Lung Cancer Research: From Prevention to Cure!

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Introduction

- Lung cancer is one of the most common cancer worldwide.
- There will be >170,000 diagnosed cases of lung cancer in 2006.
- There will be >160,000 deaths from lung cancer in 2006.
- About 75-80% of lung cancers are associated with smoking.
- However, over 50% have stopped smoking. AND over 15-20% NEVER smoked.
Lung Cancer: More Research Needed

- Every three minutes someone is diagnosed with lung cancer
- Men have a lifetime risk of 1 in 13 and women 1 in 17
- In 2003, the federal government spent $14,045/breast cancer death, $10,761/prostate cancer death, $1,632/lung cancer death
Diagnosis of Lung Cancer

- Signs and Symptoms
  - Cough (especially with blood), fevers, weight loss, facial swelling, pain, etc.

- Scans
  - CXRAY
  - CT
  - PET

- Tests
  - Blood
  - Bronchoscopies
  - Biopsies
Next Generation Scanners Can See a Pinhead-Size Spot

- Prototypes capable of 1mm resolution
- Scanning within a breath
- Look deep inside the lung

*Image Courtesy of Dianna Cody, MDAH*

*Kiessling et al, Nature Med online, 9/7/2004*
How Do You Study Lung Cancer?

- Microscopy
- Cellular biology
- Genetics
- Proteomics
Lung Cancer—Anatomy
Lung Cancer- Histology

SCLC
ADENOCARCINOMA
SQUAMOUS CELL CARCINOMA
LARGE CELL CARCINOMA
NSCLC
LARGE CELL CARCINOMA
BAC
Normal Cells
Cancer Cells
A. Molecular and Biochemical Abnormalities in a Lung Cancer Cell and its Interaction with the Extracellular Matrix
Mutations in the EGFR, erbB-2 and MET Gene in Lung Cancer

EGFR
Tyrosine kinase domain
- L861Q
- L858R
- G719C
- S752-I759
- delL747-P753insS
- delL747-T751insS
- delL747-P753insS
- delS752-T759
- delE746-A750
- R776C
- L858R

ErbB-2
Tyrosine kinase domain
- L755P
- ins779(VGS)

SEMA
PSI domain
MET
JM
Tyrosine kinase domain
- E168D
- S232G
- N375S
- delL229F
- del141bp2942-3082
- *IVS 13-(52-53)insCT
- *T1010I
- *R988C
- *S1058P
- *E168D
- N375S
- S232G
- L229F
- del141bp2942-3082
- *IVS 13-(52-53)insCT
- *T1010I
- *R988C
- *S1058P
Laser Microdissection-Assisted Sequencing

Before

During

After
EGFR Expressing Adenocarcinoma
NSCLC
EGFR Mutations in LCM-Tumor Cells (Hilar LN)
Lumbar Puncture: CSF

- NSCLC
- Leukocyte
- CSF
EGFR Mutations in LCM-Tumor Cells (CSF)
Tumor Tissue Microarray

University of Chicago TMA
B. Mechanisms of Lung Cancer Metastasis

1. Primary Lung Cancer Cells
2. Alteration in Tumor Cell Adhesion and Degradation of ECM
3. Invasion of Tumor Cell into Blood and Lymphatic Vessel
4. Circulating Tumor Cell
5. Metastasis of Lung Cancer Cell with Implantation
Biological Targets for Cancer Therapy

1. Growth factors and growth-factor receptors
   HER family, c-Met, VEGF/R, c-kit/SCFR

2. Signal-transduction pathways
   Ras, raf, MAPK, MEK, ERK, protein kinase C, PI3K

3. Tumor-associated antigens/markers
   Gangliosides, CEA, MAGE, CD20, CD22

4. Proteasome, Heat Shock Proteins

5. Cell-survival pathways
   Cyclin-dependent kinases, mTOR, cGMP, COX-2, p53, Bcl-2

6. Extracellular matrix/angiogenic pathways
   MMPs, VEGF, integrins
Therapy for Lung Cancer

- Surgery
- Radiation Therapy
- Chemotherapy
- Novel Targeted Therapies
Breakthroughs in the Treatment of Lung Cancer
Adjuvant Therapy for Lung Cancer

- Adjuvant therapy – treatment (e.g. chemotherapy) after surgery to eradicate microscopic residual cancer and prevent cancer recurrence

- 5 Large Studies have shown that Adjuvant Chemotherapy can increase cure rate in lung cancer
Drugs Recently Approved for Advanced Non-Small Cell Lung Cancer

- Gefitinib (Iressa) – May 2003 (withdrawn July 2005)

- Pemetrexed (ALIMTA) – February 2004

- Erlotinib (Tarceva) – November 2004

- Bevacizumab (Avastin) – October 2006
Pemetrexed

- Chemotherapy approved for mesothelioma and lung cancer
- Given IV, usually with platinum
- Does not cause hair loss
- Vitamin B12 and folic acid need to be taken with it.
Erlotinib

- Oral EGFR tyrosine kinase inhibitors
- Have activity in non-small-cell lung cancer (~10-15% of tumors will shrink; ~30-40% will be stable)
- Tarceva improves survival in patients with metastatic disease that have failed first-line chemotherapy
- Occasional dramatic and durable tumor responses are seen
Tarceva

- Targets a receptor found in lung cancer
- Taken by mouth
- Less side effects (no hair loss or nausea)
- Rash and diarrhea seen
How Does Tarceva Work?

1. When EGF binds to EGFR, it causes a chemical reaction within the cell.
2. This reaction results in overstimulation of cell growth and division, which produces a tumor.
3. IRESSA & TARCEVA block the internal portion of the EGF receptor and prevents the chemical reaction from occurring inside the cell, thereby halting tumor production.
Tumor Shrinkage with Tarceva:
Normal and Tumor Vasculature

Normal Blood Vessels:
- Maturation factors present (eg, Ang-1)
- Less dependent on cell survival factors
- Less permeable
- Supporting cells present
- Reduced integrin expression

Tumor Blood Vessels:
- Growth and survival factors (eg, VEGF, bFGF) present
- Leaky
- Fewer supporting cells
- Preferential expression of $\alpha_v\beta_3$, $\alpha_v\beta_5$, and $\alpha_5\beta_1$ integrins

References:
**BEVACIZUMAB**
- monoclonal antibody
- binds VEGF (ligand)
- intravenous QOW
- bleeding, arterial thrombi, proteinuria

**SORAFENIB**
- small molecule
- inhibits VEGFR2 (receptor), c-Raf, etc.
- oral twice daily
- skin toxicities, alopecia, diarrhea
Future for Lung Cancer—with Effective Research

- In the future, we will have routine:
  - Scans
  - Blood tests
  - Bronchoscopy/Sputum tests
  - Family screens
- In the future, we will have better:
  - Prevention
  - Diagnosis Ability
  - Surgery
  - Radiation Therapy
  - Chemotherapy (Including Novel Therapies)
“If you want to change the world, be that change.”

— Mahatma Gandhi