FOX CHASE CANCER CENTER 2010

Accelerating Ovarian Cancer Research: Recent Victories, Current Opportunities, Future Challenges

Michael V. Seiden, M.D., Ph.D.

Translating Science to Ovarian Cancer

Young Adult

Older Adult

Previvors

Early Detection

Diagnosis

Survivorship

Mechanisms of Translational Research

- SPORES- Specialized Programs in Organ Research
- EDRN- Early Detection Research Network
- PPACA- Patient Protection and Affordable Care Act
- TCGA- The Cancer Genome Atlas
- STRAPS- Special Translational Research Acceleration Projects
- Cooperative Groups
- Ovarian Cancer Academy

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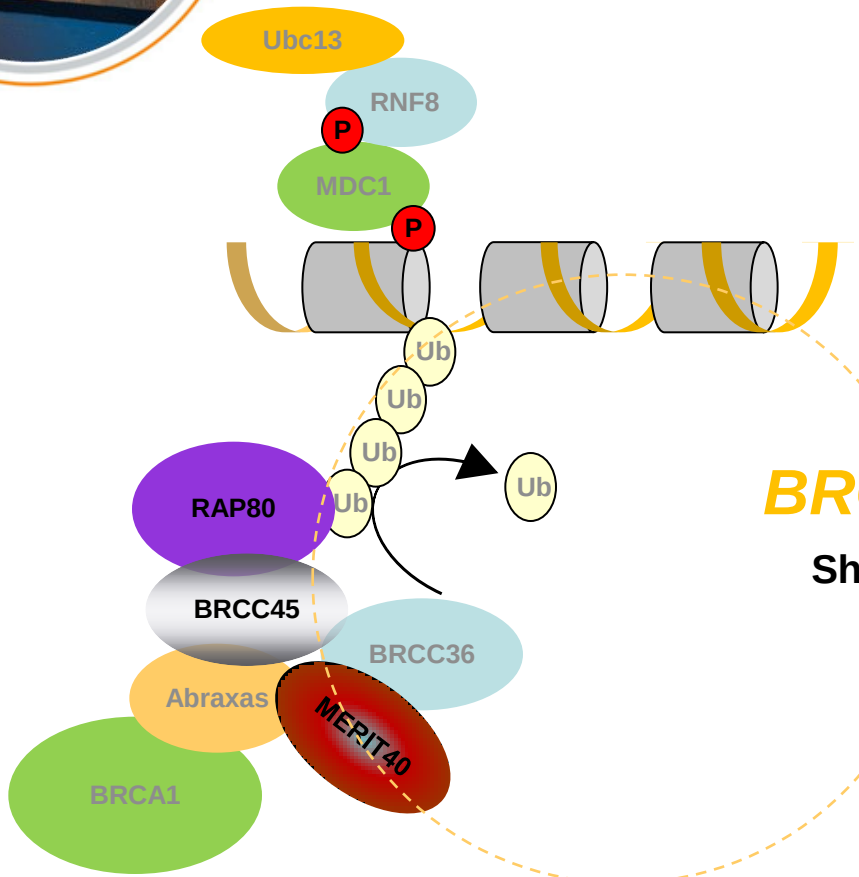
FOX CHASE CANCER CENTER 2010

Mary B. Daly
Andy Godwin
Katrina Armstrong
Susan Domchek
Nandita Mitra
Tim Rebbeck



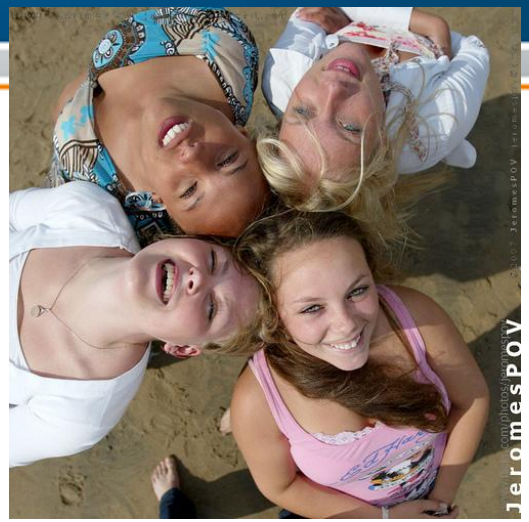
BRCA1 Interacting Complex

Shao et al. 2009, Messick and Greenberg 2009

RAD51 and Ovarian Cancer

SNP	Allele	*BRCA1* HR	*BRCA1* 95% CI	*BRCA2* HR	*BRCA2* 95% CI
rs957603 (MAF=42%)	CT	0.82	0.62-1.08	0.87	0.55-1.37
	TT	1.00	0.71-1.40	0.38	0.19-0.76
	T	0.87	0.67-1.12	0.74	0.48-1.14

SOFT: Study of Female Teens



- Evaluating knowledge and perceptions of breast cancer risk & health behaviors among adolescent girls

Angela R. Bradbury, M.D.
Fox Chase Cancer Center

Co-PI: Dr. Linda Patrick-Miller, Ph.D.
Cancer Institute of New Jersey

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Their greatest health concerns (n=25)

- None (7)
- Weight (6)
- Breast cancer (6)
  - only among high risk group
- Staying healthy NOS (6)

Perceived etiology of breast cancer (n=25)

- Any ideas how and why women get breast cancer?
- Genetic (15) or ‘runs in families’ (6)
- Not sure (13)

You have a different risk than other girls?

- 17/21 (65%) high risk girls said different and higher for breast or ovarian cancer.

Are there things one can do to reduce their chances of getting breast cancer?

- Women in general?
  - YES: 15/25 (60%)
  - NO: 7/25 (28%)
  - Not sure: 3/25 (12%)

Screening, healthy diet, Exercise, "staying healthy", Avoiding tobacco & alcohol

- Girls your age?
  - YES: 12/25 (48%)
  - NO: 8/25 (32%)
  - Not sure: 4/25 (16%)

Healthy diet, exercise, "staying healthy", developing good health habits, looking for signs.

