Aktuelle Aspekte in Diagnostik und Behandlung von Patientinnen mit Ovarialkarzinom

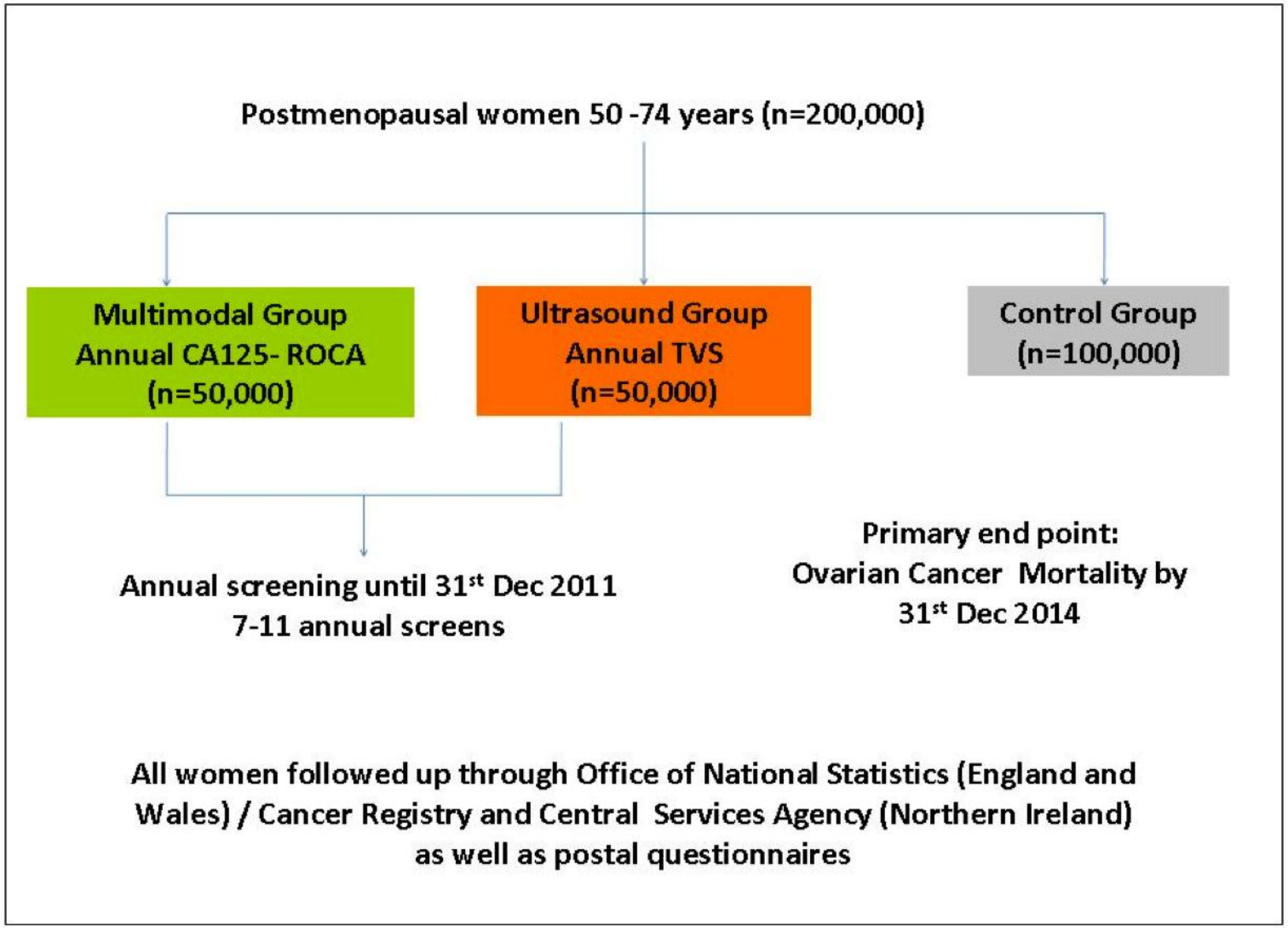
Dr. med. Elena Ioana Braicu

Gesellschaft für Geburtshilfe und Gynäkologie in Berlin
20. Januar 2016

Current status

- Ovarian Cancer – first cause of death among gynecological malignancies
- 75% of cases – stage III-IV
- No screening
- No biomarkers for early detection
- No symptoms
- Respond well to chemotherapy
- 60-80% will relapse and will develop resistance

UKCTOCS Trial



From 2003 onwards IOTA criteria for TVS

UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)

	MMS	USS	Overall
N Op	97 (0.2%)	845 (1.8%)	942 (1.0%)
N Op/OC	2.9	35.2	16.2
Sensit.	89.5%	75%	82.9%
Specif.	99.8%	98.2%	99%
PPV	35.1%	2.8%	6.2%
Stage			
I	14	10	24
II	2	2	4
III	18	10	28
IV	0	2	2
OC (I/II)	47.1%	50.0%	48.3%

Menon et al. The Lancet 2009

UK
Collaborative Trial of
Ovarian Cancer Screening (UKCTOCS)

Articles

Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

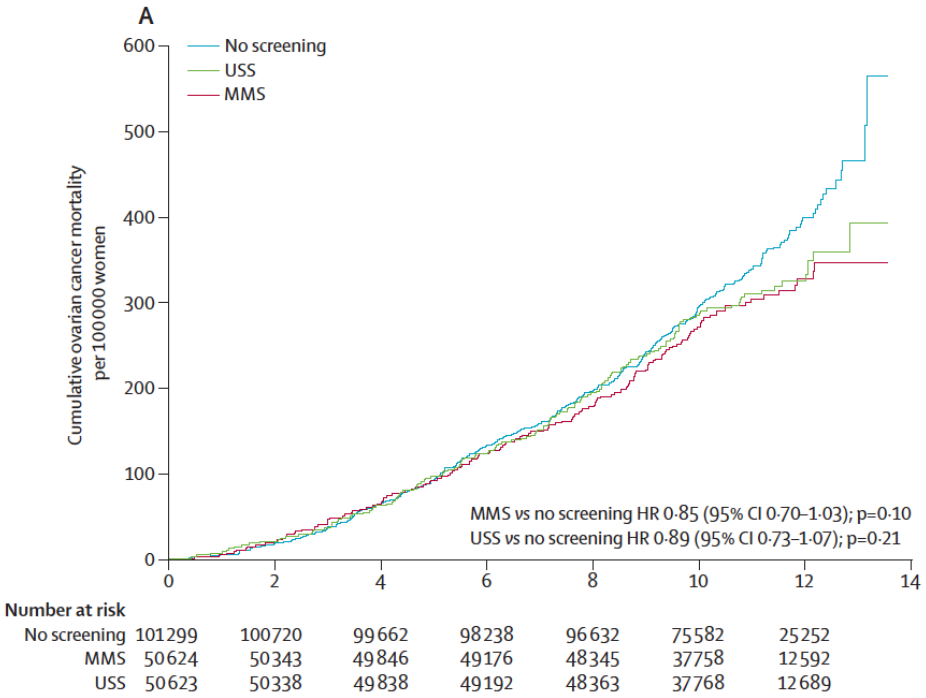
Ian J Jacobs, Usha Menon*, Andy Ryan, Aleksandra Gentry-Maharaj, Matthew Burnell, Jatinderpal K Kalsi, Nazar N Amso, Sophia Apostolidou, Elizabeth Benjamin, Derek Cruickshank, Danielle N Crump, Susan K Davies, Anne Dawnay, Stephen Dobbs, Gwendolen Fletcher, Jeremy Ford, Keith Godfrey, Richard Gunu, Mariam Habib, Rachel Hallett, Jonathan Herod, Howard Jenkins, Chloe Karpinskyj, Simon Leeson, Sara J Lewis, William R Liston, Alberto Lopes, Tim Mould, John Murdoch, David Oram, Dustin J Rabideau, Karina Reynolds, Ian Scott, Mourad W Seif, Aarti Sharma, Naveena Singh, Julie Taylor, Fiona Warburton, Martin Widschwendter, Karin Williamson, Robert Woolas, Lesley Fallowfield, Alistair J McGuire, Stuart Campbell, Mahesh Parmar†, Steven J Skates†*

Summary

Background Ovarian cancer has a poor prognosis, with just 40% of patients surviving 5 years. We designed this trial to establish the effect of early detection by screening on ovarian cancer mortality.

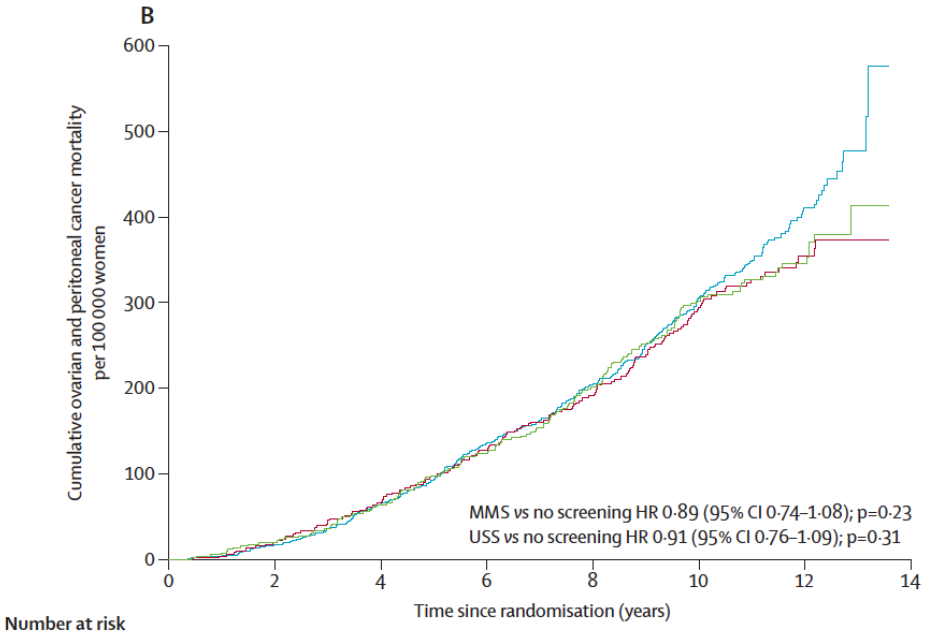
Published Online
December 17, 2015

UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)



