THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
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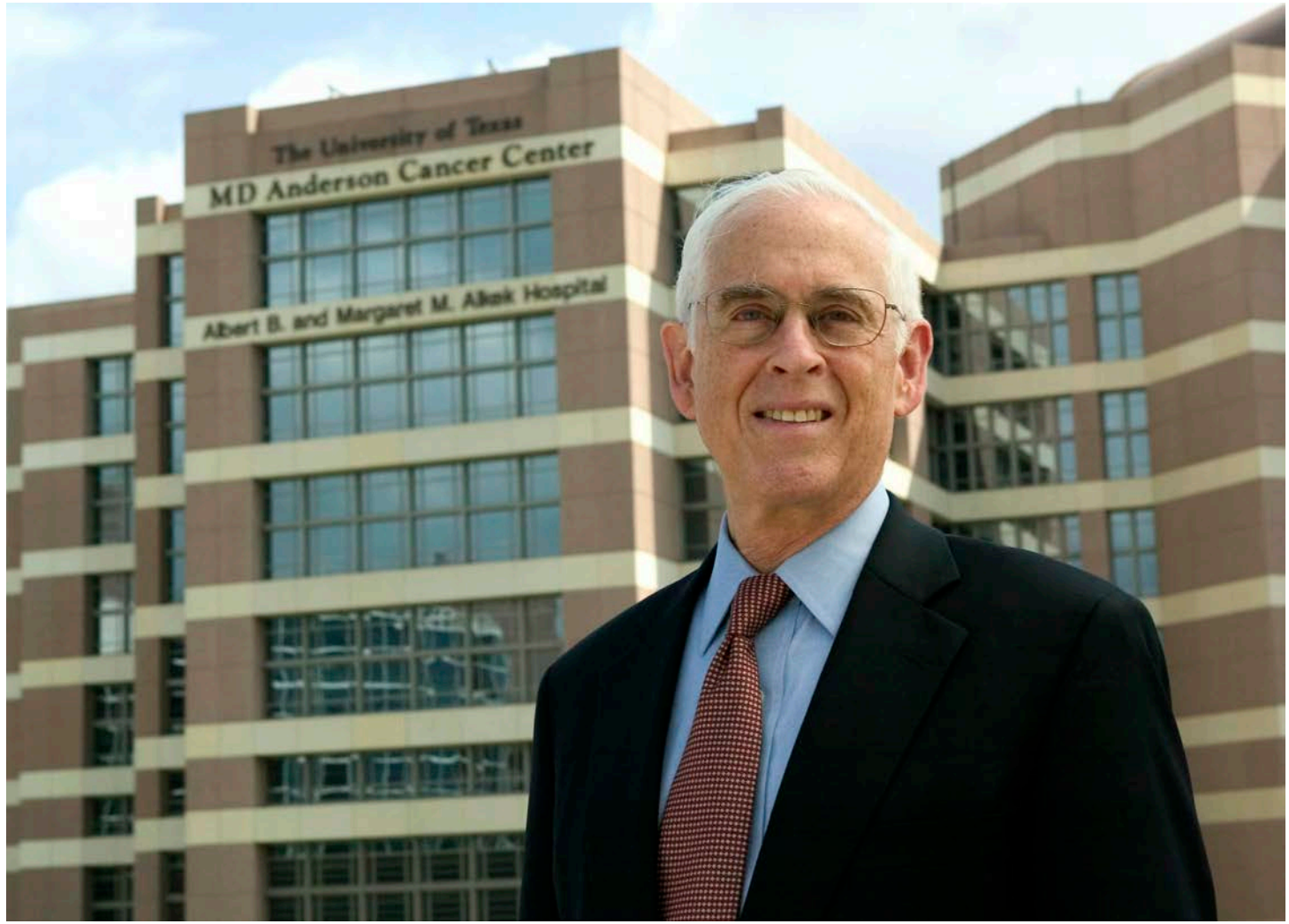
# Precision Cancer Medicine: Achievements and Prospects

**John Mendelsohn, MD**
**President Emeritus**

*Tang Prize Award Ceremony*

*September 22, 2018*

*Presented by Mien-Chie Hung, PhD*




**Dr. John Mendelsohn with M.D. Anderson’s Hospital**

# Education

- **Harvard College, Cambridge, MA, B.A., 1958, Biochemical Science**
- **University of Glasgow, Glasgow, Scotland, Fulbright Scholar, 1959, Research in Molecular Biology**
- **Harvard Medical School, M.D. 1963**

## Academic Administrative Appointments/Responsibilities

- **Founding Director of Cancer Center, University of California, San Diego, CA, 1976-85**
- **Chairman, Department of Medicine, Memorial Sloan- Kettering Cancer Center, New York, NY, 1985-96**
- **President, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 1996- 2011**
- **Director, Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 2011-18**

## Scientific Achievements

- **First hypothesis, with Dr. Gordon Sato, that inhibition of EGF receptors and of a tyrosine kinase might be an effective anticancer treatment. 1980**
- **First creation of an anti-EGF receptor/anti-tyrosine kinase agent that blocked receptor kinase activation and inhibited cell growth. 1983-84**
- **First clinical trial with an agent targeting a growth factor receptor and a tyrosine kinase, demonstrating safety and feasibility. 1990**
- **First studies demonstrating mechanisms by which inhibition of EGF receptor tyrosine kinase inhibits cell proliferation and other cellular functions. 1996**
- **First clinical trial providing proof of concept that an antireceptor agent (Herceptin) used alone could produce a clinically useful response rate (10%) in patients. 1996**
- **First clinical trial demonstrating that addition of an EGF receptor inhibitor could overcome resistance to a chemotherapeutic agent (cisplatin in head and neck cancer). 2001**

# FDA Approved Anti-cancer Drugs

- **C225 (Cetuximab/Erbitux) for advanced, irinotecan-refractory colorectal cancer, 2004**

