Ovarian Cancer in the Genomics Era

Christina M. Annunziata, MD, PhD
Women’s Malignancies Branch
National Cancer Institute
Bethesda, MD
Cancer Genomics

- Study of the genome
  - Chromosomes
  - Gene expression
  - Global analysis (not individual entities)
The Genomics Era

- 1959 – Nowell and Hungerford
  - Study of chromosomes
  - Identified recurrent abnormality
  - Philadelphia chromosome
  - Chronic leukemia
The Genomics Era

● 1959 – Nowell and Hungerford
The Genomics Era

- 1973 – Janet Rowley

Table 1  Summary of Chromosomal Analysis

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Duration of CML (yr)</th>
<th>Karyotype*6,7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1§</td>
<td>72</td>
<td>6</td>
<td>46,XY,9q+,22q−</td>
</tr>
<tr>
<td>2§</td>
<td>29</td>
<td>3 1/2</td>
<td>48,XY,9q+,+C,+mar,−17,+?F,22q−</td>
</tr>
<tr>
<td>3§</td>
<td>37</td>
<td>3 1/2</td>
<td>46,XY,9q+,22q−</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50,XY,9q+,+8,+C,+mar,22q−, +22q−</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50,XY,9q+,+8,+C,+mar,22q−, +22q−</td>
</tr>
<tr>
<td>4§</td>
<td>71</td>
<td>1 1/2</td>
<td>46,XX,9q+,+mar,−17,22q−</td>
</tr>
<tr>
<td>5§§</td>
<td>51</td>
<td>2 1/2</td>
<td>47,XX,9q+,+C,+mar,−17,22q−</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>2 mo</td>
<td>48,XY,9q+,+mar,22q−, +22q−</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>1</td>
<td>46,XX,9q+,22q−</td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>3</td>
<td>46,XX,9q+,22q−</td>
</tr>
<tr>
<td>9</td>
<td>64</td>
<td>3 1/2</td>
<td>46,XX,9q+,22q−</td>
</tr>
</tbody>
</table>
The Genomics Era

- 1984 – Groffen – BCR-ABL
The Genomics Era

- 1996 – Drucker – blocking ABL

Fig. 1 Structure of CGP 57148.
Functional Genomics

- What part of the genome is functional
- Causes an effect
- Transforms normal cells into cancer
- Looking for “driver” alterations
Functional Genomics

- 1981 – Shih – discovery of Her2/neu

Transforming genes of carcinomas and neuroblastomas introduced into mouse fibroblasts

Chiaho Shih, L. C. Padhy, Mark Murray & Robert A. Weinberg

Department of Biology and Center for Cancer Research
Functional Genomics

- 1984 – Schechter – neu and EGFR

**Fig. 1** Southern blot analysis of *erb-B*-related sequences in NIH 3T3 cells transformed with rat neuro/glioblastoma DNAs;
Functional Genomics

- 1985 – Coussens – Her2 on chromosome 17
Functional Genomics

- 1987 – Slamon – HER2 in breast cancer
Using genomics to study ovarian cancer

Do we have any “drivers”? 

Ovarian Cancer

- Most lethal gynecologic malignancy in the US
  - >16,000 deaths/yr
  - 5th most common cancer death for women
- 70% diagnosed with advanced disease
- < 35% of advanced stage patients alive at 5y
# Ovarian Cancer Stages

## Ovarian Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Incidence</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Confined to ovaries</td>
<td>20%</td>
<td>90%</td>
</tr>
<tr>
<td>II</td>
<td>Confined to pelvis</td>
<td>5%</td>
<td>65%</td>
</tr>
<tr>
<td>III</td>
<td>Spread IP or nodes</td>
<td>58%</td>
<td>45%</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastases</td>
<td>17%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>
Treatment for Newly Diagnosed Ovarian Cancer

- Complete surgical staging
- Optimal reductive surgery
- Chemotherapy
- Clinical Trials
The State of Treatment for Newly Diagnosed Ovarian Cancer

