Beyond Traditional Treatments: the Roles of Molecular Medicine and Individualized Therapies

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From where have we come?  
Where are we going?  
What can we do today to improve treatment of lung cancer?  

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SURE CANCER CAN BE CURED.

Dr. Doyen Declares That Inoculation and Electrification Are Effective.
Special Cable to THE NEW YORK TIMES.

PARIS, Oct. 9.—Dr. Doyen, addressing the Congress of Surgery now in session here, has made the sweeping assertion that in almost all cases cancer can be cured either by anti-neoplastic inoculation or bipolar electrification. He
Paul Ehrlich “father of chemotherapy”

- 1908 Nobel Prize
- Chemist who first proposed developing compounds that would combat the disease with no harmful effect on the patient
- “Magic Bullets”

Image Courtesy Edgar Fahs Smith Memorial Collection, Department of Special Collections, University of Pennsylvania Library, and The Chemical Heritage Foundation
The Biological Actions and Therapeutic Applications of the B-Chloroethyl Amines and Sulfides

Alfred Gilman, Major, and Frederick S. Philips, 1st Lieutenant, SnC, AUS
Pharmacology Section, Medical Division, CWS, Edgewood Arsenal, Maryland

Sidney Farber, 1966
May 18, 1998
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER. THESE ARE THE BULLETS.

Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?
"The history of cancer research has been a history of curing cancer in the mouse," Dr. Richard Klausner, head of the National Cancer Institute, told the Los Angeles Times. "We have cured mice of cancer for decades--and it simply didn't work in people."

March 22, 2004
Time for cautious optimism, and activism

- 3 new drugs approved in last 3 years and more to come...

- Exciting prospects for:
  - Screening to find disease early
  - Making current curative treatments such as radiation and surgery more precise and effective
  - Adjuvant “help” therapy with old and new drugs to improve cure rate
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

- Only 3% of cancer patients age 30-64 enroll in a clinical trial, only 1.3% of those 65-74 do so.*

January 15, 2001
Cancer Treatment gets Personal
Cancer Treatment Always Has Been Personal

- "If it were not for the great variability among individuals medicine might as well be a science and not an art."

- Sir William Osler, 1892
Cancer Treatment Always Has Been Personal

- Does the patient want treatment?
- Will treatment help this patient and lead to a better quality of life than no treatment? Which treatment?
- Based on results of clinical trials of agents in groups similar to patient
- Treatment dose and schedule based on what happened with those patients and study of schedules and doses (if performed)
Scientific Approaches to Personalizing Therapy

- During the 2nd half of the 20th century observant physicians noted unusual responses to drugs could run in families and determined why this happens= “Pharmacogenetics”

- Example: About 10% of persons of European Ancestry do not get relief of pain with Tylenol 3™, but Percocet ™ works just fine- related to deficiency of an enzyme CYP2D6.
Personalized Medicine Research is Best Performed on People
From where have we come?

**Where are we going?**

What can we do today to improve treatment of lung cancer?
The Future of Personalized Cancer Treatment

GOAL:
Correct Drug at the Correct Dose for every patient, everytime, leading to Maximum Efficacy and Minimum Toxicity.
New Tools to Personalize Cancer Treatment Scientifically
From where have we come?

Where are we going?

What can we do today to improve treatment of lung cancer?
Scientific Approaches to Personalizing Cancer Therapy

- What are the weaknesses/targets on the tumor?

- Will this patient handle the drug “normally?”
  - Achieve blood levels necessary to affect the tumor?
  - Will levels be much higher than normal and dangerous?
  - Special sensitivity for specific side effects?
Scientific Approaches to Personalizing Lung Cancer Therapy

- An Example with irinotecan/cpt-11

- Note, this drug is not approved by the FDA for lung cancer, but is commonly used in treating Small Cell Lung Cancer and sometimes in Non-Small Cell, too.
One Dose Does Not “Fit All”
“not-so-magic bullets”

This variability is normal.
This normal variability has consequences. This is the “average” group of patients who will have similar results to most patients in the early clinical trials.
This normal variability has consequences

These patients have higher than normal levels of drug in their blood and might be at increased risk for severe side effects.

*This variability is normal.*

From Dr. Felix Frueh, FDA
This normal variability has consequences

These patients have lower than normal levels of drug in their blood, maybe too little to have a full effect on their cancer!

From Dr. Felix Frueh, FDA
Often this variability has nothing to do with age, sex, or body size.

This variability is normal.
>10 years of clinical and lab research
For cpt-11 these groups can, in part, be identified by DNA sequencing for *UGT1A1*.

*This variability is normal.*
Evidence that 7/7 is a risk factor for a severe toxicity of cpt-11

Innocenti, *J Clin Oncol* '04
Some Pharmacogenetic tests are available today!
To make this more useful, there’s more to learn...

Can these patients handle a higher dose safely? Will this lead to better results?

This variability is normal.

From Dr. Felix Frueh, FDA
How do we collect the info and use it to advance development of lung cancer treatment?
Can we use rash from Tarceva and Erbitux to separate patients?