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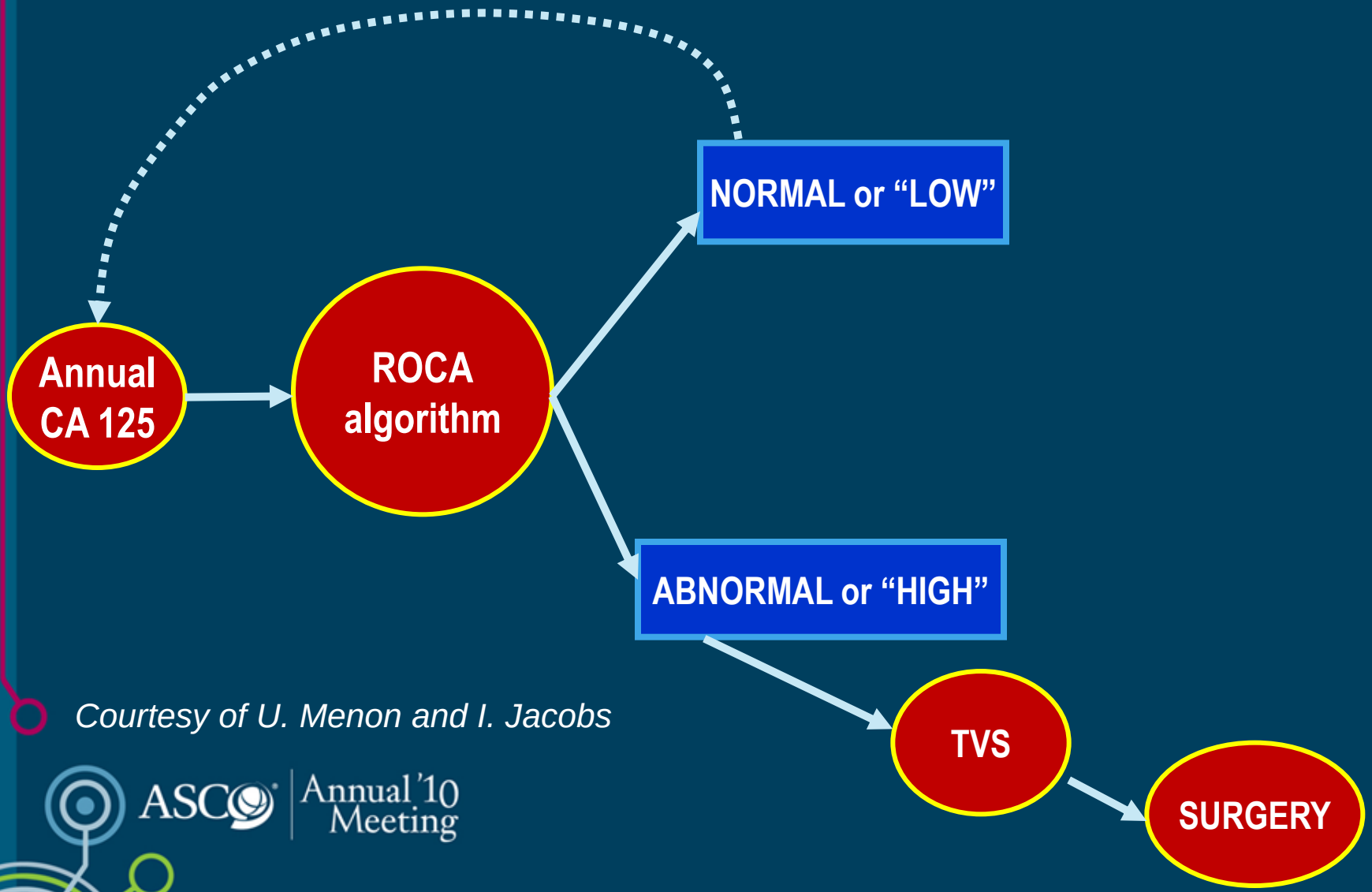
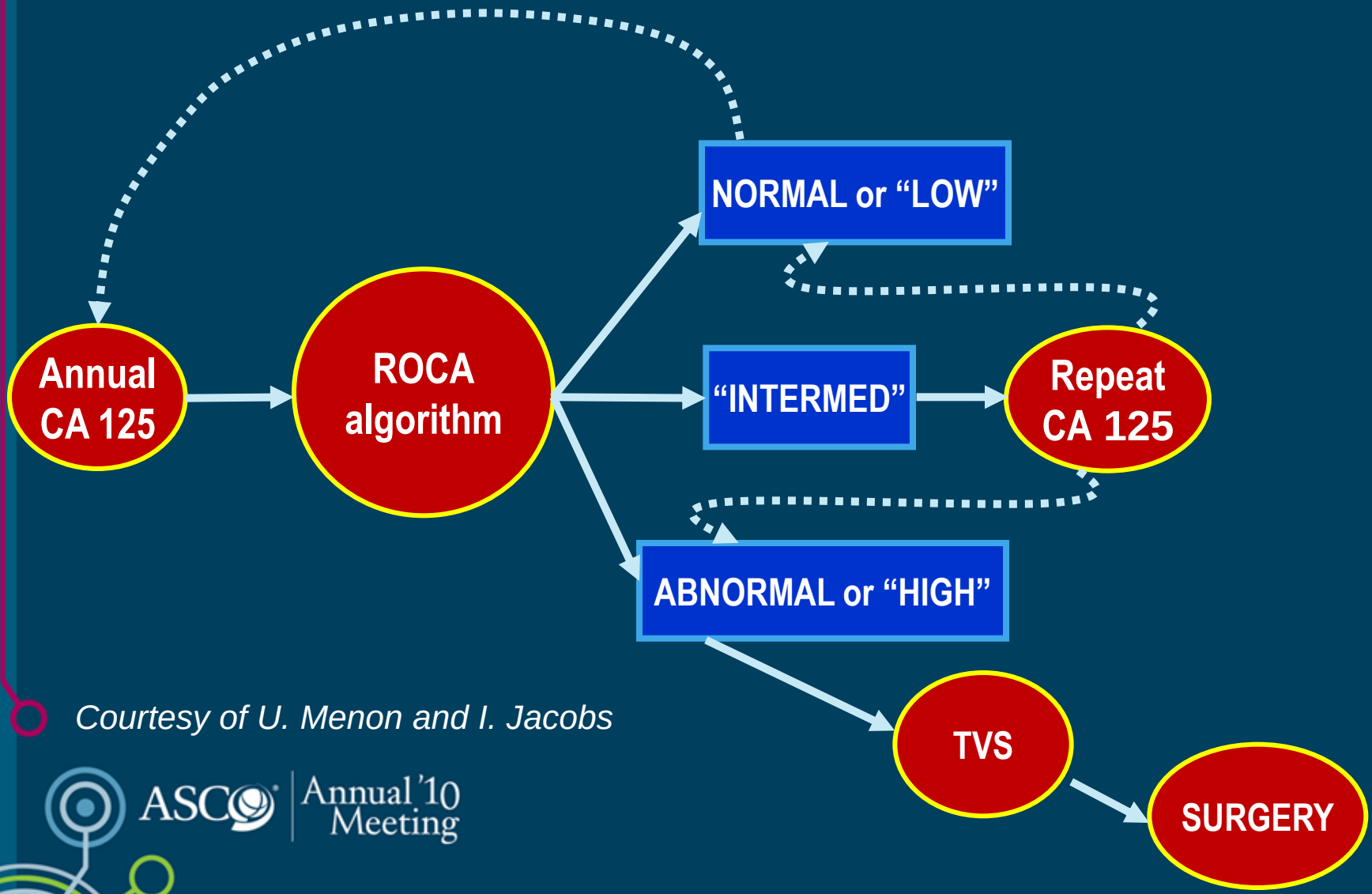
Two stage screening



Courtesy of U. Menon and I. Jacobs

Two stage screening



Courtesy of U. Menon and I. Jacobs

Purpose

- The purpose of this study was to assess the specificity and positive predictive value (PPV) of a 2-stage screening strategy to detect ovarian cancer in post-menopausal women :
  - Tailored to each individual woman's baseline
  - Only a small fraction of women referred to transvaginal sonography (TVS) and clinical evaluation

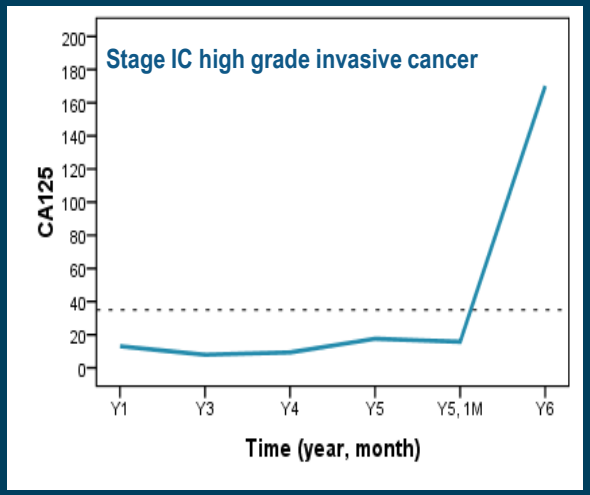
Methods

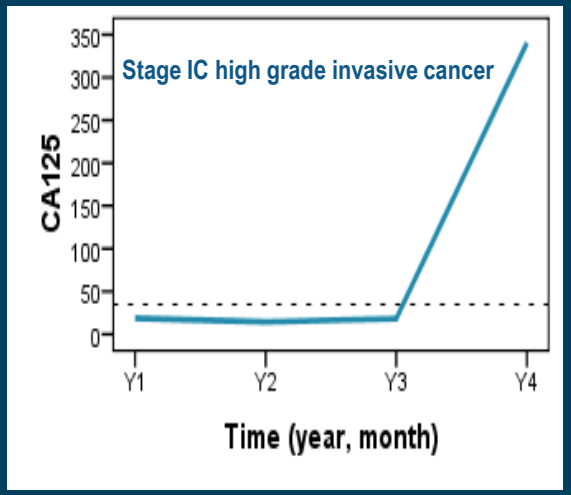
- Eligibility criteria
  - Post-menopausal women ages 50-74
  - Have at least 1 ovary
  - No significant family history of breast or ovarian cancer
  - Cancer-free and no treatment in past 12 mos, aside from hormonal adjuvant therapy

