Therapeutic Relevance of Gene Expression Signatures in Ovarian Cancer: Examining the Evidence
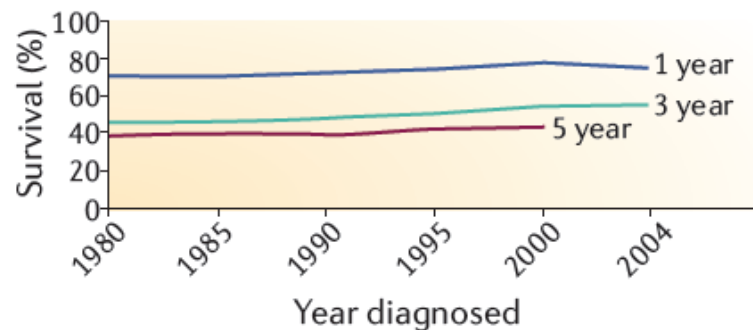
ESMO Asia, 18 Dec 2015,SUNTEC, Singapore

Ruby Yun-Ju HUANG, M.D. Ph.D.
Department of Obstetrics & Gynaecology, NUH
Cancer Science Institute of Singapore, NUS
Department of Anatomy, YLL SoM, NUS

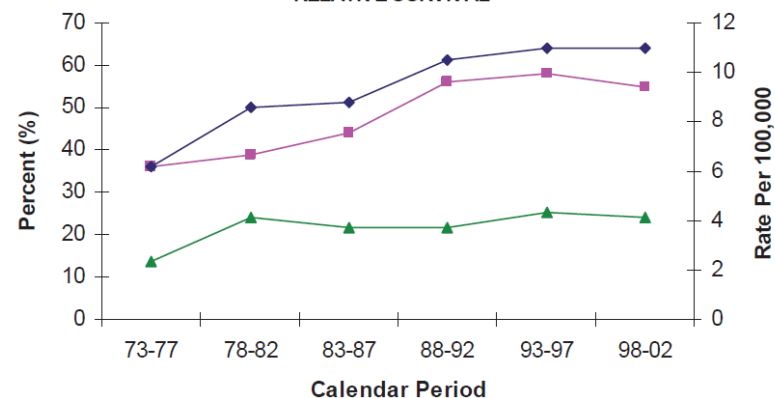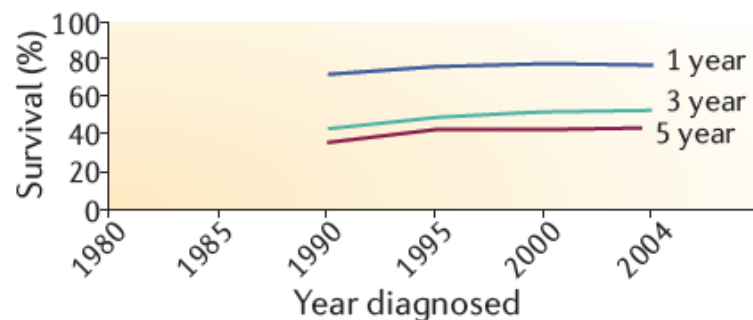# Epithelial Ovarian Cancer: Mortality Trend

US

a SEER

Australia

b The Cancer Council of Victoria

Canada

c The Cheryl Brown Outcomes Unit

SG

OVARY:
TRENDS IN INCIDENCE, MORTALITY AND 5-YEAR AGE STANDARDISED RELATIVE SURVIVAL

Legend: 5 yr ASRS — Incidence Rates/100,000 — Mortality Rates/100,000
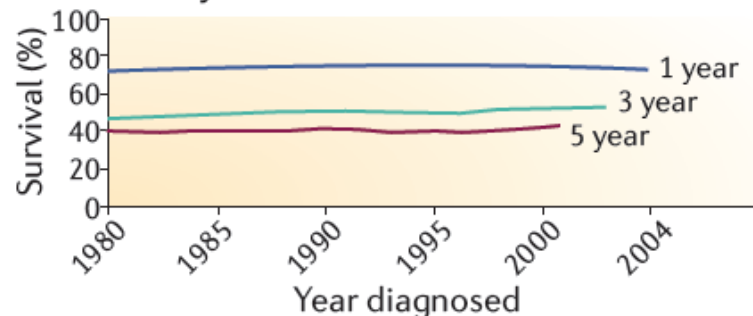
OVARY:
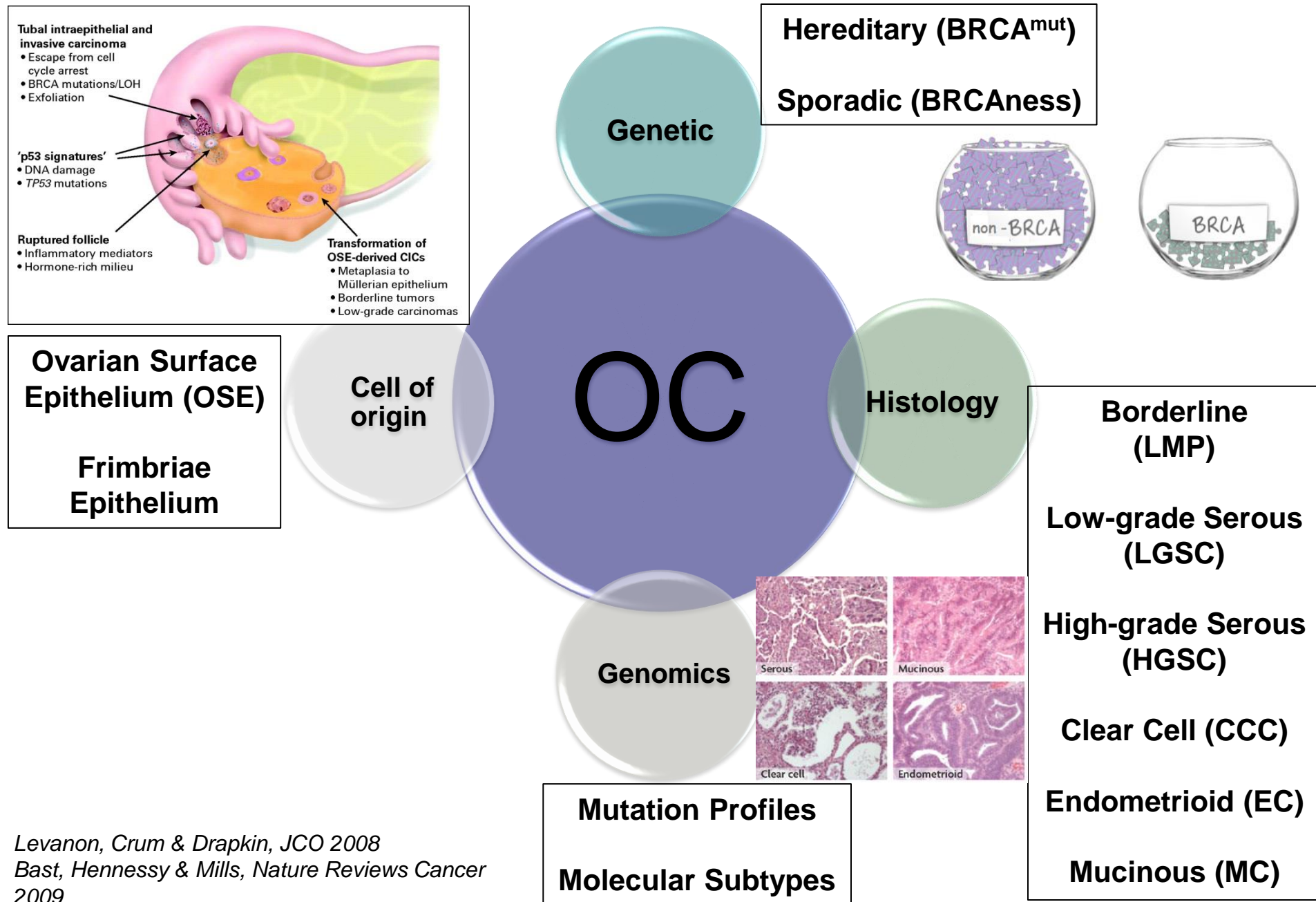1- AND 5-YEAR AGE STANDARDISED RELATIVE SURVIVAL IN SELECTED COUNTRIES
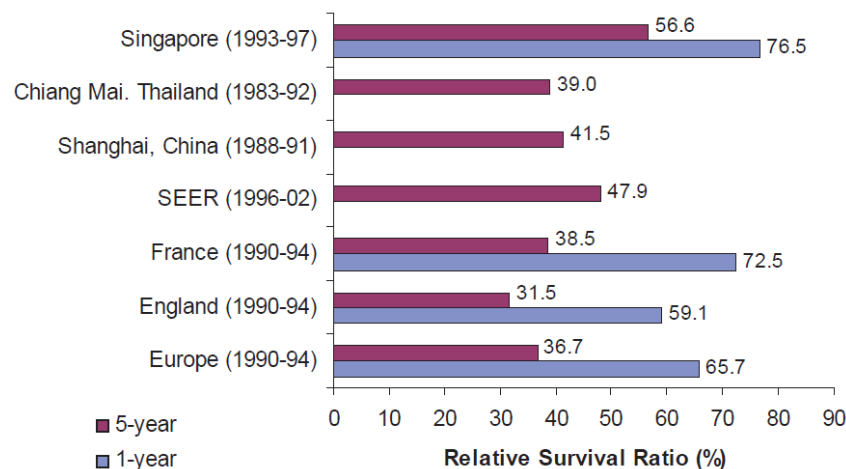
Rethinking ovarian cancer: recommendations for improving outcomes.
Vaughan et al., 2012
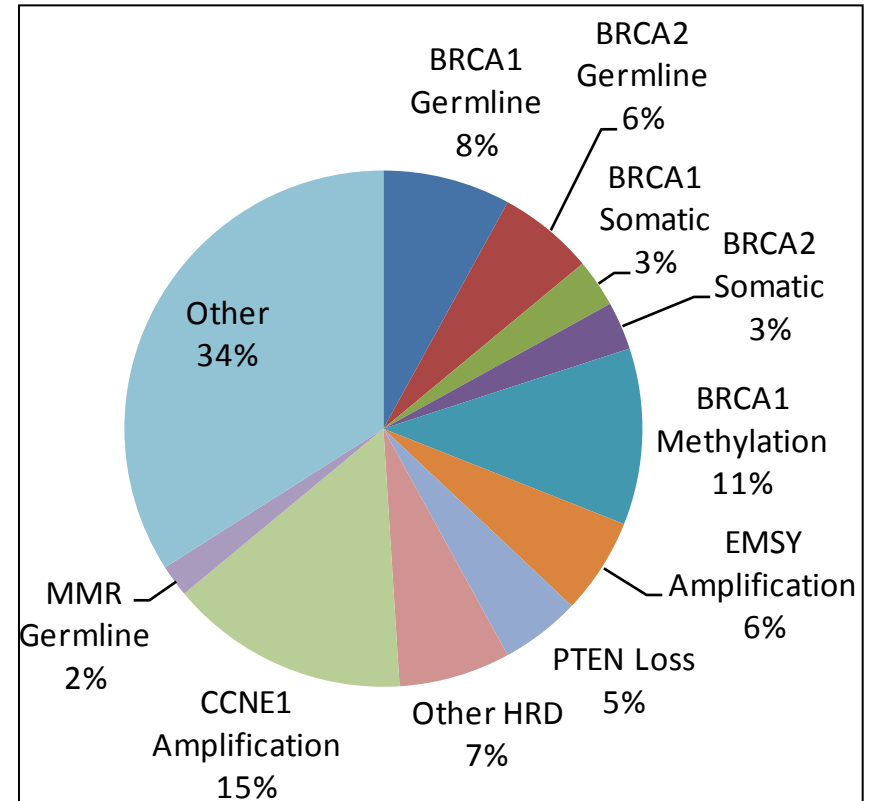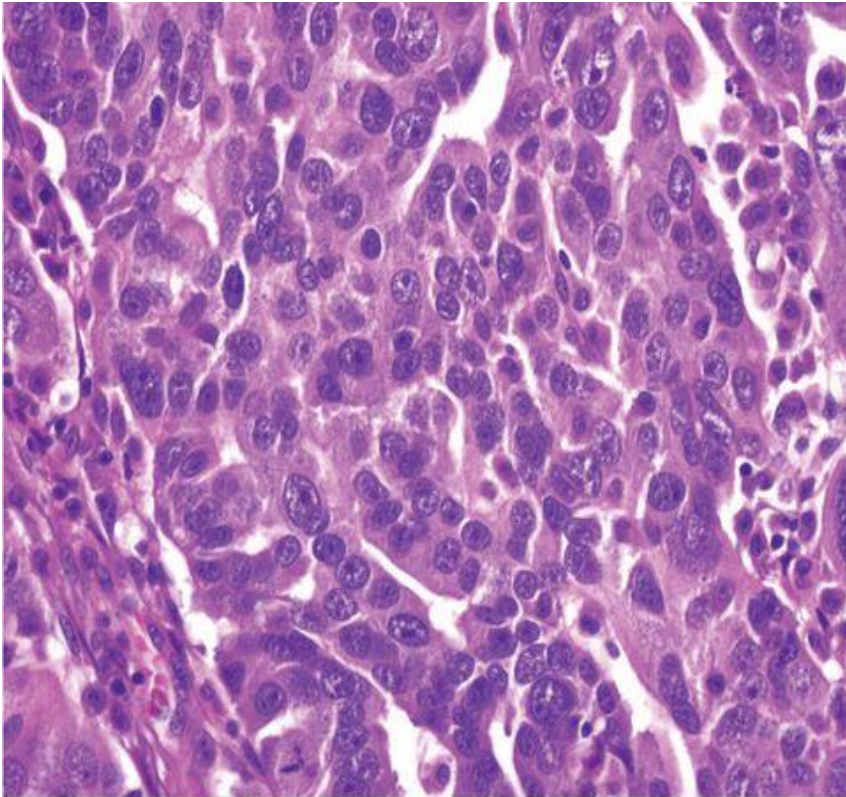*Cancer survival in Singapore 1968-2002. Singapore Cancer Registry*