Number at risk

No screening	101299	100720	99662	98238	96632	75582	25252
MMS	50624	50343	49846	49176	48345	37758	12592
USS	50623	50338	49838	49192	48363	37768	12689



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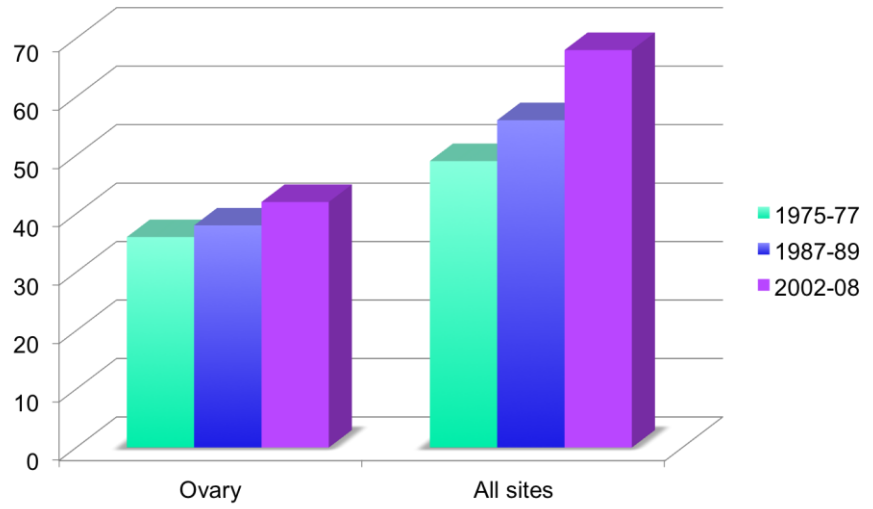
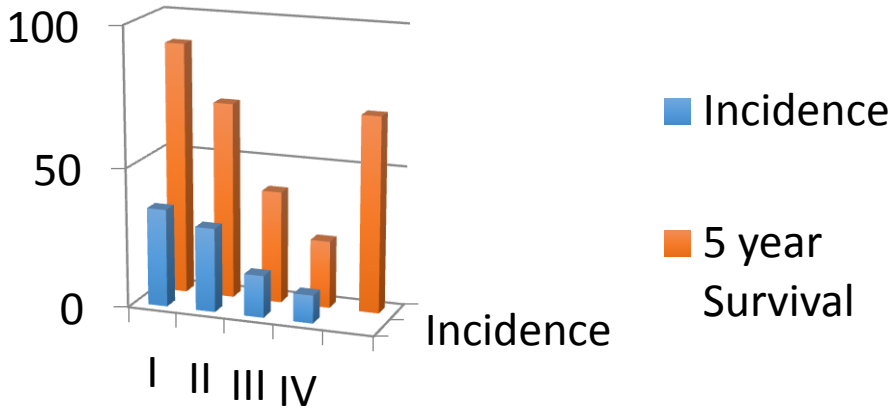
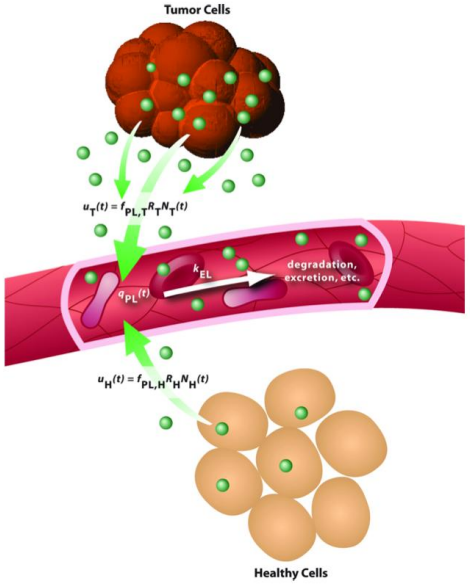
Early detection

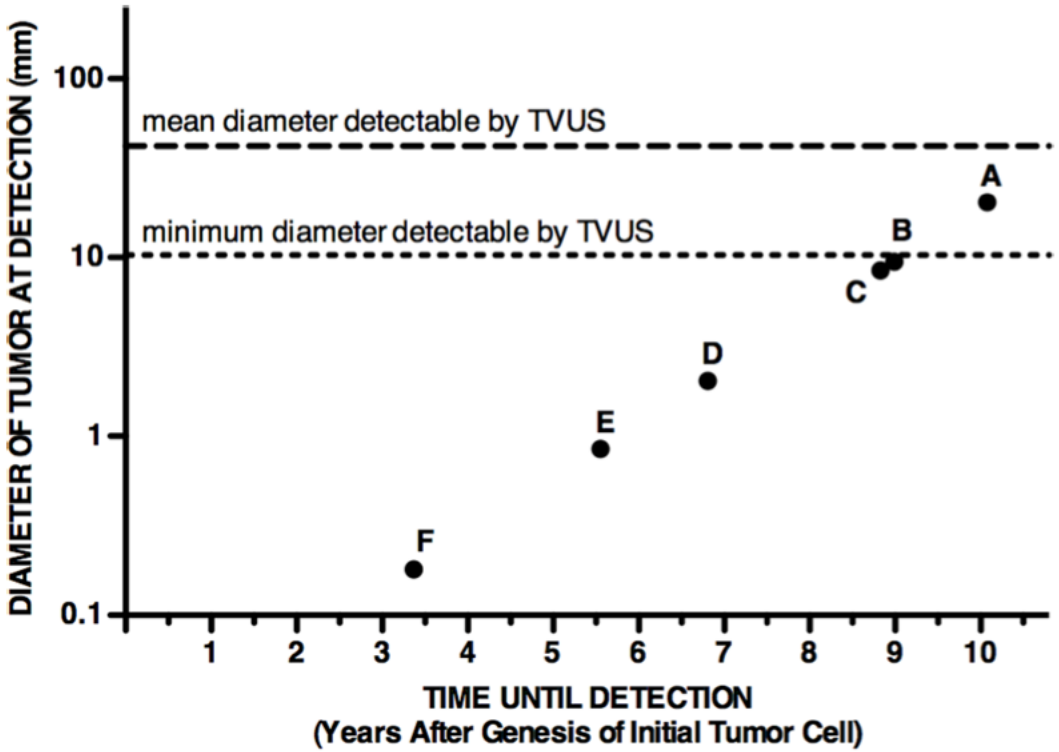
- Since the late 1980s there has been a steady improvement in 5-year survival
- allow diagnosis of early stages in asymptomatic patients





Mathematical modeling





BERLIN-ROMA

BERLINER-Studie

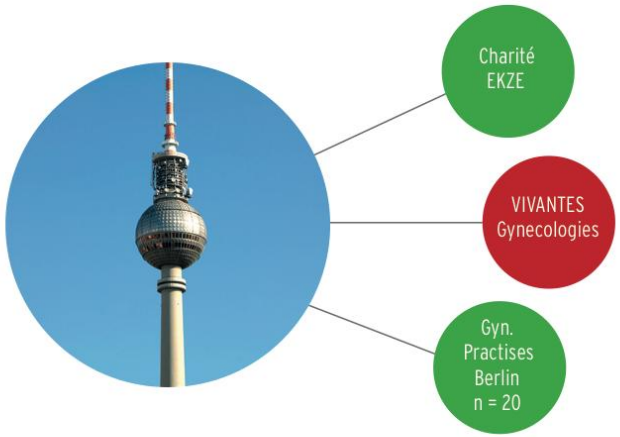
Study design

STUDY DESIGN

850 pelvic mass patients | Surgical treatment within 6-8 weeks

- Gynecological examination
- Ultrasound IOTA-
- Blood sampling HE4 and CA125
- Blood and urine sampling for Glycane analysis

- Risk assessment (IOTA)
  - High risk → Onco-gynecologist
  - Unclear → Expert-Ultrasound → Onco-gynecologist
  - Low risk → Gynecologist/LSK
- ROMA-Score Berliner-Algorithmus
- New algorithm



Aims of the study

- Primary aims:
  - Identification of a new algorithm combining biomarkers (HE4 and CA125) and ultrasound for early detection of OC in pelvic mas patients
  - New biomarker discovery
- Secondary Aims:
  - New biomarkers for prediction of platinum response and response to anti-angiogenesis therapy
  - New predictive biomarkers for surgical outcome

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TOC Tumor bank Ovarian Cancer Network advancing in understanding ovarian cancer

berliner powered by xdmed

PATIENTINNEN PRO ZENTRUM BIS 01.12.15

Zentrum	Anzahl der Patientinnen
Vivantes Auguste Viktoria Klinikum	436
Vivantes Klinikum Neukölln	431
Charité Campus Virchow Klinikum	280
Vivantes Humboldt Klinikum	110
Vivantes Klinikum im Friedrichshain	81
Vivantes Klinikum Am Urban	73
Vivantes Klinikum Hellersdorf	11
Charité Campus Mitte	7
Charité Campus Benjamin Franklin	6
Gesamt	**1435**