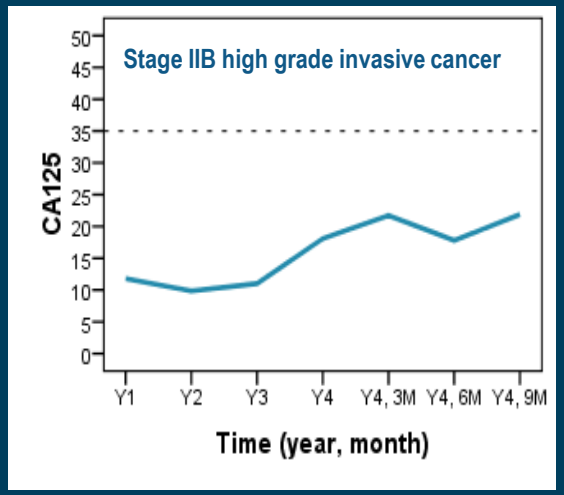
Results

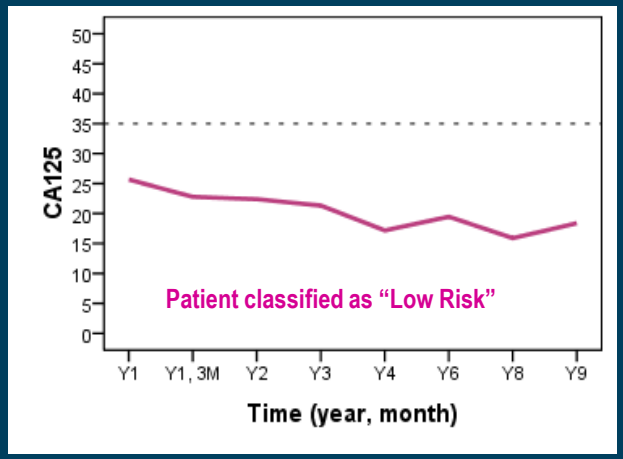
- Total number of participants = **3,252 women**
- Total number of screen years = **10,679 years**
- Average number of screen years per woman = **3.3 years**
- Median age 59, with a range of 50-74

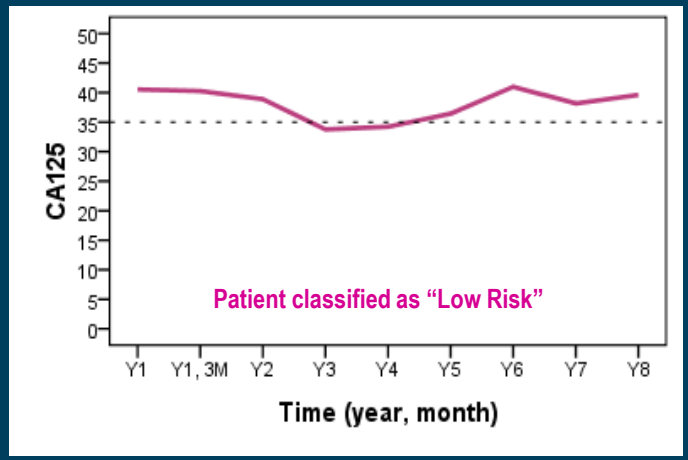
Examples of CA 125 trends











ASCO Annual '10 Meeting

Results

Average annual rates:

- **Normal risk "return in 1 year" = 92.6%**
- **Intermediate risk "repeat CA-125 in 3 mos = 6.5%**
- **High risk "TVS + referral" = 0.9%**

Overall:

- **Normal risk "return in 1 year" , n= 2666 (82%)**
- **Intermediate risk "repeat CA-125 in 3 mos, n= 501 (15.4%)**
- **High risk "TVS + referral" , n=85 (2.6%)**

Study-directed surgeries

Study Directed Surgeries (n=8)							
Pt	Age at entry	1st CA125	# annual CA125	CA 125 resulting in "High Risk"	TVS results	Symptoms	Findings at surgery
1	68	29	1	74	abnormal	No	Stage 1 serous LMP
2*	64	9	6	15	abnormal	No	Stage 1 serous LMP
3*	63	12	2	24	abnormal	No	Benign (cystadenoma)
4*	55	12	3	22	abnormal	No	Stage IIB high grade invasive cancer
5*	53	13	3	18 170	#1: normal #2: abnormal	GI	Stage IC high grade invasive cancer
6	69	75	0	75	abnormal	No	Benign (cystadenoma)
7	65	19	3	340	abnormal	No	Stage IC high grade invasive cancer
8	60	45	0	59	abnormal	No	1st surgery: no ovarian disease (sigmoid nodule with necrotic component); 2nd surgery: endometrial cancer

* Detected by ROCA only, and not by CA-125 >35

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Diagnosis &Treatment

Early Detection

Survivorship

Previvors

Phase III Trial of Bevacizumab in the Primary Treatment of Advanced Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer: A Gynecologic Oncology Group (GOG) Study

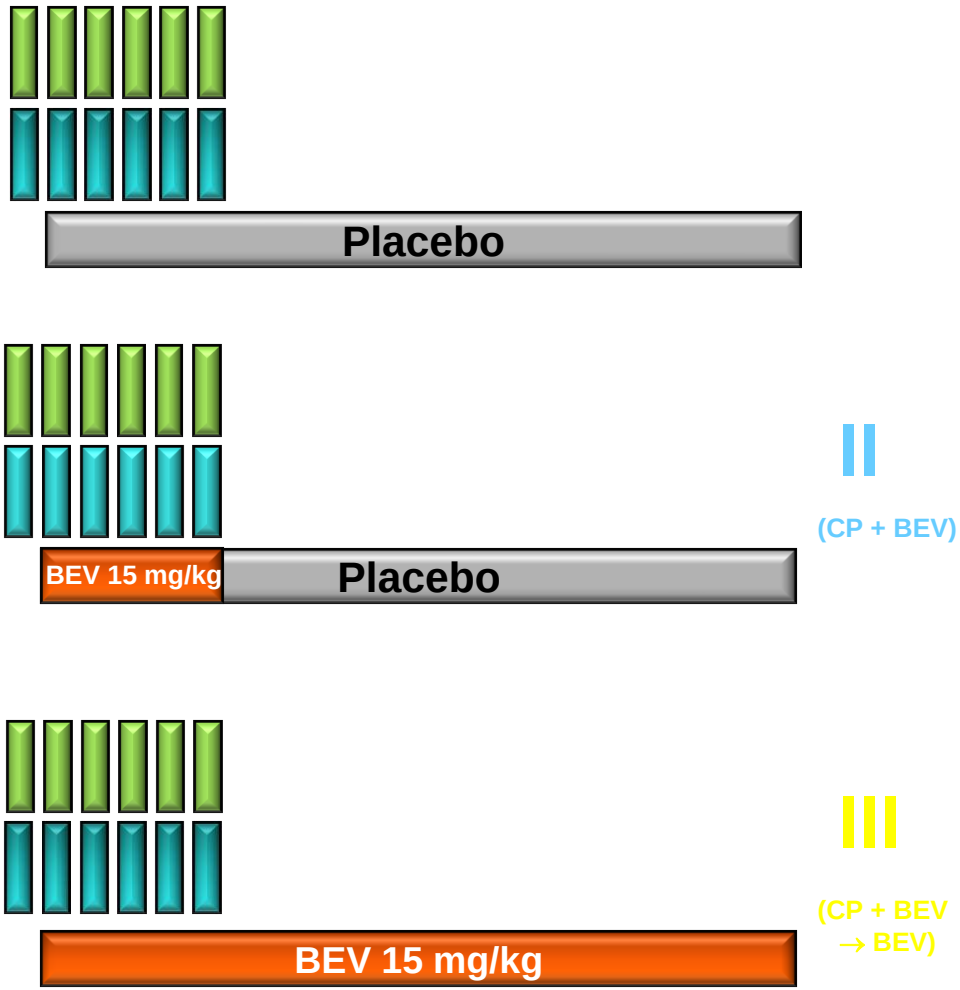
GOG-0218: Schema

Front-line: Epithelial OV, PP or FT cancer

- Stage III optimal (macroscopic)
- Stage III suboptimal
- Stage IV

n=1800 (planned)