Heterogeneity in Ovarian Cancer

Tubal intraepithelial and invasive carcinoma
- Escape from cell cycle arrest
- BRCA mutations/LOH
- Exfoliation

'p53 signatures'
- DNA damage
- TP53 mutations

Ruptured follicle
- Inflammatory mediators
- Hormone-rich milieu

Transformation of OSE-derived CICs
- Metaplasia to Müllerian epithelium
- Borderline tumors
- Low-grade carcinomas

Genetic

Hereditary (BRCA^{mut})

Sporadic (BRCAness)

non-BRCA   BRCA

OC

Cell of origin

Histology

Ovarian Surface Epithelium (OSE)

Frimbriae Epithelium

Borderline (LMP)

Low-grade Serous (LGSC)

High-grade Serous (HGSC)

Clear Cell (CCC)

Endometrioid (EC)

Mucinous (MC)

Genomics

Serous   Mucinous

Clear cell   Endometrioid

Mutation Profiles

Molecular Subtypes

Levanon, Crum & Drapkin, JCO 2008
Bast, Hennessy & Mills, Nature Reviews Cancer 2009
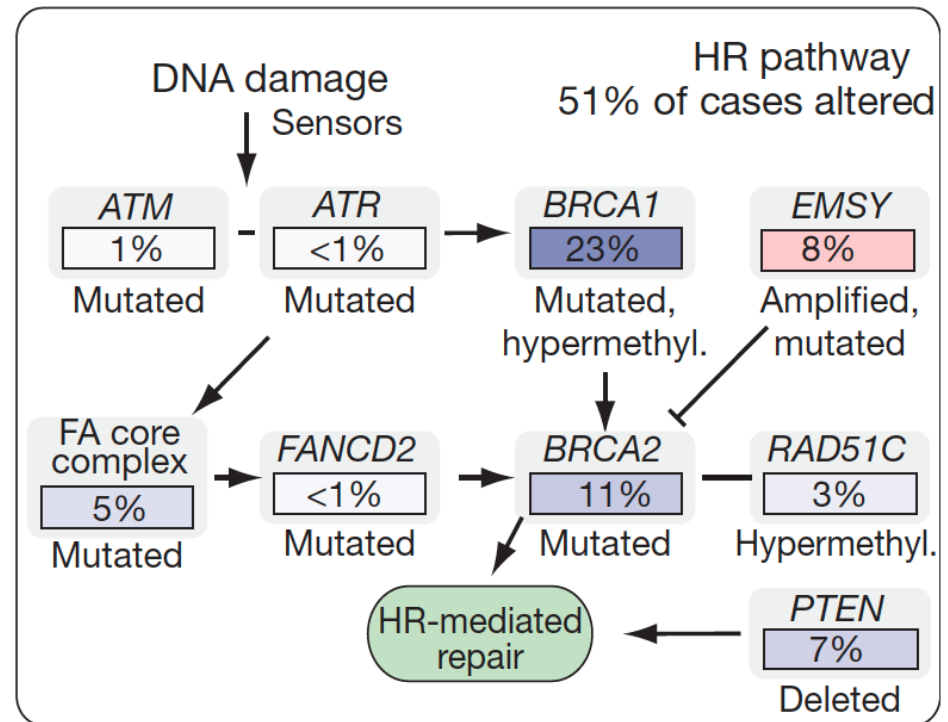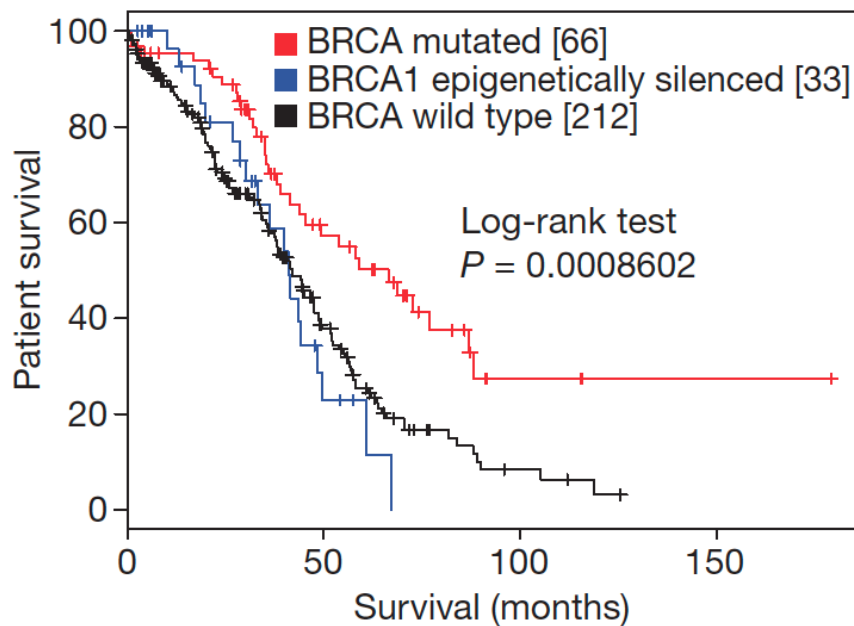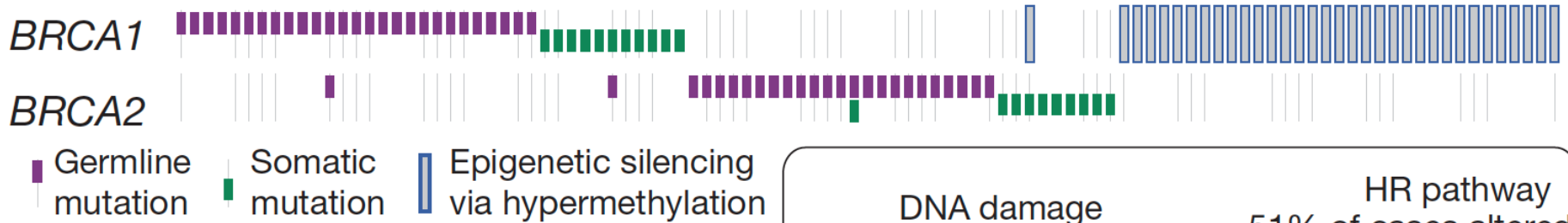
They look the same so they must be the same – right?

High grade serous ovarian cancer (HGSC)

Pie chart showing genetic alterations in HGSC:
- BRCA1 Germline 8%
- BRCA2 Germline 6%
- BRCA1 Somatic 3%
- BRCA2 Somatic 3%
- BRCA1 Methylation 11%
- EMSY Amplification 6%
- PTEN Loss 5%
- Other HRD 7%
- CCNE1 Amplification 15%
- MMR Germline 2%
- Other 34%

Approximately 50% with defects in Homologous Recombination (HR)
HR biomarker for chemo-response/outcome in Asian cohorts?

Levine et al Nature TCGA 2011

BRCAness in HGSC

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

BRCA1

BRCA2

- Germline mutation
- Somatic mutation
- Epigenetic silencing via hypermethylation

Kaplan-Meier survival curves:
- BRCA mutated [66]
- BRCA1 epigenetically silenced [33]
- BRCA wild type [212]

Log-rank test
$P = 0.0008602$

Patient survival vs Survival (months)

HR pathway
51% of cases altered

DNA damage → Sensors

ATM 1% Mutated	ATR <1% Mutated	BRCA1 23% Mutated, hypermethyl.	EMSY 8% Amplified, mutated
FA core complex 5% Mutated	FANCD2 <1% Mutated	BRCA2 11% Mutated	RAD51C 3% Hypermethyl.

HR-mediated repair

PTEN 7% Deleted

TCGA, 2011 Nature

- Lack of effective early detection (screening) methods
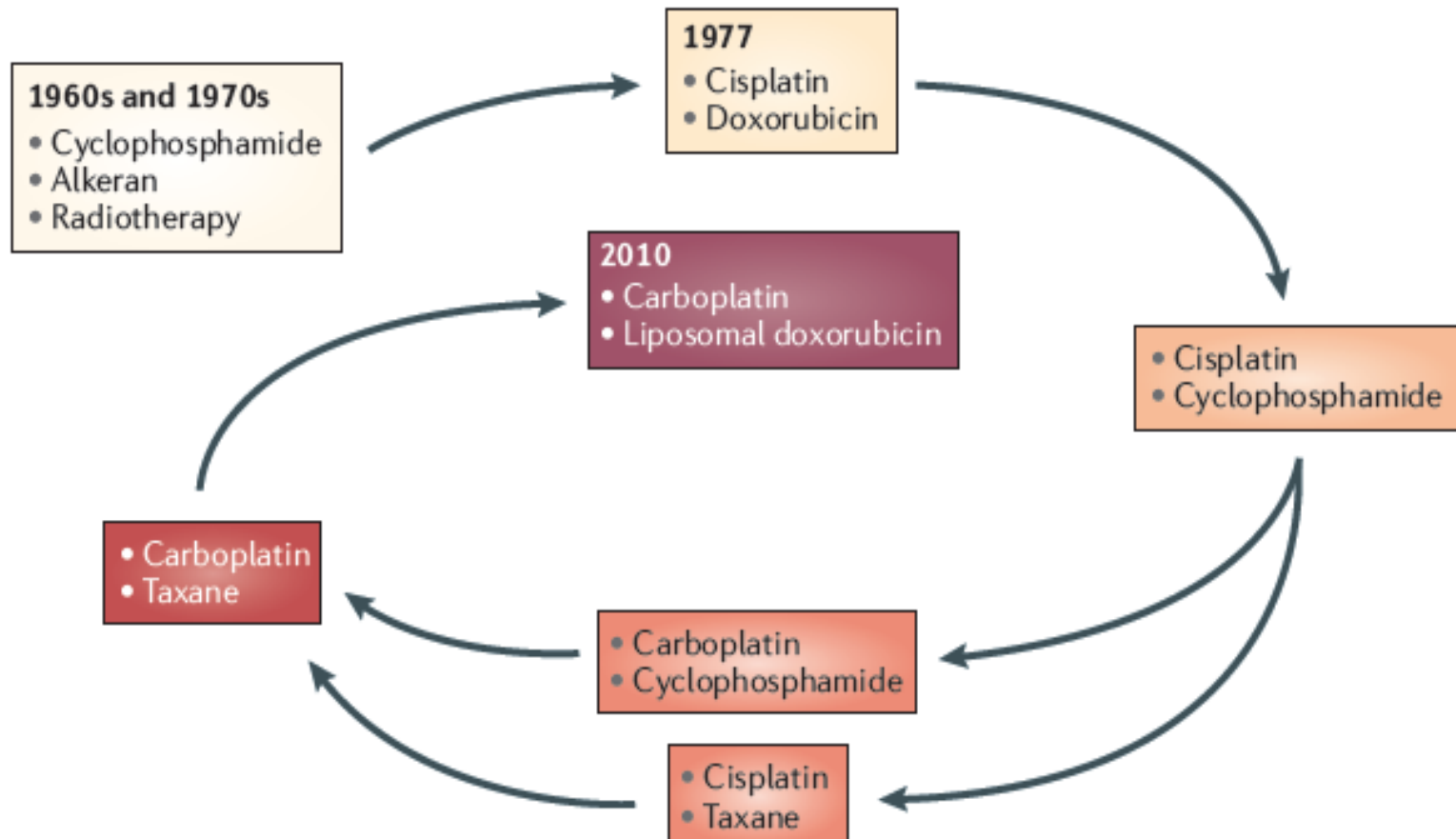
- Lack of novel patient stratification strategy

**Complexity
&
Heterogeneity**

- Emerging development of targeted therapy

Who to treat? When to treat?