- Complete surgical staging
- Optimal reductive surgery
- Chemotherapy
  - Platinum = cisplatin or carboplatin
    AND
  - Taxane = paclitaxel or docetaxel
    - Intraperitoneal if Stage III, optimal reduction

- Clinical Trials
Treatment and Outcome for Advanced Ovarian Cancer

<table>
<thead>
<tr>
<th>ALKYLATORS</th>
<th>CISPLATIN/ALKYLATOR COMBINATIONS</th>
<th>INTRA-PERITONEAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CISPLATIN</td>
<td>PAACLITAXEL/ CARBOPLATIN</td>
</tr>
<tr>
<td>0</td>
<td>5%</td>
<td>15%</td>
</tr>
<tr>
<td>1970</td>
<td></td>
<td>15%</td>
</tr>
<tr>
<td>1970</td>
<td></td>
<td>15%</td>
</tr>
<tr>
<td>1980</td>
<td>1990</td>
<td>35%</td>
</tr>
<tr>
<td>1990</td>
<td></td>
<td>35%</td>
</tr>
</tbody>
</table>

5 YR SURVIVAL ADVANCED DISEASE
Ovarian Cancer

Prevalence
- Serous – 80%
- Endometrioid – 10%
- Clear cell – 5%
- Mucinous – 3%
- Other – 2%
Ovarian Cancer

Prevalence
- Serous – 80%
- Endometrioid – 10%
- Clear cell – 5%
- Mucinous – 3%
- Other – 2%

Tissue of origin
- Fallopian tube?
  - Serous
- Endometriosis?
  - Endometrioid and clear cell
- Mullerian epithelium
  - Extra-uterine
Ovarian Cancer

- Increasing our understanding about the biological and biochemical events underlying ovarian cancer progression will create avenues for new treatments

- Can we use Genomics?
Clear cell, Endometrioid
Clear Cell cancers

- 5-10% of all cases (serous = 70%)
- Worse response to standard chemotherapy
- Associated with endometriosis (up to 40%)
Clear cell ovarian cancer

Clear cell OC – genomics

- Sequenced RNA from 18 clear cell ovarian cancers, and one cell line (discovery)
- Sequenced DNA exons from 210 samples
  - 101 more clear cell, 33 endometrioid, 76 serous, 1 more clear cell line (validation)
- Immunostain 455 more samples
  - 132 clear cell, 125 endometrioid, 198 serous
ARID1A mutations in clear cell

Weigand, NEJM 2010
ARID1A

- SWI-SNF chromatin remodeling complex
- Mutated in breast cancer, lung cancer
- 1p36: deleted 6% of all cancers
- Tumor suppressor gene?
ARID1A mutations

A

![Bar chart showing the percentage of loss of BAF250a expression in different cancer subtypes with and without ARID1A mutations.](image)

- CCC: 73% (27/37) with ARID1A mutation, 11% (4/36) without ARID1A mutation
- EC: 50% (5/10) with ARID1A mutation, 9% (2/23) without ARID1A mutation
- HGS carcinoma: 0% with ARID1A mutation, 1% (1/76) without ARID1A mutation
Clear cell and endometrioid cancer

- ARID1A mutated or lost in:
  - Over 40% clear cell
  - 30% endometrioid
  - Less than 1% serous

- Unknown oncogenic mechanism:
  - No indication of which resulting pathways affected
  - Unclear therapeutic utility

- Diagnostic utility?
  - Not a ‘functional’ experiment
Mucinous
Mucinous ovarian cancer

Median OS (95% CI)
Mucinous 12.0 mos (8.0-15.6)
Control 36.7 mos (25.2-48.2)