Previous work
New candidates

Journal of proteome research

Article

pubs.acs.org/jpr

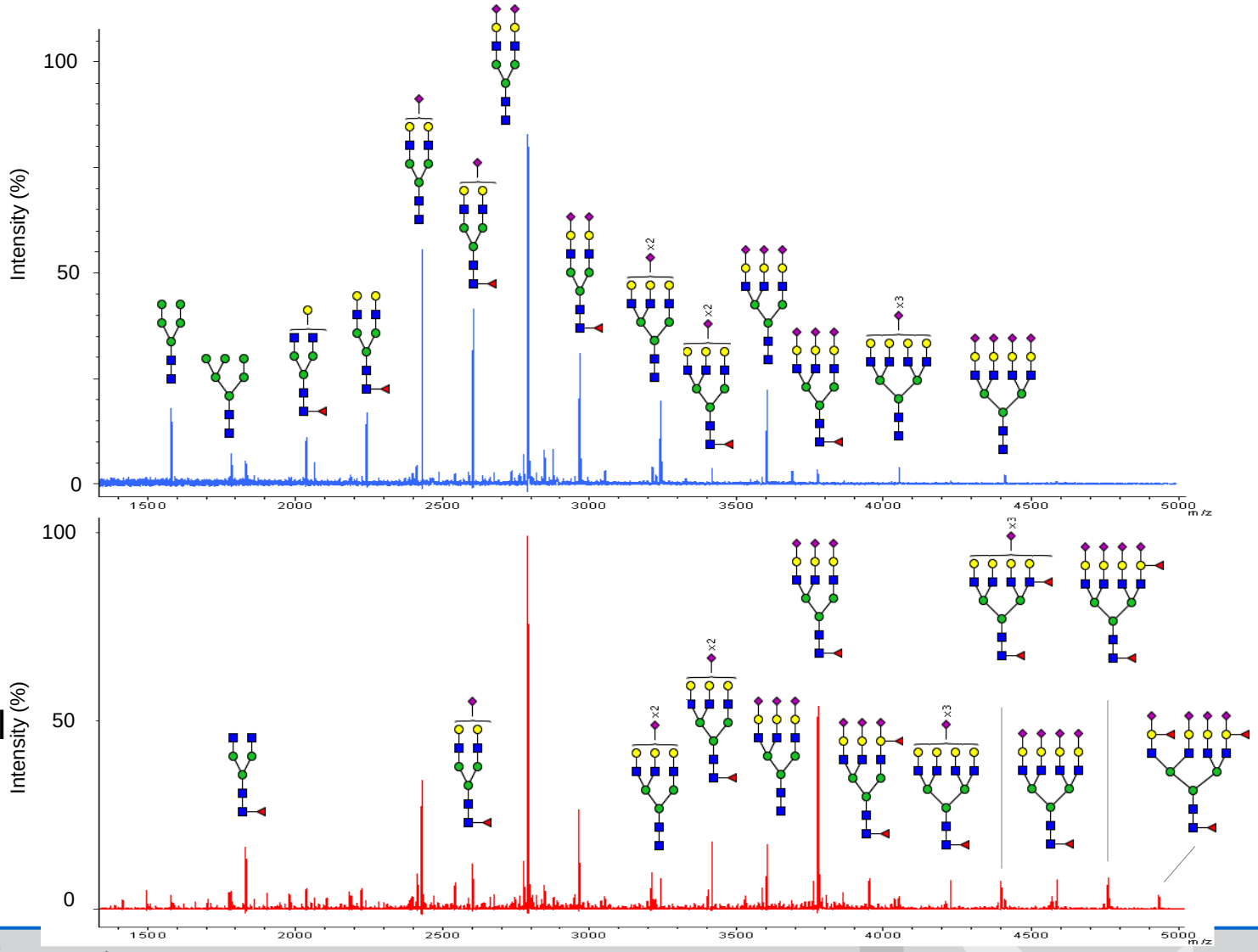
Serum Glycome Profiling: A Biomarker for Diagnosis of Ovarian Cancer

Karina Biskup,[†] Elena I. Braicu,[‡] Jalid Sehouli,[‡] Christina Fotopoulou,[‡] Rudolf Tauber,[†] Markus Berger,[†] and Véronique Blanchard*[,†]

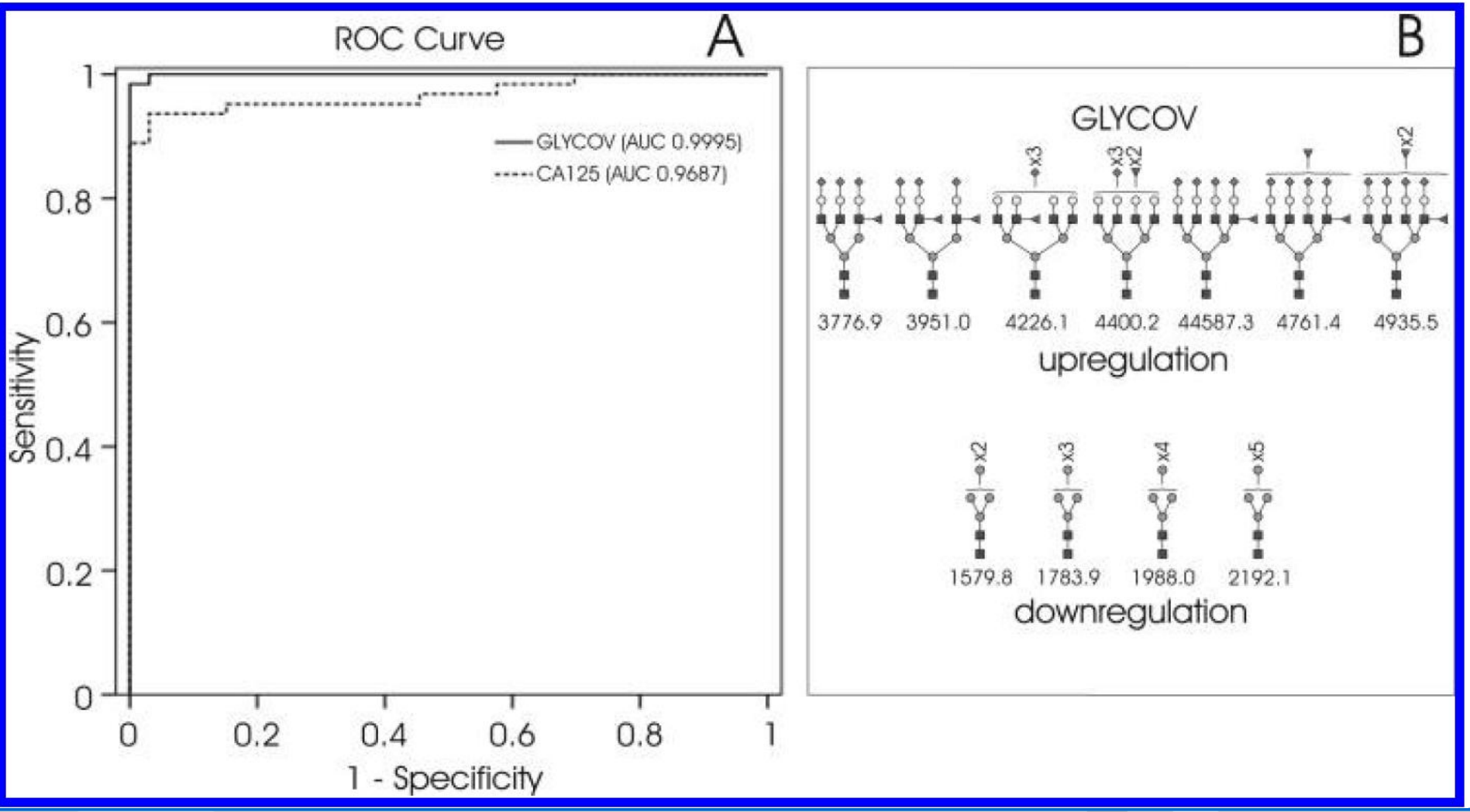
Previous Work
New candidates

Control group

EOC
CA-125 3842U/ml



Previous Work
New candidates



Previous Work
New candidates

Research Article

The Serum Glycome to Discriminate between Early-Stage Epithelial Ovarian Cancer and Benign Ovarian Diseases

Karina Biskup,[1] Elena Iona Braicu,[2] Jalid Sehouli,[2] Rudolf Tauber,[1] and Véronique Blanchard[1]

[1] *Institute of Laboratory Medicine, Clinical Chemistry and Pathobiochemistry, Charité Medical University, Augustenburger Platz 1, 13353 Berlin, Germany*

[2] *Department of Gynecology, Charité Medical University, Augustenburger Platz 1, 13353 Berlin, Germany*