Evolution of Chemotherapy in Ovarian Cancer

1960s and 1970s
- Cyclophosphamide
- Alkeran
- Radiotherapy

1977
- Cisplatin
- Doxorubicin

- Cisplatin
- Cyclophosphamide

2010
- Carboplatin
- Liposomal doxorubicin

- Carboplatin
- Cyclophosphamide

- Cisplatin
- Taxane

- Carboplatin
- Taxane

Vaughan et al, Nat Rev Ca, Oct 2011

One Model Fits All?

Heterogeneous EOC Patients   Homogeneous Treatment

❖ First study (***Tothill et al., CCR 2008***) using 285 HGSC and HGEC tumors from an Australian cohort profiled on Affymetrix U133 Plus 2.0 arrays.

    6 subgroups (C1 – C6)

    showing survival differences

❖ Subsequent study (***TCGA, Nature 2011***) using 489 HGSC tumors from an US cohort profiled on Affymetrix U133 Plus 2.0 arrays.
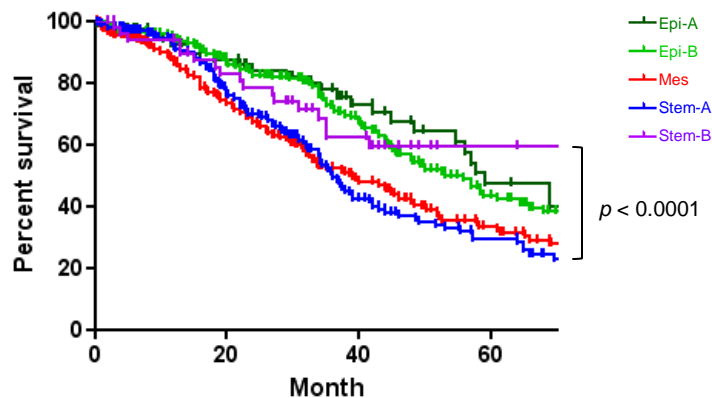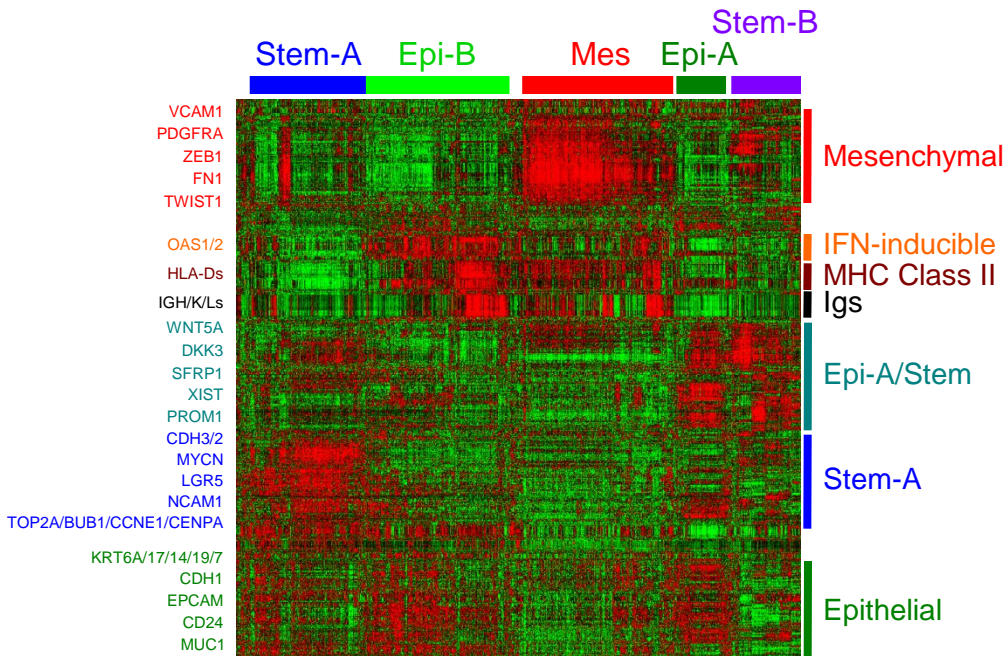
4 subgroups
(Differentiated, Immunoreactive, Mesenchymal, Proliferative)

no clear survival difference in the primary analysis

GSE9891

C1   C2   C3   C4   C5 C6

Hierarchical Gene Clustering

TCGA
489 tumours

Tumour/gene groups
Differentiated
Immunoreactive
Mesenchymal
Proliferative

Gene expression
Low   High

Tothill et al., CCR 2008   ***TCGA, Nature 2011***

Stem-B

Stem-A Epi-B Mes Epi-A

Mesenchymal

IFN-inducible
MHC Class II
Igs

Epi-A/Stem

Stem-A

Epithelial

VCAM1
PDGFRA
ZEB1
FN1
TWIST1

OAS1/2
HLA-Ds
IGH/K/Ls
WNT5A
DKK3
SFRP1
XIST
PROM1
CDH3/2
MYCN
LGR5
NCAM1
TOP2A/BUB1/CCNE1/CENPA

KRT6A/17/14/19/7
CDH1
EPCAM
CD24
MUC1

$p < 0.0001$

❖ Meta-analysis (***Tan, Miow, & Huang et al., EMBO MM, 2013***) of 1,538 EOCs including all histological types. 5 subtypes showing survival differences
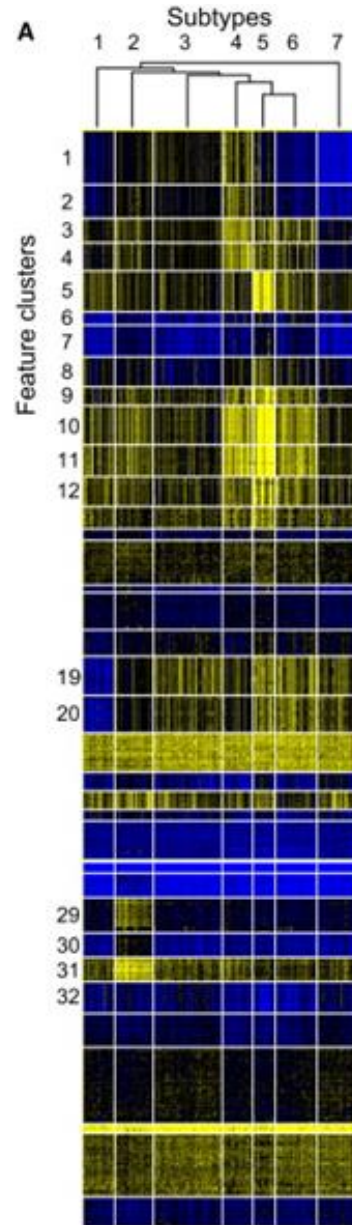
Proposed	Tothill *et al.*, 2008	TCGA, 2012
Epi-A	C3	Differentiated
Epi-B	C4	Differentiated
Epi-B	C2	Immunoreactive
Mes	C1	Mesenchymal
Stem-A	C5	Proliferative
Stem-B	C6	

Tan, Miow & Huang et al., EMBO Mol Med, 2013

Five major subgroups were identified within EOC that harbor distinctive signatures of Epithelial, Mesenchymal, or Stem-like, which confer to different clinical survival outcomes.
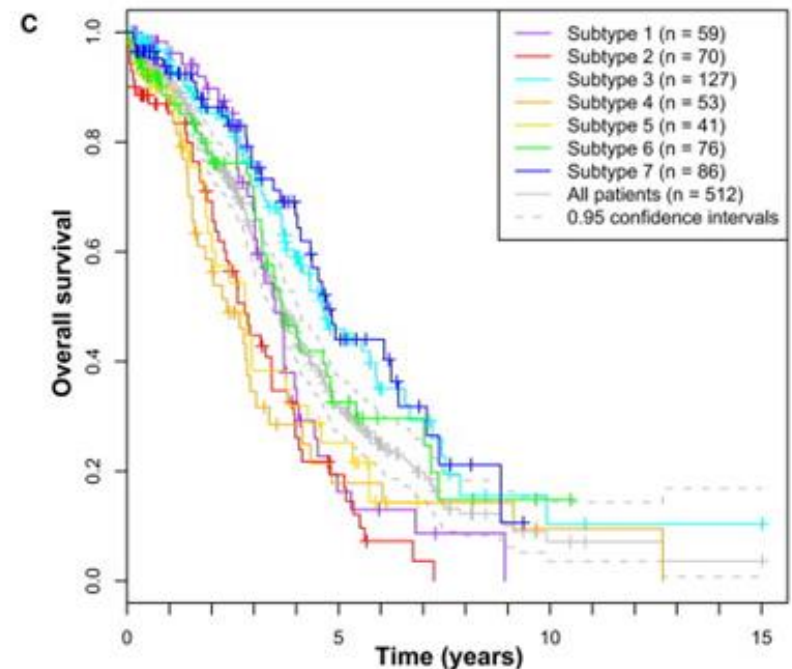
❖ Integrated Analysis (*Zhang et al., Cell Report, 2013*) of TCGA datasets.
    7 subtypes
    showing survival
differences

Challenge

Which one to treat?

What's the evidence of gene expression signature(s) in predicting therapeutic response in ovarian cancer?
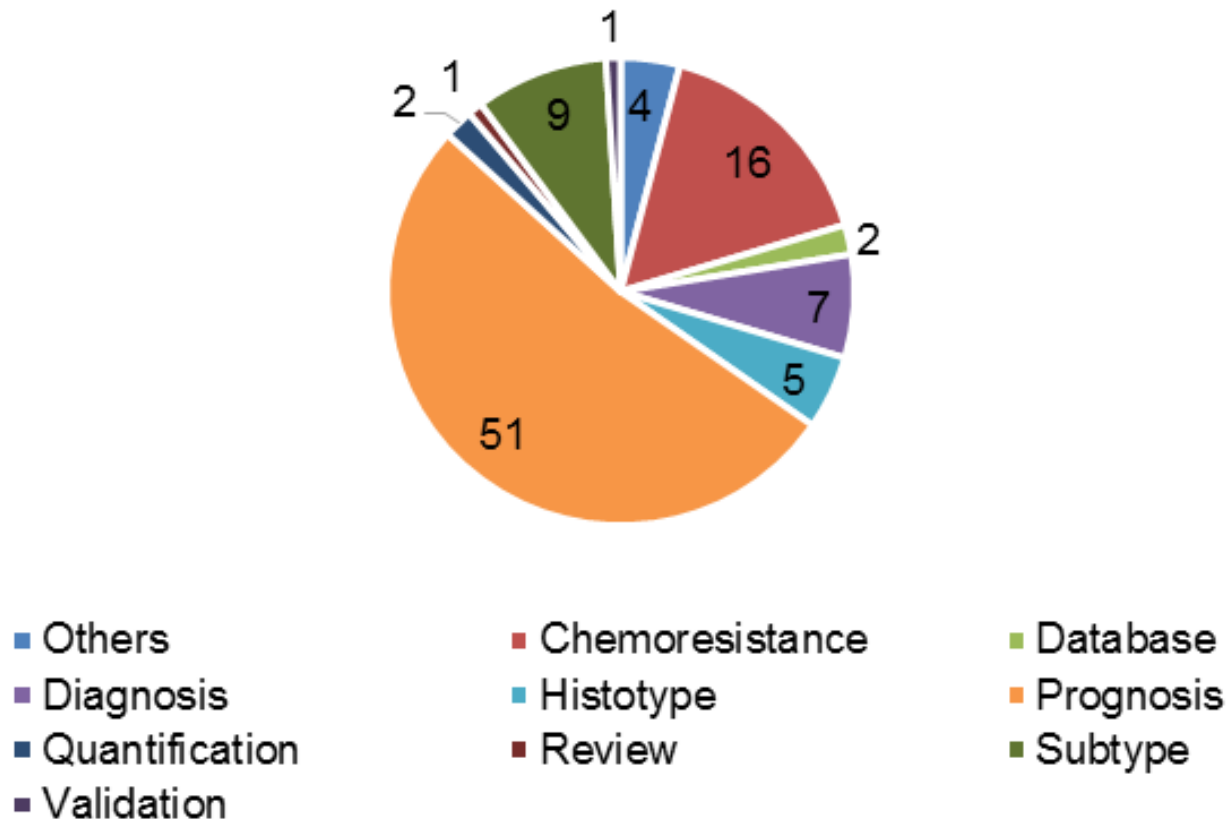
Which one for you?