RANDOMIZE



Gynecologic Oncology Group

Preliminary Results from the Ovarian TCGA Pilot Program

Thanks to Douglas A. Levine, MD
On Behalf of the TCGA investigators
Memorial Sloan-Kettering Cancer Center

TCGA Pilot Project Network

THE CANCER GENOME ATLAS

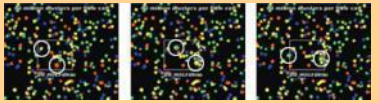
Development of New Analyses

- Tools
- Views

Data Management, Bioinformatics, and Computational Analysis

- Data Coordinating Center, DCC
- Analyses of data

Technology Development



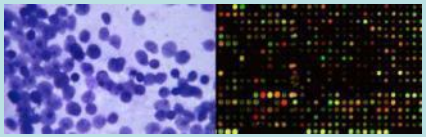
- Increased sensitivity of molecular characterization platforms
- Analysis of biomolecules from 1000 cells or less

Genome Sequencing Centers

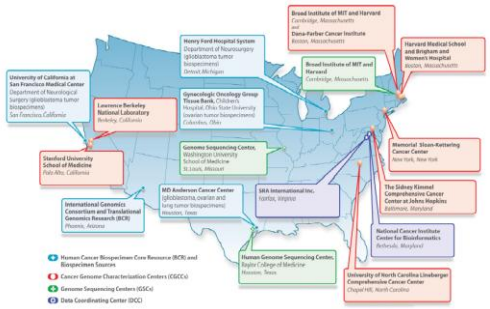
High throughput sequencing of genes and genomic regions identified through cancer characterization

Communication

Cancer Genome Characterization Centers



- Identification of expression alternation
- Detection of DNA fragment copy number changes and LOH
- Epigenetics



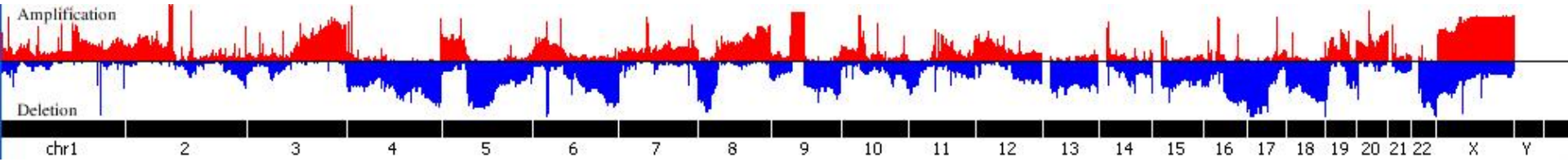
Human Cancer Biospecimen Core Resource

Biospecimens-related data storage
Histopathology confirmation performed
Biomolecules isolated, QC'ed and distributed