Previous Work
New candidates

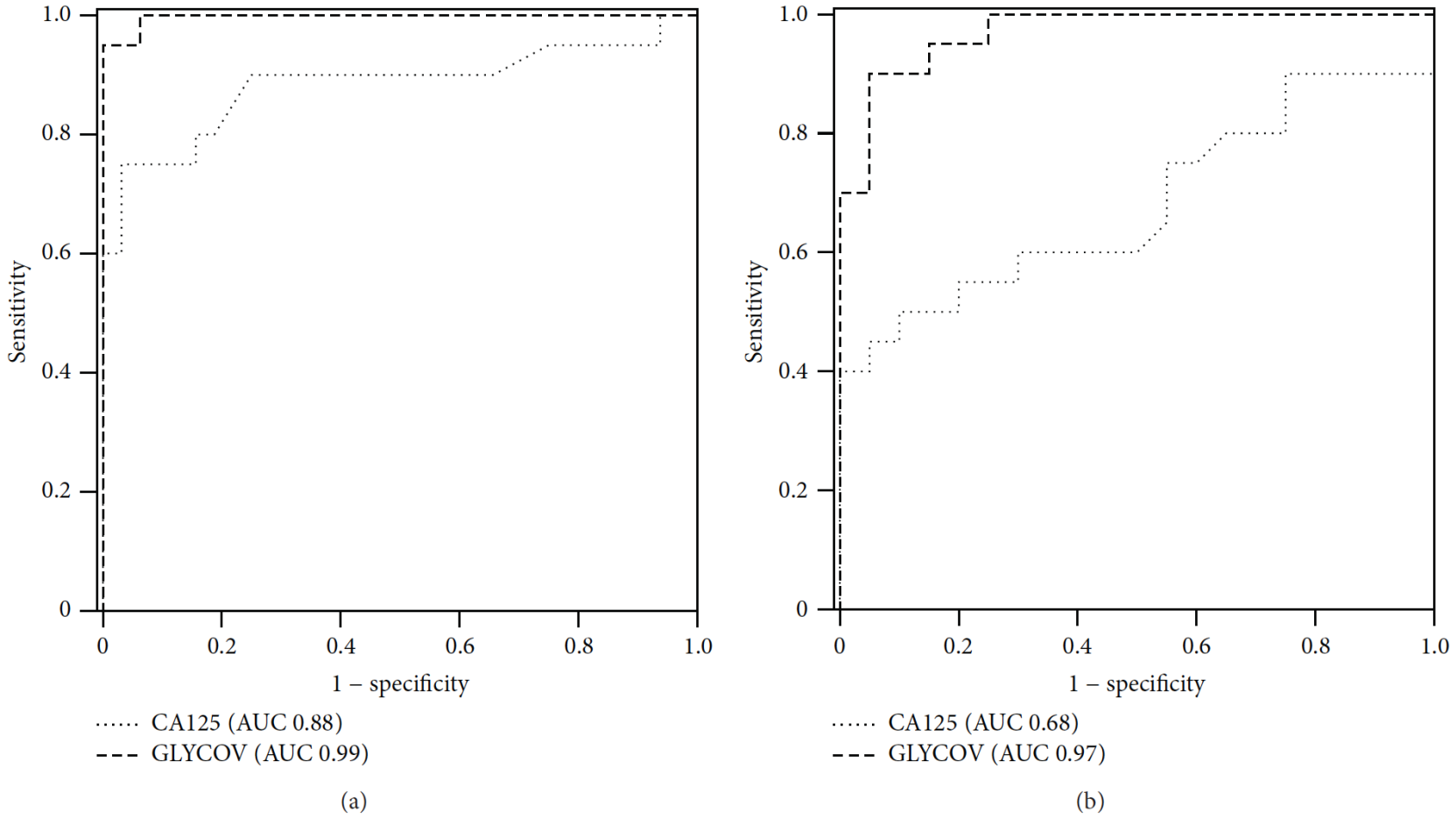
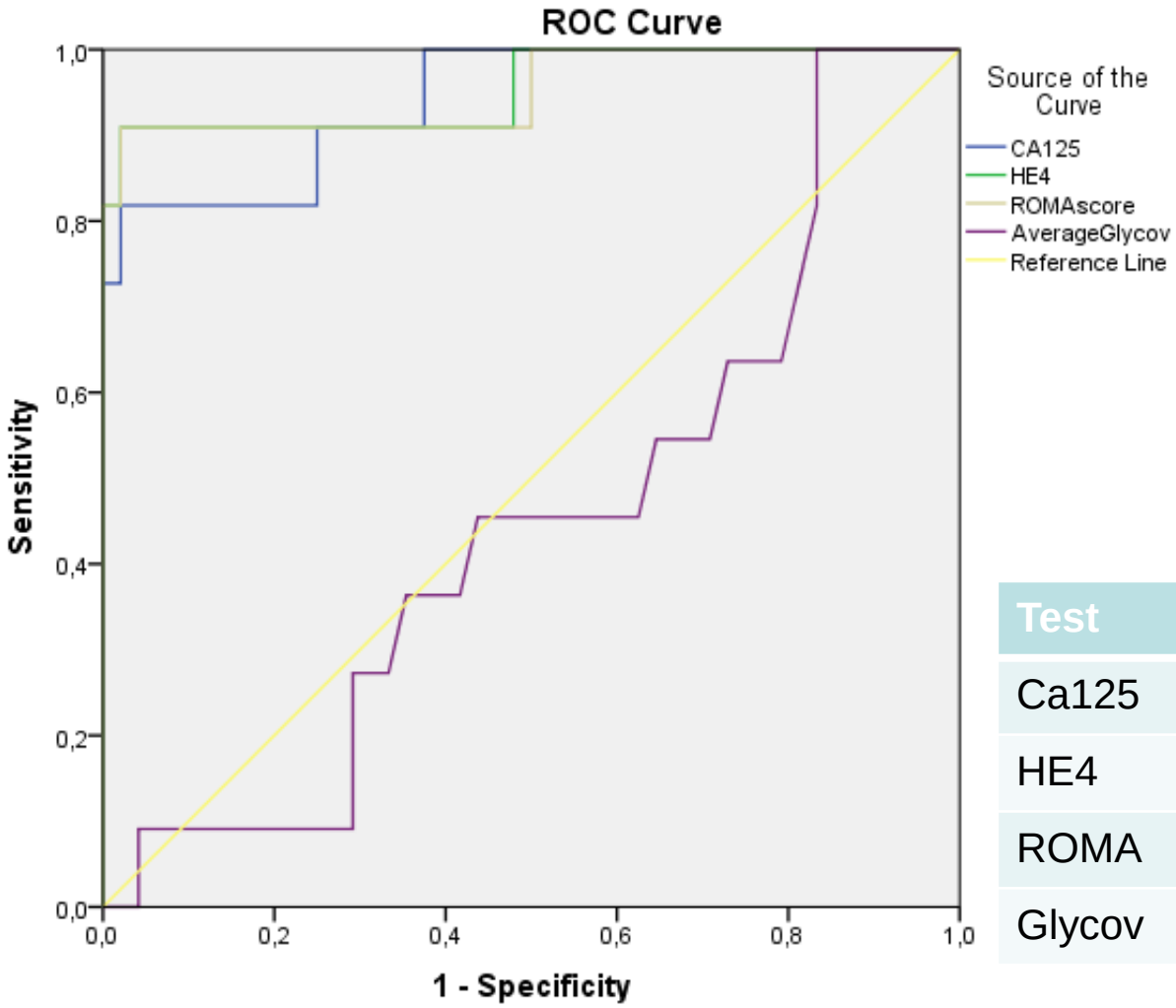


FIGURE 2: ROC curves for the GLYCOV and CA125 markers generated using 20 primary serous early-stage EOC patients and (a) 33 healthy controls or (b) 20 patients suffering from benign ovarian diseases.

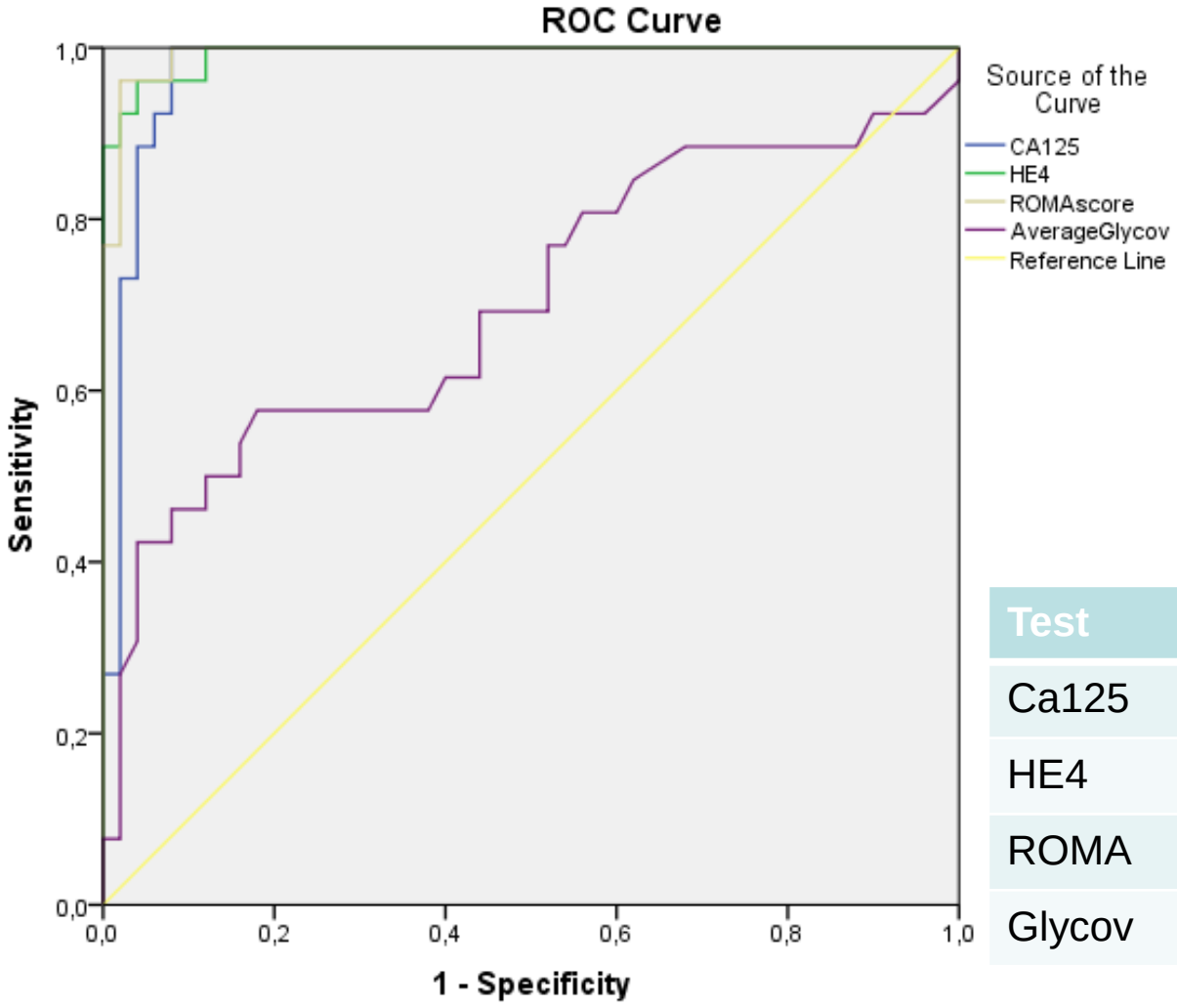
Results from Berliner Study



- 66 Premenopausal patients
- 18 ovarian cancer and Borderline Tumors
- 48 benign diseases

Test	AUC	95% CI
Ca125	0.941	0.864-1
HE4	0.955	0.871-1
ROMA	0.953	0.866-1
Glycov	0.451	0.268-0.634

Results from Berliner Study



- 82 Postmenopausal patients
- 32 ovarian cancer and BOT
- 50 benign diseases

Test	AUC	95% CI
Ca125	0.976	0.944-1
HE4	0.993	0.981-1
ROMA	0.993	0.981-1
Glycov	0.701	0.566-0837

