# Cancer Biology Course

**Tuesdays, 12 noon,**

**All students, postdocs, faculty, staff welcome**

## Schedule for 2016 Course

<table>
<thead>
<tr>
<th>Date</th>
<th>Speaker(s)</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/12</td>
<td>Cancer Biology Pathway Luncheon</td>
<td>Introduction of Oncology, chapter 2</td>
</tr>
<tr>
<td>1/19</td>
<td>Lee Ratner, MD, PhD</td>
<td>Cell Cycle Regulation, chapter 8</td>
</tr>
<tr>
<td>1/26</td>
<td>Jason Weber PhD</td>
<td>Cell Cycle Regulation, chapter 8</td>
</tr>
<tr>
<td>2/2</td>
<td>Ron Bose, MD, PhD ^</td>
<td>Cell Cycle Regulation, chapter 6</td>
</tr>
<tr>
<td>2/9</td>
<td>Amy Barone, MD *</td>
<td>Perspective on New Challenges in Oncology Drug Regulation in the Era of Genomics, chapter 16</td>
</tr>
<tr>
<td>2/16</td>
<td>Luis Batista, PhD</td>
<td>Immortalization and Cancer, chapter 10</td>
</tr>
<tr>
<td>2/23</td>
<td>Vivek Arora, MD, PhD</td>
<td>Nuclear Receptors in Prostate Cancer, chapter 5</td>
</tr>
<tr>
<td>3/1</td>
<td>Blair Madison, PhD</td>
<td>Multistep Colon Carcinogenesis, chapter 11</td>
</tr>
<tr>
<td>3/8</td>
<td>Terrence Wong, MD, PhD</td>
<td>p53 and Cancer, chapter 9</td>
</tr>
<tr>
<td>3/15</td>
<td>Chris Maher, PhD</td>
<td>Long Non-Coding RNAs in Cancer,</td>
</tr>
<tr>
<td>3/22</td>
<td>Mark Krasnow *</td>
<td>Lung Development and Cancer, chapter 13</td>
</tr>
<tr>
<td>3/29</td>
<td>Saima Waqar, MD, and Len Maggi, PhD</td>
<td>Genomics of Lung Cancer, Chapters 4 and 7</td>
</tr>
<tr>
<td>4/5</td>
<td>Jian Campian, MD, PhD and Milan Chheda, MD</td>
<td>Neural Stem Cells and Cancer, chapter 12</td>
</tr>
<tr>
<td>4/12</td>
<td>Jackie Payton, MD, PhD</td>
<td>Epigenomic Regulation of Cancer, chapter 1</td>
</tr>
<tr>
<td>4/19</td>
<td>Student Selected Speaker</td>
<td>TBD</td>
</tr>
<tr>
<td>4/26</td>
<td>Student Selected Speaker</td>
<td>TBD</td>
</tr>
</tbody>
</table>

Attendance of all sessions & **active** discussion esp during presentation classic paper
Introduction

- Nature of Cancer
- Advance in Cancer Research 2015
  See Weinberg, Chap 2, Nature of Cancer
  JCO Mar 2015, Clinical Cancer Advances
  deVita NEJM 2012 History of Cancer
  Hanahan & Weinberg Cell, 2011
Cancer – Historical Perspective