$P < .001$
Gene expression

Gene expression – mucinous versus serous

Wamunyokoli, Clin Cancer Res, 2006
K-ras mutations

KRAS mutations - mucinous

Table 2: KRAS mutation frequencies observed in borderline malignancies

<table>
<thead>
<tr>
<th>histotype</th>
<th>n</th>
<th>mutated</th>
<th>% mutated</th>
</tr>
</thead>
<tbody>
<tr>
<td>serous</td>
<td>20</td>
<td>7</td>
<td>35.00</td>
</tr>
<tr>
<td>endometroid</td>
<td>1</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>mucinous</td>
<td>6</td>
<td>3</td>
<td>50.00</td>
</tr>
<tr>
<td>unknown</td>
<td>2</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>total</td>
<td>29</td>
<td>10</td>
<td>34.48</td>
</tr>
</tbody>
</table>

Auner, BMC Cancer 2009
Low grade serous
KRAS and BRAF mutations

- BRAF codon 599
- KRAS codon 12 or 13

- 15 of 22 (68%) of low grade serous cancers
- 31 of 51 (61%) precursor lesions (SBT)
- None of 72 high grade serous cancers

Singer, JNCI 2003
KRAS and BRAF

KRAS and BRAF mutations

Singer, JNCI 2003
RAS signaling pathway - a potential driver?

EGFR* 

Sos 

Ras* 

Raf* 

MEK 

ERK 

Ras mutation:
- Pancreatic cancer (90%)
- Papillary thyroid cancer (60%)
- Colon cancer (50%)
- Non-small cell lung cancer (30%)

B-Raf mutation:
- Melanoma (70%)
- Papillary thyroid cancer (50%)
- Colon cancer (10%)

EGFR mutation:
- NSCLC (10%)
- Glioblastoma (20%)

*Mutated in human cancers
MEK inhibitor

Clinical trial: MEK inhibitor

- Recurrent Low Grade Serous ovarian cancer
- Selumetinib 50 mg twice daily
- 52 patients
  - 8 responses
  - 34 stable disease >4mo

Farley, Lancet Oncol 2013
## Selumetinib responses

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>No tumour response</th>
<th>Tumour response</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>34</td>
<td>27 (79%)</td>
<td>7 (21%)</td>
<td></td>
</tr>
<tr>
<td><strong>BRAF mutation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>32</td>
<td>25 (78%)</td>
<td>7 (22%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>2 (100%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>KRAS mutation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20</td>
<td>15 (75%)</td>
<td>5 (25%)</td>
<td>0.672</td>
</tr>
<tr>
<td>Yes</td>
<td>14</td>
<td>12 (86%)</td>
<td>2 (14%)</td>
<td></td>
</tr>
<tr>
<td><strong>BRAF or KRAS mutation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18</td>
<td>13 (72%)</td>
<td>5 (28%)</td>
<td>0.405</td>
</tr>
<tr>
<td>Yes</td>
<td>16</td>
<td>14 (88%)</td>
<td>2 (13%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are number (%), unless otherwise indicated. *Fisher’s exact test.

**Table 8: Tumour response (complete or partial) by BRAF and KRAS mutations**

Farley, *Lancet Oncol* 2013
High grade serous
High grade serous cancers

- **The Cancer Genome Atlas (TCGA)**
  - Clinically annotated HGS-OvCa samples
  - Identify molecular abnormalities that
    - influence pathophysiology,
    - affect outcome and
    - constitute therapeutic targets.
  - Microarray analyses: 489 HGS-OvCa tumours,
    - mRNA expression,
    - microRNA (miRNA) expression,
    - DNA copy number and
    - DNA promoter methylation for and
  - Whole exome DNA sequence: 316 samples.

High grade serous cancers

- **Sample inclusion criteria**
  - Newly diagnosed patients
  - ovarian serous adenocarcinoma
  - no prior treatment
  - companion normal tissue specimen
    - adjacent normal tissue,
    - peripheral lymphocytes,
    - or previously extracted germline DNA
Genome copy number

Genome copy number abnormality

Copy number profiles of 489 HGS-OvCa, compared with profiles of 197 glioblastoma multiforme (GBM) tumours.

