clin Cancer Res***. 2011;17:3341-3348.
2. Takeuchi K, et al. Identification of a novel fusion, SQSTM1-ALK, in ALK-positive large B-cell lymphoma. ***Haematologica***. 2011;96:464-467.
3. Takeuchi K, et al. KIF5B-ALK, a Novel Fusion Oncokinase Identified by an Immunohistochemistry-based Diagnostic System for ALK-positive Lung Cancer. ***Clin Cancer Res***. 2009;15:3143-3149.
4. Takeuchi K, et al. Multiplex reverse transcription-PCR screening for EML4-ALK fusion transcripts. ***Clin Cancer Res***. 2008;14:6618-6624.

Pasi Antero Jänne, M.D., Ph.D.

Current Position: Associate Professor of Medicine
Dana-Farber Cancer Institute

Office Address: Dana-Farber Cancer Institute
44 Binney Street, D820B, Boston, MA 02115

Work Phone: 617-632-6036

Work Email: pjanne@partners.org

Work FAX: 617-582-7683

EDUCATION

1989	B.A.	Chemistry, Vassar College, Poughkeepsie, NY
1996	M.D.	Medicine, University of Pennsylvania, School of Medicine, Philadelphia, PA
1996	Ph.D.	Genetics (advisor Dr. Robert Nussbaum), University of Pennsylvania, School of Medicine
2002	M.MSc.	Clinical investigation, Harvard University, Cambridge, MA

FACULTY ACADEMIC APPOINTMENTS

2001-2004	Instructor, Medicine, Harvard Medical School
2004-2008	Assistant Professor, Medicine, Harvard Medical School
2008-	Associate Professor, Medicine, Harvard Medical School
2008-	Member, Biology and Biomedical Science (BBS) Graduate Program, Harvard Medical School

APPOINTMENTS AT HOSPITALS/AFFILIATED INSTITUTIONS

2001-	Associate Physician, Medicine, Brigham and Women's Hospital
2001-2004	Instructor, Medicine, Dana-Farber Cancer Institute
2001-	Member, Dana-Farber/Harvard Cancer Center, Dana-Farber/Harvard
2004-2008	Assistant Professor of Medicine, Medicine, Dana-Farber Cancer Institute
2008-	Associate Professor of Medicine, Medicine, Dana-Farber Cancer Institute

OTHER PROFESSIONAL POSITIONS (Current)

2007-	Ad Hoc Member, Scientific Advisory Board	AVEO Pharmaceuticals
2008-	Member, Medical Advisory Board	Bonnie J. Addario Lung Cancer Foundation
2008-	Member, Scientific Advisory Board	Addario Lung Cancer Medical Institute
2008-	Ad Hoc Member, Scientific Advisory Board	Myriad Genetics
2009-	Member, Board of Directors	National Lung Cancer Partnership
2009-	Co-Founder	Gatekeeper Pharmaceuticals, Boston, MA
2010-	Member, Scientific Advisory Board	Targeted Molecular Diagnostics/Quintiles

MAJOR ADMINISTRATIVE LEADERSHIP POSITIONS (Current)

2009 -	Director, Translational Research Laboratory	Dana Farber Cancer Institute

COMMITTEE SERVICE (Current)

2001-	Thoracic Oncology Joint Venture Committee, Member, Dana-Farber/Partners Cancer Care
2005-	Respiratory core committee, Member
2006-	Scientific Executive Committee, Member
2007-	Nominating committee, Member
2008-	Data safety monitoring committee, Chair
2009-20	Chest Tumors; Faculty member, European Society for Medical Oncology; Lugano, Switzerla
2009-	Scientific Executive Committee, Chair, National Lung Cancer Partnership, Madison, WI

PROFESSIONAL SOCIETIES (Current)

1999	American Society of Clinical Oncology	Active Full Member
1999	American Association for Cancer Research	Active Member
2001	International Association for the Study of Lung Cancer	Active Member
2004	European Society of Medical Oncology	Active Full Member
2008	American Society of Clinical Investigation	Elected Member

EDITORIAL ROLES (Current)

Ad Hoc Reviewer

Journal of Clinical Oncology, Cancer Research, Clinical Cancer Research, Cancer, New England Journal of Medicine, Journal of Thoracic Oncology, American Journal of Respiratory and Critical Care Medicine , International Journal of Cancer, Nature, Science Translational Medicine, Lancet Oncology

Other Editorial Roles

2006-	Editorial Board Member	Clinical Lung Cancer
2008-	Editorial Board Member	Journal of Clinical Oncology
2009-	Editorial Board Member	Clinical Cancer Research

HONORS AND PRIZES

1985	Finalist, Westinghouse Science Talent Search
1985-89	Five academic honors in Chemistry, Vassar College, Poughkeepsie, NY
1989	General and departmental honors in Chemistry, Vassar College
1989	Phi Beta Kappa, Vassar College
1996	Alpha Omega Alpha, University of Pennsylvania, School of Medicine
2001	Merit Award, American Society of Clinical Oncology
2004	Tisch Family Award for Outstanding Achievement in Clinical Investigation, Dana Farber Cancer Institute
2005	George P. Canellos Award for Excellence in Clinical Investigation and Patient Care, Dana Farber Cancer Institute
2007	Hope Now Award for Lung Cancer Research, Joan's Legacy: The Joan Scarangello Foundation to Conquer Lung Cancer
2008	American Lung Association Award for Lung Cancer Research, American Lung Association
2010	Team Science Award, American Association for Cancer Research
2010	Richard and Hinda Rosenthal Memorial Award, American Association for Cancer Research
2010	Research Excellence Award, Uniting Against Lung Cancer

PUBLICATIONS

>100 publications in peer-reviewed journals.

NARRATIVE REPORT ON CAREER AND RESEARCH INTERESTS

My research program in thoracic oncology is focused on studying genomic abnormalities in lung cancer and translating the laboratory based observations into effective clinical treatments for patients with lung cancer. I am accomplishing this through a multi-faceted approach which includes laboratory based studies, studying tumors from patients with thoracic malignancies and by conducting clinical trials in patients with lung cancer.

A major focus of my research is translational research studies of epidermal growth factor receptor (EGFR) inhibitors in non-small cell lung cancer (NSCLC). In 2004 I was the co-first author in a seminal study that identified somatic mutations in *EGFR* in patients with NSCLC and demonstrated their association with the efficacy of EGFR tyrosine kinase inhibitor gefitinib. This discovery helped explain why, despite the almost uniform expression of EGFR in lung cancer, only 10-15% of patients actually developed tumor regressions with gefitnib. As a result, fundamental changes in the care of patients with NSCLC are occurring, as screening for mutations is being incorporated into everyday clinical practice. Recent randomized clinical trials demonstrate that EGFR kinase inhibitors are a more effective initial clinical treatment compared with systemic chemotherapy for EGFR mutant NSCLC patients and EGFR kinase inhibitors are rapidly becoming the standard of care for this molecularly defined patient population.

Since the original discovery in 2004, my laboratory has focused on understanding the biologic and clinical differences of *EGFR* mutations, on different methods of inhibiting the EGFR, on identifying mechanisms of resistance to EGFR inhibitors and on the development of technology to rapidly identify *EGFR* mutations from patient specimens. I have been involved in the discovery of resistance mechanisms to EGFR inhibitors and on developing novel pre-clinical and clinical therapeutic strategies to overcome resistance mechanisms. In 2007, my laboratory identified *MET* amplification as novel resistance mechanism to EGFR kinase inhibitors. This was a unique observation in that it was an example of how cancers develop 'bypass' signaling pathways to get around EGFR inhibition. Furthermore it spurred the development of clinical trials combining EGFR and MET inhibitors for gefitinib or erlotinib resistant NSCLC patients. More recently, together with colleagues at Dana Farber we identified a novel first in class mutant selective EGFR kinase inhibitor which is more effective in preclinical models than current clinical agents aimed at treating cancers harboring the T790M gefitinib resistance mutation.

My laboratory also focuses on studying other less common but clinically relevant genomic abnormalities (such as translocations involving *ALK* and *ROS*) in lung cancer. The overarching goal of my laboratory based studies is to identify genomically defined subsets of lung cancer and develop specific therapies for each subset of lung cancer. I lead the clinical lung cancer genomics effort at DFCI and have developed the methods to make routine genomic testing of all lung cancer patients possible.

My laboratory research has direct relevance to the clinical care of lung cancer patients. I have used the laboratory based discoveries on *EGFR* mutations and EGFR resistance mechanisms to design and conduct new clinical trials (locally, nationally and internationally) in patients with NSCLC. These trials not only provide clinical validation to the laboratory based studies and also offer novel and effective treatments for lung cancer patients in my clinic. I have developed translational tools to study tumors from NSCLC patients on such trials to help understand if my laboratory based observations and hypotheses are successful clinically. My clinical experience of treating *EGFR* mutant NSCLC patients provides me both clinical insight and access to patient specimens which I use to refine my laboratory based studies on EGFR.

Talk at IAAO2011

Session: Personalized medicine; Targeting ALK-fusion
Title; Clinical Trials with ALK Inhibitors

Abstract

Rearrangements in the anaplastic lymphoma kinase (ALK) have been detected in 3-5% of non-small cell lung cancer (NSCLC) patients. ALK kinase inhibitors, including Crizotinib, are currently undergoing evaluation in clinical trials. In the phase I trial, treatment of NSCLC patients harboring ALK rearrangements was associated with a response rate was 61% and the median PFS was 10 months. Two phase III clinical trials are currently underway. The first is randomized phase III trial of Crizotinib versus either docetaxel or pemetrexed for ALK NSCLC patients previously treated with systemic chemotherapy. A second trial compares Crizotinib to cisplatin/pemetrexed in treatment naïve ALK NSCLC patients.

Despite the efficacy of Crizotinib in ALK NSCLC acquired drug resistance is starting to emerge. To date secondary mutations in ALK that lead to acquired resistance to Crizotinib have been identified. These include the ALK mutations F1174L, L1196M and C1156Y. The exact mechanism of how these mutations lead to Crizotinib resistance has not yet been elucidated. The F1174L mutation likely promotes an active conformation of ALK. This may disfavor the binding of Crizotinib to ALK as it preferentially binds the inactive conformation. The identification of secondary mutations in ALK is leading to the pre-clinical and clinical development of second generation ALK inhibitors.