We Don't Know.

Source www.pubmed.com
Search term ovarian cancer gene expression signature
Date 2015 Dec 3, 1130am
Result of query 384
Limit to Human 328
Limit 5 years 241
Limit to English 240
Limit to transcriptome, cancer, > one gene, not method paper
98

Working definition of Signature:

A gene signature is a group of genes in a cell whose combined expression pattern is uniquely characteristic of a biological phenotype or medical condition.
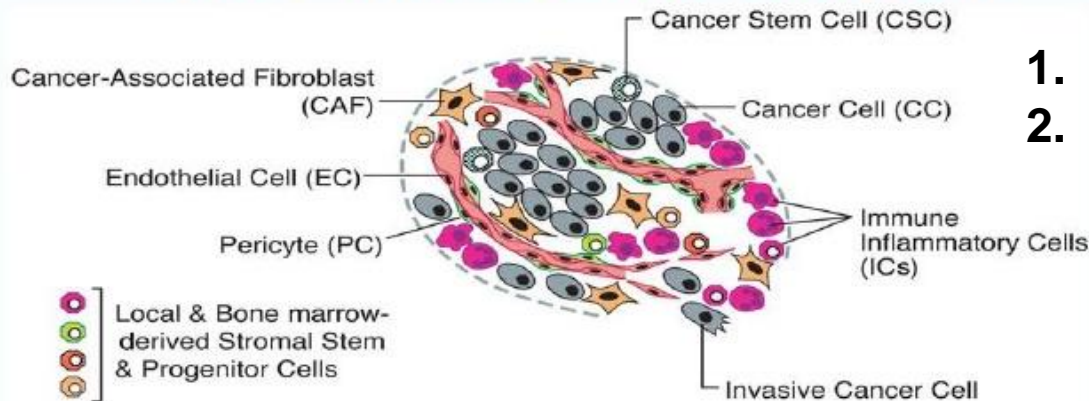
Gene expression signatures in OC: paper #

- Others
- Diagnosis
- Quantification
- Validation
- Chemoresistance
- Histotype
- Review
- Database
- Prognosis
- Subtype

Prognostic Gene Expression Signatures

Tumor Microenvironment

1. **Stromal-associated, mesenchymal**
2. **Angiogenic**

Bentink S, …., **Matulonis** UA. **Angiogenic mRNA and microRNA gene expression signature** predicts a novel subtype of serous ovarian cancer. *PLoS One. 2012;7(2):e30269.*

Siamakpour-Reihani S, …., **Alvarez Secord** A. Prognostic significance of differential expression of **angiogenic genes** in women with high-grade serous ovarian carcinoma. *Gynecol Oncol. 2015 Oct;139(1):23-9.*

Cheon DJ, …., **Orsulic** S. A **collagen-remodeling gene signature** regulated by TGF-β signaling is associated with metastasis and poor survival in serous ovarian cancer. *Clin Cancer Res. 2014 Feb 1;20(3):711-23*.

Davidowitz RA, …, **Brugge** JS. **Mesenchymal gene program**-expressing ovarian cancer spheroids exhibit enhanced mesothelial clearance. *J Clin Invest. 2014 Jun;124(6):2611-25.*

Zhang S, …., **Zhuang** G. **Stroma-associated master regulators** of molecular subtypes predict patient prognosis in ovarian cancer. *Sci Rep. 2015 Nov 4;5:16066.*

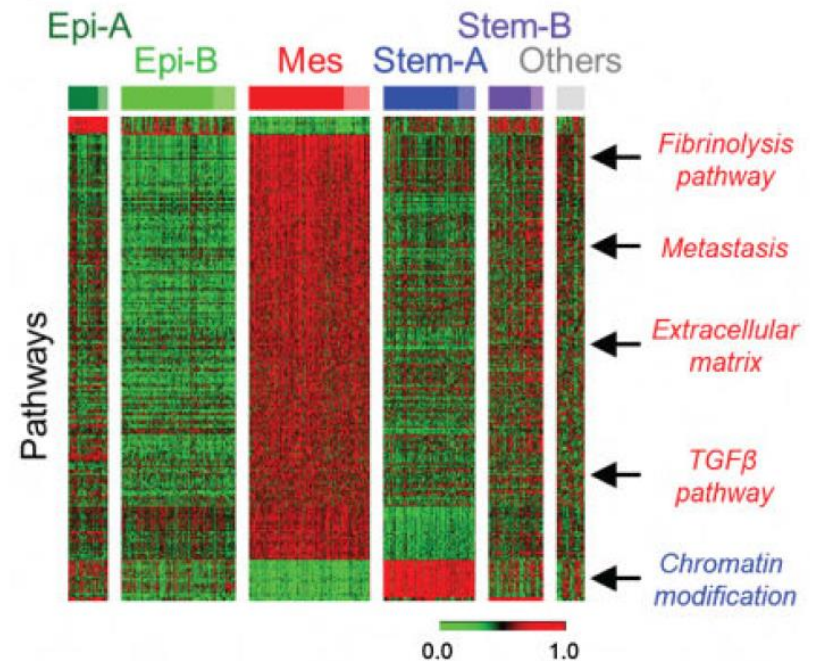# Prognostic Gene Expression Signatures: Stromal/Mesenchymal/TGFβ Pathway
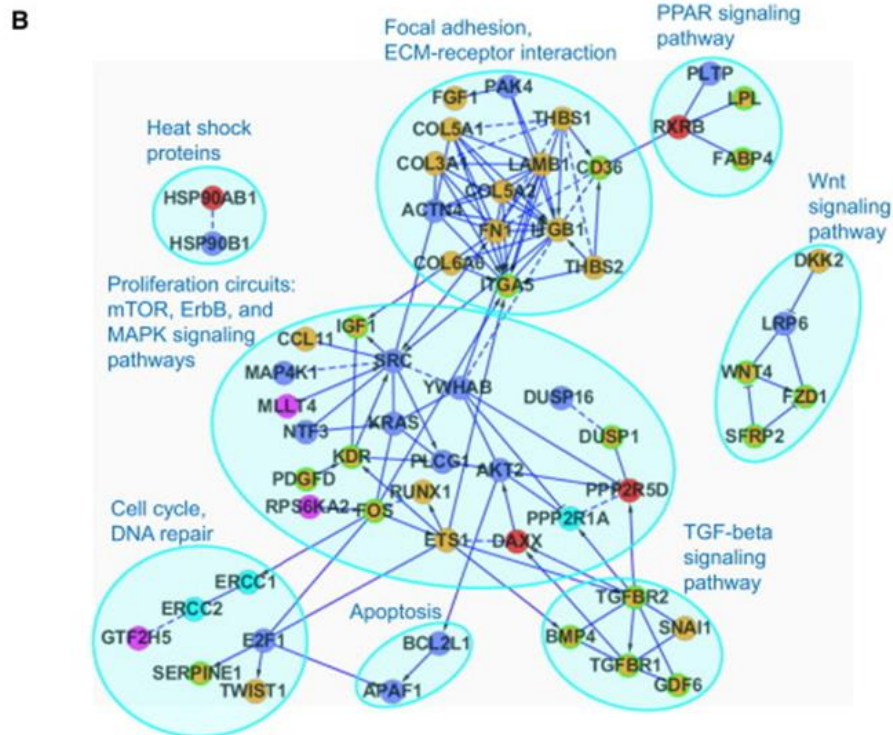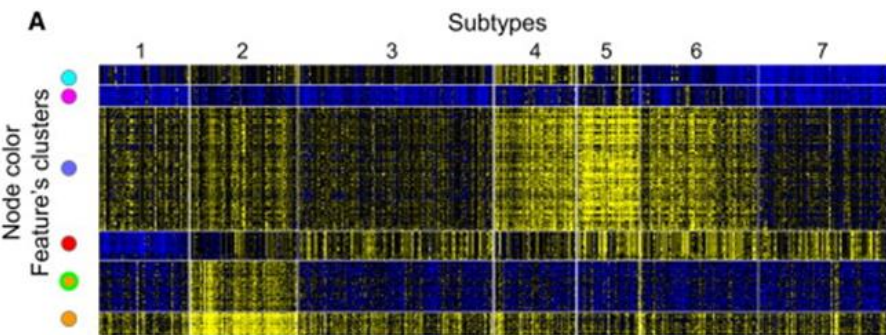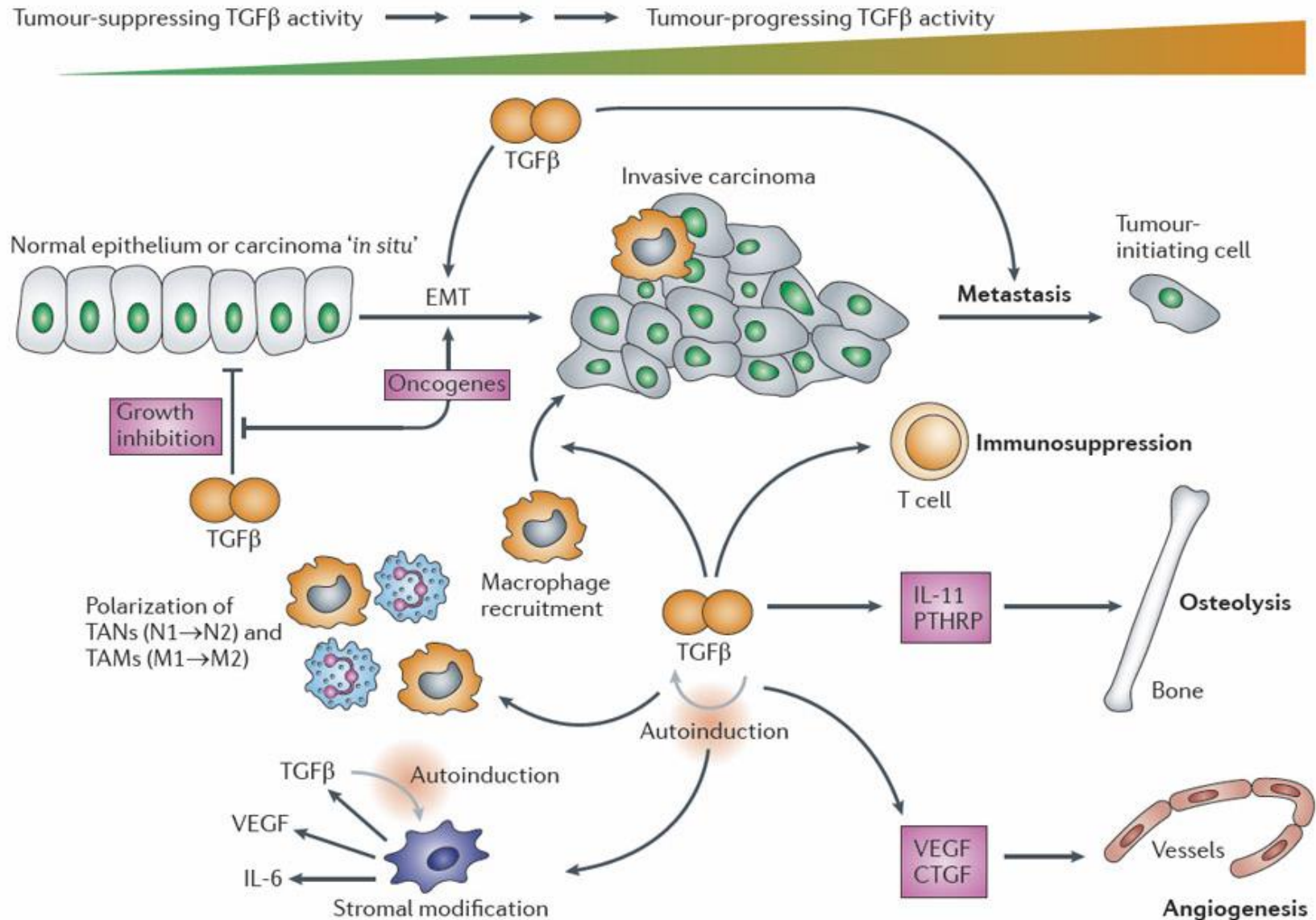

Zhang et al., Cell Report, 2013

Cheon DJ, …., **Orsulic** S. A **collagen-remodeling gene signature** regulated by **TGF-β signaling** is associated with metastasis and poor survival in serous ovarian cancer. *Clin Cancer Res. 2014 Feb 1;20(3):711-23*.