1600 BC  Egyptian physician record 1st description of breast cancer
460 BC  Hippocrates uses “carcinos” to describe tumors (Greek – crab)
129 AD  Galen attributed cancer to black bile
1660  Mastectomy for breast cancer
1713 Ramazzini noted lack of cervical ca but increased breast ca in nuns
1775 Pott described scrotal cancer in chimney sweeps
1838 Muller described cancer as abnormalities of cells
<table>
<thead>
<tr>
<th>Year</th>
<th>Discovery or Event</th>
<th>Relative Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1863</td>
<td>Cellular origin of cancer (Virchow)</td>
<td></td>
</tr>
<tr>
<td>1889</td>
<td>Seed-and-soil hypothesis (Paget)</td>
<td></td>
</tr>
<tr>
<td>1914</td>
<td>Chromosomal mutations in cancer (Boveri)</td>
<td></td>
</tr>
<tr>
<td>1937</td>
<td>Founding of NCI</td>
<td></td>
</tr>
<tr>
<td>1944</td>
<td>Transmission of cellular information by DNA (Avery)</td>
<td></td>
</tr>
<tr>
<td>1950</td>
<td>Availability of cancer drugs through Cancer Chemotherapy National Service Center</td>
<td></td>
</tr>
<tr>
<td>1953</td>
<td>Report on structure of DNA</td>
<td>35%</td>
</tr>
<tr>
<td>1961</td>
<td>Breaking of the genetic code</td>
<td></td>
</tr>
<tr>
<td>1970</td>
<td>Reverse transcriptase</td>
<td></td>
</tr>
<tr>
<td>1971</td>
<td>Restriction enzymes Passage of National Cancer Act</td>
<td></td>
</tr>
<tr>
<td>1975</td>
<td>Hybridomas and monoclonal antibodies Tracking of cancer statistics by SEER program</td>
<td>50%</td>
</tr>
<tr>
<td>1976</td>
<td>Cellular origin of retroviral oncogenes</td>
<td></td>
</tr>
<tr>
<td>1979</td>
<td>Epidermal growth factor and receptor</td>
<td></td>
</tr>
<tr>
<td>1981</td>
<td>Suppression of tumor growth by p53</td>
<td></td>
</tr>
<tr>
<td>1984</td>
<td>G proteins and cell signaling</td>
<td></td>
</tr>
<tr>
<td>1986</td>
<td>Retinoblastoma gene</td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td>First decrease in cancer incidence and mortality</td>
<td></td>
</tr>
<tr>
<td>1991</td>
<td>Association between mutation in APC gene and colorectal cancer</td>
<td></td>
</tr>
<tr>
<td>1994</td>
<td>Genetic cancer syndromes Association between BRCA1 and breast cancer</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Sequencing of the human genome</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>Epigenetics in cancer MicroRNAs in cancer</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>First decrease in total number of deaths from cancer</td>
<td>68%</td>
</tr>
<tr>
<td>2006</td>
<td>Tumor stromal interaction</td>
<td></td>
</tr>
</tbody>
</table>
Cancer in the US

1.6 million new cases this year
21% decrease in cancer-related deaths in men vs 1990s
12% decline in women
13 million cancer survivors alive in US
Cancer-related death rates decline 1.5%/yr
580,000 Americans died of cancer in 2013
Leading New Cancer Cases and Deaths – 2014 Estimates

**Estimated New Cases***

**Male**
- Prostate: 233,000 (27%)
- Lung & bronchus: 116,000 (14%)
- Colon & rectum: 71,830 (8%)
- Urinary bladder: 56,390 (7%)
- Melanoma of the skin: 43,890 (5%)
- Kidney & renal pelvis: 39,140 (5%)
- Non-Hodgkin lymphoma: 38,270 (4%)
- Oral cavity & pharynx: 30,220 (4%)
- Leukemia: 30,100 (4%)
- Liver & intrahepatic bile duct: 24,600 (3%)
- All sites: 855,220 (100%)

**Female**
- Breast: 232,670 (29%)
- Lung & bronchus: 108,210 (13%)
- Colon & rectum: 65,000 (8%)
- Uterine corpus: 52,630 (6%)
- Thyroid: 47,790 (6%)
- Non-Hodgkin lymphoma: 32,530 (4%)
- Melanoma of the skin: 32,210 (4%)
- Kidney & renal pelvis: 24,780 (3%)
- Pancreas: 22,890 (3%)
- Leukemia: 22,280 (3%)
- All sites: 810,320 (100%)