- **C225 with radiation for head and neck cancer, 2006**

- **Herceptin for HER-2/neu positive breast cancer, 1999**

## HONORS AND AWARDS

- Phi Beta Kappa, Harvard College, 1958
- United States Fulbright Scholar in Biochemistry, University of Glasgow, Scotland, 1958-59
- Alpha Omega Alpha, Harvard Medical School, 1962
- First Prize, Boylston Society Essay Contest, Harvard Medical School, 1963
- Research Career Development Award, National Institutes of Health, 1973-78
- Visiting Professor, Netherlands Cancer Institute, Amsterdam (sabbatical), 1978
- American Cancer Society Professor of Clinical Oncology, 1982-85
- "Headliner of the Year" in Medicine, Press Association, San Diego, CA, 1985
- Winthrop Rockefeller Chair in Medical Oncology, Memorial Sloan-Kettering Cancer Center, 1985-96
- Merit Award, National Cancer Institute Grant, 1990-97
- Raymond Bourgine Award for Excellence in Cancer Research, 1997

## HONORS AND AWARDS

- Bristol-Myers-Squibb Cancer Research Award, 1997
- Gold Medal of Paris, 1997
- Elected Member, Institute of Medicine of the National Academy of Science, 1997
- Breast Cancer Research Foundation's Jill Rose Award for Outstanding Breast Cancer Research, 1997
- 4th Joseph H. Burchenal American Association for Cancer Research Clinical Research Award, 1999
- Elected Member, Royal Netherlands Academy of Arts and Sciences, 1999-
- Simon M. Shubitz Award, University of Chicago Cancer Research Foundation, 2002
- David A. Karnofsky Memorial Award, American Society of Clinical Oncology, 2002
- 27th Bristol-Myers Squibb Freedom to Discover Award for Distinguished Achievement in Cancer Research, 2004
- Fulbright Lifetime Achievement Medal, 2005
- Honorary Doctor and Professor, China Medical University, Taichung, Taiwan, 2005
- Dan David Prize in Cancer Therapy, 2006

# Rationale 1980

- EGF characterized 1962[1]. EGFR characterized 1975-80.[2] (Cohen-Nobel Prize, 1986).
- Autocrine hypothesis: EGF or TGFα can autostimulate the cell's EGFRs. (Todaro and Sporn).[3]
- Tyrosine kinase activity first identified in *src* oncogene and EGFR (Cohen, Hunter, Erickson).[2,4,5]
- Overexpression of EGFR common in human cancers (Ozanne, many others).[6]
- Preferential addiction of transformed cells.
- "Experiments of nature." Circulating autoantibodies against receptors can cause stable physiologic change (disease): myasthenia gravis, thyroid disease and insulin resistance.
- Right technologies: nude mice, monoclonal antibodies.

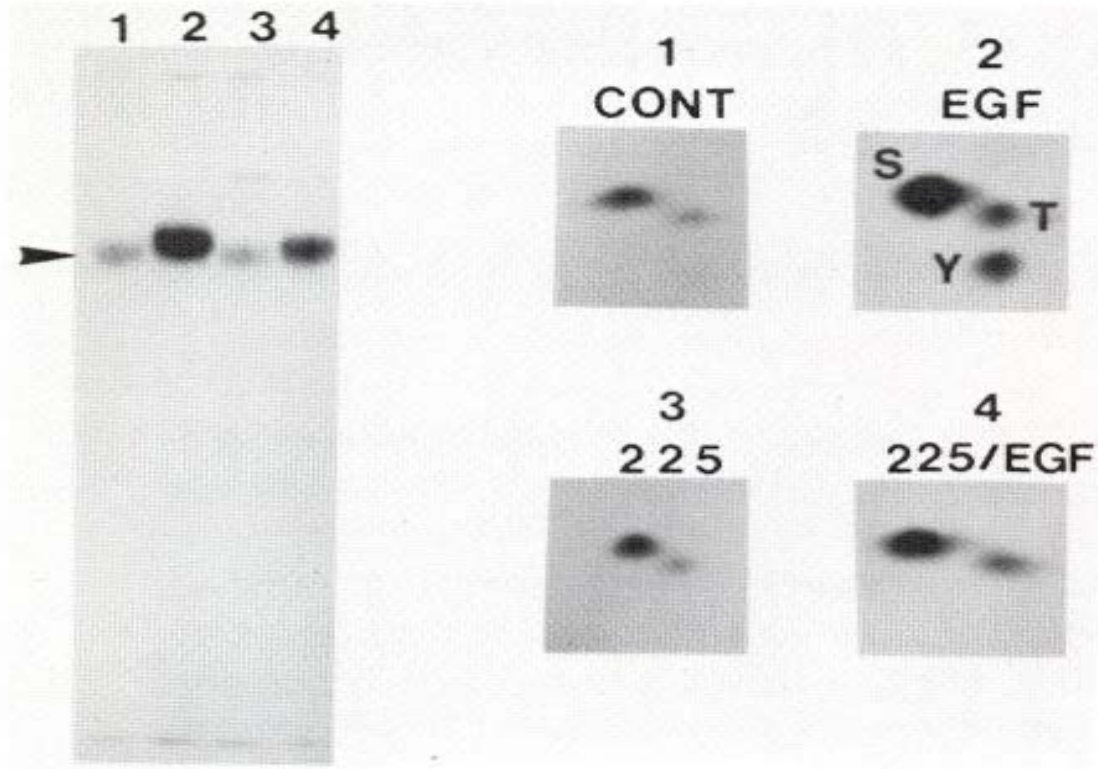
**1. Cohen S. J Biol Chem 1962;237:1555-1562; 2. Chinkers M, Cohen S. Nature 1981;290:516-519;**
**3. Sporn MB, Todaro GJ. N Engl J Med 1980;303:878-880; 4. Cooper JA, Hunter T. J Cell Biol 1981;91:878-883;**
**5. Erickson E, et al. J Biol Chem 1981;256:11381-11384; 6. Mendelsohn J, Baselga J. Oncogene 2000;19:6550-6565**

# Hypothesis: 1980

John Mendelsohn
and
Gordon H. Sato

Monoclonal antibodies which bind to EGF receptors and block access to EGF or TGF-$\alpha$ may prevent cell proliferation, by inhibiting activation of the EGF receptor tyrosine kinase.