Copy number increases (red) and decreases (blue) are plotted as a function of distance along the normal genome (vertical axis, divided into chromosomes).
Mutated genes

Table 2 | Significantly mutated genes in HGS-OvCa

<table>
<thead>
<tr>
<th>Gene</th>
<th>No. of mutations</th>
<th>No. validated</th>
<th>No. unvalidated</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>302</td>
<td>294</td>
<td>8</td>
</tr>
<tr>
<td>BRCA1</td>
<td>11</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>CSMD3</td>
<td>19</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>NF1</td>
<td>13</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>CDK12</td>
<td>9</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>FAT3</td>
<td>19</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>GABRA6</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>BRCA2</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>RB1</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

Validated mutations are those that have been confirmed with an independent assay. Most of them are validated using a second independent whole-genome-amplification sample from the same tumour. Unvalidated mutations have not been independently confirmed but have a high likelihood to be true mutations. An extra 25 mutations in TP53 were observed by hand curation.

The Cancer Genome Atlas, Nature 2011
Altered pathways

Altered pathways in HGS-OvCa

HR alterations
BRCA altered cases, $N = 103$ (33%)

BRCA1

BRCA2
Altered pathways in HGS-OvCa

- FOXM1 signalling
- 84% of cases altered

Key pathways:
- Cell cycle progression
- DNA repair

Genes involved:
- PLK1
- TP53
- ATM
- ATR
- RAD51
- CCNB1
- AURKB
- FOXM1
- CHEK2
- BRCA1
- BRCA2
- BIRC5
- CDC25B
- BRCC
TCGA – what next?

- New **therapeutic** approaches?
  - 50% with HR defects: **PARP inhibitors**
  - Commonly deregulated pathways: RB, RAS/PI3K, FOXM1, NOTCH, provide opportunities for therapeutic treatment
  - Inhibitors exist for 22 genes in regions of recurrent amplification
- Aberrant genes or **networks**: targeted therapies selected to be effective ...
Targeting deficient Homologous Recombination

PARP inhibitors
BRCA mutations

- Hall...King, *Science*, 1990
High grade serous cancers

- BRCA1 germline: 8%
- BRCA2 germline: 6%
- BRCA1 somatic: 4%
- BRCA2 somatic: 3%
- BRCA1 methylation: 11%
- EMSY amplification: 6%
- PTEN loss: 6%
- Other HRD: 5%
- Other: 31%
- MMR germline: 2%
- Rb1 loss: 4%
- CCNE1 amplification: 14%

* HRD, homologous recombination defect
BRCA mutations

BRCA mutations... and beyond

Genes associated with mutations in Homologous Recombination machinery

Peng et al, Nat Comm, 2014
PARP inhibition

PARP inhibition: BRCA-mutant cancers

- Cellular metabolism, environmental exposures
- Replicating cells
- Normal cell
- Repair by Homologous Recombination
  - Survival
- Cancer cell with BRCA deficiency
  - No effective repair
    - (No HR pathway)
PARP inhibitor

- Olaparib (AZD2281)
  - novel, orally active PARP inhibitor
  - synthetic lethality in homozygous BRCA-mut cells
Phase I/III study

Phase I/III Study of Olaparib and Carboplatin

Cohort 1
**Br/Ov** cancers
BRCA mutant
BRCApro ≥ 30%

(Lee, JNCI 2014)

- Olaparib 400mg twice daily (days 1-7)
- Carboplatin AUC 5 (every 21 days)

Cohort 2
**TNBC**
BRCA normal
BRCApro ≤ 10%

(Chiou, AACR 2014)

- Olaparib 400mg twice daily (days 1-7)
- Carboplatin AUC 4 (every 21 days)

Cohort 3
**Serous Ovarian**
BRCA normal
BRCApro ≤ 20%

(Chiou, ASCO 2015)

- Olaparib 400mg twice daily (days 1-7)
- Carboplatin AUC 4 (every 21 days)
Phase Ib Study of Olaparib and Carboplatin in BRCA1 or BRCA2 Mutation-Associated Breast or Ovarian Cancer