ALK-related publications

1. Koivunen, J.P, Mermel, C., Zejnullahu, K., Murphy, C., Lifshits, E., Holmes, A.J., Choi, H.G., Kim, Chiang, J.D., Thomas, R., Lee, J., Richards, W.G., Sugarbaker, D.J., Ducko, C., Lindeman, N., Marcoux, J.P., Engelman, J.A., Gray, N.S., Lee, C., Matthew Meyerson, M., and **Jänne, P.A.** EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. Clin Cancer Res 2008; 14(13):4275-83

2. Rodig, S.J., Mino-Kenudson, M., Dacic, S., Yeap, B.Y., Shaw, A., Barletta, J.A., Stubbs, H., Law, K., Lindeman, N., Mark, E., **Jänne, P.A.,** Lynch, T., Johnson, B.E., A.J. Iafrate, and Chirieac, L.R., Unique Clinicopathologic Features Characterize ALK-rearranged Lung Adenocarcinoma in the Western Population. Clin Cancer Res 2009; 15(16):5216-23.

3. Mino-Kenudson, M., Chirieac, L.R., Law, K., Hornick, J.L., Lindeman, N., Mark, E.J., Cohen, D.W., Johnson, B.E. **Jänne, P.A.,** Iafrate, A.J. and Rodig, S.J., A Novel, Highly Sensitive Antibody Allows for the Routine Detection of ALK-rearranged Lung Adenocarcinomas by Standard Immunohistochemistry. Clin Cancer Res 2010; 16(5):1561-71

4. Butrynski, J.E., D'Adamo, D.R.., Hornick, J.L., Dal Cin, P.S., Antonescu, C.R., M.D., Jhanwar, S.C., Ladanyi, M., Capelletti, M., Rodig, S.J., Ramaiya, N., Kwak, E.L., Clark, J.W., Wilner, K.D., Christensen, J.G., **Jänne, P.A.**, Maki, R.G., M.D., Ph.D., Demetri, G.D. and Shapiro, G.I., Crizotinib in ALK-Rearranged Inflammatory Myofibroblastic Tumor. New England Journal of Medicine 2010; October 28; 363(18): 1727–1733.

5. Kwak, E.L., Bang, Y.-J., Camidge, D.R., Shaw, A.T., Solomon, B., Maki, R.G., Ou, S.-H., I., Dezube, B., **Jänne, P.A.,** Costa, D.B. Varella-Garcia, M., Kim, W.-H., Lynch, T.J., Fidias, P.,Stubbs, H., Engelman, J.A., Sequist, L.V., Tan, W., Gandhi, L., Mino-Kenudson, M., Wei, G.C., Shreeve, S.M., Ratain, M.J., Settleman, J., Christensen, J.G., Haber, D.A., Wilner, K., Salgia, R., Shapiro, G.I., Clark, J.W. and Iafrate, A.J. Anaplastic Lymphoma Kinase (ALK) Inhibitor in Lung Cancer with ALK Gene Rearrangements. New England Journal of Medicine 2010; October 28; 363(18): 1693–1703.

6. Chen, Z., Sasaki, T., Tan, X., Carretero, J., Shimamura,T., Li, D., Xu, C., Wang, Y., Adelmant, G.O., Capelletti, M., Lee, H.J., Rodig, S., Borgman, C., Park, S.-I., Kim, H.R., Padera, R., Marto, J.A. , Gray, N.S., Kung, A.L., Shapiro, G.I., **Jänne, P.A***., and Wong, K.K. Inhibition of ALK, PI3K/MEK and HSP90 in Murine Lung Adenocaricinoma induced by *EML4-ALK* Fusion Oncogene. *Cancer Res; 70(23); 9827–36.* *co-corresponding author

Anthony John Iafrate, M.D., Ph.D.

Current Positions: Associate Pathologist
Massachusetts General Hospital
Associate Professor of Pathology
Department of Pathology
Harvard Medical School

Office Address: Massachusetts General Hospital
Department of Pathology
Diagnostic Molecular Pathology Laboratory
55 Fruit Street, Warren 501c
Boston, MA 02114

Work Phone: 617-726-0166
Work Email: aiafrate@partners.org
Work FAX: 617-726-2365

EDUCATION

1991	B.A.	Molecular Biochemistry and Biophysics / Italian Studies	Yale University, New Haven, CT
1998	Ph.D.	Molecular Microbiology	Cold Spring Harbor Laboratory, Cold Spring Harbor, NY
2000	M.D.	Medicine	State University of New York at Stony Brook, Stony Brook, NY

FACULTY ACADEMIC APPOINTMENTS

2005-2007	Instructor	Department of Pathology	Harvard Medical School
2007-2010	Assistant Professor	Department of Pathology	Harvard Medical School
2010-	Associate Professor	Department of Pathology	Harvard Medical School

APPOINTMENTS AT HOSPITALS/AFFILIATED INSTITUTIONS

2005-	Assistant Pathologist	Department of Pathology	Massachusetts General Hospital

MAJOR ADMINISTRATIVE LEADERSHIP POSITIONS (Current)

2005-	Director of Diagnostic Molecular Pathology Laboratory	Department of Pathology, Massachusetts General Hospital
2007-	Executive Director, Cancer Center-Pathology Translational Research Laboratory	Massachusetts General Hospital
2010-	Genomics committee co-chair; Lung Cancer Mutation Consortium	NIH Grand Opportunity Grant; multicenter lung cancer genotyping consortium.

COMMITTEE SERVICE (Current)

2005-	Molecular Genetic Pathology Fellowship steering committee	Harvard-wide pathology training program
2007-	Institutional Review Board committee D	Dana Farber/ Harvard Cancer Center
2008-	Clinical Services Oversight Committee	Department of Pathology, Massachusetts General Hospital

PROFESSIONAL SOCIETIES

2003	American Society of Human Genetics
2003	Association for Molecular Pathology

EDITORIAL ACTIVITIES

Ad Hoc Reviewer	Journal of Neuropathology and Exp. Neurology, Journal of Molecular Diagnostics, Archives of Pathology and Laboratory Medicine, American Journal of Surgical Pathology, Expert Opinion on Medical Diagnostics, Mutation Research, Blood, Clinical Cancer Research, Nature Medicine, Human Molecular Genetics, Journal of Thoracic Oncology

HONORS AND PRIZES

1991	*Magna cum Laude*	Yale University
1991	Academic Honors in Molecular Biochemistry and Biophysics	Yale University
1991	Academic Honors in Italian Studies	Yale University
1991-2000	Medical Scientist Training Program (MSTP)	SUNY at Stony Brook
2006	MGH Team Awards: Genetics in Medicine Implementation Team	Massachusetts General Hospital
2006	MGH Partners in Excellence Award	Massachusetts General Hospital
2007	MGH Partners in Excellence Award	Massachusetts General Hospital
2008	MGH Cancer Center "The One Hundred" awardee	Massachusetts General Hospital
2010	Dr. James Watson Healthcare Grant; Awarded Ion Torrent Next Generation Sequencer	Ion Torrent Corporation

PUBLICATIONS

>80 publicatins in the peer reviewed Journals.

NARRATIVE REPORT ON CAREER AND RESEARCH INTERESTS

1. Research

My major research interests include two areas of investigation: (1) large-scale copy number variation in the human genome and (2) molecular genetics of human neoplasia.

As a postdoctoral research fellow in the laboratory of Dr. Charles Lee at BWH, we used microarray-based comparative genomic hybridization (array CGH) to study normal human populations. We found unexpected large variations in genome segment copy number between individuals, termed large-scale copy number variants or CNVs. Subsequent studies have confirmed our findings, and have shown that CNVs are extremely common and can involve very large, contiguous regions of our genome. Current projections now suggest that any two individuals may have genomes that differ between 10-20 million bases of DNA sequence as a result of CNVs, far exceeding the total amount of DNA differences that are accounted for SNPs. Our research effort continues to explore the detailed genomic structure of these CNVs, and to assess their role in disease association. In addition we are developing probes corresponding to CNVs for *in situ* genetic analysis of identity.

My major research focus since joining the pathology department at MGH has been on applying molecular genetic techniques to the diagnosis and treatment of human neoplasia. One line of investigation has focused on diagnostics and clinico-pathologic evaluation of non-small cell lung cancer, including the description of morphologic correlates of EGFR and KRAS mutation and ALK-rearranged tumors in a large cohort of patients. We have screened large numbers of patients for entry into clinical trials of targeted agents. We found that ALK-positive lung tumors show a remarkable response to an ALK tyrosine kinase inhibitor.

We have also examined genetic alterations in tumors besides lung cancer, including FISH analysis of several hundred esophageal and stomach cancers for amplification of the *MET* gene, a recently-recognized genetic event that determines *in vitro* response to *MET* small molecular inhibitors. We have identified a subset of patients who would be eligible for a phase 1 clinical trial. As an extension of this study we have found approximately 10% of esophageal and stomach cancers also harbor *HER2* and *EGFR* amplification, and such patients will be enrolled in appropriate targeted therapy clinical trials. We are expanding our ability to screen patients for genetic signatures that will predict drug responsiveness in real time.

2.Teaching and clinical contributions

My principal teaching contributions involve direct supervision of 2-3 molecular genetic pathology fellows' 3 month clinical rotations, and organization and direct supervision of a 3 week molecular pathology clinical rotation for all pathology residents at MGH. I also give a number of didactic teaching sessions on tumor genetics each year including 6 sessions for the MGH pathology residents ("Outs" conference) and 3 sessions for MGH geneticists and fellows.

As director of Molecular Diagnostics and the Translational Research Laboratory, I oversee a new clinical laboratory service to support tumor diagnostics. The principle responsibilities include: (1) oversight of laboratory budget, including Capital and Operating budgets, (2) personnel hiring and management, (3) test development and validation using multiple advanced molecular techniques, (4) quality control and laboratory standard compliance, and (5) clinical report writing and sign-out. The lab employs 2 full-time PhD level directors, 10 full-time technicians, 1 clinical fellow and 2 post-doctoral fellows, and is in the process of expansion.