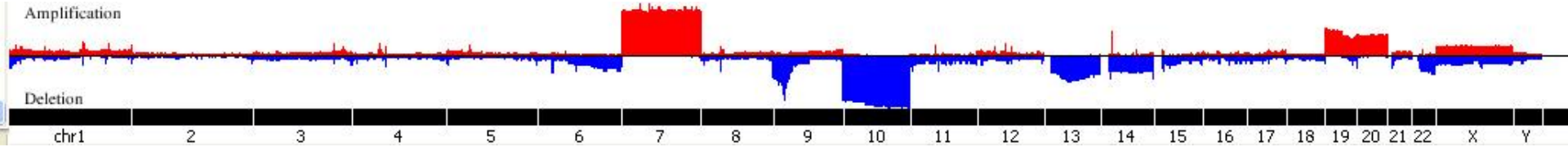
aCGH on Agilent 244K

THE CANCER GENOME ATLAS

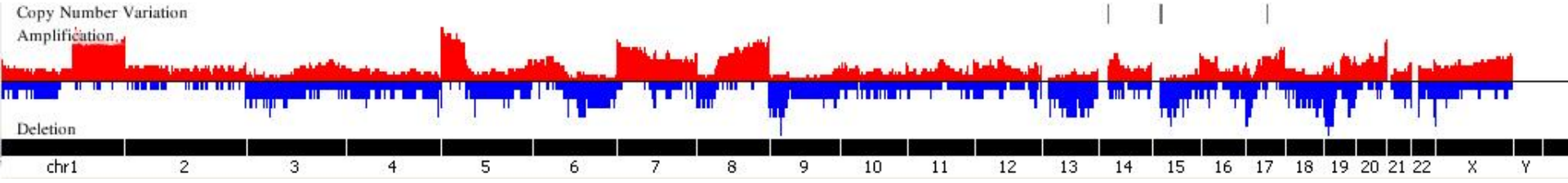
- **Ovarian - TCGA**

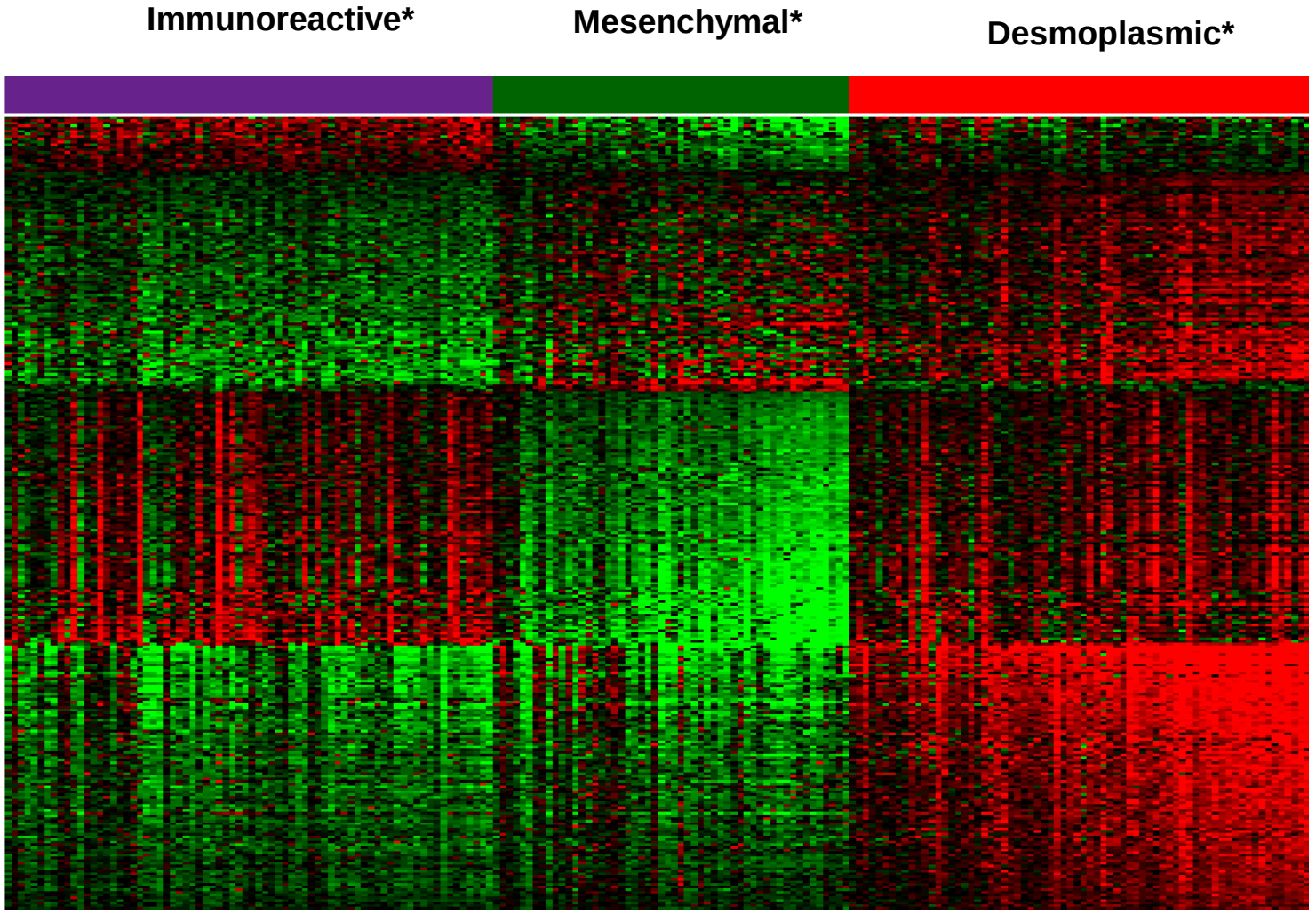


- **GBM - TCGA**



- **Lung - TSP**





Roel Verhaak

Technology and the Human Genome

- Human genome consists of nearly 4 billion chemical subunits (base-pairs) of DNA
- These subunits comprise approximately 20,000 genes
- Effort and cost
  - Ten years-to sequence 4B base pairs
  - 3 dollars per base pair = $10B
  - Cost in 2012 will be <$10K (>1 million fold reduction!)
  - Anticipated sequence information in 2010 estimated to be 150T bp= 150,000 billion!

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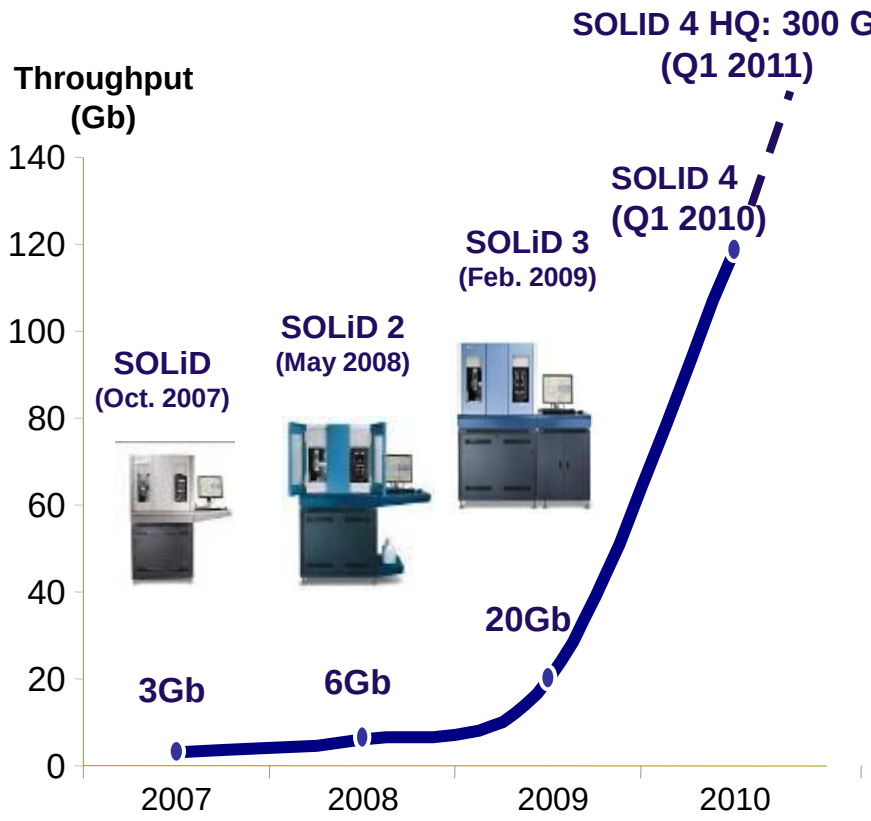
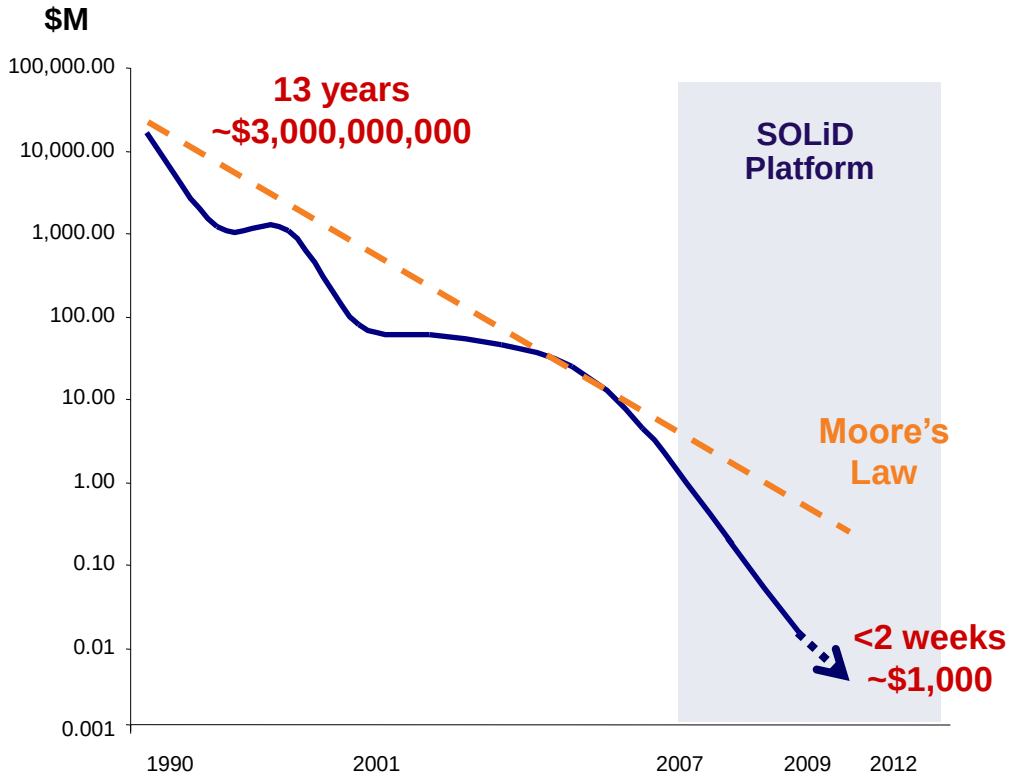
Whole Genome Sequence Analysis Is Becoming Affordable