Karlan BY, …, **Slamon** D. **POSTN/TGFBI-associated stromal signature** predicts poor prognosis in serous epithelial ovarian cancer. *Gynecol Oncol. 2014 Feb;132(2):334-42.*
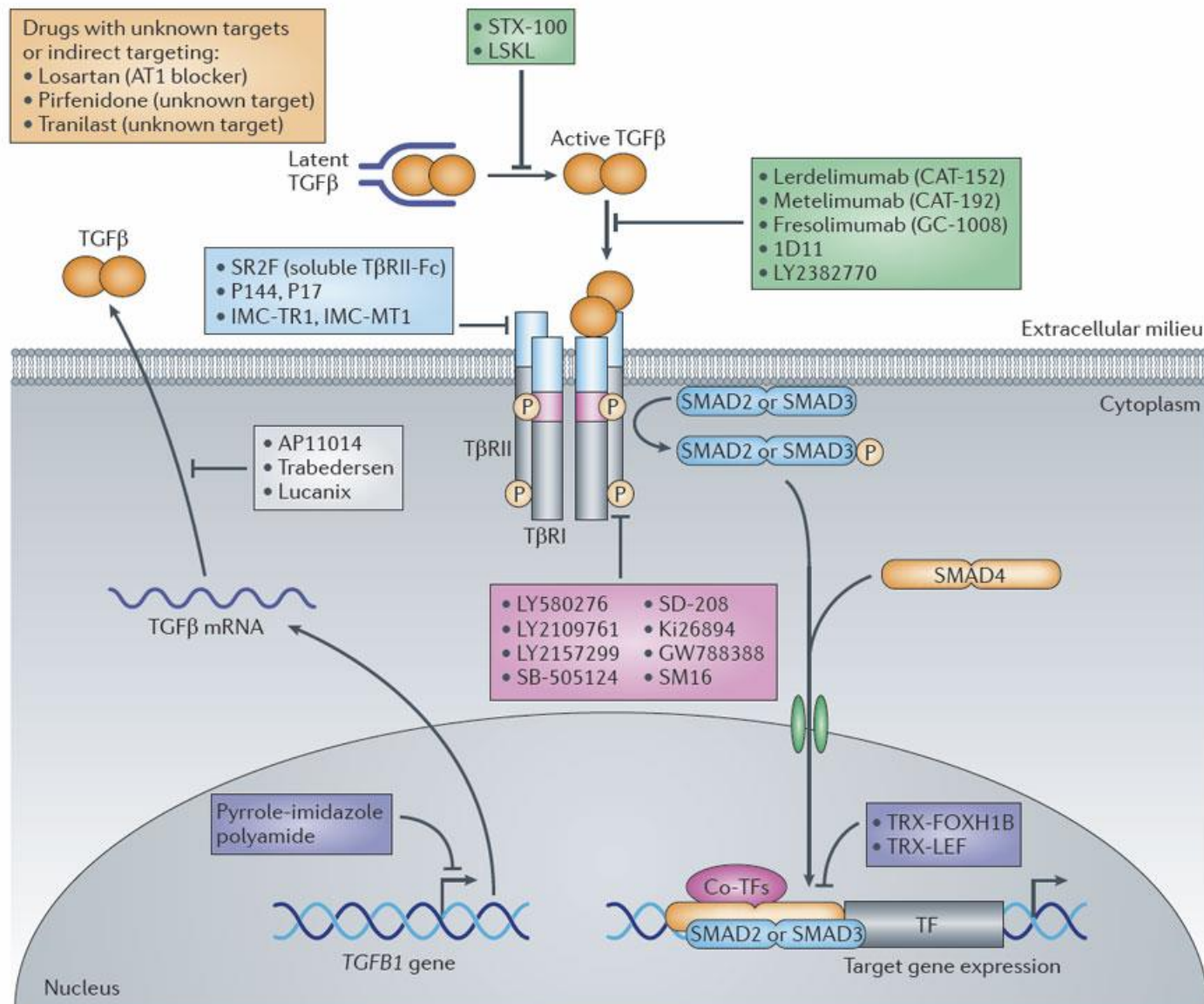

Tan, Miow & Huang et al., EMBO Mol Med, 2013

Nature Reviews | Drug Discovery

Strategies of Targeting TGFβ Pathway

Drugs with unknown targets or indirect targeting:
- Losartan (AT1 blocker)
- Pirfenidone (unknown target)
- Tranilast (unknown target)

- STX-100
- LSKL

Active TGFβ

Latent TGFβ

- Lerdelimumab (CAT-152)
- Metelimumab (CAT-192)
- Fresolimumab (GC-1008)
- 1D11
- LY2382770

TGFβ

- SR2F (soluble TβRII-Fc)
- P144, P17
- IMC-TR1, IMC-MT1

Extracellular milieu

Cytoplasm

SMAD2 or SMAD3

TβRII

- AP11014
- Trabedersen
- Lucanix

TGFβ mRNA

TβRI

- LY580276
- LY2109761
- LY2157299
- SB-505124
- SD-208
- Ki26894
- GW788388
- SM16

SMAD4

Pyrrole-imidazole polyamide

- TRX-FOXH1B
- TRX-LEF

Co-TFs

SMAD2 or SMAD3

TF

TGFB1 gene

Target gene expression

Nucleus

Nature Reviews | Drug Discovery

Akhurst and Hatta 2012

Desmoplasia, Stromal Reactions in C1/Mesenchymal/Mes Subtype
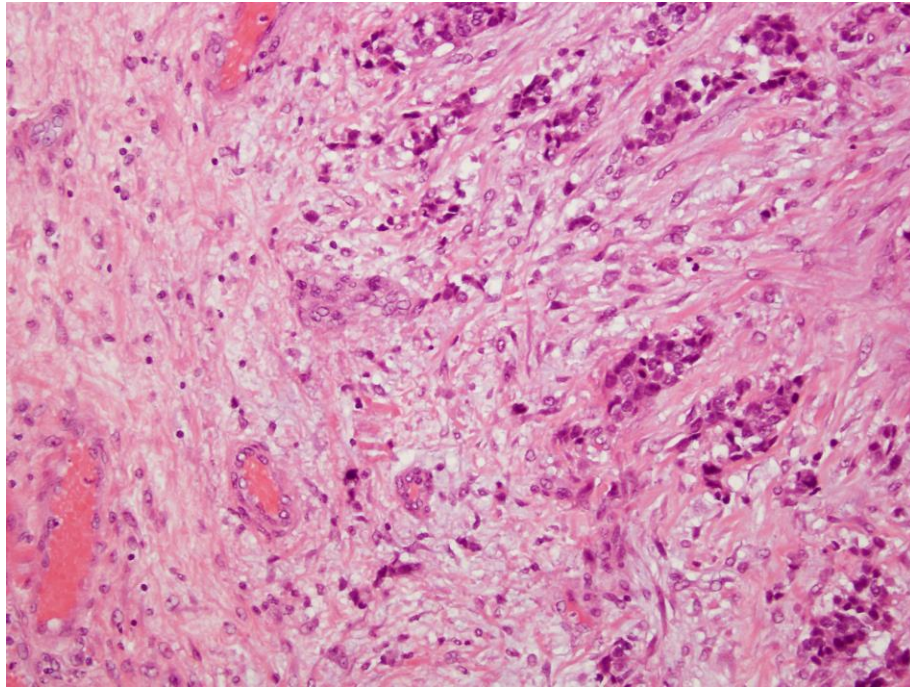
*Image courtesy of David Bowtell*
Patch et al., Nature 2015
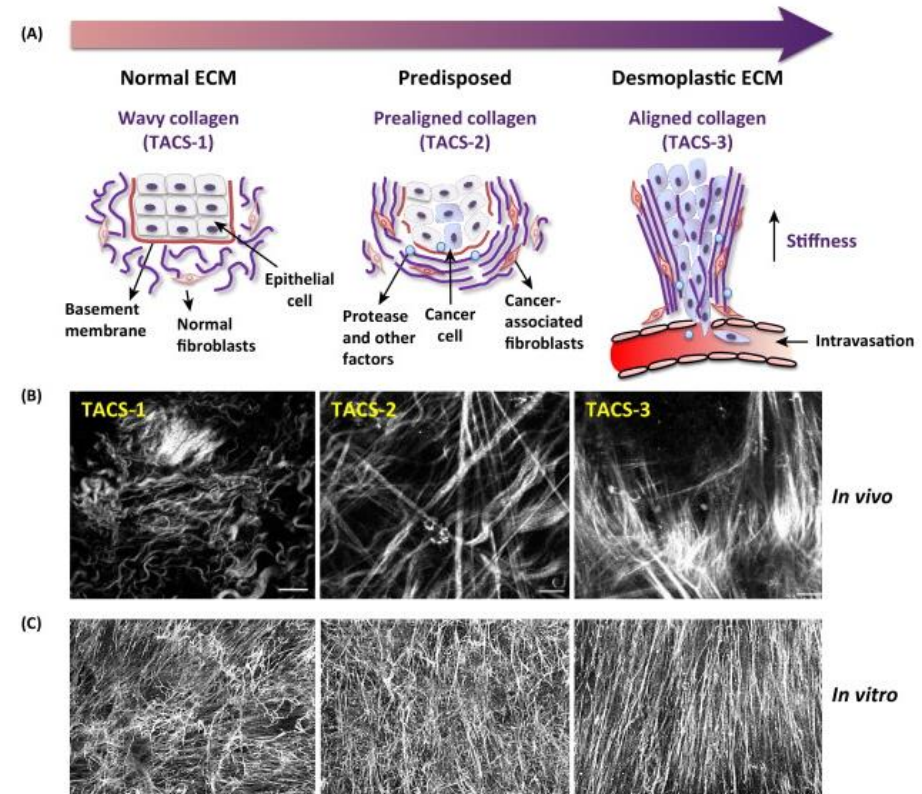
TRENDS in Biotechnology

Google:

In medicine, desmoplasia is the <u>growth of fibrous or connective tissue</u>. It is also called desmoplastic reaction to emphasize that it is <u>secondary to an insult</u>. Desmoplasia may occur around a neoplasm, causing dense fibrosis around the tumor,

Malik R, Lelkes PI, Cukierman E.
Trends Biotechnol. 2015 Apr;33(4):230-6.
Biomechanical and biochemical remodeling of stromal extracellular matrix in cancer.