# Inhibition of P- Tyrosine by mAb225



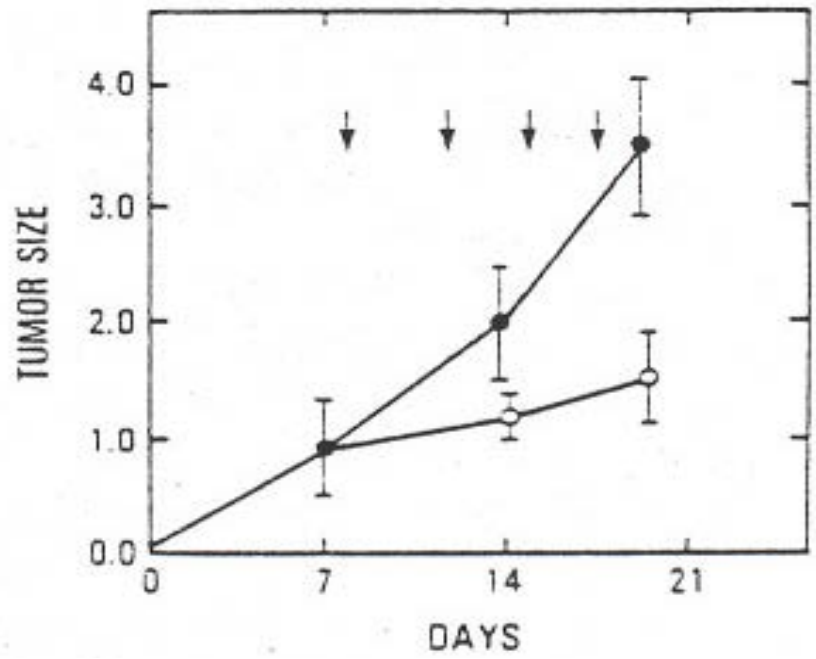

A431 cells incubated with $^{32}P$, then (1) no addition, (2) EGF, (3) mAb225, (4) EGF + mAb225: immunoprecipitated with mAb528, gel electrophoresis, hydrolysis and 2D-thin layer electrophoresis.

Sunada, J Cell Physiol. 1990

# Growth Inhibition of Human Tumor Cells in Athymic Mice by Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies[1]

Hideo Masui,[2] Tomoyuki Kawamoto, J. Denry Sato,[3] Bonnie Wolf, Gordon Sato,[4] and John Mendelsohn[5]

*Cancer Center, Q-058, University of California, San Diego, La Jolla, California 92093*




- control group, o treated group

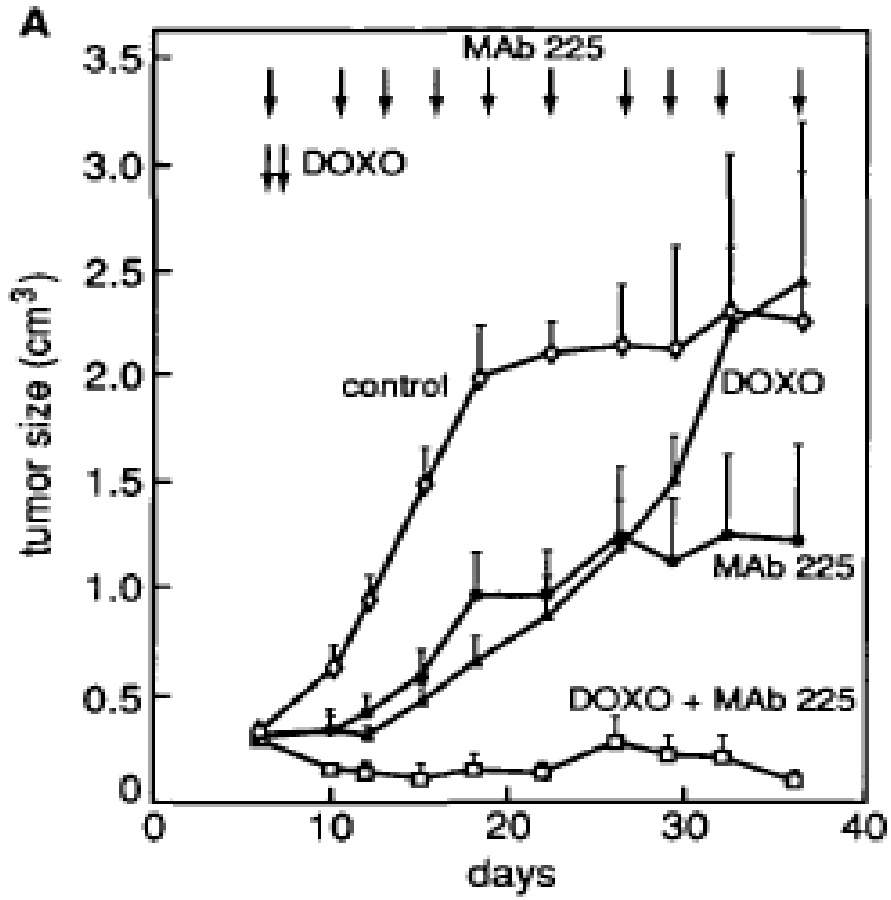
Cancer Research 44, 1002-1007, March 1984