Innovation of SOLiD throughput



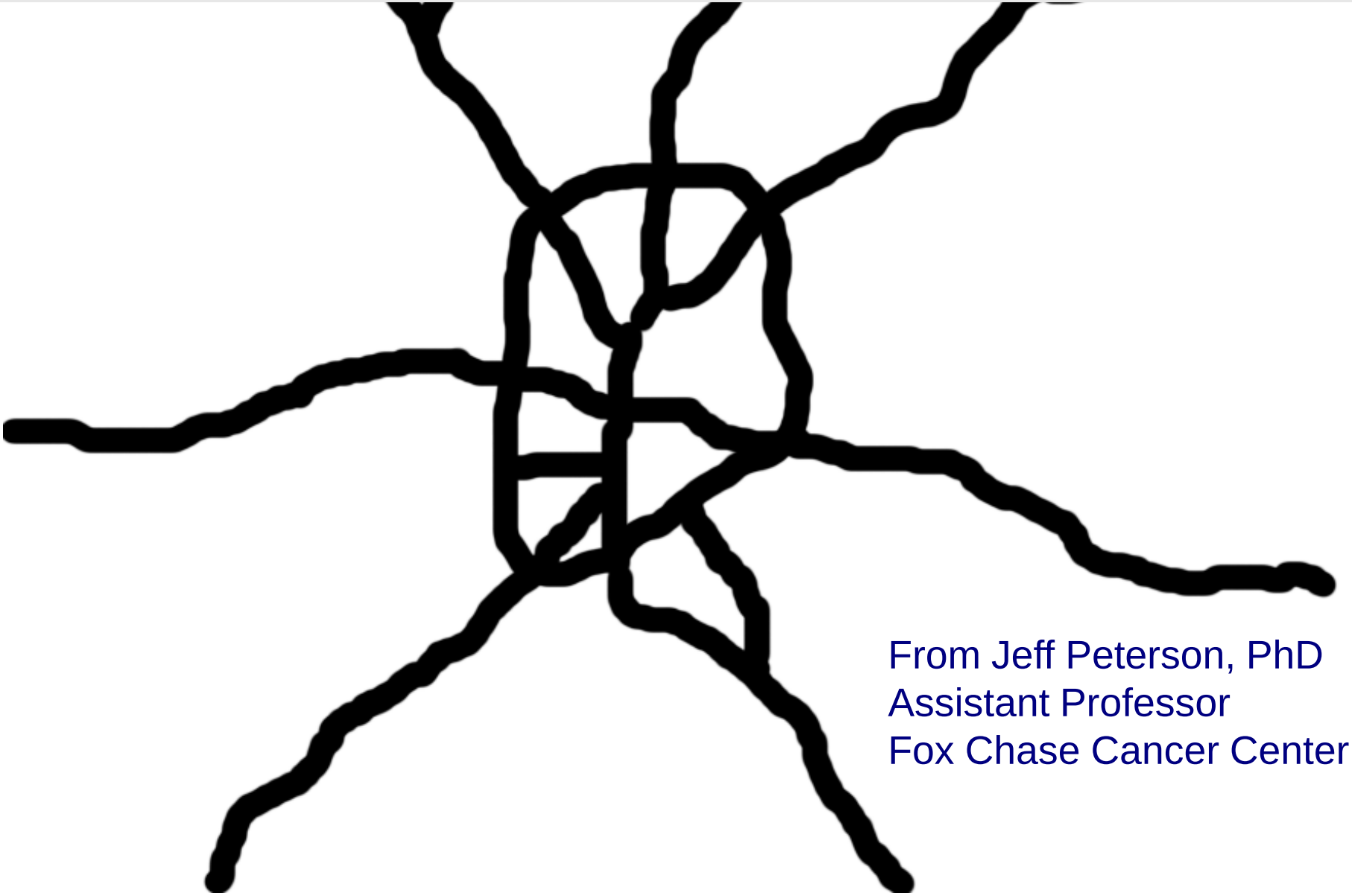
Cost per Human Genome



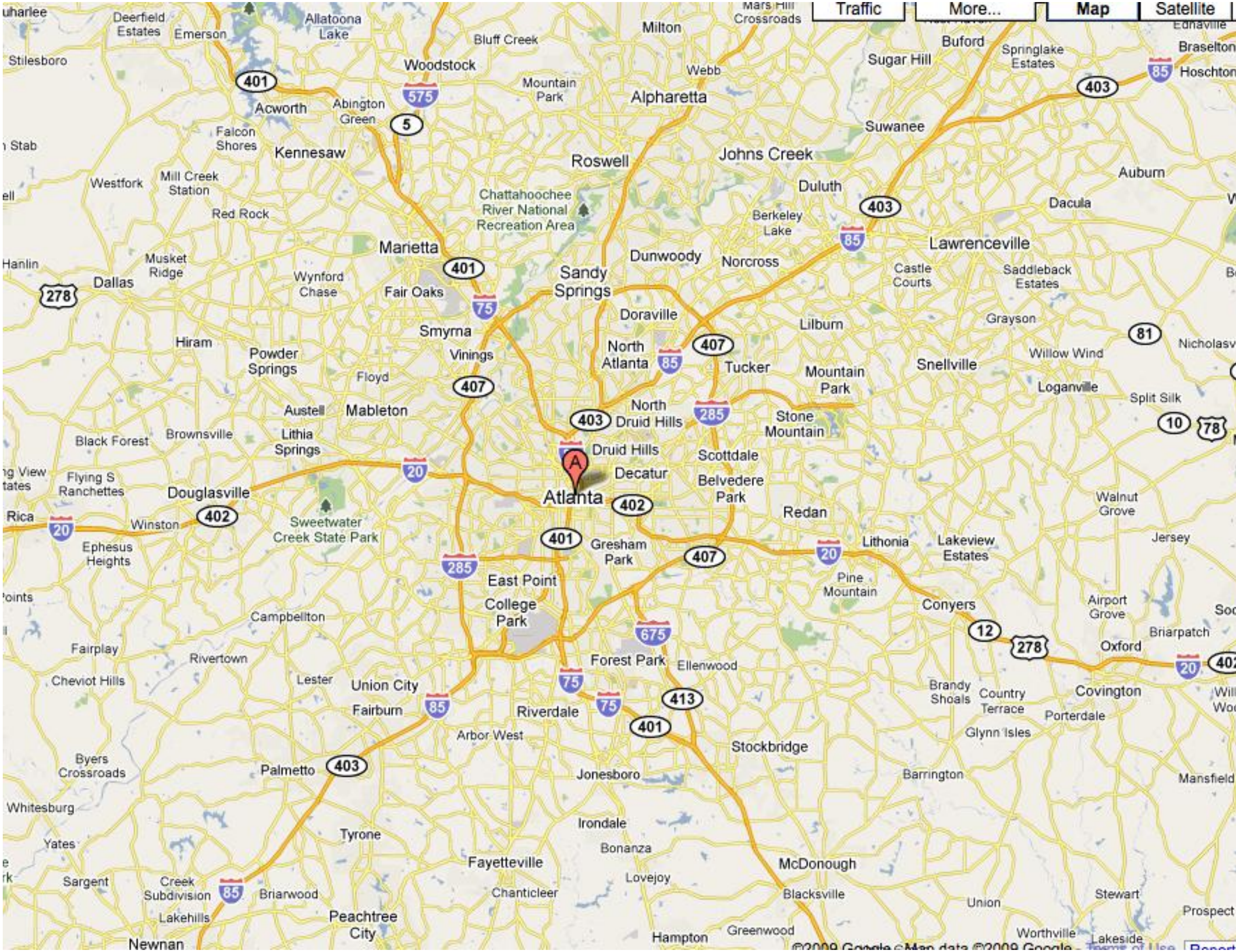
Capability, ease of use, and cost improvements make life science tools realistic for applied use