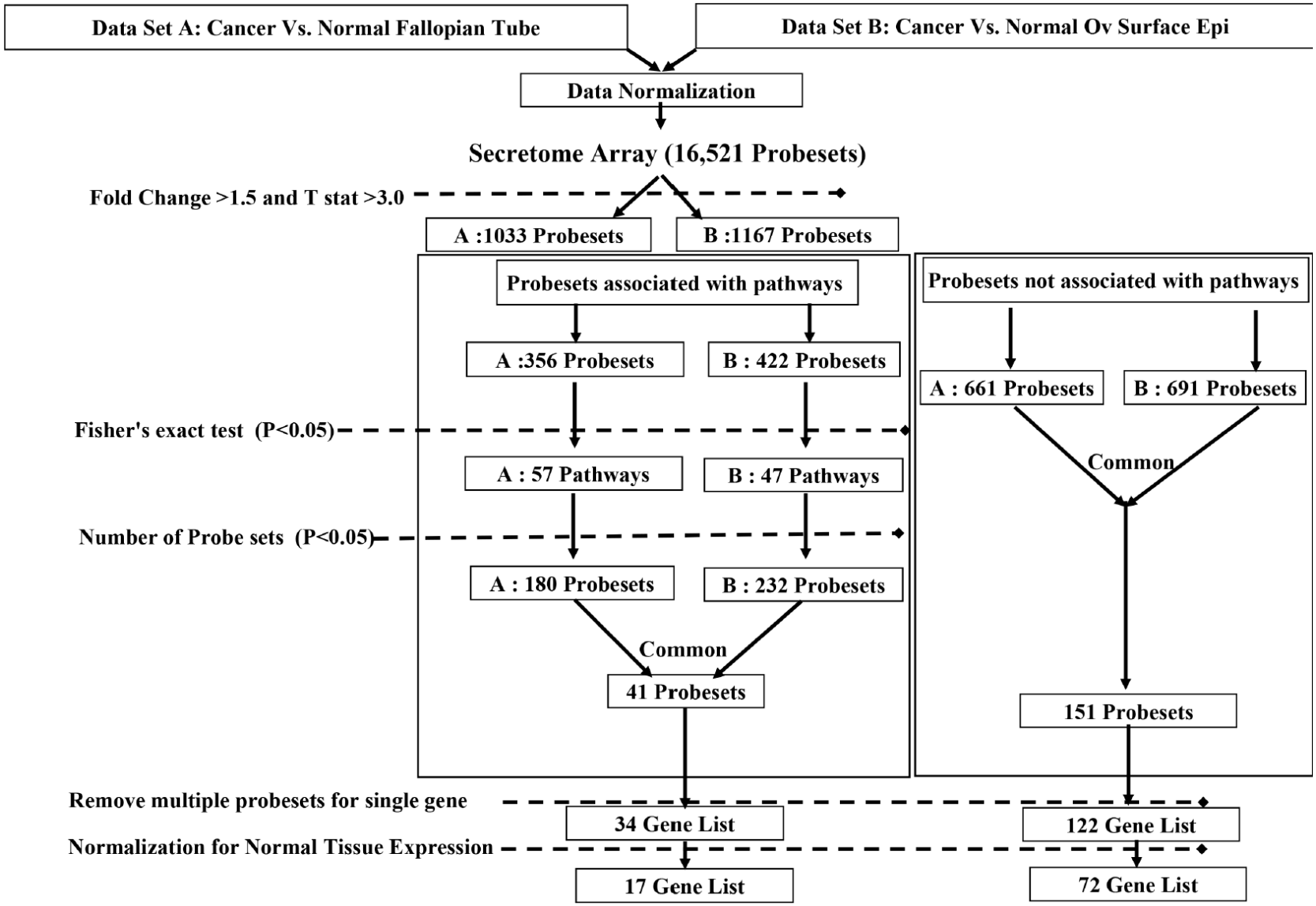
AACR American Association for Cancer Research

Clinical Cancer Research

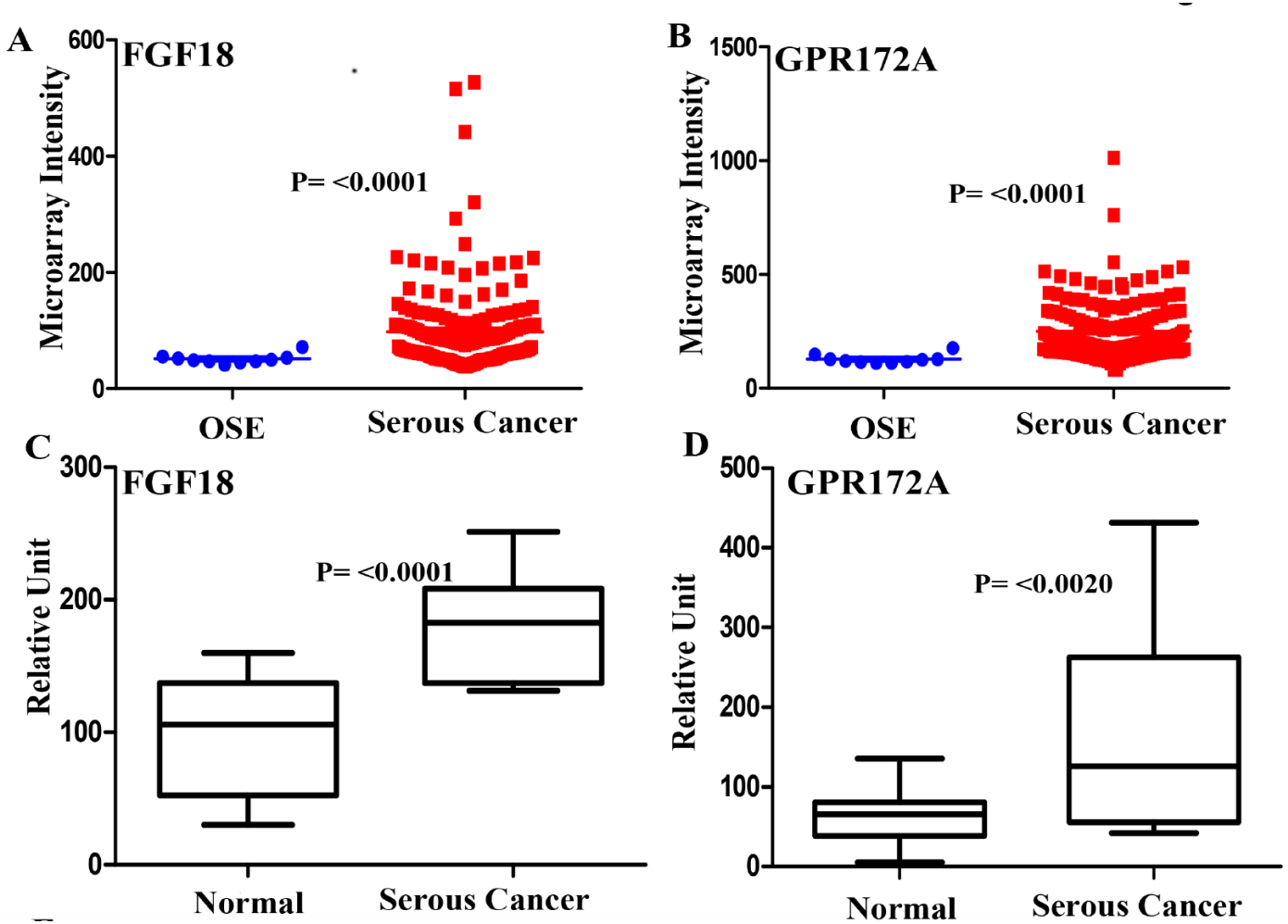
Creation of a human Secretome: Novel Composite Library of Human Secreted Proteins: Validation using Ovarian Cancer Gene Expression Data and Virtual Secretome Array

Vinod Vathipadiekal, Xin Victoria Wang, Wei Wei, et al.

Clin Cancer Res Published OnlineFirst May 5, 2015.


Data Set A: Cancer Vs. Normal Fallopian Tube
Data Set B: Cancer Vs. Normal Ov Surface Epi
Data Normalization
Secretome Array (16,521 Probesets)
Fold Change >1.5 and T stat >3.0
A :1033 Probesets
B :1167 Probesets
Probesets associated with pathways
Probesets not associated with pathways
A :356 Probesets
B : 422 Probesets
A : 661 Probesets
B : 691 Probesets
Fisher's exact test (P<0.05)
Common
A : 57 Pathways
B : 47 Pathways
Number of Probe sets (P<0.05)
A : 180 Probesets
B : 232 Probesets
Common
41 Probesets
151 Probesets
Remove multiple probesets for single gene
34 Gene List
122 Gene List
Normalization for Normal Tissue Expression
17 Gene List
72 Gene List

New approaches



New approaches

Detection and Evaluation of Molecular Biomarkers in Oavarian Cancer - BERLINER Studie

1. Gene expression profiles by in silico analysis of publically available datasets

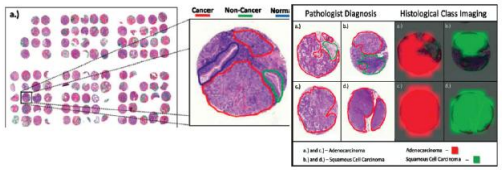
2. Protein profiles by Imaging Mass Spectrometry (IMS) on formalin-fixed ovarian cancer tissues

3. Protein profiles by mass spectrometry analysis (LC-MS/MS) in serum samples of ovarian cancer patients

Gene expression dataset of 50 human ovarian samples (GSE29156)

- 23 tissue samples from an ovary with benign serous tumour including laser capture microdisected Tumour and Stroma samples
- 27 tissue samples from an ovary with malignant serous tumour including laser capture microdisected Tumour and Stroma samples

Protein profiles of epithelial and stromal compartment by supervised analysis on TMAs as training sets
- 18 Borderline ovarian tissues samples
- 45 Low-grade serous ovarian cancer
- 54 High-grade serous ovarian cancer



Protein profiles by LC-MS/MS analysis in serum of patients with either

- Borderline (10 serum samples)
- Low-grade serous ovarian cancer (10 serum samples)
- High-grade serous ovarian cancer (10 serum samples)

Biomarker validation

Real time RT-PCR analysis for candidate genes in tumour samples of patients included in the study

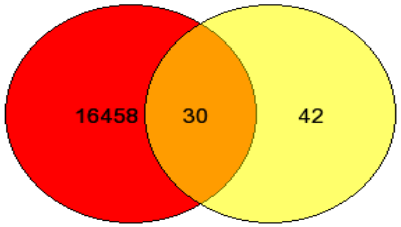
IHC for candidate biomarkers on formalin-fixed tissue samples of patients included in the study

ELISA for candidate biomarkers in serum samples of patients included in the study

