Ovarian Cancer in the Genomics Era

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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*§, 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>3½</td>
<td>48,XY,9q+,+C,+mar,-17,+?F,22q-</td>
</tr>
<tr>
<td>3§</td>
<td>37</td>
<td>3½</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>1½</td>
<td>46,XX,9q+,+mar,-17,22q-</td>
</tr>
<tr>
<td>5§‡</td>
<td>51</td>
<td>2½</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>3½</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 Biolgy 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
<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
  - 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>
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<tbody>
<tr>
<td>1960</td>
<td></td>
<td>2000</td>
</tr>
<tr>
<td>1970</td>
<td>CISPLATIN</td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td>PAACLITAXEL/ CARBOPLATIN</td>
<td>35%</td>
</tr>
<tr>
<td>1990</td>
<td></td>
<td>40%</td>
</tr>
<tr>
<td>2000</td>
<td></td>
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<table>
<thead>
<tr>
<th>5 YR SURVIVAL ADVANCED DISEASE</th>
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<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>5%</td>
</tr>
<tr>
<td>15%</td>
</tr>
<tr>
<td>35%</td>
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<tr>
<td>40%</td>
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<tbody>
<tr>
<td>0</td>
<td>5%</td>
<td>15%</td>
<td>35%</td>
<td>40%</td>
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<tr>
<td>15%</td>
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<tr>
<td>35%</td>
</tr>
<tr>
<td>40%</td>
</tr>
</tbody>
</table>
Ovarian Cancer

Prevalence

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

Soslow R. *Int J Gyneol Pathol*, 2008
Ovarian Cancer

Prevalence
- Serous – 80%
- Endometrioid – 10%
- Clear cell – 5%
- Mucinious – 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 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

Weigand, NEJM 2010
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

Weigand, *NEJM* 2010
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 – mucinous versus serous

Wamunyokoli, *Clin Cancer Res*, 2006
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>
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<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>
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<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 mutations

- Serous borderline tumors
- Invasive low grade serous cancers
- High grade serous cancers

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

http://scienceblogs.com/pharyngula/2013/09/21/16271/
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
<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>No tumour response</th>
<th>Tumour response</th>
<th>p value*</th>
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<tbody>
<tr>
<td>Total</td>
<td>34</td>
<td>27 (79%)</td>
<td>7 (21%)</td>
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</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
RAS signaling

Malumbres and Pellicer, *Fontiers Biosci* 1998
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

The Cancer Genome Atlas, Nature 2011
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).
# 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>
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<tbody>
<tr>
<td><strong>TP53</strong></td>
<td>302</td>
<td>294</td>
<td>8</td>
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<tr>
<td><strong>BRCA1</strong></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><strong>FAT3</strong></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><strong>BRCA2</strong></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.
Altered pathways in HGS-OvCa

HR alterations

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

- **BRCA1**
- **BRCA2**
Altered pathways in HGS-OvCa

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%
- MMR germline: 2%
- Rb1 loss: 4%
- CCNE1 amplification: 14%
- Other: 31%

*HRD, homologous recombination defect
BRCA mutations... and beyond

Genes associated with mutations in Homologous Recombination machinery

Survival
Normal cell
Repair by Homologous Recombination
Survival
PARP inhibition: BRCA-mutant cancers

Replicating cells
Cancer cell with BRCA deficiency
No effective repair (No HR pathway)

cellular metabolism, environmental exposures
PARP inhibitor

- PARP inhibition: BRCA-mutant cancers
- Repair by Homologous Recombination
- Survival
- Replicating cells
- Cancer cell with BRCA deficiency
- No effective repair (No HR pathway)

PARP inhibitor
PARP inhibitor

- Olaparib (AZD2281)
  - novel, orally active PARP inhibitor
  - synthetic lethality in homozygous BRCA-mut cells
Phase I/Ib 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 Ib Study of Olaparib and Carboplatin in BRCA1 or BRCA2 Mutation-Associated Breast or Ovarian Cancer

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

Redig and Janne, *J Clin Oncol* 2015
“Actionable” targets

- Need a functional experiment
- 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

shRNA that blocks cell proliferation or 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”?
Common targets in ovarian cancer – “drivers”?

BRD4
BUB1B
DCLK2
GRK6
ITK
PDGFRB
RET
SGK2
STK36

DDR2
ERN2
INSRR
MAP2K7
RRM1

GUCY2F
MKNK2
PDK3
PIK3AP1
WEE1

AURKA
CDC2L5
CDC7
CDK7
CSNK12
ERBB2
FER
KSR1
LRRK2
MAP3K7
MARK3
MGC42105
NLK
NUAK1
PLK1
PNCK
PRKCA
PRKCB
STK32A
TAOK1
TEK
TRRAP
TSSK3
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
Gene expression – subgroups

The Cancer Genome Atlas, Nature 2011
Gene expression – immunoreactive

**NF-κB complex**
NF-κB signaling

TNFα

TNFR1

Cell membrane

TRAF2

TAK1

cIAP

IKKβ

IKKγ

IKKα

IKKε

IkBα

p50

p65

NF-κB activity

proteasome

Nucleus

NF-κB target genes

survival, proliferation

TNF, tumor necrosis factor
IAP, inhibitor of apoptosis protein
IKK, IkB kinase
IkB, Inhibitor of NF-κB
NF-κB, nuclear factor κB
IKKε related targets

shRNA Bar code
shRNA retroviral library

Infect cancer cells

IKKε-low

IKKε-high

shRNA that works in conjunction with IKKε
CHEK1

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

CHEK signaling

DNA damage → DDR

Therapeutic inhibition

ATM

Chk1/Chk2

Cdc25A/B/C

CyclinB-cdk2

Cell Cycle

Mitosis

G1

G1/S

G2

G2/M

S to G2

Normal cells

p21waf1 → p53

G1/S checkpoint disrupted

Mutated p53

Cancer cells

Biodiscoveryjournal.co.uk
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
Ovarian cancer genomics

Summary
Ovarian cancer genomics

Ovarian cancer

Epithelial

High-grade serous
- TP53
- BRCA1 and 2
- NF1
- RB1
- CDK12
- Homologous recombination repair genes*

Low-grade serous
- BRAF
- KRAS
- NRAS
- ERBB2

Mucinous
- KRAS
- HER2 amplification

Clear cell
- ARID1A
- PIK3CA
- PTEN
- CTNNB1
- PPP2R1α

Endometrioid
- ARID1A
- PIK3CA
- PTEN
- PPP2R1α

Sex cord-stromal
- Granulosa cell
- FOXL2
- Sertoli-Leydig cell
- DICER1

Others, including germ cell

Nonepithelial

Pattern of spread
- Early, trans-coelomic
- Trans-coelomic
- Usually confined

Molecular aberration
- BRCA, p53, network
- BRAF
- KRAS
- HER2
- ARID1A
- PTEN
- HNF1

Chemo-sensitivity
- High
- Intermed
- Low

Prognosis
- Poor
- Intermed.
- Favorable

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
shRNA Library Screen for Genes Controlling Cancer Cell Proliferation and Survival

- **shRNA Library Screen**
  - Infect cancer cells with shRNA retroviral library
  - Induce shRNA expression
  - 21 day growth in vitro
  - PCR amplify bar codes
  - Barcode microarray assay of shRNA abundance
  - shRNA that blocks cell proliferation or survival
Ovarian Cancer in the Genomics Era

Functional genomic screen

“Driver” aberration/pathway

Clinical trial

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Patients and their families