Talk at IAAO2011

Session; Personalized medicine; Targeting ALK-fusion
Title; A large scale screening of ALK fusions

Publications on ALK-related studies and those published in 2011.

1. Shaw AT, Forcione DG, Digumarthy SR, **Iafrate AJ**. "Case records of the Massachusetts General Hospital. Case 21-2011. A 31-year-old man with ALK-positive adenocarcinoma of the lung." N Engl J Med. 2011 Jul 14;365(2):158-67.
2. Chiang S, Fazlollahi L, Nguyen A, Betensky RA, Roberts DJ, **Iafrate AJ**. "Diagnosis of hydatidiform moles by polymorphic deletion probe fluorescence in situ hybridization." J Mol Diagn. 2011 Jul;13(4):406-15. Epub 2011 Apr 29.
3. Farris AB, Taheri D, Kawai T, Fazlollahi L, Wong W, Tolkoff-Rubin N, Spitzer TR, **Iafrate AJ**, Preffer FI, Locascio SA, Sprangers B, Saidman S, Smith RN, Cosimi AB, Sykes M, Sachs DH, Colvin RB. "Acute renal endothelial injury during marrow recovery in a cohort of

combined kidney and bone marrow allografts." Am J Transplant. 2011 Jul;11(7):1464-77. doi: 10.1111/j.1600-6143.2011.03572.x. Epub 2011 Jun 10.

4. Ou SH, Kwak EL, Siwak-Tapp C, Dy J, Bergethon K, Clark JW, Camidge DR, Solomon BJ, Maki RG, Bang YJ, Kim DW, Christensen J, Tan W, Wilner KD, Salgia R, **Iafrate AJ**. "Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification." J Thorac Oncol. 2011 May;6(5):942-6.
5. Le LP, Nielsen GP, Rosenberg AE, Thomas D, Batten JM, Deshpande V, Schwab J, Duan Z, Xavier RJ, Hornicek FJ, **Iafrate AJ**. "Recurrent chromosomal copy number alterations in sporadic chordomas." PLoS One. 2011;6(5):e18846. Epub 2011 May 13.
6. Demicco EG, Farris AB 3rd, Baba Y, Agbor-Etang B, Bergethon K, Mandal R, Daives D, Fukuoka J, Shimizu M, Dias-Santagata D, Ogino S, **Iafrate AJ**, Gaissert HA, Mino-Kenudson M. "The dichotomy in carcinogenesis of the distal esophagus and esophagogastric junction: intestinal-type vs cardiac-type mucosa-associated adenocarcinoma." Mod Pathol. 2011 May 13. [Epub ahead of print]
7. Zhu AX, Abrams TA, Miksad R, Blaszkowsky LS, Meyerhardt JA, Zheng H, Muzikansky A, Clark JW, Kwak EL, Schrag D, Jors KR, Fuchs CS, **Iafrate AJ**, Borger DR, Ryan DP. "Phase 1/2 study of everolimus in advanced hepatocellular carcinoma." Cancer. 2011 Apr 27. doi: 10.1002/cncr.26165. [Epub ahead of print]
8. Katayama R, Khan TM, Benes C, Lifshits E, Ebi H, Rivera VM, Shakespeare WC, **Iafrate AJ**, Engelman JA, Shaw AT. "Therapeutic strategies to overcome crizotinib resistance in non-small cell lung cancers harboring the fusion oncogene EML4-ALK." Proc Natl Acad Sci U S A. 2011 May 3;108(18):7535-40. Epub 2011 Apr 18.
9. Dias-Santagata D, Lam Q, Vernovsky K, Vena N, Lennerz JK, Borger DR, Batchelor TT, Ligon KL, **Iafrate AJ**, Ligon AH, Louis DN, Santagata S. "BRAF V600E mutations are common in pleomorphic xanthoastrocytoma: diagnostic and therapeutic implications." PLoS One. 2011 Mar 29;6(3):e17948.
10. Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, Bergethon K, Shaw AT, Gettinger S, Cosper AK, Akhavanfard S, Heist RS, Temel J, Christensen JG, Wain JC, Lynch TJ, Vernovsky K, Mark EJ, Lanuti M, **Iafrate AJ**, Mino-Kenudson M, Engelman JA. "Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors." Sci Transl Med. 2011 Mar 23;3(75):75ra26.
11. Dias-Santagata D, Lam Q, Bergethon K, Baker GM, **Iafrate AJ**, Rakheja D, Hoang MP. "A potential role for targeted therapy in a subset of metastasizing adnexal carcinomas." Mod Pathol. 2011 Jul;24(7):974-82. doi: 10.1038/modpathol.2011.48. Epub 2011 Mar 18.
12. Growdon WB, Roussel BN, Scialabba VL, Foster R, Dias-Santagata D, **Iafrate AJ**, Ellisen LW, Tambouret RH, Rueda BR, Borger DR. "Tissue-specific signatures of activating PIK3CA and RAS mutations in carcinosarcomas of gynecologic origin." Gynecol Oncol. 2011 Apr;121(1):212-7. Epub 2010 Dec 17.
13. Farris AB 3rd, Demicco EG, Le LP, Finberg KE, Miller J, Mandal R, Fukuoka J, Cohen C, Gaissert HA, Zukerberg LR, Lauwers GY, **Iafrate AJ**, Mino-Kenudson M. "Clinicopathologic and molecular profiles of microsatellite unstable Barrett Esophagus-associated adenocarcinoma." Am J Surg Pathol. 2011 May;35(5):647-55.
14. Camelo-Piragua S, Jansen M, Ganguly A, Kim JC, Cosper AK, Dias-Santagata D, Nutt CL, **Iafrate AJ**, Louis DN. "A sensitive and specific diagnostic panel to distinguish diffuse astrocytoma from astrocytosis: chromosome 7 gain with mutant isocitrate dehydrogenase 1 and p53." J Neuropathol Exp Neurol. 2011 Feb;70(2):110-5.
15. Ting DT, Lipson D, Paul S, Brannigan BW, Akhavanfard S, Coffman EJ, Contino G, Deshpande V, **Iafrate AJ**, Letovsky S, Rivera MN, Bardeesy N, Maheswaran S, Haber DA. "Aberrant overexpression of satellite repeats in pancreatic and other epithelial cancers." Science. 2011 Feb 4;331(6017):593-6. Epub 2011 Jan 13.
16. Corcoran RB, Dias-Santagata D, Bergethon K, **Iafrate AJ**, Settleman J, Engelman JA. "BRAF gene amplification can promote acquired resistance to MEK inhibitors in cancer cells harboring the BRAF V600E mutation." Sci Signal. 2010 Nov 23;3(149):ra84.
17. Ou SH, Bazhenova L, Camidge DR, Solomon BJ, Herman J, Kain T, Bang YJ, Kwak EL, Shaw AT, Salgia R, Maki RG, Clark JW, Wilner KD, **Iafrate AJ**. "Rapid and dramatic radiographic and clinical response to an ALK inhibitor (crizotinib, PF02341066) in an ALK translocation-positive patient with non-small cell lung cancer." J Thorac Oncol. 2010 Dec;5(12):2044-6.
18. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, Ou SH, Dezube BJ, Jänne PA, Costa DB, Varella-Garcia M, Kim WH, Lynch TJ, Fidias P, Stubbs H, Engelman JA, Sequist LV, Tan W, Gandhi L, Mino-Kenudson M, Wei GC, Shreeve SM, Ratain MJ, Settleman J, Christensen JG, Haber DA, Wilner K, Salgia R, Shapiro GI, Clark JW, **Iafrate AJ**. "Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer." N Engl J Med. 2010 Oct 28;363(18):1693-703.
19. Dias-Santagata D, Akhavanfard S, David SS, Vernovsky K, Kuhlmann G, Boisvert SL, Stubbs H, McDermott U, Settleman J, Kwak EL, Clark JW, Isakoff SJ, Sequist LV, Engelman JA, Lynch TJ, Haber DA, Louis DN, Ellisen LW, Borger DR, **Iafrate AJ**. "Rapid targeted mutational analysis of human tumours: a clinical platform to guide personalized cancer medicine." EMBO Mol Med. 2010 May;2(5):146-58.
20. Mino-Kenudson M, Chirieac LR, Law K, Hornick JL, Lindeman N, Mark EJ, Cohen DW, Johnson BE, Jänne PA, **Iafrate AJ**, Rodig SJ. "A novel, highly sensitive antibody allows for the routine detection of ALK-rearranged lung adenocarcinomas by standard immunohistochemistry." Clin Cancer Res. 2010 Mar 1;16(5):1561-71. Epub 2010 Feb 23.
21. Shaw AT, Yeap BY, Mino-Kenudson M, Digumarthy SR, Costa DB, Heist RS, Solomon B, Stubbs H, Admane S, McDermott U, Settleman J, Kobayashi S, Mark EJ, Rodig SJ, Chirieac LR, Kwak EL, Lynch TJ, **Iafrate AJ**. "Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK." J Clin Oncol. 2009 Sep 10;27(26):4247-53. Epub 2009 Aug 10.
22. Pao W, Kris MG, **Iafrate AJ**, Ladanyi M, Jänne PA, Wistuba II, Miake-Lye R, Herbst RS, Carbone DP, Johnson BE, Lynch TJ. "Integration of molecular profiling into the lung cancer clinic." Clin Cancer Res. 2009 Sep 1;15(17):5317-22. Epub 2009 Aug 25.
23. Rodig SJ, Mino-Kenudson M, Dacic S, Yeap BY, Shaw A, Barletta JA, Stubbs H, Law K, Lindeman N, Mark E, Janne PA, Lynch T, Johnson BE, **Iafrate AJ**, Chirieac LR. "Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population." Clin Cancer Res. 2009 Aug 15;15(16):5216-23. Epub 2009 Aug 11.
24. McDermott U, **Iafrate AJ**, Gray NS, Shioda T, Classon M, Maheswaran S, Zhou W, Choi HG, Smith SL, Dowell L, Ulkus LE, Kuhlmann G, Greninger P, Christensen JG, Haber DA, Settleman J. "Genomic alterations of anaplastic lymphoma kinase may sensitize tumors to anaplastic lymphoma kinase inhibitors." Cancer Res. 2008 May 1;68(9):3389-95.
25. McDermott U, Sharma SV, Dowell L, Greninger P, Montagut C, Lamb J, Archibald H, Raudales R, Tam A, Lee D, Rothenberg SM, Supko JG, Sordella R, Ulkus LE, **Iafrate AJ**, Maheswaran S, Njauw CN, Tsao H, Drew L, Hanke JH, Ma XJ, Erlander MG, Gray NS, Haber DA, Settleman J. "Identification of genotype-correlated sensitivity to selective kinase inhibitors by using high-throughput tumor cell line profiling." Proc Natl Acad Sci U S A. 2007 Dec 11;104(50):19936-41. Epub 2007 Dec 6.