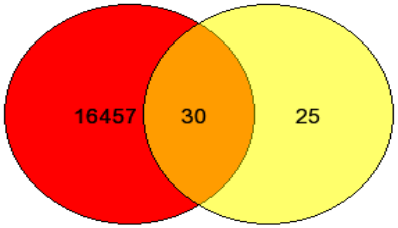
New approaches

In silico data analysis

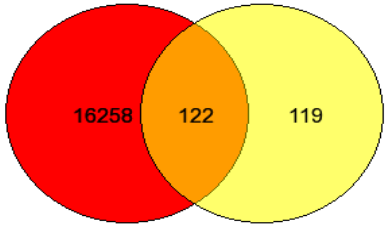
Secretome Malignant versus benign



Malignant versus benign Stroma



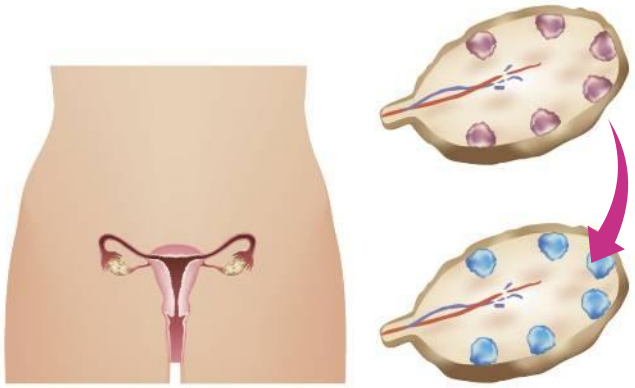
Malignant versus benign Combined



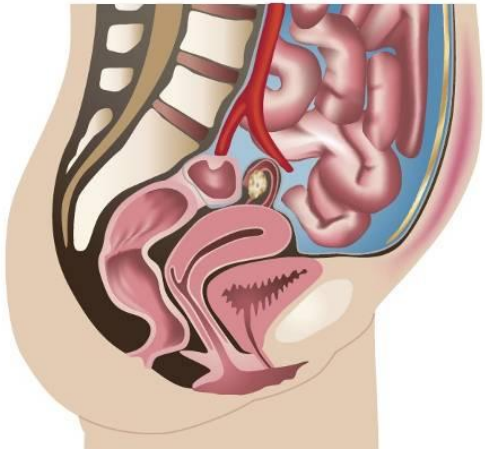
- Validation of the top 25% (n=38) in the 155 gene signature by NanoString technology In 10 serum and 10 tissue samples of benign and malignant biopsies
- Validation of the top 5 gene in Serum samples and by IHC on TMAs
- ELISA of top 5 overrepresented proteins in serum

Therapy resistance Models

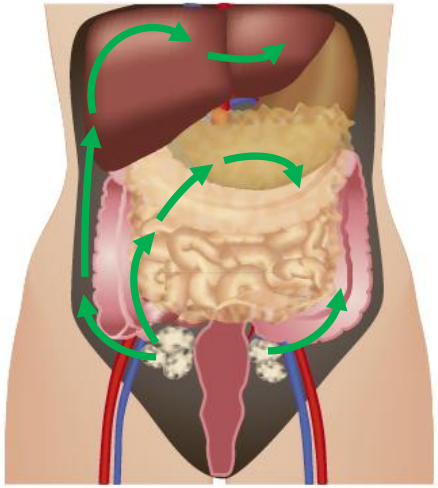
VEGF is highly expressed in ovarian cancer, with multiple effects



Switch from benign to malignant growth pattern[1]



Accumulation of ascites, by increasing peritoneal blood vessel permeability[1–5]



Formation of the metastases typical of ovarian cancer on the peritoneum[3]

1. Schumacher et al. Cancer Res 2007, 2. Ramakrishnan et al. Angiogenesis 2005; 3. Zhang et al. Am J Pathol 2002, 4. Trinh, et al. Br J Cancer 2009; 5. Belotti, et al. Cancer Res 2003

Bevacizumab provides proof of concept for anti-VEGF therapy

Five positive phase III trials of bevacizumab in ovarian cancer patients

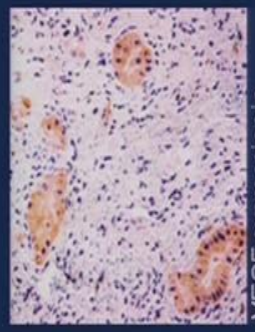
Front-line		Recurrent		
GOG 218	ICON7	OCEANS	AURELIA	GOG 213
Advanced, stage III/IV patients	Early and advanced stage patients	Recurrent, platinum sensitive	Recurrent, platinum resistant	Recurrent, platinum sensitive
PFS HR=0.717[1]	**PFS HR=0.81[2]**	**PFS HR=0.48[3]**	**PFS HR=0.48[4]**	**PFS HR=0.61[5]**

1. Burger, et al. NEJM 2011; 2. Perren, et al. NEJM 2011 3. Aghajanian, et al. JCO 2012;
4. Pujade-Lauraine, et al. ASCO 2012, 5. Coleman et al., SGO 2015

Cediranib

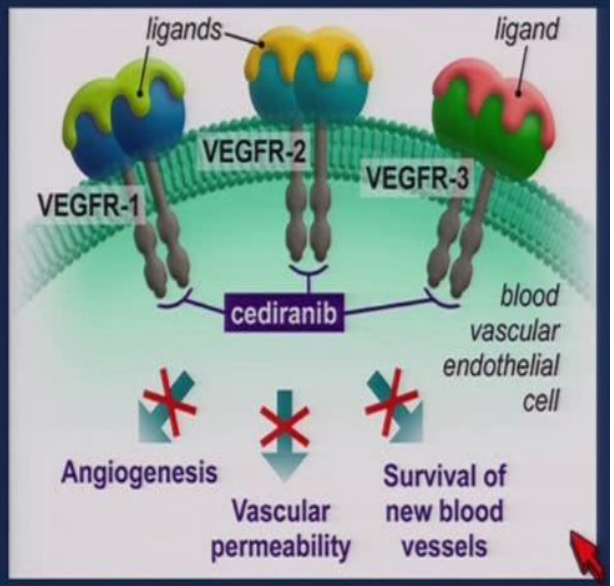
Targeting VEGF | Rationale

- VEGF is over-expressed in 40-75% of BTCs [1-3]
- VEGFR-1 and -2 are also over-expressed in adjacent endothelial cells [4]
- VEGF expression associated with
  - ⇧ metastases (IH-CC) [1]
  - ⇧ micro-vessel density [2,3]
  - ⇩ OS (EH-CC) [5]
- Cediranib is a pan-VEGF receptor TKI (with some activity against PDGF receptors and c-Kit) [6]



VEGF expression in Gallbladder carcinoma [3]

VEGF expression in CC tumour cells [4]



[1] Yoshikawa *BJC* 2008; [2] Tang *Oncol Rep* 2006; [3] Giatromanolaki EJSO 2003; [4] Benckert, *Cancer Res* 2003; [5] Hida *Anticancer Res* 1999; [6] Wedge *Cancer Res* 2005

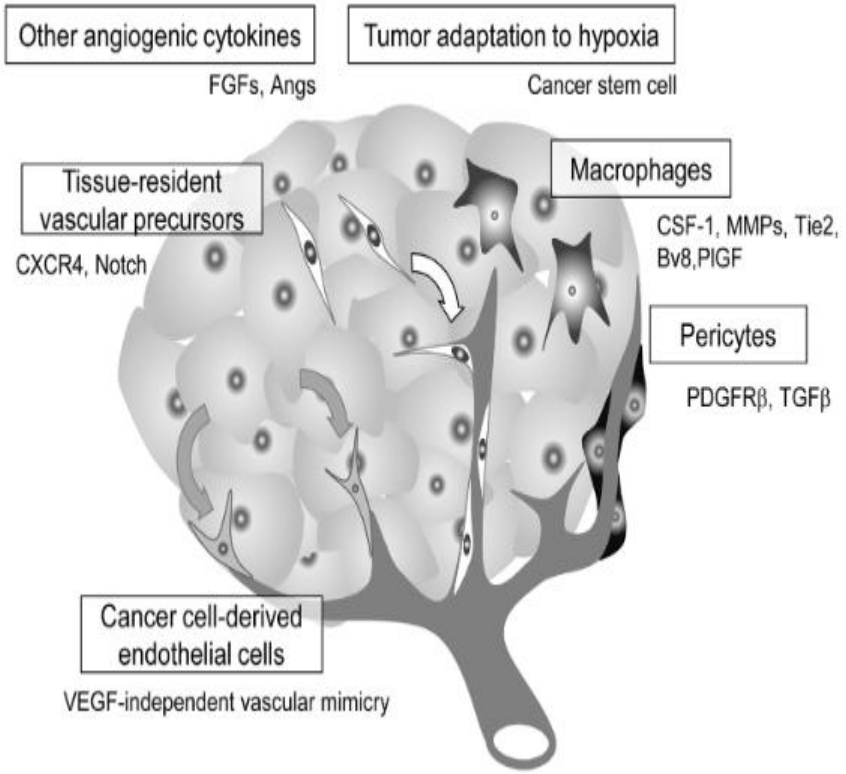
Presented by: Juan W Valle

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Cediranib

- Encouraging results from ICON 6:
  - significant improvement in PFS and OS in ChTh concurrent with Ced followed by Ced maintenance arm compared to ChTh alone (11.1 vs. 8.7 mo and 26.3 vs. 20.0 mo, respectively).