# Summary of Accomplishments 1980 - 1990

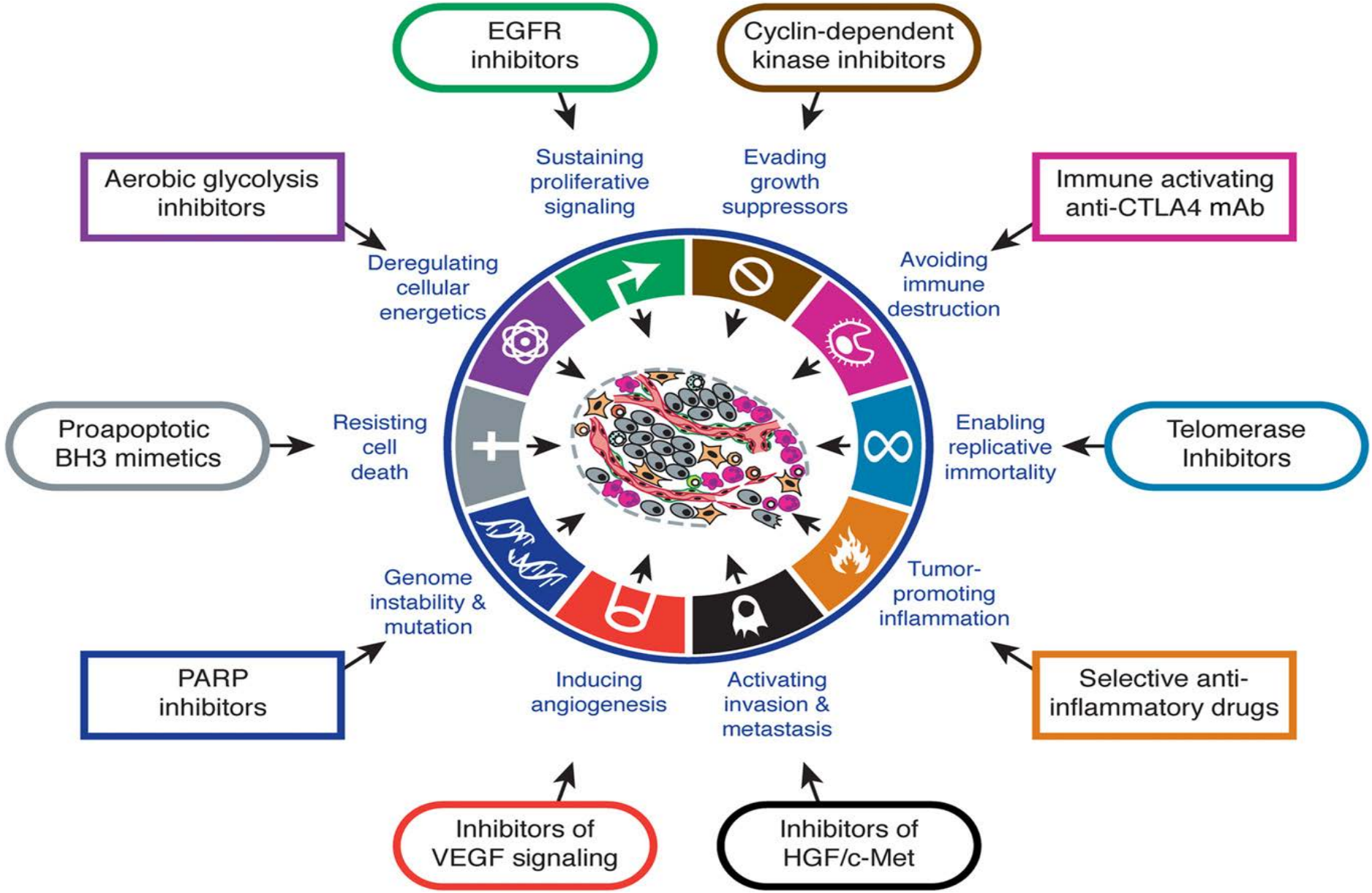
1. First hypothesis, with Dr. Gordon Sato, that an agent blocking activation of a growth factor receptor could inhibit cell proliferation.
2. First production of an agent that inhibited a receptor tyrosine kinase.
3. First clinical trial in humans with an agent targeting a growth factor receptor and a tyrosine kinase.
4. First clinical trial with a monoclonal antibody specifically designed to alter a biologic function, not to elicit an immunological response. In fact, it can do both.

# Antitumor Effects of Doxorubicin in Combination With Anti-epidermal Growth Factor Receptor Monoclonal Antibodies

*Jose Baselga, Larry Norton, Hideo Masui, Atanasio Pandiella, Keren Coplan, Wilson H. Miller, Jr., John Mendelsohn*




J Natl Cancer Instit 85:1327-1333, 1993




**HALLMARKS OF CANCER**

Hanahan D and Weinberg RA, *Cell* 144, 5:646-674, 2011

# Molecularly Targeted Oncology Agents – FDA Approved

| Agent | Target | Class | Disease |
|---|---|---|---|
| Alemtuzumab (Campath) | CD52 | mAb | B-CLL |
| Anastrozole (Arimidex) | Aromatase | Aromatase inhibitor | Breast Cancer |
| Bevacuzumab (Avastin) | VEGF | mAb | NSCLC, T Cell Lymphoma, CRC |
| Bortezomib (Velcade) | Proteasome | Proteasome inhibitor | Multiple Myeloma |
| Cetuximab (Erbitux) | EGFR | mAb-TKI | CRC, HNSCC |
| Dasatinib (Sprycel) | Bcr-Abl, Src | TKI | CML |
| Erlotinib (Tarceva) | EGFR | TKI | NSCLC, Pancreatic Cancer |
| Gefitinib (Iressa) | EGFR | TKI | NSCLC |
| Gemtuzumab (Mylotarg) | CD33 | mAb | B Cell NHL |
| ***Imatinib (Gleevac)*** | cKit, Bcr-Abl, PDGFR | TKI | CML, GIST |
| Irbitumomab (Zevalin) | CD20 | mAb | B Cell NHL |
| Lapitinib (Tykerb) | EGFR/Her2 | TKI | Breast Cancer |
| Nilotinib (Tasigna) | Bcr-Abl, cKit, PDGF | TKI | CML |
| Panitumumab (Vectibix) | EGFR | mAb-TKI | CRC |
| Rituximab (Rituxan) | CD20 | mAb | B Cell NHL |
| Sorafenib (Nexavar) | Raf, MAPK, VEGFR2, PDGFR | TKI | RCC |
| Sunitinib (Sutent) | VEGFR2, PDGFR, cKit, FGFR | TKI | RCC, GIST |
| Temsirolimus (Torisel) | mTOR | Ser/Thr kinase inhibitor | RCC |
| Tositumomab (Bexxar) | CD20 | mAb | Follicular NHL |
| Trastuzumab (Herceptin) | Her2/neu (Erb2) | mAb-TKI | Breast Cancer |