- **Results:** 45 enrolled patients
  - 37 ovarian cancer
  - 8 breast cancer

- Phase 1 dose escalation = 30 patients
- Phase 1b expansion = 15 patients

- **MTD** = Carboplatin AUC5 on day 1 + Olaparib 400mg twice daily on days 1-7, every 21 days

Phase 1b Study of Olaparib and Carboplatin in BRCA1 or BRCA2 Mutation-Associated Breast or Ovarian Cancer

Phase 1b study

Phase Ib Study of Olaparib and Carboplatin in BRCA1 or BRCA2 Mutation-Associated Breast or Ovarian Cancer

<table>
<thead>
<tr>
<th>Best response</th>
<th>Ovarian cancer (n = 34)†</th>
<th>No. (%)</th>
<th>Median duration in months (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>15 (44.1)</td>
<td>16 (4 to &gt;45)</td>
<td></td>
</tr>
<tr>
<td>SD ≥ 4 mo</td>
<td>13 (38.2)</td>
<td>11 (6 to 24)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>6 (17.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response rate</td>
<td>15/34 (44.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical benefit rate</td>
<td>28/34 (82.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions:

- Oral olaparib is well tolerated in combination with carboplatin
- Highly active in advanced, chemotherapy-refractory BRCA-deficient cancer
- Greater activity seen at the higher dose
- Positive proof of the concept of the activity and tolerability of genetically defined targeted therapy with olaparib in BRCA-deficient cancers
- Results of sporadic HGSOC cohort to be presented at ASCO meeting 2015
Exploration of new targets

Functional Genomics
“Actionable” mutations

- Commercially available testing
  - e.g., Caris, Foundation One
  - Report “possible” or “unlikely” benefit
- “Basket” clinical trials
  - e.g., NCI-MPACT
  - Assign treatment based on mutation
- Typically no functional link
“Actionable” mutations

- “…depends in large part on the strength of the data linking the target and targeted therapy.”
- “For this trial design to work, two key conditions must be met:
  - the tumor must depend on the target pathway, and
  - the targeted therapy must reliably inhibit the target.”
- “Achieving both goals can be a matter of some complexity.”
“Actionable” targets

- Need a functional experiment
- Functional genomics
Functional genomics

Using a functional genomics screen to identify targets

Creation of an Inducible shRNA Retroviral Library for Functional Genomics Studies of Cancer Phenotypes

- shRNAs targeting **2500** human genes
- 3 shRNA constructs per gene
- All sequence verified
- All containing identified **60-mer bar code sequence**
- shRNA expression is inducible by doxycycline
- Library target genes:
  - All protein kinases
  - All PI3 kinase
  - All deubiquitinating enzymes
  - NF-kB pathway regulators
  - Differentially expressed genes among lymphoma types
  - Apoptosis regulators, oncogenes, tumor suppressors

shRNA Library Screen for Genes Controlling Cancer Cell Proliferation and Survival
Functional Genomics of ovarian cancer

- Four ovarian cancer cell lines
  - OVCAR3 – serous
  - OVCAR5 – serous
  - Igrov1 – non-serous
  - A2780 – non-serous
Common targets in ovarian cancer – “drivers”?

63 shRNAs representing 55 genes
Common targets

Common targets in ovarian cancer – “drivers”?

[Diagram with overlapping circles and gene names]

- Common targets
- serous
  - Ovcar3
  - Ovcar5
- non-serous
  - Igrov1
  - A2780

- Brd4
- Bub1b
- Dclk2
- Grk6
- Itk
- Pdgfrb
- Ret
- Sgk2
- Stk36
- Ddr2
- Ern2
- Insrr
- Map2k7
- Rrm1
- Gucy2f
- Mnk2
- Pdk3
- Pik3ap1
- Wee1

- Aurka
- Cdc2l5
- Cdc7
- Dclk3
- Ephb1
- Fgr
- Gsk3a
- Hipk4
- Ksr1
- Lrrk2
- Map3k7
- Trrap
- Mark3