VEGF-independent pro-angiogenic mechanisms: novel targets for anti-angiogenic therapy



LETTERS

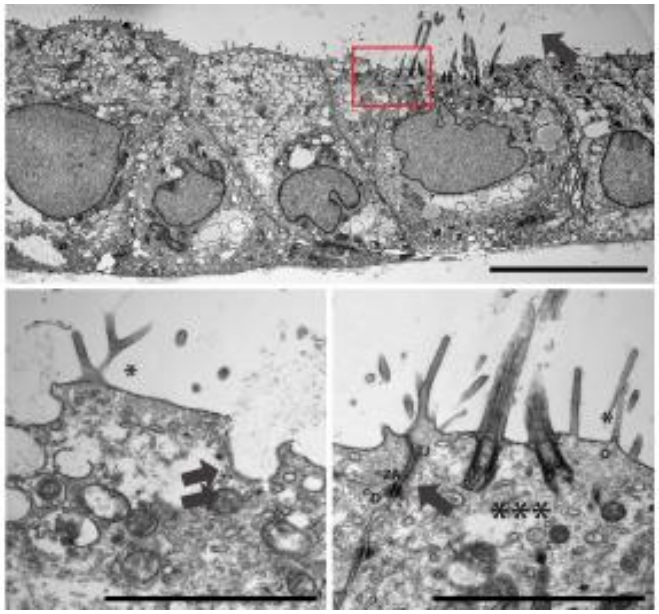
nature medicine

Induction of interleukin-8 preserves the angiogenic response in HIF-1α–deficient colon cancer cells

Yusuke Mizukami[1], Won-Seok Jo[1], Eva-Maria Duerr[1], Manish Gala[1], Jingnan Li[1], Xiaobo Zhang[1], Michael A Zimmer[2], Othon Iliopoulos[2], Lawrence R Zukerberg[3], Yutaka Kohgo[4], Maureen P Lynch[5], Bo R Rueda[5] & Daniel C Chung[1]

ure.com/naturemedicine

Human Fallopian tube organoids- long term culture of polarized differentiated Epithelia



Polarized monolayer

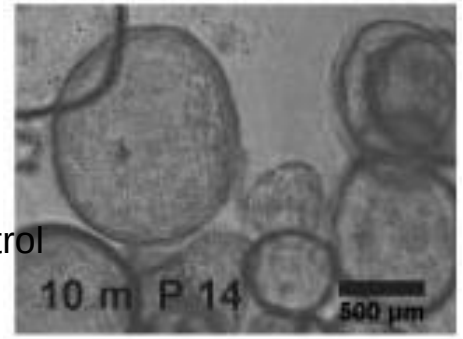
Complete development of cilia
(first time in long term culture)

Mature zonula adherens, tight junctions,
active secretion (arrows)

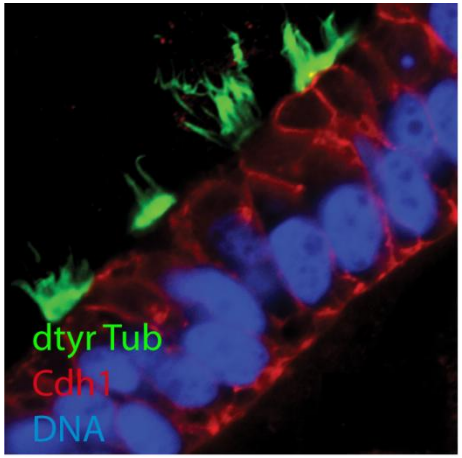
Based on expansion of
stem cells >50 donors

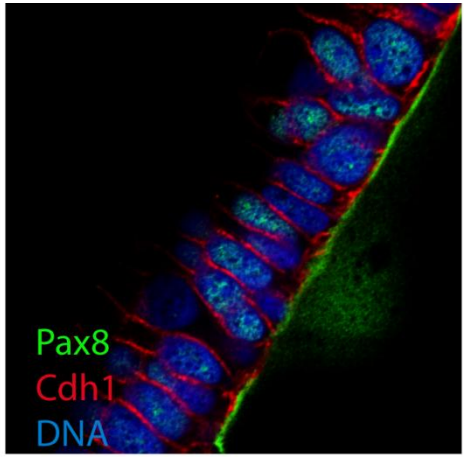
>1 year in culture

WNT and Notch pathways control
differentiation:



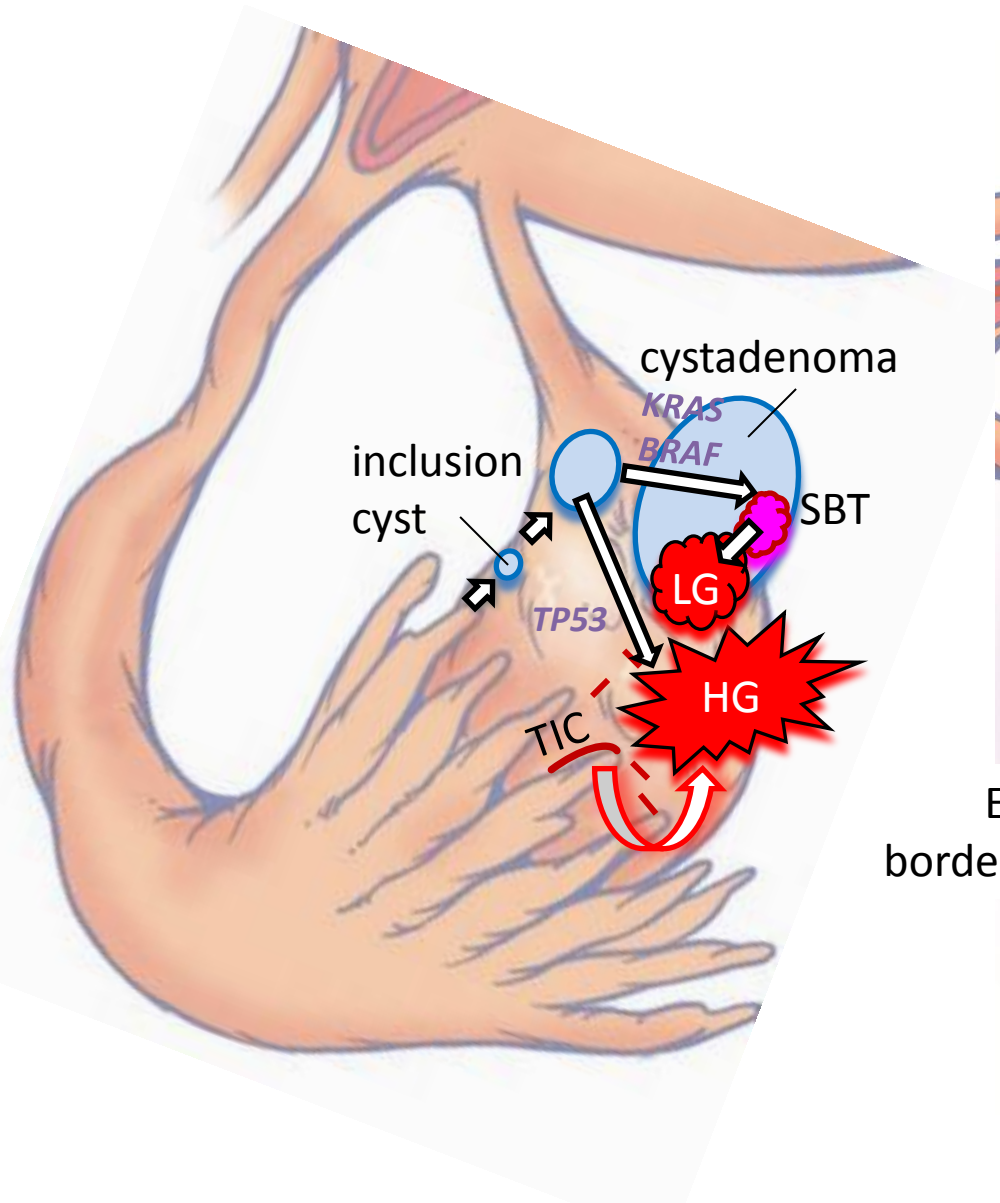
Cilliated and secretory cells (PAX8)