**11/20 target**
**TK**
**5/20 target**
**EGFR**

# Personalized Cancer Therapy: The Paradigm of Cancer as a Genetic Disease

1. We have identified most of the genetic abnormalities that cause cancer.
2. There are over 800 drugs in the pipeline that target the products of those abnormal genes.
3. We can detect aberrant genes (biomarkers) in an individual patient's cancer in a reasonable time frame, and at a reasonable cost.
4. Clinical trials assigning a targeted therapy on the basis of the genetic aberrations in a patient's cancer have resulted in successes.

# Personalized Cancer Therapy – Recent Successes: Importance of Biomarkers

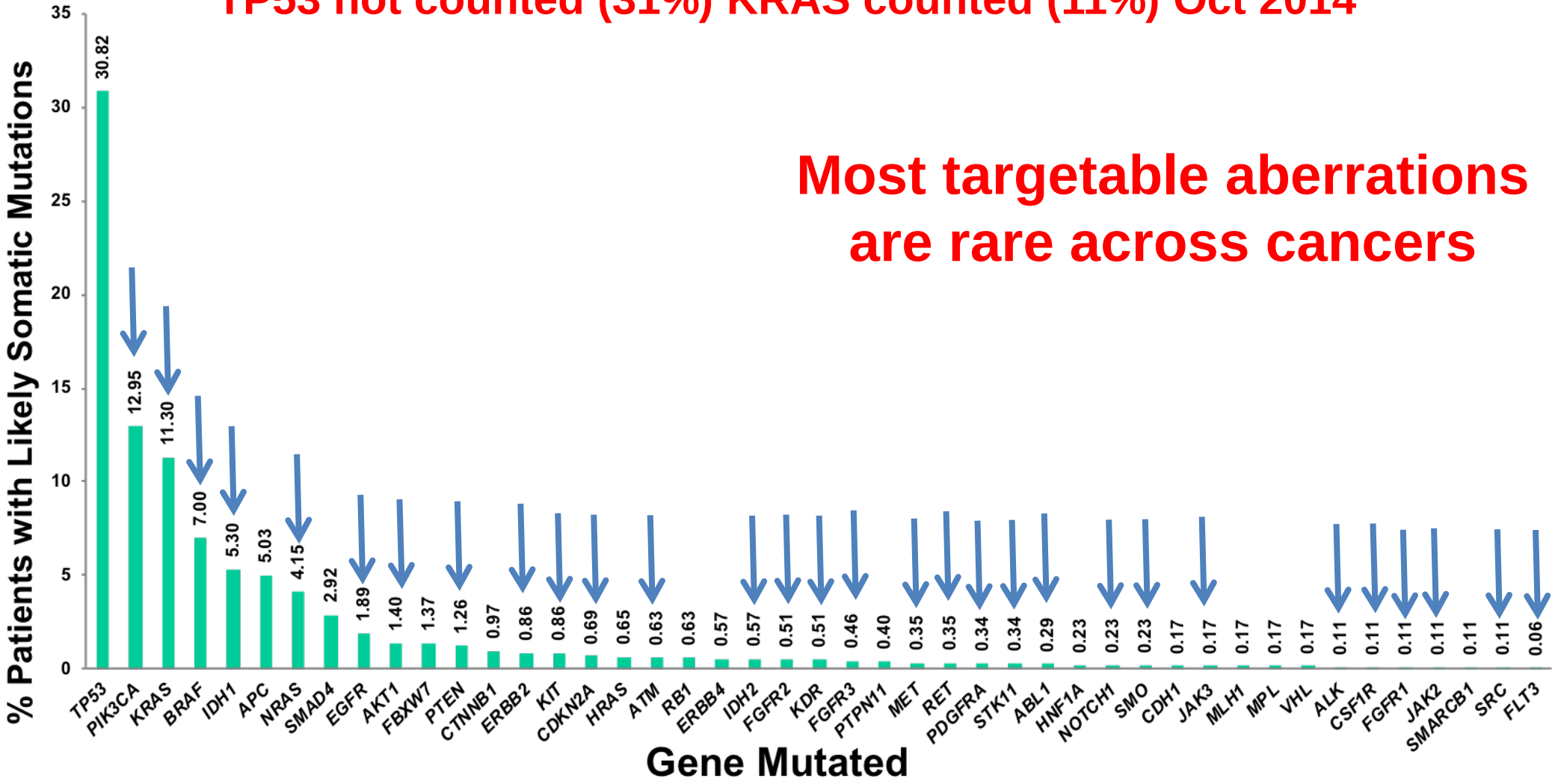
1. Trastuzumab for high-HER2 breast cancer. Slamon, NEJM, 2001
2. Imatinib, first for CML, then for GI stromal tumors with cKit mutations. Drucker, NEJM, 2001, Demitri, NEJM, 2002.
3. PARP inhibitor olaparib for BRCA 1/2-associated cancers. Fong, NEJM, 2009.
4. Gefitinib against the EGF receptor as first line therapy for advanced NSCLC. Mok, NEJM 2009
5. Crizotinib for lung cancers with ALK-EML rearrangements. Kwak, NEJM, 2010.
6. Vemurafenib for melanomas with BRAF V600E mutations. Flaherty, NEJM, 2010.