Severity of Skin Rash
Can we use blood pressure changes from Nexavar or Avastin to separate patients?

Change in Blood Pressure
From where have we come?

Where are we going?

What can we do today to improve treatment of lung cancer?
What can we do today to improve treatment of lung cancer?
<table>
<thead>
<tr>
<th>Protocol Title</th>
<th>IRB #</th>
<th>Physician</th>
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<tbody>
<tr>
<td>A Phase Ib Study of Rapamycin (Sirolimus) in Patients with Advanced Malignancies</td>
<td>13142A</td>
<td>Cohen</td>
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<tr>
<td>A combined Phase 1 and 2 Study Investigating the Combination RAD001 and Erlotinib in Patients With Advanced NSCLC After Failure of Chemotherapy</td>
<td>14125B</td>
<td>Salgia</td>
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<tr>
<td>CALGB 30302* 90223: A Phase II Trial of Induction Chemotherapy with Capetinib/Erbitux Followed by Surgical Resection, Followed by Docetaxel, for Non-Small Cell Lung Cancer Involving the Superior Sutures (Mimic Tumors)</td>
<td>14165A</td>
<td>Mallick</td>
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<td>CALGB 30400: A Phase II Randomized Study of 536-774 (erlotinib) With or Without Carboplatin/Paclitaxel in Patients With Previously Untreated Adenocarcinomas of the Lung Who Never Smoked or Were Former Light Smokers</td>
<td>14312A</td>
<td>Velas</td>
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<td>CALGB 30407: A Randomized Phase II Study of Radiation Therapy, Paclitaxel and Carboplatin With or Without Cetuximab in Stage III Non-Small Cell Lung Cancer</td>
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<td>A Phase I Study of CCR11-107 in Subjects With Advanced Refractory Solid Tumors</td>
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<td>A phase I single institution, open-label, dose-escalating, clinical and pharmacokinetic study of PF02374 administered every three weeks, intravenously, over 30 minutes, to subjects with advanced malignant solid tumors</td>
<td>13991B</td>
<td>Ratan</td>
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<td>Two Phase, Open-Label, Sequential, Ascending Dose Study of the Tolerability Safety, and Pharmacokinetics of CRA-02477I IV Following Infusion Delivery in Cancer Patients</td>
<td>13937B</td>
<td>Undeva</td>
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<td>Phase II Trial of Vatalanib, Capecitabine and Paclitaxel (400mg/m2) for Secondline# #E2241/Line Treatment in Patients With Non-Small Cell Lung Cancer</td>
<td>14347B</td>
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<td>A Phase I, Sequential Cohort, Dose Escalation Trial to Determine the Safety, Tolerability, Maximum Tolerated Dose, and Optimal Infusion Duration of Vatalanib Administration of CRA-02477I in Patients With Refractory Or Relapsed Solid Tumor Malignancies</td>
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<td>A Phase II Study of Polyethylene Glycolated FerrumX in a Combination With Bevacizumab, Paclitaxel and Carboplatin in Patients at High Risk for Bevacizumab-Associated Hemorrhage</td>
<td>14574A</td>
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<td>A Safety and Feasibility Study of Bevacizumab With Paclitaxel, Carboplatin and Chest Radiation Therapy in Patients With Locally Advanced Non-Small Cell Lung Cancer</td>
<td>14576A</td>
<td>Maier</td>
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<td>Tissue Procurement for Lung Cancer, Stomach Cancer, Ovarian Cancer, and Mesothelioma in Patients Undergoing Surgery of Biopsy</td>
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<td>Phase III Study of Carboplatin in Patients With Advanced Solid Tumors and Lymphoma</td>
<td>11130B</td>
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<td>CALGB 300301: Pharmacokinetic and Phase I Study of Sorafenib (450 mg PO) in Patients With Solid Tumors</td>
<td>12774A</td>
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<tr>
<td>CALGB 60010: Pharmacokinetic and Safety I Study of Sorafenib (450 mg PO) and Docetaxel (75 mg/m2) for Solid Tumors and Hematologic Malignancies in Patients With Hepatic or Renal Dysfunction</td>
<td>13557A</td>
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<td>Utilization of Previously-Sampled Tissue From Patients With Lung Cancer, Mesothelioma, Thymoma/Thymic Carcinoma, and Biphasic Cancer and Correlation with Clinical Data</td>
<td>13947A</td>
<td>Salgia</td>
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<td>A Phase Ib, Open-Label, Dose Escalating Study of PDX1777/1k 225B/1h in Combination With Velcide in Patients With Advanced Cancer</td>
<td>11083B</td>
<td>Schlesky</td>
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If you want to learn more about the program and the trials underway or planned, please call 800-343-3742 for more information or to make an appointment.

Although our objective is to provide an up-to-date list of available clinical trials, it is subject to change. For more information, please visit our website:

http://uccrc.uchicago.edu/patients/clinicaltrials.html
What can we do today to improve treatment of lung cancer?

- Find a treatment team you trust
- Utilize available resources
- Network with advocates for quality care and research
- Seek opportunities to participate in clinical research