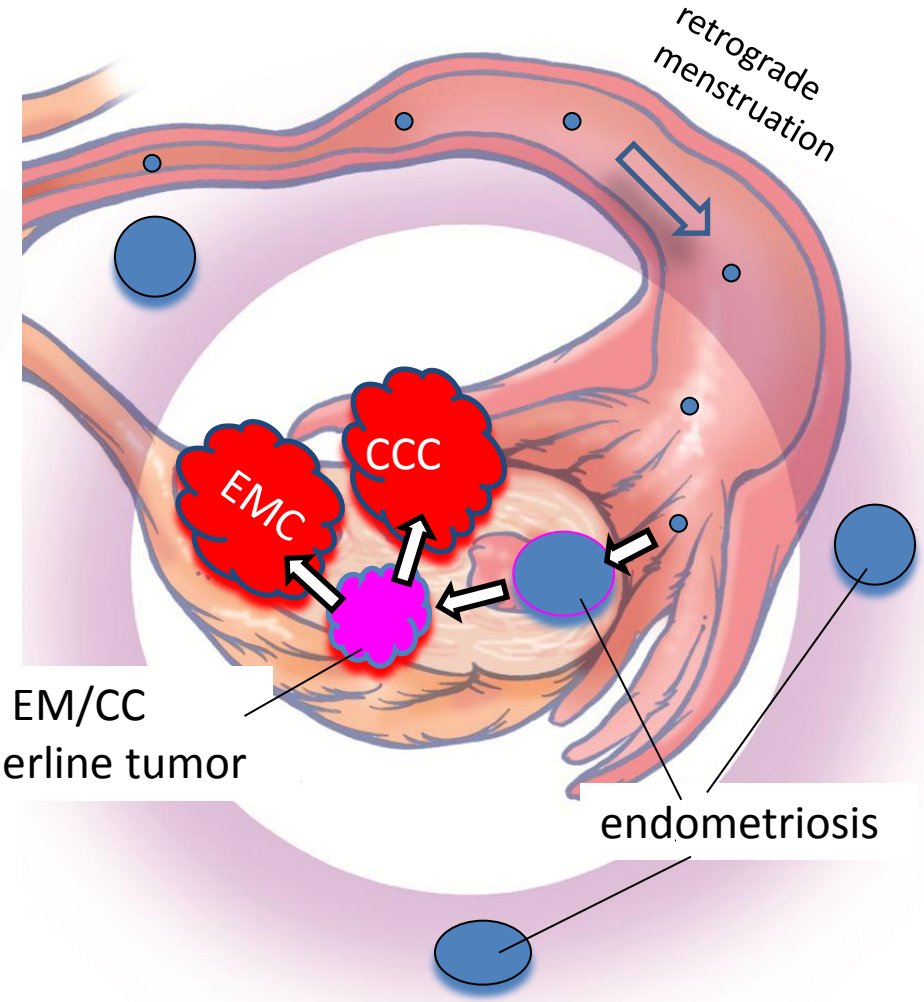




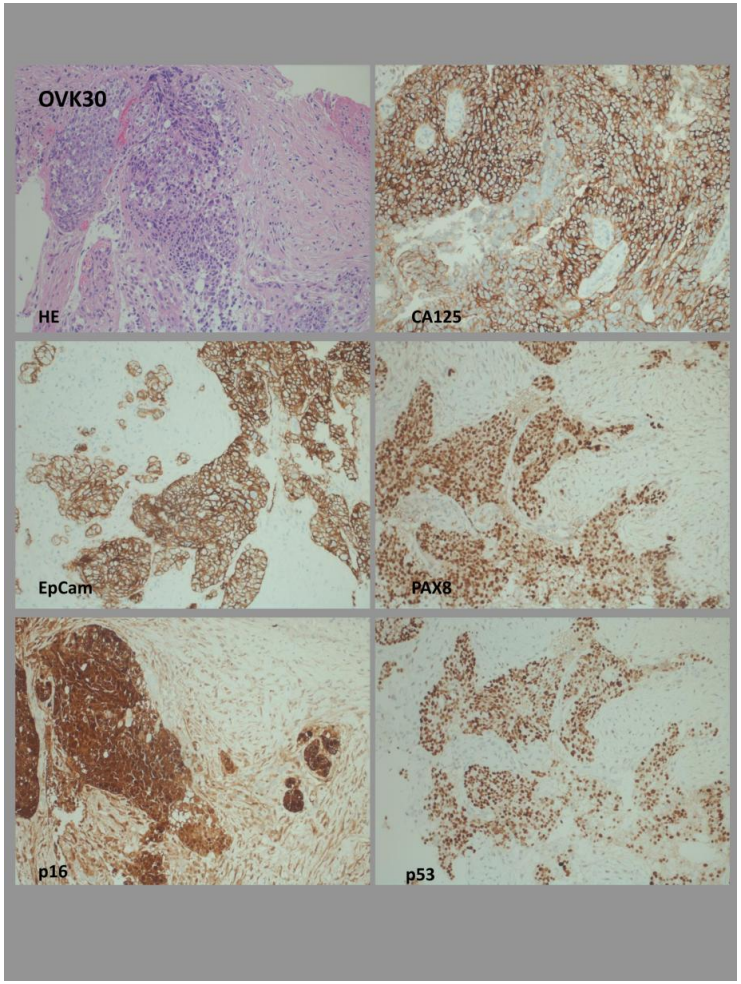
Kessler et al 2015. *Nature communications*

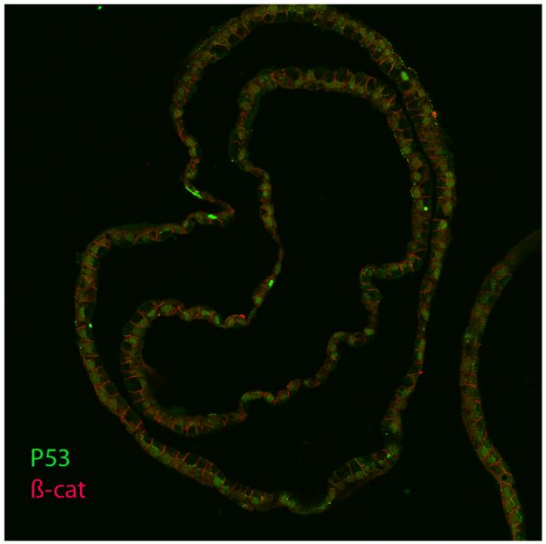
Cell of origin in ovarian cancer subtypes

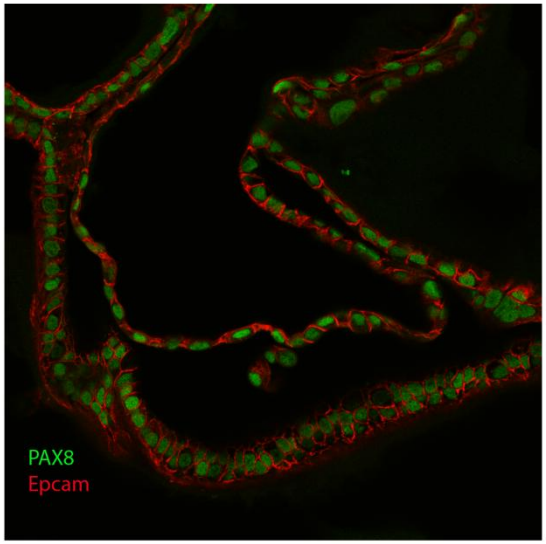




Comparative phenotypic analysis of cancer tissue and organoids from HGSOvCa







3D organoid culture recapitulates main characteristics of cancer tissue

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JOURNAL OF CLINICAL ONCOLOGY

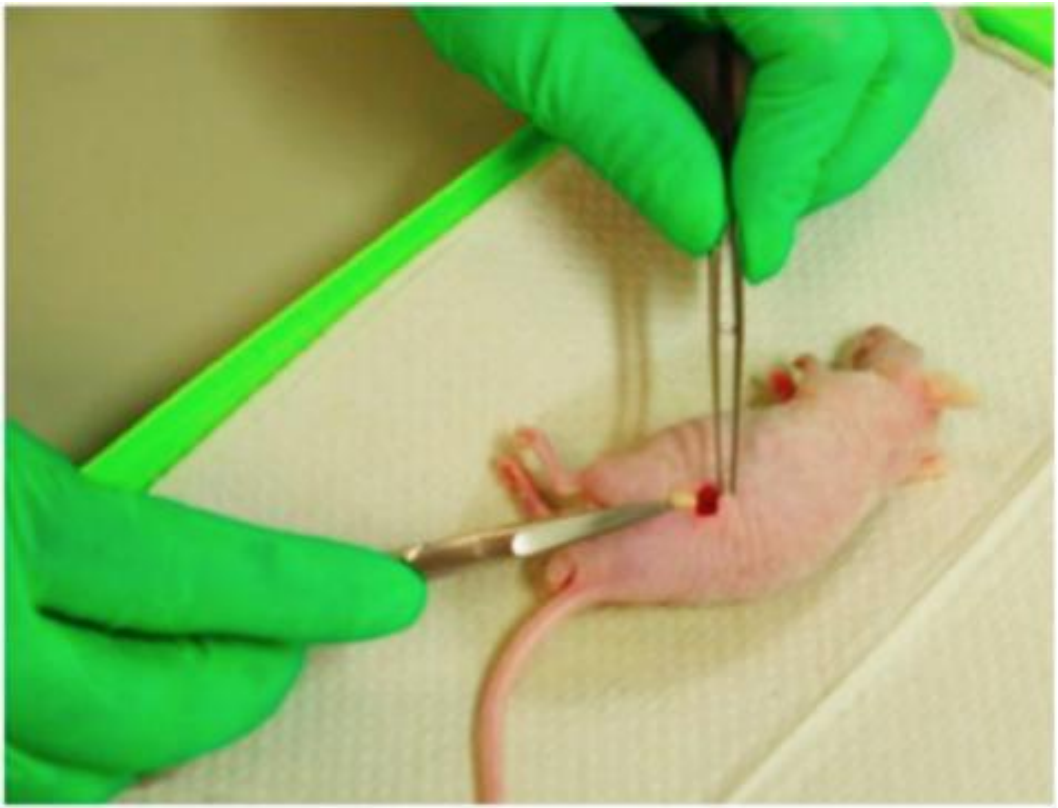
ORIGINAL REPORT

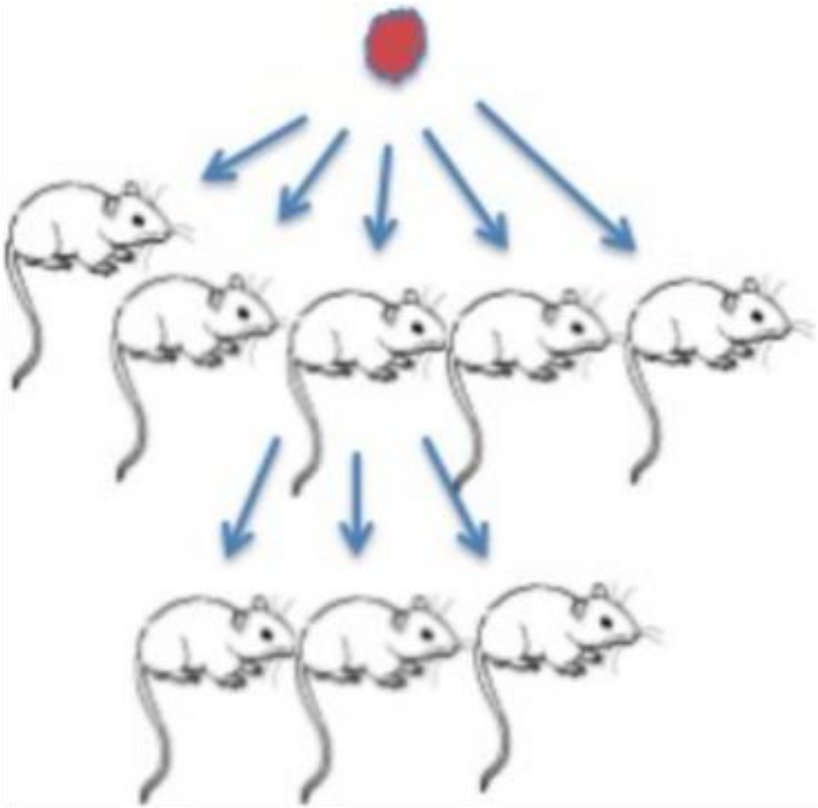
Lavage of the Uterine Cavity for Molecular Detection of Müllerian Duct Carcinomas: A Proof-of-Concept Study

Elisabeth Maritschnegg, Yuxuan Wang, Nina Pecha, Reinhard Horvat, Els Van Nieuwenhuysen, Ignace Vergote, Florian Heitz, Jalid Sehouli, Isaac Kinde, Luis A. Diaz Jr, Nickolas Papadopoulos, Kenneth W. Kinzler, Bert Vogelstein, Paul Speiser, and Robert Zeillinger

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

Therapy resistance Models





From 18 patients
Molecular genetic characterization
Sensitivity to Carboplatin, Avastin, Paclitaxel, Gemcitabine

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