# Sheikh Khalifa Institute for Personalized Cancer Therapy: 2011 Goals

1. Create the infrastructure and platforms for genetic analysis of large numbers of clinical cancer specimens. Other "omics" to follow.
2. Support clinical trials bringing therapies to patients that target the genetic aberrations in their cancers.
3. Provide decision support to create personalized cancer treatment plans.
4. Promote research into the mechanisms of response and resistance to targeted therapies.
5. Demonstrate the value of this approach so that it will become standard of practice and reimbursed.
6. Educate the next generation of clinical investigators.

# 2000 patients likely to enter trials
# Hot Spot Mutation: 50 Gene Panel
# Potentially actionable 39%

## TP53 not counted (31%) KRAS counted (11%) Oct 2014




## Most targetable aberrations are rare across cancers

IPCT: F. Meric-Bernstam, G. Mills, K. Shaw, J. Mendelsohn

# Patients Screened for **Non-Standard** of Care Potentially Actionable Genomic Aberrations: first 2,000 patients, updated 2016

| | 50 gene panel | 400 gene* panel |
|---|---|---|
| **Potentially actionable somatic mutations** (not including TP53) | **39%** | **47%** |
| **Non-actionable somatic mutations** | **21%** | |
| **Likely germline variants** | **10%** | |
| **No mutations/variants** | **30%** | |
| **Treated on genotype matched trials** | **11%** | **24%** |

***More genes, includes copy number, decision support provided, increased number of trials available.

IPCT: F. Meric-Bernstam, G. Mills, K. Shaw, J. Mendelsohn

# Genotype/Biomarker-Selected Basket Trials in ICT

| | |
|---|---|
| Akt | AZD5363, MSC2363318A |
| PTEN | Buparlisib, MSC2363318A, Talazoparib |
| PIK3R1/2 | MSC2363318A |
| PIK3CA | AZD536, GDC-0032, MSC2363318A |
| FGFR1/2/3 | BGJ398, TAS-120, Debio1347 |
| FGFR4 | TAS-120 |
| FGFs | BGJ398, TAS-120 |
| NRAS | BGJ398, TAS-120 |
| KRAS | CB-839, Selumetinib |
| BRAF | Dabrafenib+Trametinib, LGK974, Sorafenib, Vemurafenib, BVD-523 |
| N-MYC | GSK525762 |
| NUTM1 | GSK525762 |
| EGFR | Erlotinib, KBP-5209, Neratinib |
| HER3 | KBP-5209, Neratinib |
| HER2 | Everolimus, KBP-5209, Neratinib, Pertuzumab, Trastuzumab |
| CDKN2A | Crizotinib+Dasatinib, ABT-348 |
| DDR2 | Crizotinib+Dasatinib |
| MET | Crizotinib+Dasatinib, INC280 |
| SMO | Vismodegib, LY2940680 |
| PTCH | Vismodegib, LY2940680 |
| PD-L1 | MK-3475 |

| | |
|---|---|
| TP53 | MLN9708+Vorinostat, Pazopanib+Vorinostat |
| KIT | Imatinib |
| IDH1 | IDH305, AG-221 |
| DHH/IHH | LY2940680 |
| MLL | EPZ-5676 |
| RNF43 | LGK974 |
| RSPO | LGK974 |
| MRCA1 | Talazoparib |
| ATM/ATR | Talazoparib |
| FANCs | Talazoparib |
| EMSY | Talazoparib |
| MRE11A | Talazoparib |
| NBS1 | Talazoparib |
| PALB2 | Talazoparib |
| RAD50/51 C | Talazoparib |
| BRCA1/2 | Olaparib, Talazoparib |
| MAP2K1/3 | BVD-523 |
| NTRK1/2/3 | LOXO-101, RXDX-101 |
| ROS1 | Ceritinib, Crizotinib,RXDX-101 |
| ALK | Ceritinib, Crizotinib, RXDX-101, X-396 |
| NOTCH1 | OMP-52M51 |

**Cocktail?**

**~80 alterations; 44 drugs, 47 trials**

# Dream List for the Future

1. Longitudinal surveillance of biomarkers during diagnosis and treatment.
2. Biomarkers beyond genes from tumors and body fluids.
3. Integration and sharing of clinical, biomarker, immunologic and imaging “Big Data”.
4. Physician decision support tools and algorithms for selecting optimal targeted therapies.
5. Evidence-based combinations of therapies. (Targeted therapy and immune therapy)