Targeting the Stroma
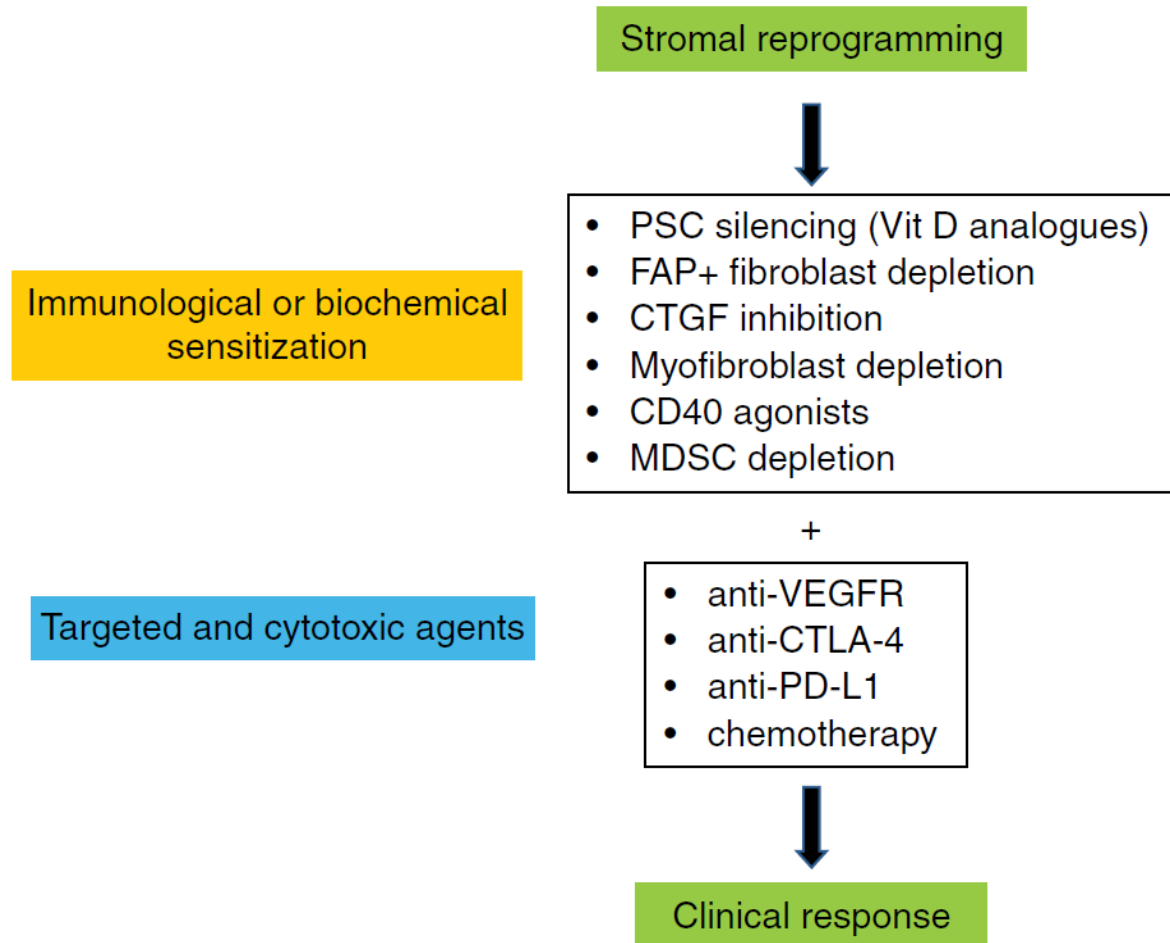
Neesse A, Algül H, Tuveson DA, Gress TM.
Gut. 2015 Sep;64(9):1476-84.
Stromal biology and therapy in pancreatic cancer: a changing paradigm.

Anti-Angiogenesis: ICON7 Bevacizumab Trial

ICON7 Phase III Trial

Ovarian Cancer
- Stage I–IIa (grade 3 or clear cell)
- Stage IIb–IV (all grades/histologic types)

Debulked to ≤1cm or >1cm

n=1,528

Primary endpoint: investigator-assessed PFS
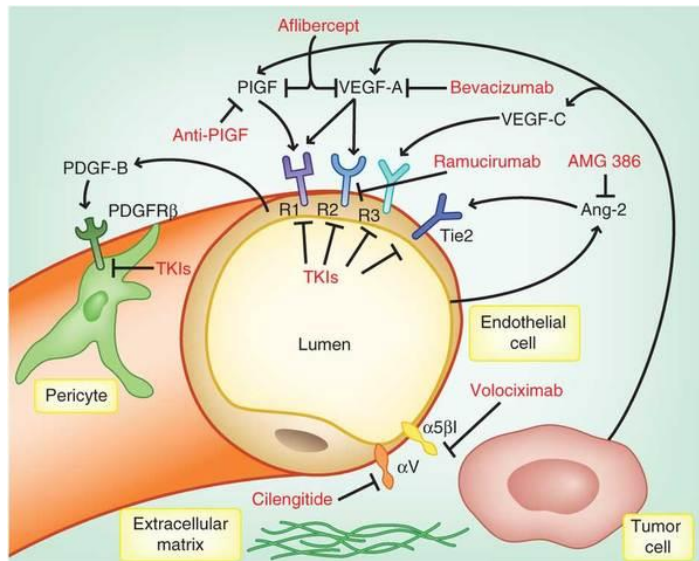
RANDOMISE 1:1

Carboplatin / paclitaxel → CP
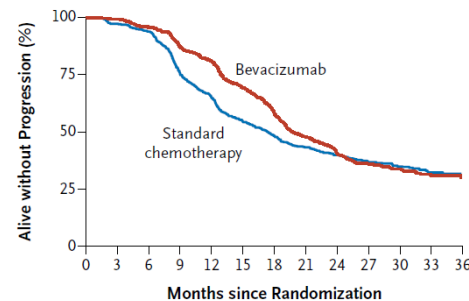
Carboplatin / paclitaxel → Avastin 7.5mg/kg q3w → CP + Avastin → Avastin 7.5mg/kg
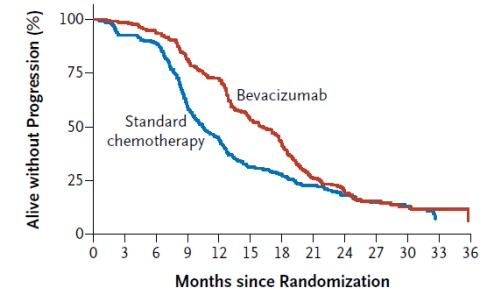
12 months or disease progression
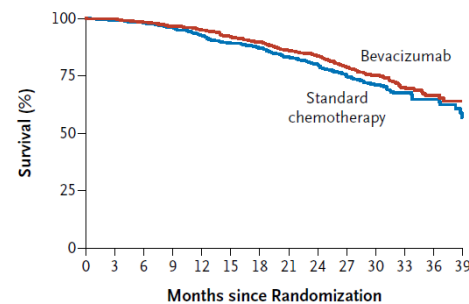
A Updated Data, Progression-free Survival

No. at Risk
Standard chemotherapy	764	693	474	350	221	114	39
Bevacizumab	764	716	599	430	229	107	27

B Updated Data, Progression-free Survival in Patients at High Risk for Progression

No. at Risk
Standard chemotherapy	234	205	100	63	30	13	5
Bevacizumab	231	213	163	94	35	13	1

C Updated Data, Overall Survival

No. at Risk
Standard chemotherapy	764	741	724	703	672	646	623	542	421	304	212	132	71	26
Bevacizumab	764	753	737	717	702	680	657	592	459	329	228	129	69	19

D Updated Data, Overall Survival in Patients at High Risk for Progression
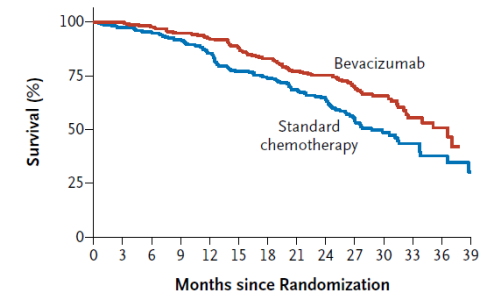
No. at Risk
Standard chemotherapy	234	226	219	208	194	175	166	137	107	67	46	25	15	6
Bevacizumab	231	227	222	214	208	199	186	164	134	94	65	31	18	4

Singh & Ferrara, 2012 Nat Biotech
Perren et al., 2011 NEJM
Spannuth, Sood and Coleman, 2008
Nature Clinical Practice Oncology

# Molecular Subtypes as Predictive Biomarker for ICON7

- Mesenchymal (C1/Mes) and Proliferative (C5/Stem-A) subtypes show improved progress-free survival (PFS) with Bevacizumab combined with standard first-line chemotherapy in ICON7 trial. *(Winterhoff et al., ASCO Annual Meeting, 2014)*

- EOC with an Immuno signature (Epi-B?) show less benefit to Bevacizumab combined with standard first-line chemotherapy in ICON7 trial. *(Gourley et al., ASCO Annual Meeting, 2014)*

| Group	Median Δ PFS months	OS HR
Overall	6.5, p=0.004	0.68 (0.45-1.03), p=0.067
High risk for progression	6.7, p=0.006	0.52 (0.29-0.94), p=0.031
Proliferative HGS	12.8, p=0.032	0.51 (0.2-1.26), p=0.136
Proliferative	10.1, p=0.015	0.52 (0.25-1.08), p=0.074
Mesenchymal HGS	7.2, p=0.096	0.27 (0.08-0.96), p=0.030
Mesenchymal	8.2, p=0.405	0.56 (0.23-1.34), p=0.187
Differentiated	3.7, p=0.610	1.41 (0.53-3.71), p=0.486
Immunoreactive	3.8, p=0.080	0.76 (0.33-1.76), p=0.518

Immune subgroup
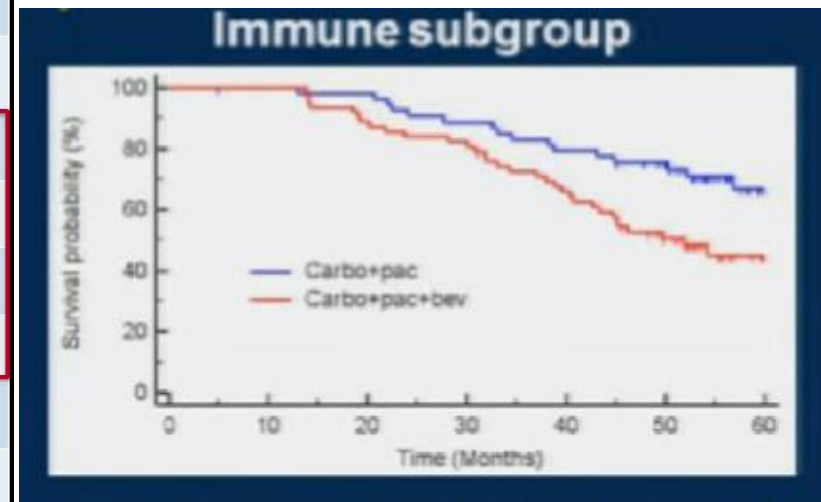
Molecular Subtypes and Immunotherapy?

Yoshihara K, …., **Tanaka** K; Japanese Serous Ovarian Cancer Study Group. High-risk ovarian cancer based on **126-gene expression signature** is uniquely characterized by **downregulation of antigen presentation pathway**. *Clin Cancer Res. 2012 Mar 1;18(5):1374-85.*
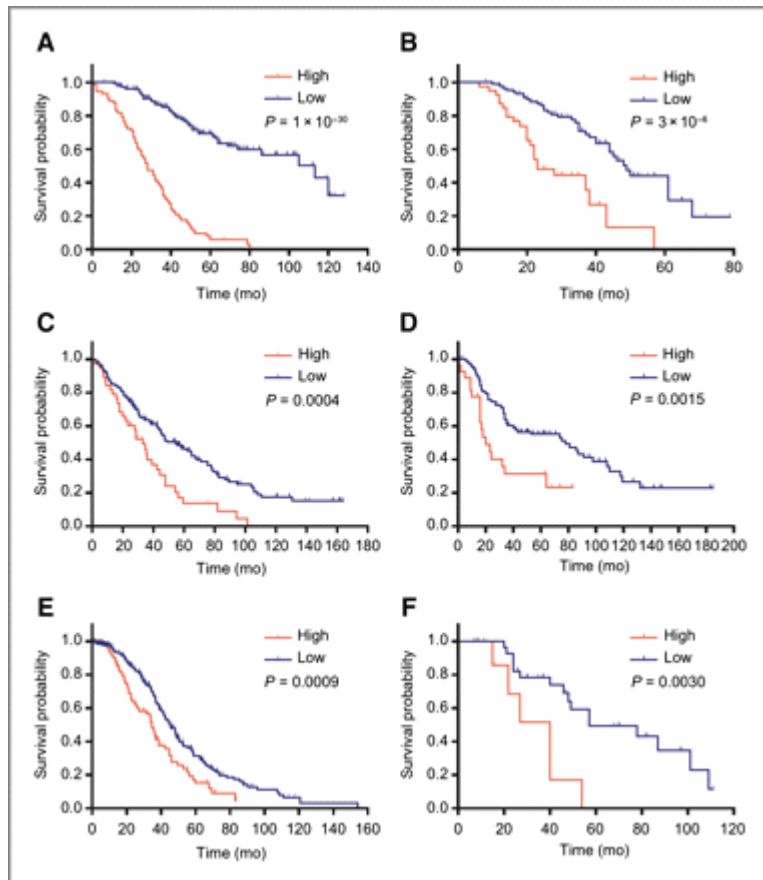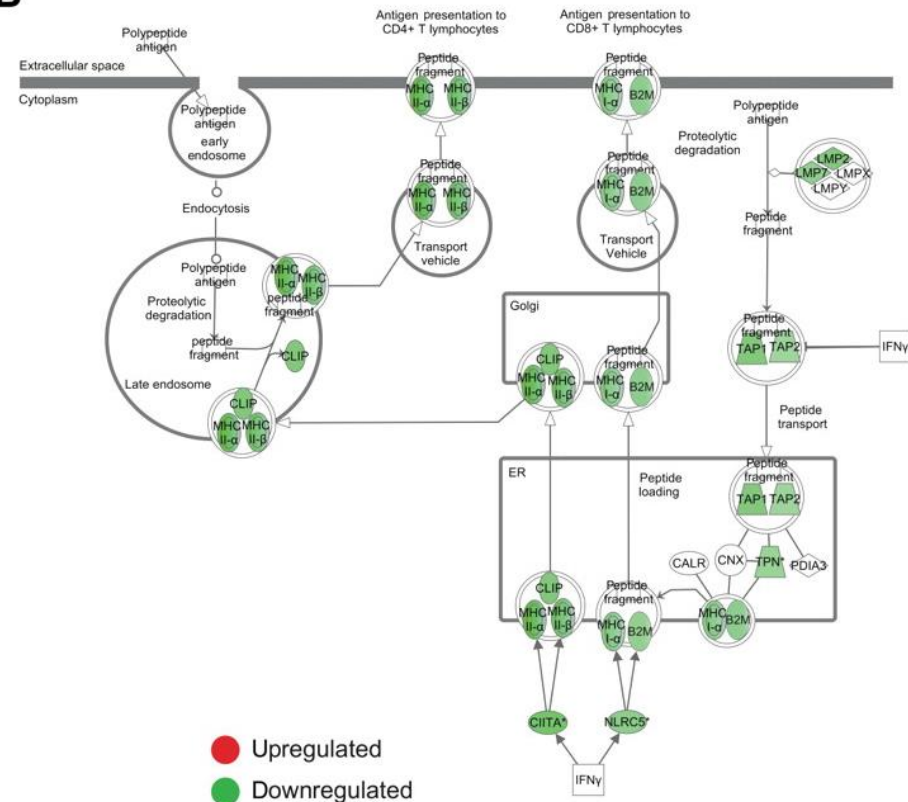
Kaplan–Meier survival analysis in 6 microarray data sets (A, Japanese data set A; B, Tothill's data set; C, Bonome's data set; D, Dressman's data set; E, TCGA data set; F, Japanese data set B). Based on 126-gene signature, ovarian cancer patients were divided into 2 risk groups (red, high risk; blue, low risk).