Symposium 2

Synthetic lethality; Theory and Practice

Chairperson:

Kiyohiko Hatake

Cancer Institute Hospital, Japanese Foundation for Cancer Research, Japan

Chairperson:

Yuko Kitagawa

Keio University School of Medicine, Japan

Christopher Lord, Ph.D.

Current Position: Senior Staff Scientist
The Breakthrough Breast Cancer Research Centre
The Institute of Cancer Research

Office Address: The Breakthrough Breast Cancer Research Centre
The Institute of Cancer Research
Fulham Road
London, SW3 6JB

Work Phone: +44 (0) 207 153 5334 (work-direct)

Work Email: chris.lord@icr.ac.uk

EDUCATION

1997	DPhil	University of Oxford, UK
1993	BSc (Hons)	University of Surrey, UK

PREVIOUS POSTS HELD

Aug 2005-Sep 2008	Staff Scientist	Institute of Cancer Research, UK
Oct 2000-Aug 2005	Postdoctoral Fellow	Institute of Cancer Research, UK
Jul 1997-Oct 2000	Postdoctoral Fellow	Cambridge Institute for Medical Research, University of Cambridge, UK

BIOGRAPHY

Chris Lord received his PhD in 1997 (University of Oxford), working in the field of complex trait genetics. Since 2000, Chris has worked at the Breakthrough Breast Cancer Research Centre at the Institute of Cancer Research, London. Here Chris' work has focussed upon the use of genetics to identify novel therapeutic approaches to cancer as well as using high-throughput genetic screens to optimise the use of existing cancer drugs. In 2005, Chris was a member of the team that demonstrated the potential of PARP inhibitors in BRCA mutant cancers and his subsequent work has also shown that PARP inhibitors could be used in patients with tumours that carry PTEN defects.

CURRENT PROJECTS

Refining the clinical use of PARP inhibitors in cancer; development of biomarkers for use with PARP inhibitors; oncogenomics; DNA repair; drug resistance; drug development

CAREER HIGHLIGHTS

- Identifying BRCA dysfunction as a determinant of PARP inhibitor sensitivity (Nature 2005).
- Identification of additional determinants of PARP inhibitor sensitivity (publications in 2005, 2006, 2008).
- Identifying a genetic mechanism of resistance to PARP inhibitors (Nature 2008).
- Identifying novel determinants of tamoxifen sensitivity (Cancer Cell 2008)
- Identifying novel synthetic lethal strategies for MMR deficient cancers (Cancer Cell 2010)

PUBLICATIONS

60 publications in peer-reviewed journal

Publications selected for PARP and BRCA (* corresponding or joint first author)

1. Sourisseau T, Maniotis D, McCarthy A, Tang C, Lord CJ, Ashworth A, Linardopoulos S.: Aurora-A expressing tumour cells are deficient for homology-directed DNA double strand-break repair and sensitive to PARP inhibition. EMBO Mol Med. 2010 Apr;2(4):130-42.
2. Mendes-Pereira AM, Martin SA, Brough R, McCarthy A, Taylor JR, Kim JS, Waldman T, Lord CJ, Ashworth A.: *Synthetic lethal targeting of PTEN mutant cells with PARP inhibitors. EMBO Mol Med. 2009 Sep;1(6-7):315-22.
3. Martin SA, Hewish M, Lord CJ, Ashworth A.: *Genomic instability and the selection of treatments for cancer. J Pathol. 2010 Jan;220(2):281-9.
4. Oliver AW, Swift S, Lord CJ, Ashworth A, Pearl LH.: Structural basis for recruitment of BRCA2 by PALB2. EMBO Rep. 2009 Sep;10(9):990-6
5. McCabe N, Cerone MA, Ohishi T, Seimiya H, Lord CJ, Ashworth A.: *Targeting Tankyrase 1 as a therapeutic strategy for BRCA-associated cancer. Oncogene. 2009 Mar 19;28(11):1465-70.
6. Lord CJ, McDonald S, Swift S, Turner NC, Ashworth A.: *A high-throughput RNA interference screen for DNA repair determinants of PARP inhibitor sensitivity. DNA Repair (Amst). 2008 Dec 1;7(12):2010-9.
7. Lord CJ, Ashworth A.: *Targeted therapy for cancer using PARP inhibitors. Curr Opin Pharmacol. 2008 Aug;8(4):363-9
8. Turner NC, Lord CJ, Iorns E, Brough R, Swift S, Elliott R, Rayter S, Tutt AN, Ashworth A.: A synthetic lethal siRNA screen identifying genes mediating sensitivity to a PARP inhibitor. EMBO J. 2008 May 7;27(9):1368-77.
9. Martin SA, Lord CJ, Ashworth A.: *DNA repair deficiency as a therapeutic target in cancer. Curr Opin Genet Dev. 2008 Feb;18(1):80-6.
10. Edwards SL, Brough R, Lord CJ, Natrajan R, Vatcheva R, Levine DA, Boyd J, Reis-Filho JS, Ashworth A.: Resistance to therapy caused by intragenic deletion in BRCA2. Nature. 2008 Feb 28;451(7182):1111-5
11. Brough R, Wei D, Leulier S, Lord CJ, Rong YS, Ashworth A.: Functional analysis of Drosophila melanogaster BRCA2 in DNA repair. DNA Repair (Amst). 2008 Jan 1;7(1):10-9.
12. Gudmundsdottir K, Lord CJ, Ashworth A.: The proteasome is involved in determining differential utilization of double-strand break repair pathways. Oncogene. 2007 Nov 29;26(54):7601-6.
13. Lord CJ, Ashworth A.: RAD51, BRCA2 and DNA repair: a partial resolution. Nat Struct Mol Biol. 2007 Jun;14(6):461-2.
14. Tutt AN, Lord CJ, McCabe N, Farmer H, Turner N, Martin NM, Jackson SP, Smith GC, Ashworth A.: Exploiting the DNA repair defect in BRCA mutant cells in the design of new therapeutic strategies for cancer. Cold Spring Harb Symp Quant Biol. 2005;70:139-48.
15. McCabe N, Lord CJ, Tutt AN, Martin NM, Smith GC, Ashworth A.: BRCA2-deficient CAPAN-1 cells are extremely sensitive to the inhibition of Poly (ADP-Ribose) polymerase: an issue of potency. Cancer Biol Ther. 2005 Sep;4(9):934-6
16. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC, Ashworth A.: Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005 Apr 14;434(7035):917-21.
17. Warren M, Lord CJ, Masabanda J, Griffin D, Ashworth A.: Phenotypic effects of heterozygosity for a BRCA2 mutation. Hum Mol Genet. 2003 Oct 15;12(20):2645-56.

Talk at IAAC2011
Session: Synthetic Lethality; Theory and Practice
Title: Using Synthetic Lethality Approaches to Design Novel Therapeutic

Abstract

Approaches to Cancer Treatment

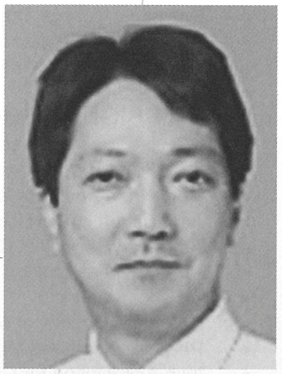
As the search for suitable cancer drug targets becomes ever more difficult, the need for novel approaches to this problem is becoming more apparent. Although first proposed in the 1940s, it is only recently that the concept of using synthetic lethality (SL) to design new therapeutic approaches is being tested both in the laboratory and in the clinic. Two genes or proteins are synthetic lethal when deficiency in either is compatible with cellular viability but loss of both is not. Where one partner of a synthetic lethal relationship is a tumour suppressor gene that is lost in tumours, the other synthetic lethal partner, once identified, becomes a candidate drug target. Using this approach, we have identified PARP inhibition as being SL with loss of either the *BRCA1* or *BRCA2* tumour suppressor genes and clinical trials testing this approach are now showing considerable promise. Using this and other examples, I will illustrate how the SL approach can be exploited, how novel targets can be identified and how tumour types as diverse as colorectal, breast, prostate and endometrial cancer could be treated using a SL approach.

Special Lecture

Chairperson:

Kiyohiko Hatake

Cancer Institute Hospital, Japanese Foundation for Cancer Research, Japan



Chairperson:

Nobuyuki Mizunuma

Cancer Institute Hospital, Japanese Foundation for Cancer Research, Japan

Patrick Gerard Johnston, M.D., Ph.D.