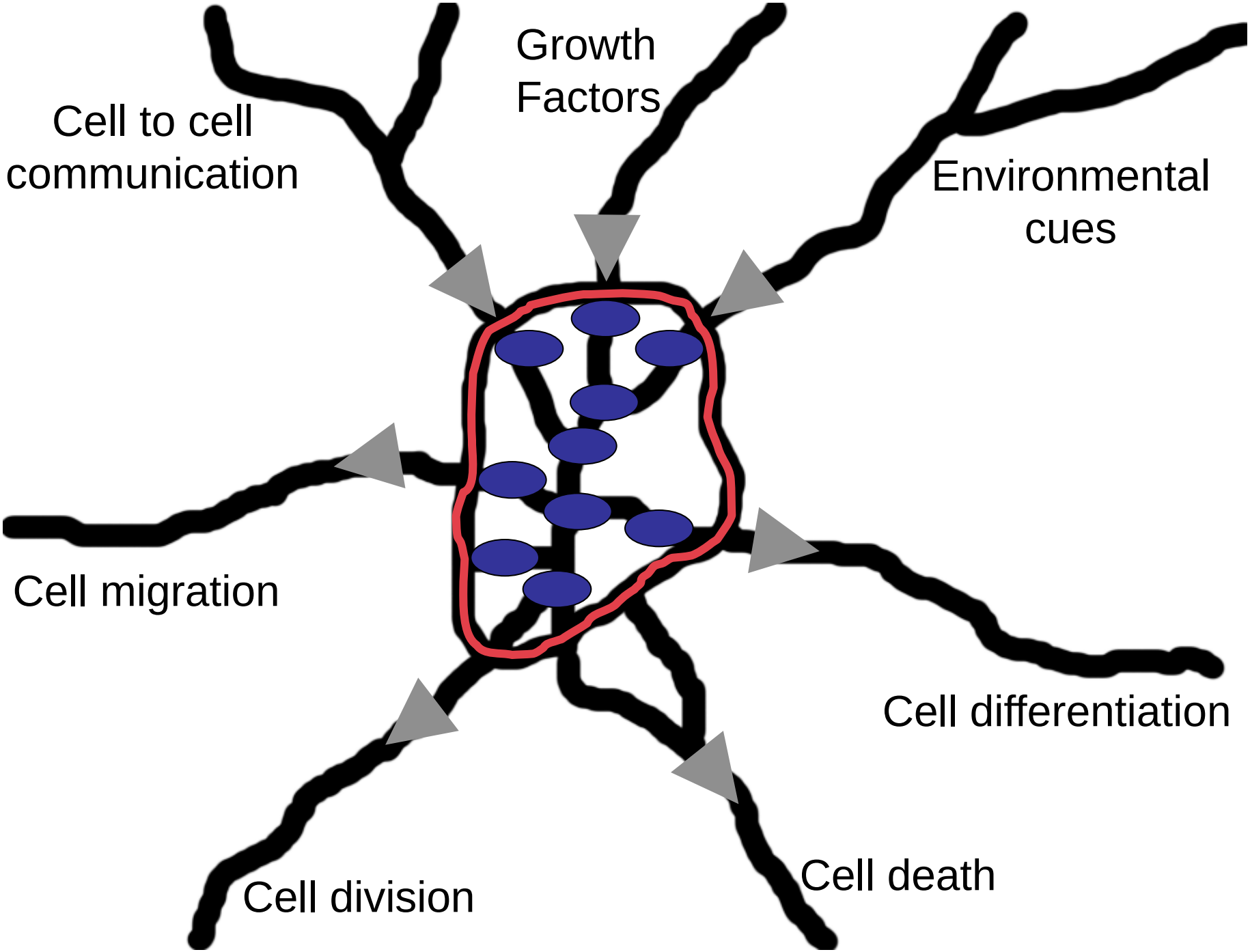
life technologies™

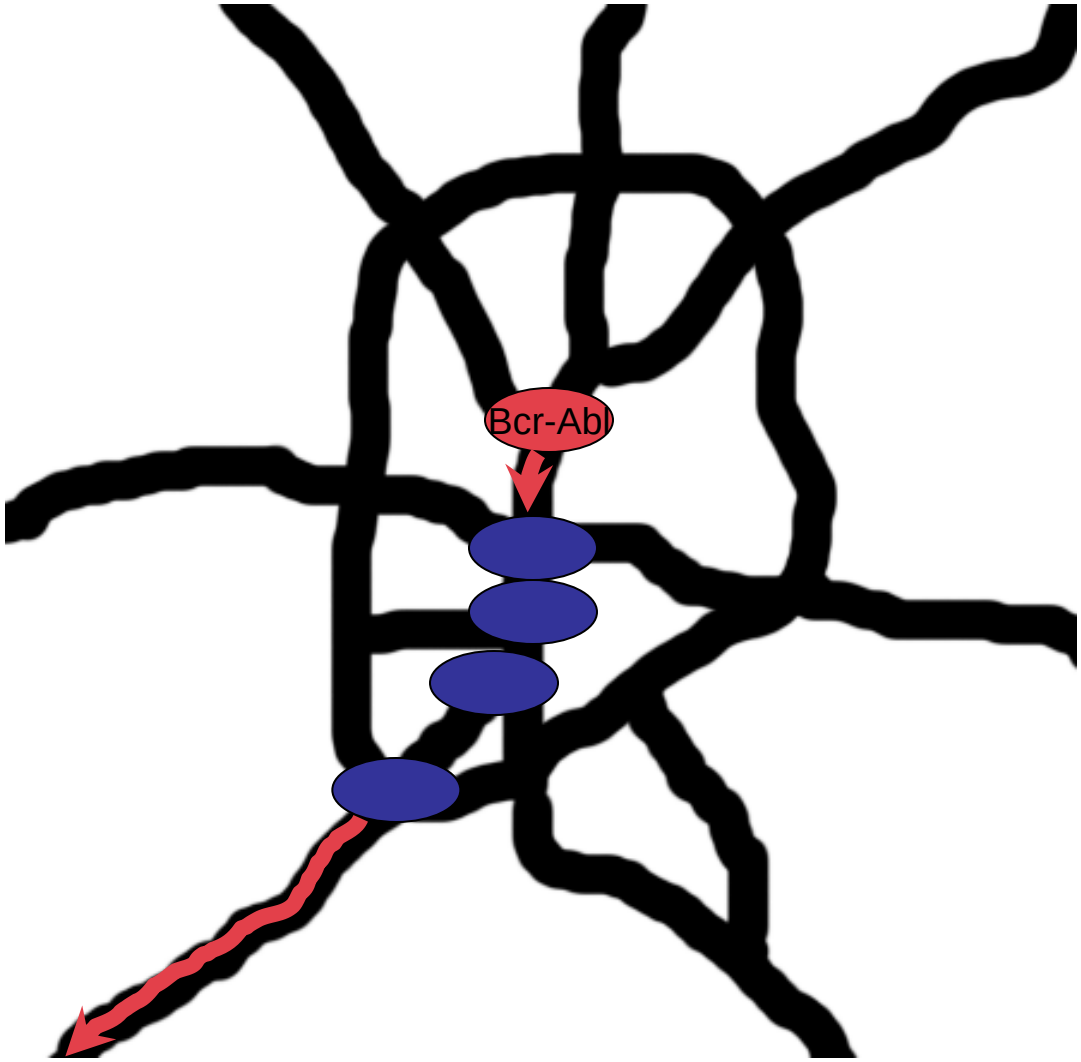
Cancer Signaling Perhaps Another Reason Why it is Hard to Cure Ovarian Cancer!