# 黃帝內經

# ”正氣存內,邪不可干”

## 去邪　扶正

**Eliminating evil　Strenthen body resistance**

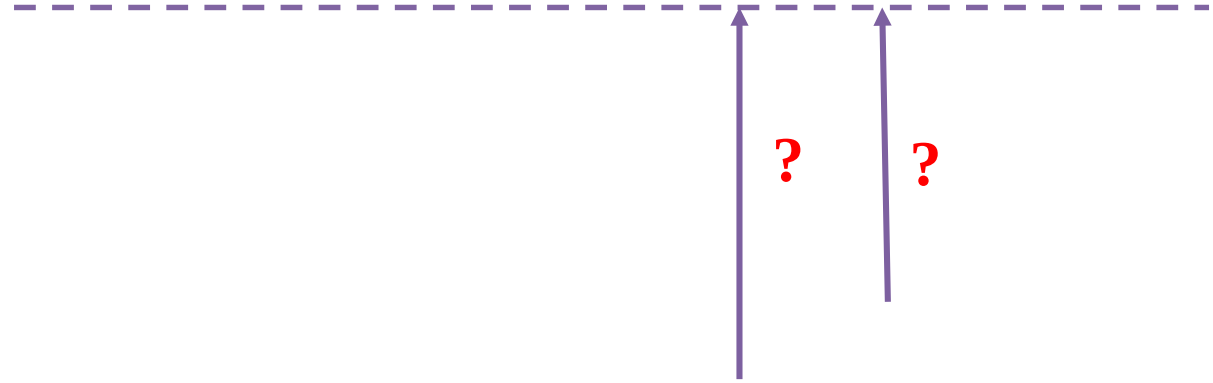
**The first Chinese medicine book**

# Monoclonal antibodies for Immune Checkpoint Therapy

**Nivolumab – anti-PD-1**
**Ipilimumab – anti –CTLA4**

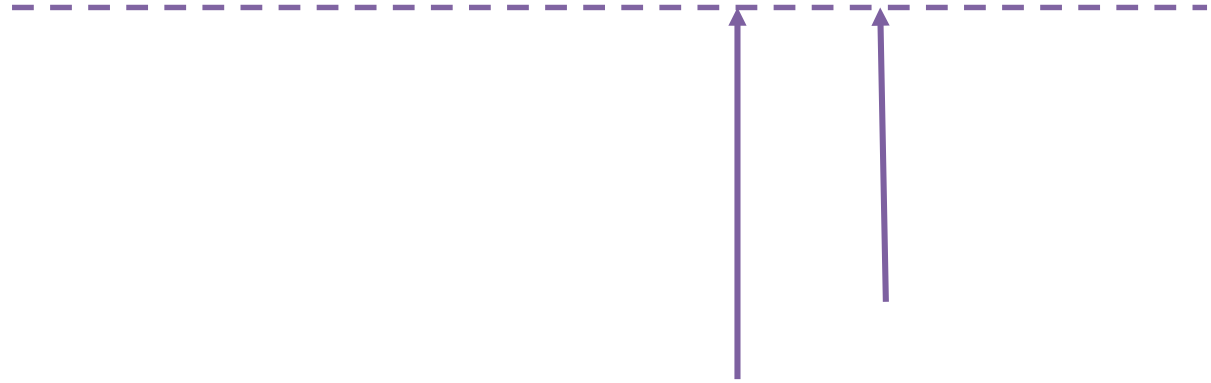
**N Engl J Med 2015; 373:23-34, July 2, 2015**
**N Engl J Med 2017; 377:1345-1356,Oct 5,2017**

# Monoclonal antibodies for Immune Checkpoint Therapy




N Engl J Med 2015; 373:23-34, July 2, 2015
N Engl J Med 2017: 377;1345, Oct 5,2017

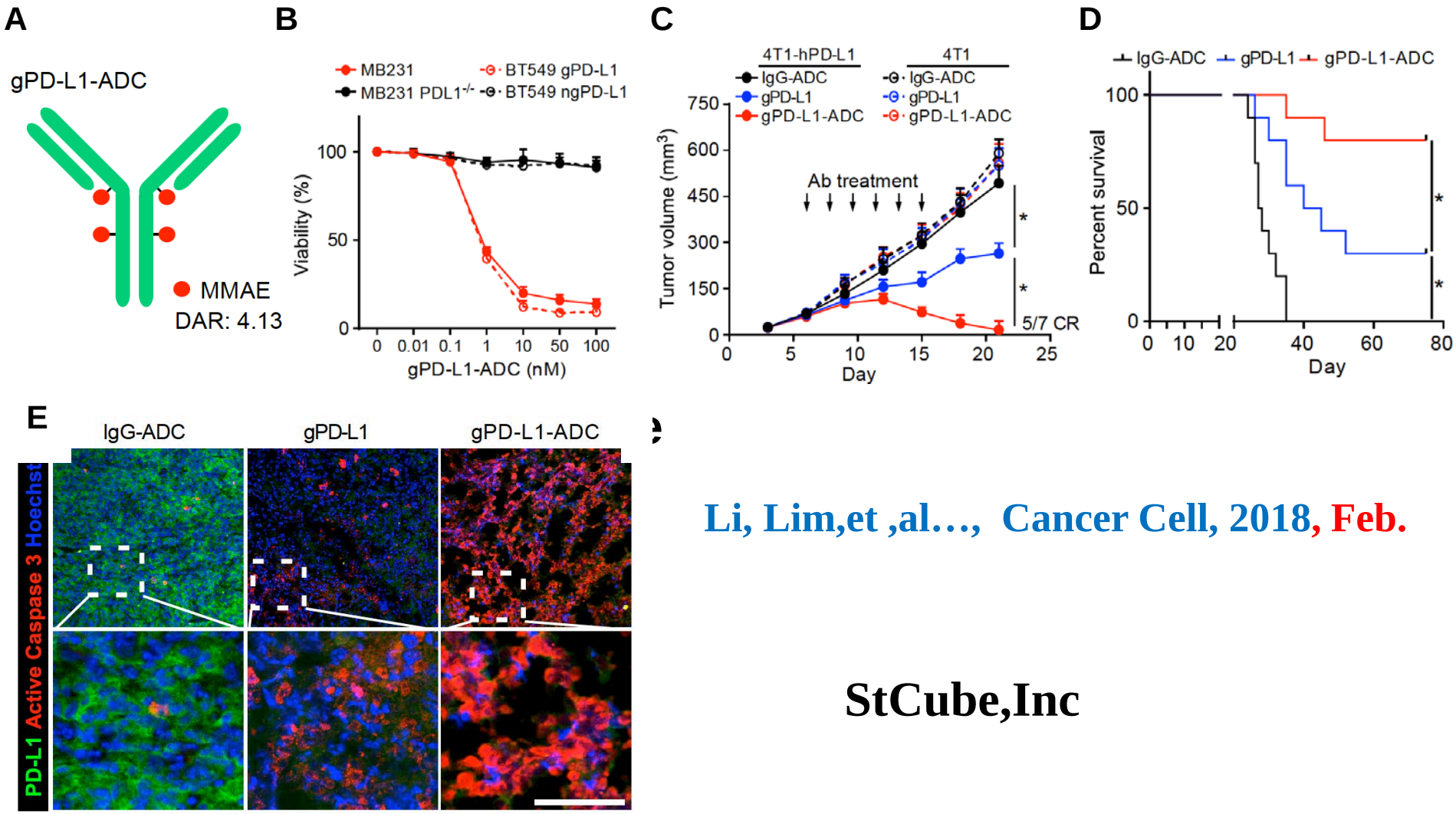
# Monoclonal antibodies for Immune Checkpoint Therapy



**Tumor heterogeneity,**
**Effective combination therapy,**

**N Engl J Med 2015; 373:23-34, July 2, 2015**
**N Engl J Med 2017: 377;1345, Oct 5,2017**

# Monoclonal antibody targeting PD-L1 glycosylation enhances anti-tumor immunity




Li, Lim,et ,al…, Cancer Cell, 2018, Feb.