Current Position: Dean, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast
Director, Institute of Health & Life Sciences, Queen's University Belfast

Office Address: H.S.N.B, Block 10 Health Sciences
School of Medicine, Dentistry and Biomedical Sciences
97 Lisburn Road Belfast, BT9 7BL
Northern Ireland, UK

Work Phone: +44 (0)28 9097 2764
Work Email: p.johnston@qub.ac.uk

EDUCATION

1976-1982	MB, BCh, BAO (Honours)	University College Dublin, Ireland.
June 1985	MRCPI	Royal College of Physicians of Ireland, Dublin, Ireland.
December 1985	Diploma in Child Health	University College Dublin, Ireland.
December 1990	MD	University College Dublin, Ireland.
June 1995	PhD	University College Dublin, Ireland.
June 1997	FRCPI	Fellow of the Royal College of Physicians of Ireland
June 1998	FRCP	Fellow of the Royal College of Physicians, London

ACADEMIC APPOINTMENTS

Jan 1991 - June 96	Senior Investigator, Medical Oncology, NCI-Navy Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD.USA
July 1996 - Present	Professor and Chair of Department of Oncology, Queens University Belfast, Belfast, Northern Ireland, UK
April 1999 - 2004	Director, Cancer Research Centre, Queen's University Belfast, N. Ireland
Mar 2004 - Feb 2008	Director, Centre for Cancer Research & Cell Biology, Queen's University Belfast
Sep 2007 - Present	Dean, School of Medicine, Dentistry & Biomedical Sciences, Queen's University Belfast
Sep 2007 - Present	Director, Institute of Health & Life Sciences, Queen's University Belfast

HONOURS AND AWARDS

- MB, BCh, BAO (Honours Degree)
- National Cancer Institute Fellowship - 1987
- Irish Society of Gastroenterology Gold Medal, November 1987
- Alton Gold Medal Prize, Mater Hospital, University College Dublin, November 1990
- Young Investigator Award, American Society of Clinical Oncology, 1991
- National Cancer Institute Technology Award, October 1993
- National Cancer Institute Grand Rounds, National Institutes of Health, 2000
- American Cancer Society Presidential Lecture and Address, Atlanta, 2003
- Tom Connors Award Lecture – National Cancer Research Institute, 2005
- Biolink USA – Ireland Life Science Award 2007
- University College Dublin – Distinguished Graduate Award 2008
- Institute of Molecular Medicine, Dublin – Cancer Award 2008
- Alumnus Illustrissimus Award, St Columb's College, Derry, N Ireland, 2008

PROFESSIONAL SOCIETIES

- Royal College of Physicians Ireland
- Royal College of Physicians (London)
- Royal Irish Academy of Medicine
- Association of Physicians of Great Britain and Ireland
- American Society of Clinical Oncology
- American Association for Cancer Research
- American Association for Advancement of Science
- European Society of Medical Oncology
- Pharmacology and Molecular Mechanisms Group, EORTC
- Irish Association for Cancer Research

CURRENT MEMBERSHIP OF COMMITTEES/BOARDS

Europe

- European Organisation for Research and Treatment of Cancer (EORTC) - Gastrointestinal Cancer Group Committee
- EORTC PAMM Group
- Scientific Advisory Board of VUmc Cancer Center Amsterdam
- Chair, International Selection Committee for the Bob Pinedo Award for Cancer Care

International

- NCI-All-Ireland Cancer Consortium Implementation Board
- Singapore Cancer Advisory Board
- Society for Translational Oncology (Founder and Co-Chair)
- Almac Diagnostics (Founder and Director)
- American Society for Clinical Oncology Scientific Program Committee
- International Academy for Advanced Oncology (IAAO), Japan - EU Board Member

MEMBERSHIP OF EDITORIAL BOARDS

- The Oncologist (Senior Editor; Gastrointestinal Cancer Section Editor)
- Journal of the National Cancer Institute (2001-2010)
- Journal of Clinical Oncology (2002-06)
- Clinical Cancer Research (2002-2006)
- Clinical Colorectal Cancer
- PLoS Medicine

PUBLICATIONS

>150 publications in peer-reviewed journals.

Talk at IAAO 2011

Session; Special Lecture

Title: The Methodological Challenge of Delivering Personalised Therapy for Cancer Patients

Abstract

Over the last two decades there have been very significant improvements in cancer treatment and patient outcomes in a wide variety of cancers such as breast, colorectal and lung cancer. These improvements have been followed by a plethora of biomarker studies to refine patient prognostic information and to try and predict which patient group may benefit most from systemic chemotherapy or targeted therapy. Biomarkers such as ER status HER2 in breast cancer and most recently KRAS status in colorectal cancer represent important biomarkers that help refine both prognostic and predictive information and improve the precision with which we are able to define those patient cohorts that benefit from specific therapies.

More recently the introduction of high throughput technologies has enabled us to classify tumours at a molecular level that traditionally have the same clinical and pathological features such as tumour grade and stage. However, despite the revolution that has occurred in the field of genomic and biomarker research, none of these genomics markers are as yet commonly used in clinical practice. These studies often have poorly defined study endpoints and are mostly retrospective sub-group analysis from larger clinical trials, or studies based on available tumour biopsies from heterogeneous patient cohorts. The challenge going forward in drug development is to move away from routine clinical trial approaches and move more towards a "Stratified Medicine" approach targeting well defined populations. In order to do this we must focus on designing clinical trials with enough statistically power, with clearly defined study endpoints, in stratified patient populations that allow us to evaluate and validate potential biomarkers of response to therapy. Novel adoptive clinical trial design incorporating putative genomic prognostic/predictive markers in randomised perspective phase II or III studies will enable clinical validation of these markers and may facilitate rapid implementation of biomarkers into routine medical practice.

My talk will focus on the challenges of adapting existing and novel biomarkers into clinical trial development and explore some of the hurdles that need to be addressed in order to do this effectively.

Symposium 3

Therapeutic Inhibition of oncogenic signaling

Chairperson:

Masakazu Toi

Kyoto University School of Medicine, Japan

Chairperson:

Chikashi Ishioka

Tohoku University School of Medicine, Japan

Jose Baselga, M.D., Ph.D.

Current Position: Professor, Department of Medicine, Harvard Medical School
Associate Director, MGH Cancer Center, Medicine, Massachusetts General Hospital
Chief, Hematology/Oncology, Medicine, Massachusetts General Hospital

Office Address: Massachusetts General Hospital
Lawrence House, Room 108
55 Fruit Street
Boston, MA. 02114

Work Phone: 617-643-2438
Work Email: jbaselga@partners.org
Work FAX: 617-643-9686

EDUCATION

9/76-6/82	MD	Medicine	Universitat Autonoma de Barcelona, Spain
11/92	Ph.D.		Universitat Autonoma de Barcelona, Spain
	Cum Laude and Extraordinary Award		

FACULTY ACADEMIC APPOINTMENTS

7/94-6/96	Instructor, Medical, Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, New York, NY.
1/95-7/10	Professor, Medicine, Universitat Autonoma de Barcelona, Spain
2010-	Professor, Medicine, Harvard Medical School, Boston, MA

APPOINTMENTS AT HOSPITALS/AFFILIATED INSTITUTIONS

7/94-6/96	Clinical Assistant Physician, Breast/Gynecology Oncology Service, Department of Medicine
1/96-7/10	Chairman, Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain
7/10 -	Physician, Medicine, Massachusetts General Hospital, Boston, MA.

MAJOR ADMINISTRATIVE LEADERSHIP POSITIONS (2010—Present)

1996-2010	Chairman, Medical Oncology Service, Vall d'Hebron University Hospital, Barcelona, Spain
1996-2010	Director, Medical Oncology, Hematology and Radiation Oncology, Vall d'Hebron University Hospital, Barcelona, Spain
2007-2010	Director, Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain
2010-	Associate Director, MGH Cancer Center, Massachusetts General Hospital
2010-	Division Chief, Division of Hematology/Oncology, Massachusetts General Hospital

PROFESSIONAL SOCIETIES (Current)

1990	American Society of Clinical Oncology	
	2004-2006	Member, Board of Directors.
	2008-2011	Member, Trials in Progress Track, Scientific Program Committee
1990	American Association for Cancer Research	
	2008-2011	Member, Board of Directors
1996	Spanish Cooperative Breast Cancer Group (SOLTI)	
	2009-	President
1996	European Society for Medical Oncology	
	2008-2009	President
	2006-2012	Member, Board of Directors
2002	European Cancer Organization	
	2010-2011	Member, Board of Directors, Re-elected
2006	Ludwing Institute for Cancer Research	
	2006-	Member, Scientific Advisory Committee
2008	American-Italian Cancer Foundation	
	2008-	Member, Board of Directors
	2008-2011	Member, Scientific Advisory Board
2010	Breast International Group	
	2010-	Member, Board of Directors

EDITORIAL ACTIVITIES (Current)

1995-2011	Member, Editorial Advisory Board, Clinical Cancer Research 2009-2011 Senior Editor,
2001-	Member, Editorial Advisory Board, Investigational New Drugs
2002-	Member, Editorial Advisory Board, Annals of Oncology
2002-2011	Member, Editorial Advisory Board, Cancer Cell
2008-	Member, Editorial Advisory Board, Cancer Prevention Research
2009-	Advisor of the Highlights Section, Nature Reviews Cancer
2011-	Founding Editor in Chief, Cancer Discovery
1995-	Ad Hoc Reviewer: Journal of the National Cancer Institute Cancer Research, International Journal of Cancer European Journal of Cancer, Cancer, New England Journal of Medicine, Cell

HONORS AND PRIZES

1989	Annual Research Competition for Residents, First Prize, Department of Medicine, State University of New York, Health Sciences Center
1990	Lederle Scholar in Clinical Oncology, Memorial Sloan-Kettering Cancer Center
1992	Travel Award, American Society of Clinical Oncology (ASCO)
1992-1993	Young Investigator Award, American Society of Clinical Oncology (ASCO)
1999	Young Investigator Award, American Association for Cancer Research (AACR)
2003	Honorary Membership Award, The European Society for Therapeutic Radiology and Oncology (ESTRO)
2004	Waun Ki Hong Visiting Professorship, UTMD Anderson Cancer Center
2004	Distinguished Alumni Award, 29th Annual Alumni Society Meeting, Memorial Sloan-Kettering Cancer Center
2005	Annual Award, European Society of Medical Oncology (ESMO), Career Recognition Award
2005	Professional Excellence Award in Biomedicine Research, Barcelona College of Physicians
2006	City Award "The Key to the City of Barcelona", Francisco Godia Foundation, Civic leadership in Barcelona
2006	Michael Clavel Lecture Award, 18th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, Contributions in early drug development
2006	San Salvatore Prize 2006, San Salvatore Foundation, Achievements in breast cancer research
2007	AICF Prize For Scientific Excellence in Medicine, American Italian Cancer Foundation
2008	Civil Order of Health – Commander with Plaque, Ministry of Health, Government of Spain; Contribution to the advanced of biomedical science in Spain
2008	Rosenthal Family Foundation Award, American Association for Cancer Research, Academic career in translational oncology
2008	Rey Jaime I Award in Medical Research, King Jaime I Foundation, Achievements in biomedical research in cancer
2010	Bruce A. Chabner Chair in Hematology Oncology, Massachusetts General Hospital Cancer Center, Academic career achievements in Hematology/Oncology
2010	Bob Pinedo Cancer Care Prize, The Society for Translational Oncology (STO), Exceptional contribution to improved care for cancer patients
2010	Gold Medal, Queen Sofia Spanish Institute, Achievements in biomedical research in cancer
2011	Honorary Doctoral Degree, Valencia University, Career excellence and innovation in biomedical research in cancer

PUBLICATIONS

>250 publications in peer-reviewed journals.