Chemoresistance Gene Expression Signature

Gillet JP, …., **Gottesman** MM. Clinical relevance of **multidrug resistance gene expression** in ovarian serous carcinoma effusions. *Mol Pharm. 2011 Dec 5;8(6):2080-8.*

Liu Y, …., **Zhang** W. Integrated analysis of **gene expression and tumor nuclear image profiles** associated with chemotherapy response in serous ovarian carcinoma. *PLoS One. 2012;7(5):e36383.*

Latifi A, …, **Ahmed** N. Isolation and characterization of tumor cells from the ascites of ovarian cancer patients: **molecular phenotype** of chemoresistant ovarian tumors. *PLoS One. 2012;7(10):e46858.*

Koti M, …., **Squire** JA. Identification of the **IGF1/PI3K/NF κB/ERK gene signalling networks** associated with chemotherapy resistance and treatment response in high-grade serous epithelial ovarian cancer. *BMC Cancer. 2013 Nov 16;13:549.*

Huh JH, …, **An** HJ. Dysregulation of **miR-106a and miR-591** confers paclitaxel resistance to ovarian cancer. *Br J Cancer. 2013 Jul 23;109(2):452-61.*

Frederick PJ, …, **McNally** LR. Chemoresistance in ovarian cancer linked to expression of **microRNAs**. *Biotech Histochem. 2013 Oct;88(7):403-9.*

Vecchione A, …, **Croce** CM. A **microRNA signature** defines chemoresistance in ovarian cancer through modulation of angiogenesis. *Proc Natl Acad Sci U S A. 2013 Jun 11;110(24):9845-50.*

Chen P, …., **Hautaniemi** S. Identification of **Prognostic Groups** in High-Grade Serous Ovarian Cancer Treated with Platinum-Taxane Chemotherapy. *Cancer Res. 2015 Aug 1;75(15):2987-98.*

No significant consensus

Chemoresistance & Gene Expression Molecular Subtype

	Malek et al., 2012	Brodsky et al., 2014	Marchini et al., 2013
	Primary vs Peritoneum	**Primary vs Omentum**	**Primary vs Relapse**
	11 pairs	9 pairs	23 pairs
Same Subtype	6 (54.5 %)	4 (44.4 %)	10 (43.4 %)
Subtype Switch	5 (45.5 %)	5 (55.6 %)	13 (56.5 %)
Epi to Mes	1 (9.1 %)	3 (33.3 %)	9 (39.1 %)
Epi to Stem-A	1 (9.1 %)	0 (0.0 %)	0 (0.0 %)
Stem-A to Mes	0 (0.0 %)	2 (22.2 %)	2 (8.7 %)
Others	3 (27.2 %)	0 (0.0 %)	2 (8.7 %)

C1/Mesenchymal/Mes subtype appeared to be the "default" state for disease progression and chemoresistance
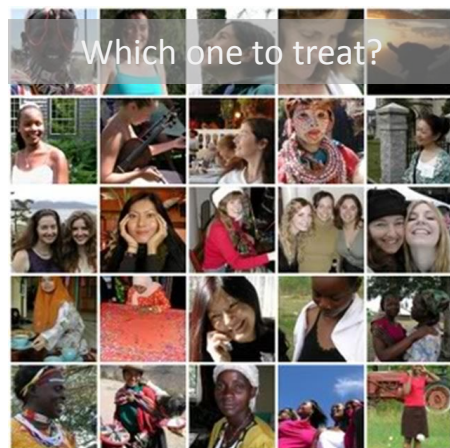
Challenge

Which one to treat?

What's the evidence of gene expression signature(s) in predicting therapeutic response in ovarian cancer?

Which one for you?

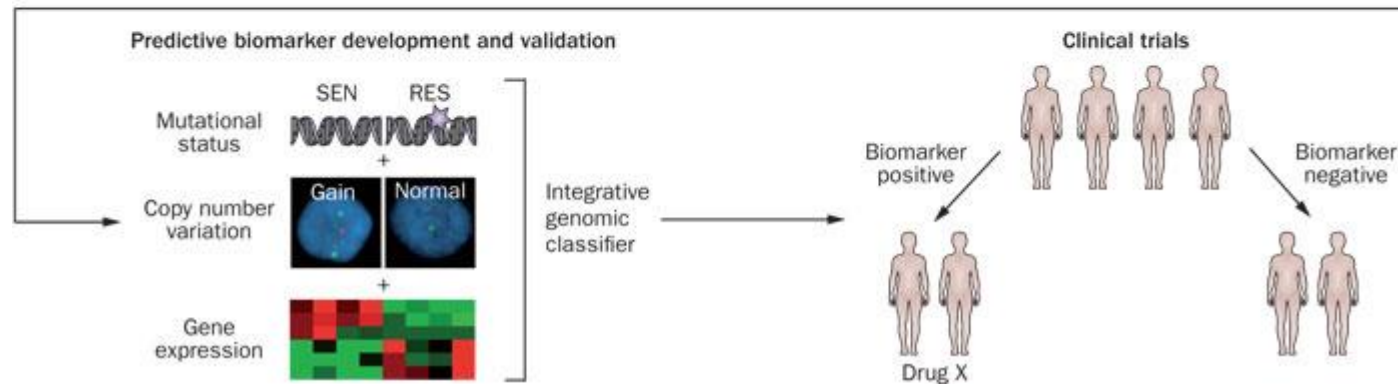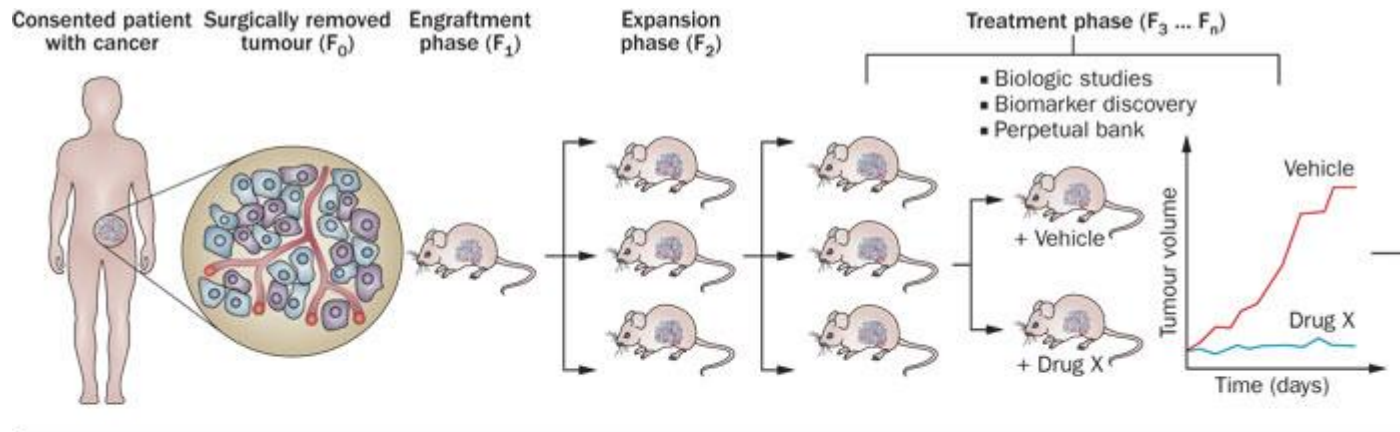We Don't Know.

What's the feasibility of integrating gene expression signature(s) in clinical trials?

- Stem-A (C5) subtype show increased sensitivity to vinca-biders of anti-microtubule agents, such as vincristine or vinorelbine. *(Tan, Miow, & Huang et al., EMBO Mol Med, 2013)*
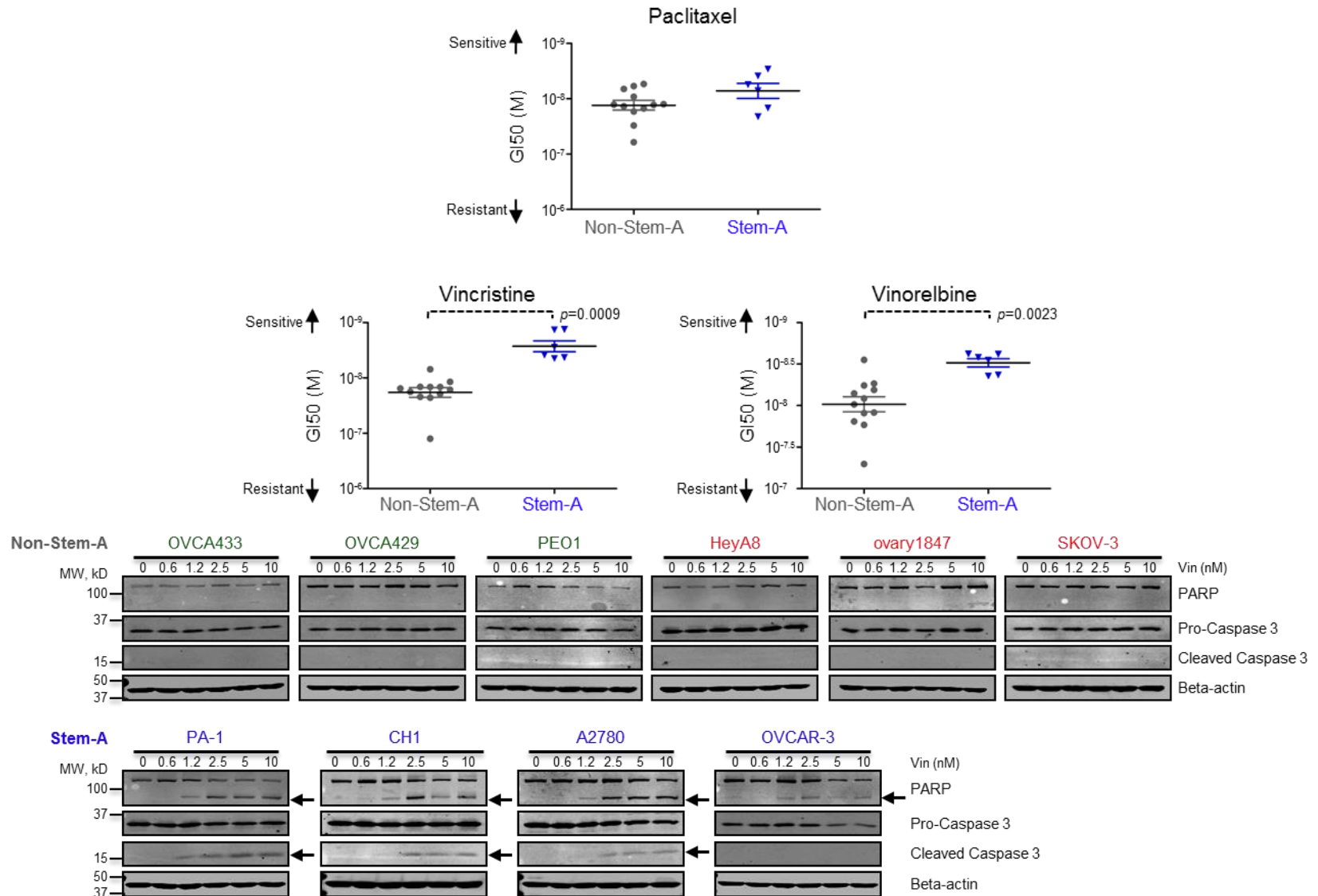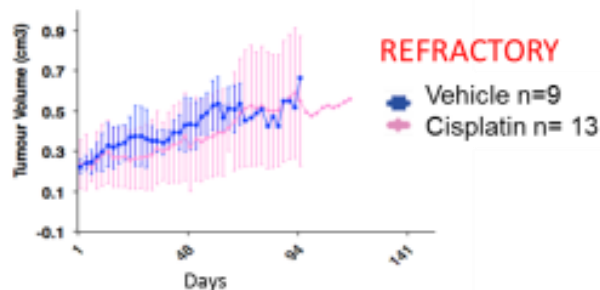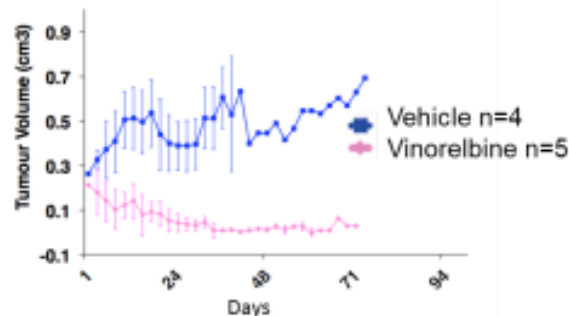
Tentler et al., Nature Review Clinical Oncology 2012