**Estimated Deaths**

**Male**
- Lung & bronchus: 86,930 (28%)
- Prostate: 29,480 (10%)
- Colon & rectum: 26,270 (8%)
- Pancreas: 20,170 (7%)
- Liver & intrahepatic bile duct: 15,870 (5%)
- Leukemia: 14,040 (5%)
- Esophagus: 12,450 (4%)
- Urinary bladder: 11,170 (4%)
- Non-Hodgkin lymphoma: 10,470 (3%)
- Kidney & renal pelvis: 8,900 (3%)
- All sites: 310,010 (100%)

**Female**
- Lung & bronchus: 72,330 (26%)
- Breast: 40,000 (15%)
- Colon & rectum: 24,040 (9%)
- Pancreas: 19,420 (7%)
- Ovary: 14,270 (5%)
- Leukemia: 10,050 (4%)
- Uterine corpus: 8,590 (3%)
- Non-Hodgkin lymphoma: 8,520 (3%)
- Liver & intrahepatic bile duct: 7,130 (3%)
- Brain & other nervous system: 6,230 (2%)
- All sites: 275,710 (100%)

*Excludes basal and squamous cell skin cancers and in situ carcinoma except urinary bladder.

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Therapeutic Targeting of the Hallmarks of Cancer

- **EGFR inhibitors**
  - Sustaining proliferative signaling
  - Deregulating cellular energetics

- **Cyclin-dependent kinase inhibitors**
  - Evading growth suppressors
  - Avoiding immune destruction

- **Immune activating anti-CTLA4 mAb**
  - Enabling replicative immortality
  - Tumor-promoting inflammation

- **Aerobic glycolysis inhibitors**
  - Resisting cell death
  - Genome instability & mutation

- **Proapoptotic BH3 mimetics**
  - Inducing angiogenesis
  - Activating invasion & metastasis

- **PARP inhibitors**
  - Selective anti-inflammatory drugs

- **Inhibitors of VEGF signaling**
  - Inhibitors of HGF/c-Met
Normal vs Neoplastic Tissue
What are characteristic pathologic features of cancer?
### Tumor Classification Hierarchy

#### I - Differentiation State
1. Epithelial
2. Nonepithelial
3. Mixed

#### II - Embryonic Origin
1. Ectoderm
2. Endoderm
3. Mesoderm

#### III - Biological Behavior
1. Benign
2. Malignant

#### Differentiation State - I: Epithelial
- **Embryonic Derivation:**
  - Ectoderm
    - Bilayer epithelium
    - Cell Type: breast, sweat glands, salivary glands
    - Benign: adenoma, Malignant: adenocarcinoma
  - Endoderm
    - Single-layer epithelium
    - Cell Type: thyroid, lung, stomach, liver, pancreas, small intestine, colon, prostate
    - Benign: adenoma, Malignant: adenocarcinoma
  - Mesoderm
    - Single-layer epithelium
    - Cell Type: kidney, testis, endometrium

#### Differentiation State - II: Nonepithelial
- **Embryonic Derivation:**
  - Mesoderm
    - Stromal (mesenchymal)
      - Benign: fibroma, lipoma, osteoma, chondroma, leiomyoma, hemangioma
      - Tumor Name: fibrosarcoma, liposarcoma, osteosarcoma, chondrosarcoma, leiomyosarcoma, hemangiosarcoma
    - Hematopoietic
      - Cell Type: lymphocyte, leukocyte
      - Tumor Name: lymphoma, leukemia
  - Neuro-ectoderm
    - Nervous system
      - Cell Type: astrocyte, retina, oligodendrocyte, schwann
      - Tumor Name: astrocytoma, retinoblastoma, oligodendroglioma, schwannoma
      - Other
        - melanocyte, melanoma
Monoclonal tumors:
- Normal tissue
- Normal behavior
- Transformation
- Cancerous behavior
- Tumors

Polyclonal tumors:
- Normal tissue
- Normal behavior
- Transformation
- Cancerous behavior
- Tumors
Abnormal Metabolism in Cancer
New Drug Approvals 2014