NARRATIVE REPORT ON CAREER AND RESEARCH INTERESTS

My career is focused towards the development of novel molecular targeted agents, with special emphasis in breast cancer. I have directed the pre-clinical and early clinical development of therapies against the Epidermal Growth Factor Receptor (EGFR) and the closely related HER2 receptor. My current work has expanded towards the early clinical development of mTOR and PI3Kinase inhibitors. In the process, I have been deeply involved in the creation of a new paradigm for translational and clinical research, generating hypotheses in the lab and moving them swiftly into clinical trials. On the administration front, I have led the transformation of the Vall d´Hebron Hospital Oncology from a small clinical service to a full cancer center with a large multidisciplinary research program and currently among the largest in Europe. I have recently moved to the Mass General Hospital Cancer Center.

I have devoted 20 years to the development of anti-EGFR agents in the laboratory and in the clinic. I lead the initial clinical studies that identified the optimal dose and schedule of a series of EGFR agents. I was also the first one to report clinical activity with anti-EGFR (and anti-HER2) agents and have led the full clinical development of this class of agents. Our latest work is focused in triple negative breast cancer.

I have also been closely involved in the development of anti-HER2 therapies, being the lead investigator in the first publication that demonstrated the clinical activity of the anti-HER2 monoclonal antibody trastuzumab (Herceptin) in patients with advanced HER2 over expressing breast cancer. I continue to lead state-of the art world-wide clinical trials with trastuzumab including in the neo-adjuvant and adjuvant setting. In the laboratory, I reported the synergy between paclitaxel and trastuzumab that lead to the registration clinical trial. We have also been able over the years to identify a number of mechanisms of resistance to anti-HER2 agents. Some of them including p95HER2 and hyper-activation of the PI3K-AKT-mTOR pathway are therapeutic targets themselves and we are exploring them. Our latest work includes the clinical development of novel anti-HER2 antibodies such as pertuzumab that have shown remarkable activity.

I have pioneered the development of pharmacodynamic markers of target inhibition with signal transduction inhibitors in preclinical models and translated into early clinical trials where we sequentially interrogate tumors. Among a long list of findings, we observed that inhibition of mTOR induced intra-tumoral activation of compensatory feedback loops that resulted in activation of multiple pathways. We have now identified that this activation is mediated via the IGF-1R and clinical trials with anti-mTOR and anti-IGF-1R agents given combined have shown remarkable results in patients with Luminal B hormone refractory breast cancer.

In addition to my research and administrative functions described above, I have also been deeply involved in teaching. I established the first elective in oncology at the medical school in Barcelona in 1996 and I have also been involved in teaching of residents and fellows. At the European level, I created a number of International Fellowships during my ESMO presidency from which a large number of oncologists have benefited.

Talk at IAAO2011

Session: Therapeutic Inhibition of Oncogenic Signaling

Title: PI3K pathway: Therapeutic Targeting of Malignancy

Publications selected for PI3K, mTOR and AKT, and those published in 2011

1. O'Reilly KE, Rojo F, She QB, Solit D, Mills GB, Smith D, Lane H, Hofmann F, Hicklin DJ, Ludwig DL, **Baselga J**, Rosen N. "mTOR inhibition induces upstream receptor tyrosine kinase signaling and activates AKT". Cancer Res. 2006 Feb 1;66(3):1500-8.
2. Carracedo A, Ma L, Teruya-Feldstein J, Rojo F, Salmena L, Alimonti A, Egia A, Sasaki AT, Thomas G, Kozma SC, Papa A, Nardella C, Cantley LC, **Baselga J**, Pandolfi PP. "Inhibition of mTORC1 leads to MAPK pathway activation through a PI3K-dependent feedback loop in human cancer". J Clin Invest. 2008 Sep;118(9):3065-74.
3. **Baselga J**. "Novel agents in the era of targeted therapy: what have we learned and how has our practice changed?" Ann Oncol. 2008 Sep;19 Suppl 7:vii281-8.
4. Serra V, Markman B, Scaltriti M, Eichhorn P, Valero V, Guzman M, Botero ML, Llonch E, Atzori F, Di Cosimo S, Maira M, Garcia-Echeverria C, Parra JL, Arribas J, and **Baselga J**. " NVP-BEZ235, a dual PI3K/mTOR inhibitor, prevents PI3K signaling and inhibits growth of cancer cells with activating PI3K mutations" Cancer Res. 2008 Oct 1;68(19):8022-30.
5. Eichhorn P, Gili M, Scaltriti M, Serra V, Guzman M, Nijkamp W, Beijersbergen R, Valero V, Seoane J, Bernards R and **Baselga J**. "Phosphatidylinositol 3-kinase hyperactivation results in lapatinib resistance that is reversed by the mTOR/phosphatidylinositol 3-kinase inhibitor NVP-BEZ235." Cancer Res. 2008 Nov 15;68(22):9221-30.
6. Di Cosimo S, **Baselga J**. "Targeted therapies in breast cancer: Where are we now ?" Eur J Cancer. 2008 Dec;44(18):2781-90.
7. Carracedo A, **Baselga J**, Pandolfi PP. "Deconstructing feedback-signaling networks to improve anticancer therapy with mTORC1 inhibitors." Cell Cycle. 2008 Dec 15:7(24):3805-9
8. **Baselga J**, Semiglazov V, Van Dam P, Manikhas A, Bellet M, Mayordomo J, Campone M, Kubista E, Greil R, Bianchi G, Steinseifer J, Molloy B, Tokaji E, Gardner H, Phillips P, Stumm M, Lane HA, Dixon JM, Jonat W and Rugo HS. "Phase II randomized neoadjuvant study of the mTOR inhibitor everolimus (RAD001) in combination with letrozole versus placebo and letrozole in patients witHer+ breast cancer." J Clin Oncol. 2009 Jun 1;27(16):2630-7.
9. **Baselga J**. Targeting the phosphoinositide-3 (PI3) kinase pathway in breast cancer. Oncologist. 2011;16 Suppl 1:12-9.
10. Chandarlapaty S, Sawai A, Scaltriti M, Rodrik-Outmezguine V, Grbovic-Huezo O, Serra V, Majumder PK, **Baselga J**, Rosen N. AKT inhibition relieves feedback suppression of receptor tyrosine kinase expression and activity. Cancer Cell. 2011 Jan 18;19(1):58-71.
11. Isakoff SJ, **Baselga J**. Trastuzumab-DM1: building a chemotherapy-free road in the treatment of human ePIdermal growth factor receptor 2-positive breast cancer. J Clin Oncol. 2011 Feb 1;29(4):351-4.
12. Scaltriti M, Eichhorn PJ, Cortés J, Prudkin L, Aura C, Jiménez J, Chandarlapaty S, Serra V, Prat A, Ibrahim YH, Guzmán M, Gili M, Rodríguez O, Rodríguez S, Pérez J, Green SR, Mai S, Rosen N, Hudis C, **Baselga J**. Cyclin E amplification/overexpression is a mechanism of trastuzumab resistance in HER2+ breast cancer patients. Proc Natl Acad Sci U S A. 2011 Mar 1;108(9):3761-6.
13. Gianni L, Dafni U, Gelber RD, Azambuja E, Muehlbauer S, Goldhirsch A, Untch M, Smith I, **Baselga J**, Jackisch C, Cameron D, Mano M, Pedrini JL, Veronesi A, Mendio la C, Pluzanska A, Semiglazov V, Vrdoljak E, Eckart MJ, Shen Z, Skiadopoulos G, Procter M, Pritchard KI, Piccart-Gebhart MJ, Bell R; Herceptin Adjuvant (HERA) Trial Study Team. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. Lancet Oncol. 2011 Mar;12(3):236-44.
14. Wu Y, Amonkar MM, Sherrill BH, O'Shaughnessy J, Ellis C, Baselga J, Blackwell KL, Burstein HJ. Impact of lapatinib plus trastuzumab versus single-agent lapatinib on quality of life of patients with trastuzumab-refractory HER2+ metastatic breast cancer. Ann Oncol. 2011 Mar 15.
15. Scaltriti M, Serra V, Normant E, Guzman M, Rodriguez O, Lim AR, Slocum KL, West KA, Rodriguez V, Prudkin L, Jimenez J, Aura C, **Baselga J**. Antitumor Activity of the Hsp90 Inhibitor. IPI-504 in HER2-Positive Trastuzumab-Resistant Breast Cancer. Mol Cancer THer. 2011 May;10(5):817-24.
16. Fuentes G, Scaltriti M, **Baselga J**, Verma CS. Synergy between trastuzumab and pertuzumab for human ePIdermal growth factor 2 (Her2) from colocalization: an in silico based mechanism. Breast Cancer Res. 2011 May 22;13(3):R54.
17. Serra V, Scaltriti M, Prudkin L, Eichhorn PJ, Ibrahim YH, Chandarlapaty S, Markman B, Rodriguez O, Guzman M, Rodriguez S, Gili M, Russillo M, Parra JL, Singh S, Arribas J, Rosen N, **Baselga J**. PI3K inhibition results in enhanced HER signaling and acquired ERK dependency in HER2-overexpressing breast cancer. Oncogene. 2011 Jun 2;30(22):2547-57.

David B. Solit, M.D.