C5/Stem-A PDX
Valerie Heong & Clare Scott
(unpublished)
In collaboration with WEHI

CISPLATIN 4mg/kg (D1, D8, D18)

REFRACTORY
Vehicle n=9
Cisplatin n= 13

VINORELBINE 15mg/kg (D1, D8, D18)

Vehicle n=4
Vinorelbine n=5

PDX PH041

Marginal efficacy of oral vinorelbine in platinum resistant settings (un-selected patients):

❖ Single agent navelbine; RR: 3% Gynecol Oncol. 2004 Dec;95(3):506-12.

❖ Navelbine + gemcitabine; ORR: 11% Cancer Chemother Pharmacol. 2011 Jan;67(1):69-73.

❖ Navelbine + topotecan; ORR: 18% Gynecol Oncol. 2008 Dec;111(3):467-73.

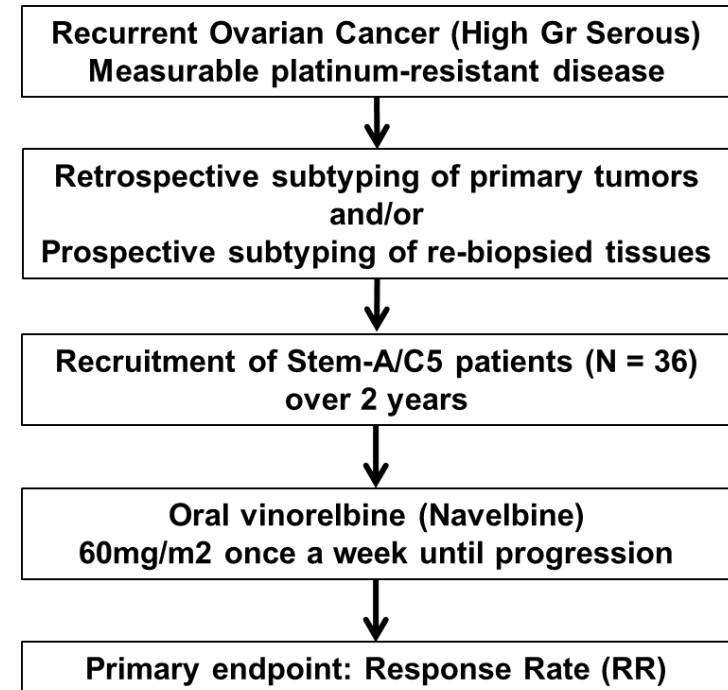**Molecular Subtype Specific Clinical Trial in Ovarian Cancer**

National University Cancer Institute, Singapore

Gynae Onc Group Singapore (GOGS)

ANZGOG

Australian New Zealand Gynae Onc Group

Phase II, Single-arm

Recurrent Ovarian Cancer (High Gr Serous) Measurable platinum-resistant disease

↓

Retrospective subtyping of primary tumors and/or Prospective subtyping of re-biopsied tissues

↓

Recruitment of Stem-A/C5 patients (N = 36) over 2 years

↓

Oral vinorelbine (Navelbine) 60mg/m2 once a week until progression

↓

Primary endpoint: Response Rate (RR)

SG site: Ruby Huang & David Tan
Australia site: Linda Mileshkin & David Bowtell

Underpinning the C5/Stem-A Subtype:
from Pre-Clinical to Clinical

BOWTELL LAB (PMCC)
Cell lines
Generic drug library screen
Nanostring classifyer

SCOTT LAB (WEHI)
Annotated C5 PDX
Candidate pathway inhibitors
PDX cell lines incl CRISPR
GEMM (incl premalignant)

HUANG LAB (Singapore)
Microtubulin dynamics
Discovery and targeting

C5/Stem-A CLINICAL TRIALS
SG: Huang, Tan,
AU: Bowtell, Scott, Melishkin
Navelbine
as proof of principle of
trials targeting HGSOC subsets

BRIEF DEFINITIVE REPORT

Efficient molecular subtype classification of high-grade serous ovarian cancer

Huei San Leong,[1] Laura Galletta,[1] Dariush Etemadmoghadam,[1,2,3] Joshy George,[4] The Australian Ovarian Cancer Study[1,5,6] Martin Köbel,[7] Susan J Ramus[8] and David Bowtell[1,2,3,9,10,*]

Table 1. Classification accuracies of fresh frozen and FFPE samples on TaqMan-based low-density arrays, Fluidigm, Illumina targeted RNA, and Nanostring platforms compared with Affymetrix microarrays

Subtype	Taqman (48 genes) Fresh frozen (post-optimization) Score (%)	Fluidigm (48 genes) Fresh frozen Score (%)	FFPE Score (%)	Illumina (42 genes) Fresh frozen Score (%)	FFPE (modified protocol) Score (%)	Nanostring (48 genes) Fresh frozen Score (%)	FFPE Score (%)
C1	20/23 (87)	10/12 (83.3)	14/16 (87.5)	7/7 (100)	6/7 (85.7)	4/4 (100)	15/15 (100)
C2	19/20 (95)	13/13 (100)	12/14 (85.7)	6/6 (100)	5/7 (71.4)	4/4 (100)	10/13 (77)
C4	17/20 (85)	9/11 (81.8)	11/22 (50)	5/5 (100)	5/7 (71.4)	4/4 (100)	10/16 (62.5)
C5	18/21 (85.7)	11/12 (91.7)	8/14 (57.1)	4/5 (80)	6/7 (85.7)	5/5 (100)	11/14 (79)
Overall	74/84 (88)	43/48 (89.6)	45/66 (68.2)	22/23 (95.7)	22/28 (78.6)	17/17 (100)	46/58 (79.3)

Application of Gene Expression Signatures

Gene Expression Signature(s)
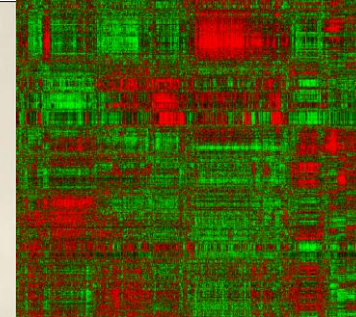
Lab-based Diagnostic Assays

IVD

1 Gene Expression Signature Stratification

Prospective Clinical Trials

2 Translational Research Pipeline

Randomized Controlled Trials

Clinical Trials with Gene Expression Signatures

| Clinical Trials ID	Official Title	Type
NCT00897806	Feasibility of Measuring Gene Expression Patterns Using Tissue Acquisition of Primary Stage 3 & 4 Epithelial Ovarian Cx or Primary Peritoneal Cx & Gene Expression Array Technology for Predicting Paclitaxel Chemotherapy	Identify gene expression signature
NCT01074398	ERCC1 Expression as a Predictor of Progression Free and Overall Survival in Patients With Epithelial Ovarian Cancer Treated on GOG Protocols 0172 and 0182	Validation of gene expression signature
NCT01391351	Search for Predictors of Therapeutic Response in Patients With Carcinoma of the Ovary, the Fallopian Tube or Peritoneal Serous-type Advanced	Identify gene expression signature (miRNA)
NCT01770535	A Single-Centre Prospective Phase 0 Translational Study for Predicting Response of High Grade Serous Ovarian Cancers to Paclitaxel Chemotherapy	Identify gene expression signature
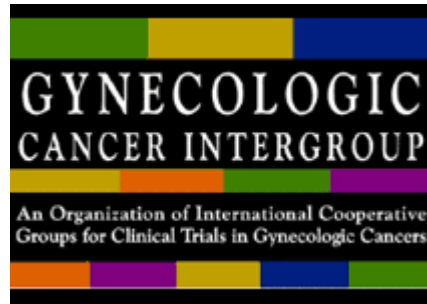
❖ **Ovarian cancer is a heterogeneous entity and the field should start to move towards stratifying patients for better treatment outcome.**

❖ **From the gene expression microarray analysis, four to seven major molecular subtypes have been identified within EOC that harbors distinctive signatures, which confer survival prognostication.**

❖ **The C1/Mesenchymal/Mes subtype is hallmarked by deposition of ECM forming desmoplastic stroma, TGFβ pathway, and angiogenesis.**

❖ **The growth of C5/Proliferative/Stem-A subtype tumors is dependent on genes/pathways related to microtubule dynamics and non-canonical Wnt signaling and show preferential sensitivity to vinca-binders.**

❖ **A molecular subtyping diagnostic scheme has been developed for patient stratification. The first clinical trial targeting the C5/Stem-A subtype is planned.**

❖ **Incorporation of gene expression subtype analysis in ovarian cancer RCTs**

RH Lab

CSI Singapore

Jean Paul Thiery (guru)

Tony Tan (Bioinformatics)

Eddie Miow (shRNA library screen)

Valerie Heong (PDX)

Jieru Ye (TR Coordinator)

Collaborators

Seiichi Mori

Richie Soong

Goh Boon Cher

Henry Yang

David Tan

Jeffrey Low

Mahesh Choolani

Noriomi Matsumura

Ben Davidson

Clare Scott

Linda Mileshkin

David Bowtell

CSIOVDB: a microarray gene expression database of epithelial ovarian cancer subtype

Tuan Zea Tan[1], He Yang[1], Jieru Ye[1], Jeffrey Low[2], Mahesh Choolani[2], David Shao Peng Tan[1,2,3], Jean-Paul Thiery[1,4,5], Ruby Yun-Ju Huang[1,2,5,6]

http://csibio.nus.edu.sg/CSIOVDB/CSIOVDB.html

- A transcriptomic microarray database of **3,431** human ovarian cancers, including carcinoma of the ovary, fallopian tube, and peritoneum, and metastasis to the ovary from other sites.
- over 400 early-stage ovarian cancers
- molecular subtype and EMT status
- major histologies (clear cell, endometrioid, mucinous, low-grade serous, serous)
- Clinicopathological parameters (tumor grade, surgical debulking status, clinical response and age)
- Of **1,868** and **1,516** samples with information pertaining to overall and disease-free survival rates, respectively