- Targeted
- Chemotherapy
- Immunotherapy

Year

No. of Approvals
2015 Cancer Drug Approvals

**Alecensa (alectinib)**: Roche; For the treatment of ALK-positive, metastatic non-small cell lung cancer, Approved December 2015

**Cotellic (cobimetinib)**: Genentech; For the treatment of BRAF V600E or V600K melanoma, Approved November 2015

**Darzalex (daratumumab)**: (anti-CD38) Janssen Biotech; For the treatment of multiple myeloma, Approved November 2015

**Empliciti (elotuzumab)**: (anti-SLAMF7) Bristol-Myers Squibb; For the treatment of patients with multiple myeloma who have received prior therapies, Approved November 2015

**Farydak (panobinostat)**: Novartis; For the treatment of multiple myeloma, Approved February 2015

**Ibrance (palbociclib)**: Pfizer; For the treatment of ER-positive, HER2-negative breast cancer, Approved February 2015

**Imlygic (talimogene laherparepvec)**: (HSV) Amgen; For the treatment of unresectable recurrent melanoma, Approved October 2015

**Lenvima (lenvatinib)**: Eisai; For the treatment of thyroid cancer, Approved February 2015

**Lonsurf (trifluridine and tipiracil)**: Taiho Oncology; For the treatment of metastatic colorectal cancer, Approved September 2015

**Ninlaro (ixazomib)**: Millennium Pharmaceuticals; For the treatment of multiple myeloma, Approved November 2015

**Odomzo (sonidegib)**: Novartis; For the treatment of locally advanced basal cell carcinoma, July 2015

**Onivyde (irinotecan liposome injection)**: Merrimack; For the treatment of metastatic pancreatic cancer following gemcitabine-based therapy, Approved October 2015

**Opdivo (nivolumab)**: Bristol-Myers Squibb; For the treatment of metastatic squamous non-small cell lung cancer, Approved March 2015

**Portrazza (necitumumab) (anti-EGFR)**: Eli Lilly; For the treatment of metastatic squamous non-small cell lung cancer, Approved November 2015

**Tagrisso (osimertinib)**: AstraZeneca; For the treatment of EGFR T790M mutation positive non-small cell lung cancer, Approved November 2015

**Unituxin (dinutuximab)**: United Therapeutics; For the treatment of pediatrics with high-risk neuroblastoma, Approved March 2015

**Varubi (rolapitant)**: Tesaro; For the prevention of delayed nausea and vomiting associated with chemotherapy, Approved September 2015

**Yondelis (trabectedin)**: Janssen; For the treatment of liposarcoma or leiomyosarcoma, Approved October 2015
Advance of the Year – CLL - 2014

- Newly Diagnosed CLL
  - Obinutuzumab (obinut-chlorambucil vs rituximab-chlorambucil 23 vs 11 m DFS)
  - Ofatumumab (ofat-chlorambucil vs chlorambucil 22.4 vs 13.1 m DFS)

- Relapsed CLL
  - Ibrutinib (Ibrutinib vs Ofatumumab 90% vs 81% 12 m OS)
  - Idelalisib (Idelalisib-Rit vs Rit 10.7 vs 5.5 m DFS)
Overcoming Treatment Resistance

- **EGFR mut lung cancer T790M**
  - AZD9291 (osimertinib) and CO-1686
- **EML4-ALK lung cancer**
  - Ceritinib
## Therapy-Resistant Gastric Cancer

- Ramucirumab (5.2 vs 3.8 mo OS)

### Agents Targeting VEGF Receptors

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Targets</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyrosine kinase inhibitors</td>
<td>Sunitinib</td>
<td>VEGFR-2, PDGFR, c-Kit</td>
<td>Approved RCC and GIST</td>
</tr>
<tr>
<td></td>
<td>Sorafenib</td>
<td>VEGFR-2, Raf, VEGFR-1</td>
<td>Approved RCC and HCC</td>
</tr>
<tr>
<td></td>
<td>Pazopanib</td>
<td>VEGFR-2, PDGFR, c-Kit</td>
<td>Approved RCC</td>
</tr>
<tr>
<td></td>
<td>Axitinib</td>
<td>VEGFR-1/2, c-Kit, PDGFR</td>
<td>Approved RCC</td>
</tr>
<tr>
<td></td>
<td>Tivozanib</td>
<td>VEGFR-1, -2, -3</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>