Current Position: Elizabeth and Felix Rohatyn Chair for Junior Faculty
Memorial Sloan-Kettering Cancer Center
Office Address: Memorial Sloan Kettering Cancer Center
415 E. 68th Street, Room 603, New York, NY 10065
Office Phone: 646-888-2641
Office Fax: 646-888-2595
E-mail: solitd@mskcc.org

EDUCATION:
BA, University of Pennsylvania, Philadelphia, PA, 1991
MD, University of Pennsylvania School of Medicine, Philadelphia, PA, 1995

ACADEMIC POSITIONS

Assistant Member	Memorial Sloan-Kettering Cancer Center, New York, NY	2001-2005
Instructor in Medicine	Joan and Sanford I. Weill Medical College of Cornell University, New York, NY	2001-2006
Assistant Member	Memorial Sloan-Kettering Cancer Center, New York, NY	2005-2011
Assistant Professor of Medicine	Weill Cornell Medical College, New York, NY	2006-present
Associate Member	Memorial Sloan-Kettering Cancer Center, New York, NY	2011-present

HOSPITAL POSITIONS

Assistant Attending Physician	Genitourinary Oncology Service Memorial Hospital for Cancer and Allied Diseases, NY, NY	2001-2011
Laboratory Head	Memorial Hospital for Cancer and Allied Diseases, NY, NY	2006-present
Assistant Attending Physician	Human Oncology & Pathogenesis Program (HOPP)	2007-2011
Elizabeth and Felix Rohatyn Chair for Junior Faculty	Memorial Hospital for Cancer and Allied Diseases, NY, NY	2007-2011
Associate Attending Physician	Genitourinary Oncology Service Memorial Hospital for Cancer and Allied Diseases, NY, NY	2011-present
Associate Attending Physician	Human Oncology & Pathogenesis Program (HOPP)	2011-present

PROFESSIONAL MEMBERSHIPS (medical and scientific societies)

• Member, American Society of Clinical Oncology	1999-present
• Member, American Association for Cancer Research	1999-present
• Member, American Society for Clinical Investigation	2011-present

HONORS AND AWARDS

• Inductee, American Society for Clinical Investigation	2011
• Boyer Award for Excellence in Clinical Research	2007
• Elizabeth and Felix Rohatyn Chair for Junior Faculty	2007
• Kimmel Scholars Award	2007
• Prostate Cancer Foundation Investigator Award	2004
• ASCO Career Development Award	2002
• ASCO Young Investigator Award	2001
• ASCO Merit Award	2001
• Doris Duke Translational Award	2001
• NIH Clinical Scholars Research Fellow	2000
• Phi Beta Kappa, University of Pennsylvania	1992
• Summa Cum Laude, University of Pennsylvania	1991
• Rensselaer Math and Science Medal	1987
• National Merit Scholar	1987

MEETING FACULTY/PROGRAM COMMITTEES (Current)
- Co-Chair, Program Committee, AACR Annual Meeting, 2011.
- Faculty, AACR Annual Meeting: 2004, 2007, 2008, 2010, and 2011.
- Faculty, ASCO Annual Meeting: 2006, 2007, 2008, 2009, 2010, and 2011.

Other Committees
- Co-chair, GI Tissue committee, CALGB (2010 – present).
- Scientific Advisory Board, Prostate Cancer Foundation (2008-present)
- Grant Review Committee, Melanoma Research Alliance (2010-present)
- MSKCC whole genome working group (2010-present)

JOURNAL EDITORIAL BOARDS, REVIEWER
- Editorial Board, Clinical Cancer Research
- Editorial Board, Molecular Cancer Therapeutics
- Ad Hoc Reviewer: Nature, Journal of Clinical Investigation, PLOS Medicine, PLOS One, Cancer Research, Clinical Cancer Research, Molecular Cancer Therapeutics, Oncogene, Cancer Chemotherapy and Pharmacology, Journal of the National Cancer, Science Translational Medicine, Journal of Clinical Oncology, International Journal of Cancer, The Prostate, Journal of Investigative Dermatology.

PUBLICATIONS

>60 publications in peer-reviewed journals.

Publications in 2011

1. Bachleitner-Hofmann T, Sun M, Chen C-T, Liska D, Zeng Z, Viale A, Olshen A, Mittlboeck M, Chistensen J, Rosen N, **Solit D**, Weiser M, Antitumor activity of SNX-2112, a synthetic heat shock protein-90 inhibitor, in MET-amplified tumor cells with or without resistance to selective MET inhibition. *Clin Cancer Res* 2011; 17(1):122-33. PMID: 21208906.
2. Al-Ahmadie H, Iyer G, Janakiraman M, Lin O, Tickoo S, Fine S, Gopalan A, Chen Y, Balar A, Riches J, Bochner B, Dalbagni G, Bajorin D, Reuter V, Milowsky M, **Solit D**, Somatic mutation of Fibroblast Growth Factor Receptor-3 (FGFR3) defines a distinct morphologic subtype of high-grade urothelial carcinoma. *J Pathol;* 224(2):270-9, 2011. PMID: 21547910
3. Modi S, Stopeck A, Linden H, **Solit D**, Chandarlapaty S, Rosen N, D'Andrea G, Dickler MN, Moynahan M, Sugarman S, Ma W, Patil S, Norton L, Hannah A, Hudis C. HSP90 Inhibition is Effective in Breast Cancer: A Phase 2 Trial of Tanespimycin (17AAG) plus Trastuzumab in Patients with HER2-Positive Metastatic Breast Cancer Progressing on Trastuzumab. *Clin Cancer Res,* Epub, May 2011. PMID: 21558407.
4. Xing F, Persaud Y, Pratilas C, Taylor B, Janakiraman M, She QB, Gallardo H, Liu C, Merghoub T, Hefter B, Dolgalev I, Viale A, Heguy A, De Stanchina E, Cobrinik D, Bollag G, Wolchok J, Houghton A, **Solit D**, Concurrent loss of the PTEN and RB1 tumor suppressors attenuates RAF-dependence in melanomas harboring ^{V600E}BRAF, *Oncogene*, in press, 2011.

NARRATIVE REPORT ON CAREER AND RESEARCH INTERESTS

The focus of my laboratory is the development of cancer therapies that target pathways responsible for cancer initiation and progression. I am particularly interested in the study of cancers dependent upon alterations in tyrosine kinase and steroid receptor signaling. In pursuit of this goal, we have established relevant model systems in which changes in a drugs proposed molecular target can be correlated with drug dose, serum level, and anticancer activity. Our hypothesis is that the consequences of pathway inhibition will vary as a function of cell lineage and the complement of mutations within a tumor cells. Therefore, in order to improve the treat of cancer patients, one must understand not only which genetic changes are commonly found within particular tumor types but the mechanisms whereby these genetic alterations support tumor growth, survival, metastasis or other hallmarks of the cancer phenotype.

One focus of the laboratory is understanding the role played by activated Ras and Raf in mediating transformation. The RAS/RAF/MEK/ERK cascade (MAPK pathway) transduces growth factor initiated signals that regulate cell proliferation and survival. Constitutive activation of this pathway is a common event in human tumors and activating mutations in this pathway occur in Ras, B-Raf and upstream receptor tyrosine kinases (RTK) in a mutually exclusive fashion. We find that tumor cells with activating BRAF mutations are selectively sensitivity to MEK inhibition (Solit et al., Nature 2006). Tumors in which MAP kinase is activated by other upstream activating mutations (RAS, RTKs, unknown) are typically less sensitive or resistant to MEK inhibition.

Using pharmacologic and genetic methods, current studies are focused on identifying which downstream effector pathways are most responsible for mediating growth and survival in tumors with Ras and B-Raf mutations. These studies are of interest as selective inhibitors of these downstream pathways are currently being testing in patients at MSKCC and elsewhere. Concurrent mutations that mediate resistance to Raf and MEK inhibitors are also being studied using preclinical model systems and human tumor samples. One goal of such studies is to use the data generated to develop rational combination therapies.

Talk at IAAO2011

Session: Therapeutic Inhibition of oncogenic signaling

Title; Genetic predictors of RAF-dependence.

Abstract

Abstract: There is a desperate need for more effective treatments for patients with advanced cancer. Approximately half of melanomas have an activating mutation of the BRAF gene. PLX4032 (also called vemurafinib) is a potent and selective inhibitor of the most common mutant form of BRAF. In a Phase I trial of PLX4032, approximately 80% of patients with melanoma whose tumors express the BRAF mutation experienced significant tumor shrinkage with minimal side effects. In contrast, none of the patients with melanomas without a BRAF mutation responded to the drug. These promising results demonstrate what can be achieved with personalized, molecularly targeted therapy for melanoma and other solid tumors. However, the degree of tumor shrinkage varied greatly among patients and many of the patients who initially responded to PLX4032 subsequently developed resistance. The experience with targeted therapies in other diseases suggests that understanding the causes of resistance can lead to improved patient selection for treatments like PLX4032 and the development of more effective drug combinations. My laboratory is focused on identifying the mechanisms of resistance to PLX4032 and other targeted kinase inhibitors. In this lecture, I will review the genetic basis for RAF inhibitor resistance and highlight ways in which real time genetic evaluation of human tumors is altering the development of novel targeted cancer therapies.

Five selected references for the IAAO2011 Talk.

1. Al-Ahmadie H, Iyer G, Janakiraman M, Lin O, Tickoo S, Fine S, Gopalan A, Chen Y, Balar A, Riches J, Bochner B, Dalbagni G, Bajorin D, Reuter V, Milowsky M, **Solit D**, Somatic mutation of Fibroblast Growth Factor Receptor-3 (FGFR3) defines a distinct morphologic subtype of high-grade urothelial carcinoma. *J Pathol;* 224(2):270-9, 2011. PMID: 21547910

2. Xing F, Persaud Y, Pratilas C, Taylor B, Janakiraman M, She QB, Gallardo H, Liu C, Merghoub T, Hefter B, Dolgalev I, Viale A, Heguy A, De Stanchina E, Cobrinik D, Bollag G, Wolchok J, Houghton A, **Solit D**. Concurrent loss of the PTEN and RB1 tumor suppressors attenuates RAF-dependence in melanomas harboring ^{V600E}BRAF, *Oncogene*, 1-12, 2011.

3. Janakiraman M, Vakiani E, Zeng Z, Pratilas C, Taylor B, Chitale D, Halilovic E, Ricarte-Filho J, Persaud Y, Levine D, Fagin J, Lash A, Jhanwar S, Mariadason J, Ladanyi M, Saltz L, Heguy A, Paty P, **Solit D**, Genomic and biological characterization of exon 4 KRAS mutations in human cancer. *Cancer Res* 2010; 70(14). PMID: 20570890.