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**MM Auristatin E**

This is time to


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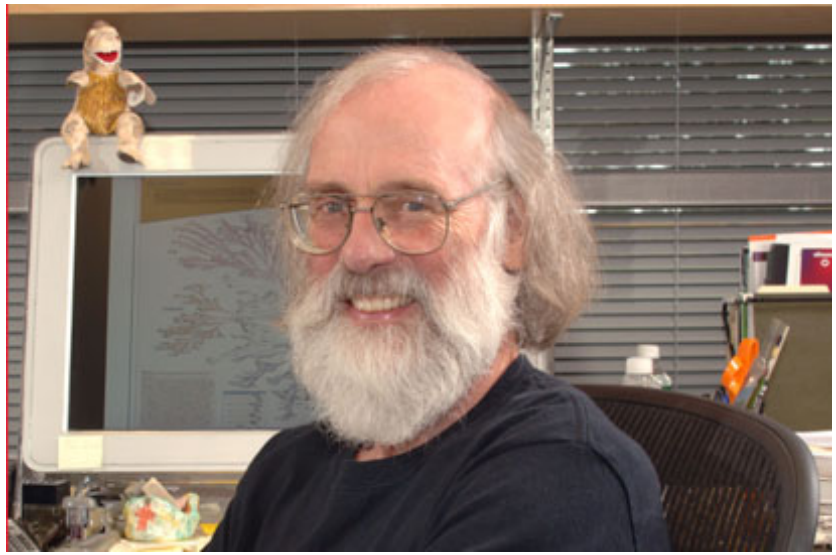
**Tony Hunter, PhD**
**Professor Molecular and Cell Biology Laboratory American Cancer Society Professor**
**Renato Dulbecco Chair**
**Salk Institute for Biological Studies**
**University of California, San Diego**



**Originality of discovery: tyrosine kinase**

**Contribution to Biopharmaceutical/biomedical advance: inhibitors of tyrosine kinase are first line defense to treat cancer patients.**

**Impact on human health: cancer patients receive benefits from the treatments of tyrosine kinase inhibitors**

**Role in development history of the field: Kinase King (2008, Journal of Cell Biology)**

**Brian Druker, MD**
**Director, Knight Cancer Institute at Oregon Health & Science University**
**JELD-WEN Chair of Leukemia Research**
**Investigator, Howard Hughes Medical Institute**

**Originality of discovery: development of small molecules as tyrosine kinase inhibitor**

**Contribution to Biopharmaceutical/biomedical advance: first TKI to treat patients with Philadelphia chromosome.**

**Impact on human health: CML/ALL cancer patients receive benefits from the treatments of Gleevec (imatinib)**

**Role in development history of the field: open new era of targeted therapy using small molecules to target tyrosine kinases**

**John Mendelsohn, MD**
**L.E. & Virginia Simmons Senior Fellow, James A. Baker III Institute for Public Policy, Rice University**
**Professor, Genomic Medicine**
**Former President**
**The University of Texas MD Anderson Cancer Center**

**Originality of discovery: development of monoclonal antibody against EGFR**

**Contribution to Biopharmaceutical/biomedical advance: first monoclonal antibody against EGFR approved by FDA to treat cancer patients**

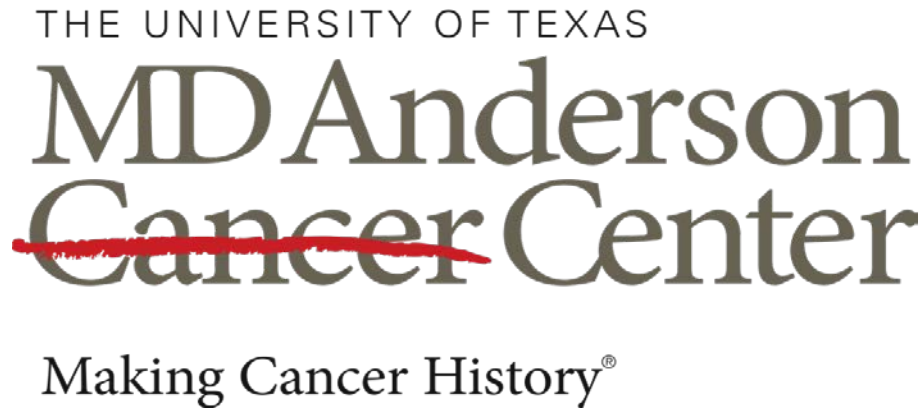
**Impact on human health: colorectal and head and neck cancer patients receive benefits from the treatments of cetuximab (Erbitux)**

**Role in development history of the field: open new era of targeted therapy using monoclonal antibody to target EGFR, a receptor tyrosine kinase.**

# Congratulations and Salute to

- **Dr. Tony Hunter for his seminal discovery on role of tyrosine kinase in critical cellular functions including cellular transformation, which paved a way to later development of blocking of Tyrosine Kinases .**
- **Dr. Brian Druker for his relentless effort to open up small molecules as tyrosine kinase inhibitor to treat CML/ALL with Phil+ patients.**
- **Dr. John Mendelsohn for his diligence to develop monoclonal antibody as a method to block tyrosine kinase of EGFR to treat cancer patients including colon as well as head and neck cancer.**

# THANK YOU!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松下問童子，言師採藥去，
只在此山中，雲深不知處