- Alpk2
- Cdc2l6
- Cdk7
- Csnk12
- Erbb2
- Fer
- Ksr2
- Map3k8
- Nek2
- Ripk5
- Tlk1
- Wnk1

- Aurka
- Cdc2l5
- Cdc7
- Dclk3
- Ephb1
- Fgr
- Gsk3a
- Hipk4
- Ksr1
- Lrrk2
- Map3k7
- Trrap
- Mark3

- Alpk2
- Cdc2l6
- Cdk7
- Csnk12
- Erbb2
- Fer
- Ksr2
- Map3k8
- Nek2
- Ripk5
- Tlk1
- Wnk1

- Aurka
- Cdc2l5
- Cdc7
- Dclk3
- Ephb1
- Fgr
- Gsk3a
- Hipk4
- Ksr1
- Lrrk2
- Map3k7
- Trrap
- Mark3
Functional genomics of ovarian cancer

- Following up in
  - 6 additional cell lines
  - 2 different RNAi constructs
  - Select “druggable” targets

- Focused functional screens
  - Specific subgroup of serous ovarian cancer
  - NF-kappaB signaling pathway
**CHEK1**

- Highly synergistic with IKKε
- Over-expressed in nearly all ovarian cancers

---

CHEK signaling

DNA damage → DDR

ATM

Chk1/Chk2

Cdc25A/B/C

CyclinB-cdk2

Therapeutic inhibition

Cell Cycle

G1

G1/S

G2

G2/M

M

S

S to G2

Mitosis

Normal cells

p21waf1

p53

G1/S checkpoint disrupted

Mutated p53

Cancer cells
CHEK inhibitor

- Most potent in HGSOC

CHEK inhibitor

- Clinical trial ongoing
  - NCT02203513
  - Promising results in High grade serous non BRCA

- Highlighted by a Functional Genomics approach
Best response on clinical trial

Germline BRCA mutation

High grade serous ovarian cancer

Change from baseline in sum of longest diameters (%)
Duration on clinical trial

Duration on clinical trial

High grade serous ovarian cancer

Germline BRCA mutation

Time on study (months)

- Partial response
- Platinum-sensitive
- Platinum-resistant
Ovarian cancer genomics

Summary
Ovarian cancer genomics

Ovarian cancer genomics

![Diagram showing the genomics of ovarian cancer with epithelial and nonepithelial categories, detailing gene alterations and pathway modifications.](image)

Functional Genomics

- 1981 – Shih – discovery of Her2/neu

Transforming genes of carcinomas and neuroblastomas introduced into mouse fibroblasts

Chiaho Shih, L. C. Padhy, Mark Murray & Robert A. Weinberg

Department of Biostat and Center for Cancer Research
Controlling genes

shRNA Library Screen for Genes Controlling Cancer Cell Proliferation and Survival

shRNA retroviral library

Induce shRNA expression

21 day growth in vitro

shRNA ON

shRNA OFF

shRNA that blocks cell proliferation or survival

PCR amplify bar codes

Barcode microarray assay of shRNA abundance
Ovarian cancer and genomics

Ovarian Cancer in the Genomics Era

Transforming genes of carcinomas and neuroblastomas introduced into mouse fibroblasts

Chiaho Shih, L. C. Padhy, Mark Murray & Robert A. Weinberg

Department of Biology and Center for Cancer Research
Women’s Cancer Team:
Stan Lipkowitz, MD, PhD
Jung-Min Lee, MD
Alexandra Zimmer, MD
Victoria Chiou, MD
Ciara O’Sullivan, MD
Anne Noonan, MD
Elise C. Kohn, MD
Nicole Houston, RN
Irene Ekwede, RN
MOS Fellows and Nursing Staff

Collaborators:
Lou Staudt, MD, PhD
George Wright, PhD

Funding:
National Cancer Institute, IRP

Women’s Cancer Foundation

Patients and their families