**Antibodies**
- Ramucirumab (IMC 1121B) VEGFR-2 Phase 2

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RAI-Resistant Thyroid Cancer

- Lenvatinib – (NEJM Feb 2015) – blocks VEGFR2 and 3

**Graph:**
- Progression-free survival over time for Lenvatinib vs Placebo.
- Median (95% CI):
  - Lenvatinib: 18.3 mo (15.1–NE)
  - Placebo: 3.6 mo (2.2–3.7)
- Hazard ratio for progression or death: 0.21 (99% CI, 0.14–0.31)
- P < 0.001

**No. at Risk:**
- Lenvatinib: 261 225 198 176 159 148 136 92 66 44 24 11 3 0
- Placebo: 131 71 43 29 19 13 11 5 4 2 2 0 0
### Geographic Variation in Cancer Incidence & Death Rates

#### Countries showing highest and lowest incidence of specific types of cancer

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Country of highest risk</th>
<th>Country of lowest risk</th>
<th>Relative risk H/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin (melanoma)</td>
<td>Australia (Queensland)</td>
<td>Japan</td>
<td>155</td>
</tr>
<tr>
<td>Lip</td>
<td>Canada (Newfoundland)</td>
<td>Japan</td>
<td>151</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>Hong Kong</td>
<td>United Kingdom</td>
<td>100</td>
</tr>
<tr>
<td>Prostate</td>
<td>U.S. (African American)</td>
<td>China</td>
<td>70</td>
</tr>
<tr>
<td>Liver</td>
<td>China (Shanghai)</td>
<td>Canada (Nova Scotia)</td>
<td>49</td>
</tr>
<tr>
<td>Penis</td>
<td>Brazil</td>
<td>Israel (Ashkenazic)</td>
<td>42</td>
</tr>
<tr>
<td>Cervix (uterus)</td>
<td>Brazil</td>
<td>Israel (non-Jews)</td>
<td>28</td>
</tr>
<tr>
<td>Stomach</td>
<td>Japan</td>
<td>Kuwait</td>
<td>22</td>
</tr>
<tr>
<td>Lung</td>
<td>U.S. (Louisiana, African American)</td>
<td>India (Madras)</td>
<td>19</td>
</tr>
<tr>
<td>Pancreas</td>
<td>U.S. (Los Angeles, Korean American)</td>
<td>India</td>
<td>11</td>
</tr>
<tr>
<td>Ovary</td>
<td>New Zealand (Polynesian)</td>
<td>Kuwait</td>
<td>8</td>
</tr>
</tbody>
</table>

#### Geographic areas showing highest and lowest death rates from specific types of cancer

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Area of highest risk</th>
<th>Area of lowest risk</th>
<th>Relative risk H/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung, male</td>
<td>Eastern Europe</td>
<td>West Africa</td>
<td>33</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Southern Africa</td>
<td>West Africa</td>
<td>16</td>
</tr>
<tr>
<td>Colon, male</td>
<td>Australia, New Zealand</td>
<td>Middle Africa</td>
<td>15</td>
</tr>
<tr>
<td>Breast, female</td>
<td>Northern Europe</td>
<td>China</td>
<td>6</td>
</tr>
</tbody>
</table>
Environmental and lifestyle factors known or suspected to be etiologic for human cancers in the United States\(^a\)