4. Joseph E, Pratilas C, Poulikakos P, Tadi M, Wang W, Taylor B, Persaud Y, Halilovic E, Xing F, Viale A, Tsai J, Bollag G, **Solit D**, Rosen N, The pan-RAF inhibitor PLX4032 inhibits ERK signaling and tumor cell proliferation in a (V600E) mutant B-RAF-selective manner. *Proc Natl Acad Sci USA* 2010; 107(33):14903-8. PMID: 20668238. (The last two authors contributed equally to this study).

5. Halilovic E, She QB, Ye Q, Pagliarinis R Sellers W, **Solit D**, Rosen N, PIK3CA Mutation Uncouples Tumor Growth and Cyclin D1 Regulation from MEK/ERK and Mutant KRAS Signaling. *Cancer Res* 2010; 70(17):6804-14. PMID: 20699365.

NEAL ROSEN, M.D., Ph.D.

Current Positions: Enid A. Haupt Chair in Medical Oncology
Member, Department of Medicine
Member, Program in Molecular Pharmacology and Chemistry
Memorial Sloan-Kettering Cancer Center, New York, NY

Professor of Pharmacology, Cornell University Graduate School of Medical Sciences, New York, NY
Professor of Medicine, Joan and Sanford I. Weill Medical College, Cornell University, New York, NY

Addresses: Memorial Sloan-Kettering Cancer Center
Mail: 1275 York Avenue – Box 271
Office: 415-17 East 68th Street – Room Z-1760
New York, NY 10065

Office Phone: 646 / 888-2075
Office Fax: 646 / 422-0246
E-mail: rosenn@mskcc.org

EDUCATION

1971 BA, Columbia College, New York, NY
1979 MD, PhD (Molecular Biology), Albert Einstein College of Medicine, New York, NY

ACADEMIC APPOINTMENTS

1985—1988 Senior Investigator, Medicine Branch, National Cancer Institute, Bethesda, MD
1988—1991 Associate Professor of Medicine, Georgetown University Medical School, Washington, DC
1992—1998 Associate Member, Program in Cell Biology and Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY
Associate Professor of Cell Biology, Cornell University Graduate School of Medical Sciences, New York, NY
1992—2000 Associate Professor of Medicine, Joan and Sanford I. Weill Medical College, Cornell University, New York, NY
1998— Member, Departments of Medicine and Neurology; and Program in Molecular Pharmacology and Chemistry, Memorial Sloan-Kettering Cancer Center, New York, NY
Professor of Pharmacology, Cornell University Graduate School of Medical Sciences, New York, NY
2000— Professor of Medicine, Joan and Sanford I. Weill Medical College, Cornell University, New York, NY

HOSPITAL APPOINTMENTS

1988—1991 Director, Gastrointestinal Oncology Clinic, Lombardi Cancer Center, Georgetown University Medical School, Washington, DC
1991—1998 Associate Attending Physician, Department of Medicine, Memorial Hospital for Cancer and Allied Diseases
1998— Attending Physician, Department of Medicine, Memorial Hospital for Cancer and Allied Diseases (Breast, Gastroenterology, and Genitourinary Services)

RESEARCH INTERESTS

- The biologic and therapeutic implications of oncogene-mediated feedback inhibition of the signaling network.
- Integration of RAS and PI3K pathway function.
- The Hsp90 chaperone as a therapeutic target.
- Development of inhibitors of mitogenic signaling as therapeutics for cancer.

PUBLICATIONS

>150 publications in peer-reviewed journals.

Selected Publications 2010 – 2011

1. Chandarlapaty S, Scaltriti M, Angelini P, Ye Q, Guzman M, Hudis CA, Norton L, Solit DB, Arribas J, Baselga J, Rosen N. Inhibitors of HSP90 block p95-HER2 signaling in Trastuzumab-resistant tumors and suppress their growth. Oncogene; Jan 21; 29(3): 325-34. 2010. [PMID # 19855434]
2. Scaltriti M, Chandarlapaty S, Prudkin L, Aura C, Jimenez J, Angelini PD, Sanchez G, Guzman M, Parra JL, Ellis C, Gagnon R, Koehler M, Gomez H, Geyer C, Cameron D, Arribas J, Rosen N, Baselga J. Clinical benefit of lapatinib-based therapy in patients with human epidermal growth factor receptor 2-positive breast tumors coexpressing the truncated p95HER2 receptor. Clin Cancer Res; 16(9): 2688-95. 2010.
3. Poulikakos, PI, Zhang C, Bollag G, Shokat KM, and Rosen N. RAF inhibitors transactivate RAF dimers and ERK signaling in cells with wild-type BRAF. Nature; 464(7287): 427-30. 2010. [PMID # 20179705]
4. She QB, Halilovic E, Ye Q, Zhen W, Shirasawa S, Sasazuki T, Solit DB, and Rosen N. 4E-BP1 is a key effector of the oncogenic activation of the AKT and ERK signaling pathways that integrates their function in tumors. Cancer Cell; 18(1): 39-51. 2010.
5. Halilovic E, She QB, Ye Q, Pagliarini R, Sellers WR, Solit DB, and Rosen N. PIK3CA mutation uncouples tumor growth and cyclin D1 regulation from MEK/ERK and mutant KRAS signaling. Cancer Res; 70(17): 6804-14. 2010.
6. Joseph EW, Pratilas CA, Poulikakos PI, Tadi M, Wang W, Taylor BS, Halilovic E, Persaud Y, Xing F, Viale A, Tsai J, Chapman PB, Bollag G, Solit DB, and Rosen N. The RAF inhibitor PLX4032 inhibits ERK signaling and tumor cell proliferation in a V600E BRAF-selective manner. Proc Natl Acad Sci U S A; 107(33):14903-8. 2010. PMCID: PMC2930420
7. Chandarlapaty S, Sawai A, Scaltriti M, Rodrik-Outmezguine V, Grbovic-Huezo O, Serra V, Majumder PK, Baselga J, and Rosen N. AKT inhibition relieves feedback suppression of receptor tyrosine kinase expression and activity. Cancer Cell; 19(1):58-71. 2011. PMCID: PMC3025058
8. Poulikos PI, and Rosen N. Mutant BRAF melanomas: Dependence and resistance. Cancer Cell; 19(1): 11-5. 2011.
9. Solit DB, Rosen N. Resistance to BRAF inhibition in melanomas. N Engl J Med; 364(8): 772-4. 2011.
10. Serra V, Scaltriti M, Prudkin L, Eichorn P, Ibrahim YH, Chandarlapaty S, Markman B, Rodriguez O, Guzman M, Rodriguez S, Gili M, Russillo M, Parra JL, Singh S, Arribas J, Rosen N, Baselga J. PI3K inhibition results in enhanced HER signaling and acquired ERK dependency in HER2-overexpressing breast cancer, Oncogene; 30(22): 2547-57. 2011.
11. Carver BS, Chapinski C, Wongvipat J, Hieronymous H, Chen Y, Chandarlapaty S, Arora VK, Le C, Koutcher J, Scher H, Scardino PT, Rosen N, Sawyers CL. Reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. Cancer Cell; 19(5): 575-86. 2011.
12. Modi S, Stopeck AT, Linden HM, Solit DB, Chandarlapaty S, Rosen N, D'Andrea G, Dickler MN, Moynahan ME, Sugarman S, Ma W, Patil S, Norton L, Hannah AL, Hudis C. Hsp90 inhibition is effective in breast cancer: A phase 2 trial of Tanespimycin (17AAG) plus Trastuzumab in patients with Her2-positive metastatic breast cancer progressing on Trastuzumab. (May 10, 2011) Clin Cancer Res, 10.1158/1078-0432.CCR-11-0072.
13. Rodrik-Outmezguine VS, Chandarlapaty S, Pagano NC, Poulikakos PI, Scaltriti M, Moskatel E, Baselga J, Guichard S, Rosen N. mTOR kinase inhibition causes feedback-dependent biphasic regulation of AKT signaling. (June 17, 2011) Cancer Discovery, 10.1158/2159-8290.CD-11-0085.

Talk at IAAO 2011

Session: Therapeutic Inhibition of Oncogenic Signaling

Title: Feedback and redundancy of oncogenic signaling pathways

Neal Rosen's suggested 5 (maximum) journal articles that would provide useful background for his IAAO 2011 talk:

1 O'Reilly KE, Rojo F, She Q-B, Solit D, Mills GB, Smith D, Lane H, Hofmann F, Hicklin DJ, Ludwig DL, Baselga J, and Rosen N. m-TOR inhibition induces upstream receptor tyrosine kinase signaling and activates Akt. Cancer Res; 66(3): 1500-08. 2006.

2 Pratilas CA, Taylor BS, Ye Q, Viale A, Sander C, Solit DB , Rosen N. (V600E) BRAF is associated with disabled feedback inhibition of RAF-MEK signaling and elevated transcriptional output of the pathway. Proc Natl Acad Sci USA; 106(11): 4519-24. 2009. PMCID #: PMC2649208

3 She QB, Halilovic E, Ye Q, Zhen W, Shirasawa S, Sasazuki T, Solit DB, and Rosen N. 4E-BP1 is a key effector of the oncogenic activation of the AKT and ERK signaling pathways that integrates their function in tumors. Cancer Cell; 18(1): 39-51. 2010.

4 Chandarlapaty S, Sawai A, Scaltriti M, Rodrik-Outmezguine V, Grbovic-Huezo O, Serra V, Majumder PK, Baselga J, and Rosen N. AKT inhibition relieves feedback suppression of receptor tyrosine kinase expression and activity. Cancer Cell; 19(1):58-71. 2011. PMCID: PMC3025058

5 Rodrik-Outmezguine VS, Chandarlapaty S, Pagano NC, Poulikakos PI, Scaltriti M, Moskatel E, Baselga J, Guichard S, Rosen N. mTOR kinase inhibition causes feedback-dependent biphasic regulation of AKT signaling. (June 17, 2011) Cancer Discovery, 10.1158/2159-8290.CD-11-0085.