<table>
<thead>
<tr>
<th>Type</th>
<th>% of total cases(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancers due to occupational exposures</td>
<td>1–2</td>
</tr>
<tr>
<td><strong>Lifestyle cancers</strong></td>
<td></td>
</tr>
<tr>
<td>Tobacco-related (sites: e.g., lung, bladder, kidney)</td>
<td>34</td>
</tr>
<tr>
<td>Diet (low in vegetables, high in nitrates, salt) (sites: e.g., stomach, esophagus)</td>
<td>5</td>
</tr>
<tr>
<td>Diet (high fat, low fiber, broiled/fried foods) (sites: e.g., bowel, pancreas, prostate, breast)</td>
<td>37</td>
</tr>
<tr>
<td>Tobacco plus alcohol (sites: mouth, throat)</td>
<td>2</td>
</tr>
</tbody>
</table>

**Specific carcinogenic agents implicated in the causation of certain cancers\(^c\)**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scrotal carcinomas</td>
<td>chimney smoke condensates</td>
</tr>
<tr>
<td>Liver angiosarcoma</td>
<td>vinyl chloride</td>
</tr>
<tr>
<td>Acute leukemias</td>
<td>benzene</td>
</tr>
<tr>
<td>Nasal adenocarcinoma</td>
<td>hardwood dust</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>radium</td>
</tr>
<tr>
<td>Skin carcinoma</td>
<td>arsenic</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>asbestos</td>
</tr>
<tr>
<td>Vaginal carcinoma</td>
<td>diethylstilbestrol</td>
</tr>
<tr>
<td>Oral carcinoma</td>
<td>snuff</td>
</tr>
<tr>
<td>ER+ breast cancer(^d)</td>
<td>hormone replacement therapy (E + P)(^e)</td>
</tr>
</tbody>
</table>
Advances in Prevention & Screening

- Obesity – 84,000 cancers/yr – esophagus, pancreas, colon, breast, endometrium, kidney, thyroid, gall bladder
- HPV screening with Pap q 3 yrs
- Breast Cancer
  - Anastrazole decreased risk of breast cancer 50% in high risk women (similar or greater than tamoxifen, raloxifene, exemestane)
- Lung Cancer
  - Low dose CT screening for age 55-80 with >30 pack-yr smoking and have quit <15 yo ago
  - miRNA profiling may decrease false-positive 5-fold
A total of 53,439 eligible participants were randomly assigned to a study group (26,715 to low-dose CT and 26,724 to chest radiography).

Lung cancer was diagnosed in 292 participants (1.1%) in the low-dose CT group versus 190 (0.7%) in the radiography group (stage 1 in 158 vs. 70 participants).

Sensitivity and specificity were 73.4% and 93.8% for low-dose CT and 73.5% and 91.3% for chest radiography, respectively.
CANCER RESEARCH PROGRESS THREATENED

Cancer touches us all. The need for continued progress is urgent and growing.

Over 1.6 MILLION AMERICANS received a new cancer diagnosis in the past year. By 2030, this number will increase 45%.

Yet federal funding for cancer research is at the lowest point in decades...

...Putting U.S. scientific leadership in jeopardy

National Institutes of Health Budget FY2003-2013

NIH funding down 23% since 2003, after adjusting for inflation

Russia increasing basic research funding 65%

Europe increasing research spending 40% over seven years

China announced a 26% boost in basic research funding in 2012

NIH research funding cuts harm us all

FEWER CLINICAL TRIAL OPTIONS FOR CANCER PATIENTS

Patient Enrollment in NIH’s Clinical Trials Network

29,000 PATIENTS IN 2009

20,000 PATIENTS IN 2013

NEW TREATMENTS DELAYED

U.S. oncologists report:

75% Current funding situation is directly impacting their ability to conduct cancer research

38% Reduced time spent on research

26% Delayed launching a clinical trial

HARM TO LOCAL ECONOMIES

For every one NIH grant dollar cut, $2.21 will be lost in local economies through lost business activity, jobs and wages

IT’S TIME TO RE-IGNITE OUR NATION’S COMMITMENT TO CANCER RESEARCH.

ASCO is calling on Congress to provide a strong investment for NIH in 2016 to sustain the search for cures.

For more information, go to: www.CancerProgress.Net

Gregory A. Masters et al. JCO
doi:10.1200/JCO.2014.59.9746
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