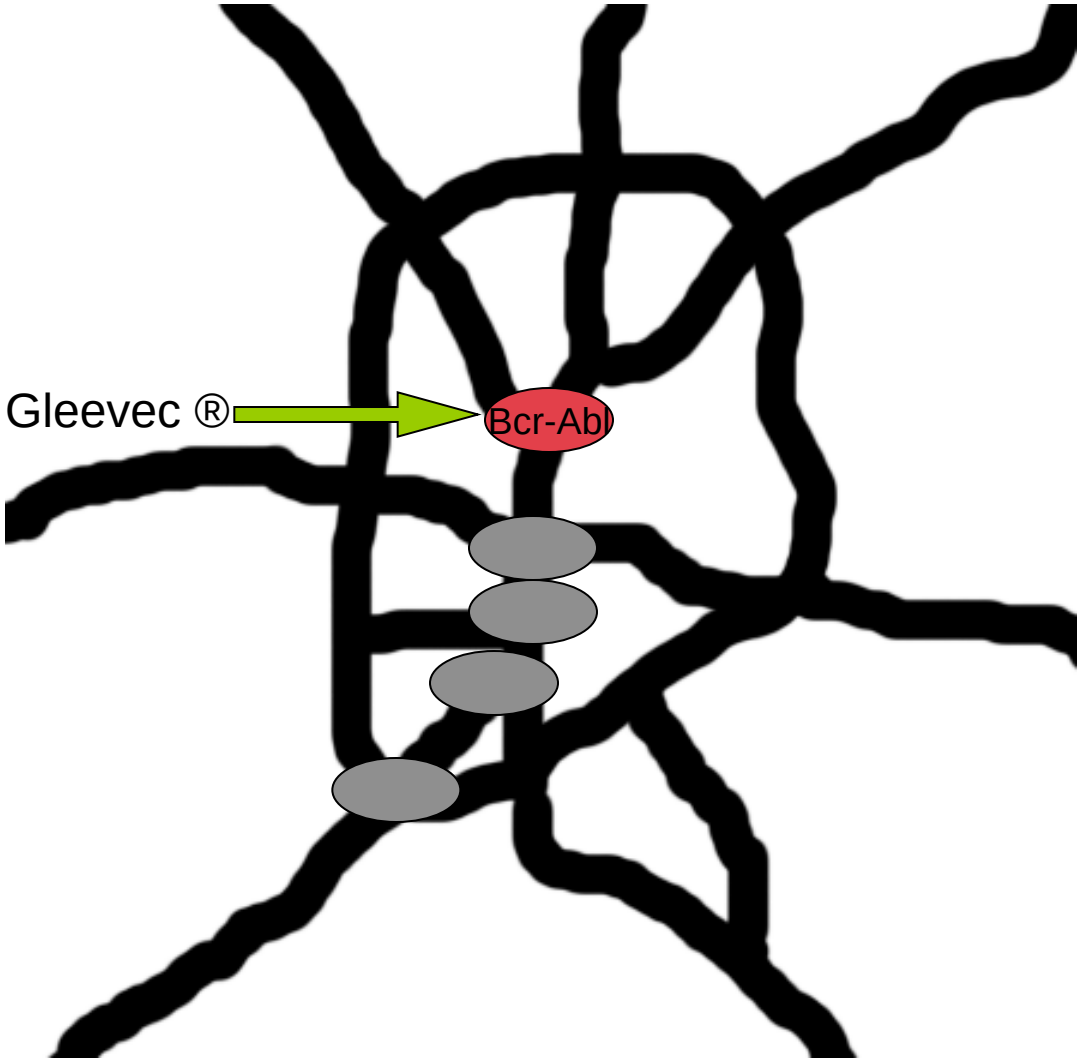
From Jeff Peterson, PhD
Assistant Professor
Fox Chase Cancer Center


Traffic
More...
Map
Satellite
Deerfield Estates
Emerson
Allatoona Lake
Bluff Creek
Milton
Mars Hill Crossroads
Buford
Springlake Estates
Braselton
Hoschton
Stilesboro
401
Woodstock
575
Mountain Park
Webb
Sugar Hill
Alpharetta
403
85
Acworth
Abington Green
5
Suwanee
Falcon Shores
Kennesaw
Roswell
Johns Creek
Westfork
Mill Creek Station
Chattahoochee River National Recreation Area
Duluth
Auburn
Red Rock
Berkeley Lake
Dacula
Marietta
Lawrenceville
Hanlin
Musket Ridge
Dunwoody
Norcross
Castle Courts
Saddleback Estates
Dallas
Wynford Chase
Fair Oaks
75
Sandy Springs
278
Doraville
Grayson
Smyrna
Lilburn
81
Hiram
Powder Springs
Vinings
North Atlanta
407
Tucker
Nicholasville
Floyd
Mountain Park
Snellville
Willow Wind
Loganville
Split Silk
Austell
Mableton
North Druid Hills
285
Stone Mountain
10
78
Black Forest
Brownsville
Lithia Springs
Druid Hills
Scottdale
Flying S Ranchettes
Douglasville
20
Decatur
Belvedere Park
Walnut Grove
Atlanta
402
Redan
Rica
Winston
Sweetwater Creek State Park
Ephesus Heights
Gresham Park
Lithonia
Lakeview Estates
Jersey
East Point
Pine Mountain
College Park
Campbellton
Conyers
Airport Grove
12
Briarpatch
675
Fairplay
Rivertown
Forest Park
Ellenwood
Oxford
Cheviot Hills
Lester
Union City
413
Brandy Shoals
Country Terrace
Covington
Fairburn
Riverdale
Porterdale
Arbor West
Glynn Isles
Stockbridge
Byers Crossroads
Palmetto
Jonesboro
Barrington
Mansfield
Whitesburg
Irondale
Yates
Tyrone
Bonanza
Fayetteville
McDonough
Sargent
Creek Subdivision
Briarwood
Lovejoy
Blacksville
Stewart
Lakehills
Peachtree City
Chanticleer
Union
Prospect
Newnan
Hampton
Greenwood
Worthville
Lakeside

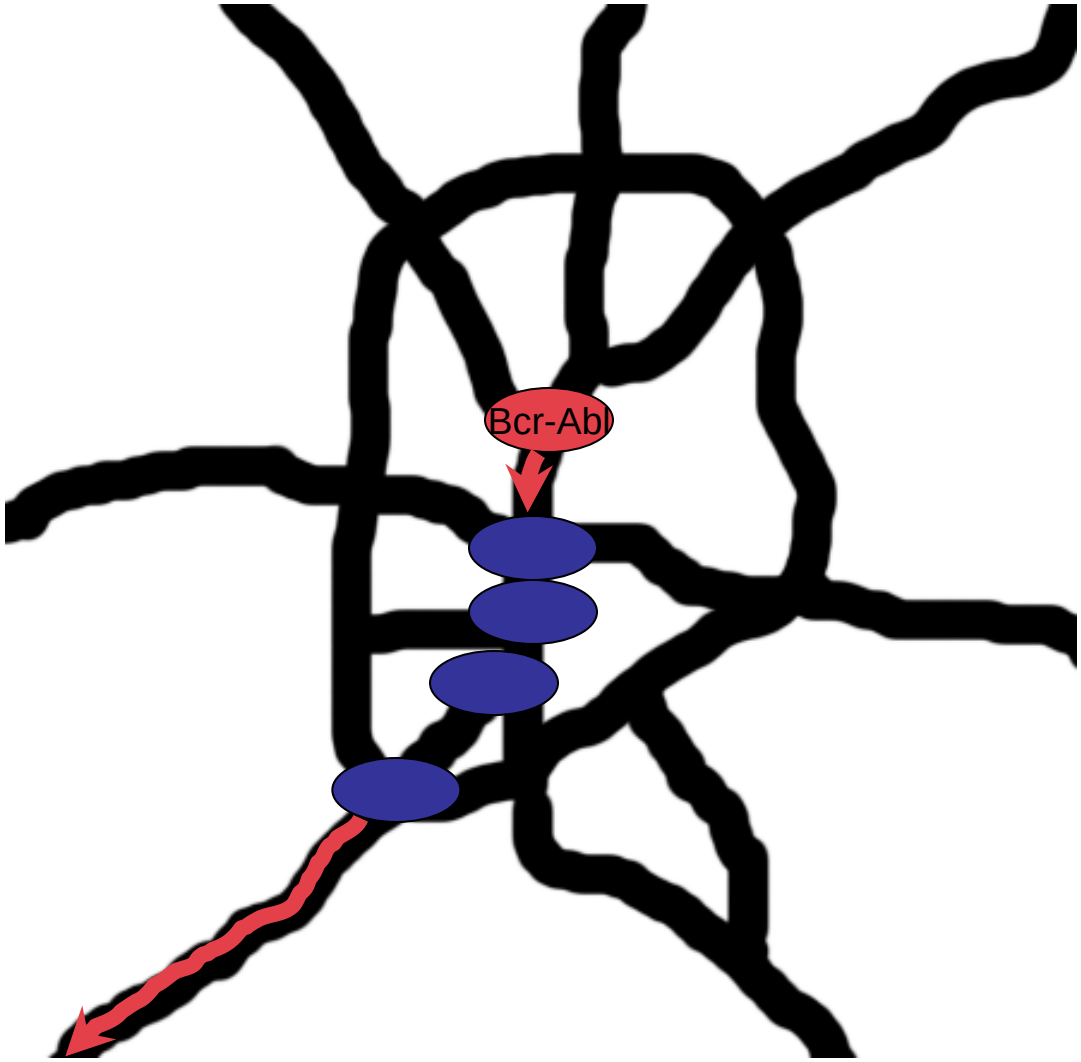

Growth Factors
Cell to cell communication
Environmental cues
Cell migration
Cell differentiation
Cell division
Cell death



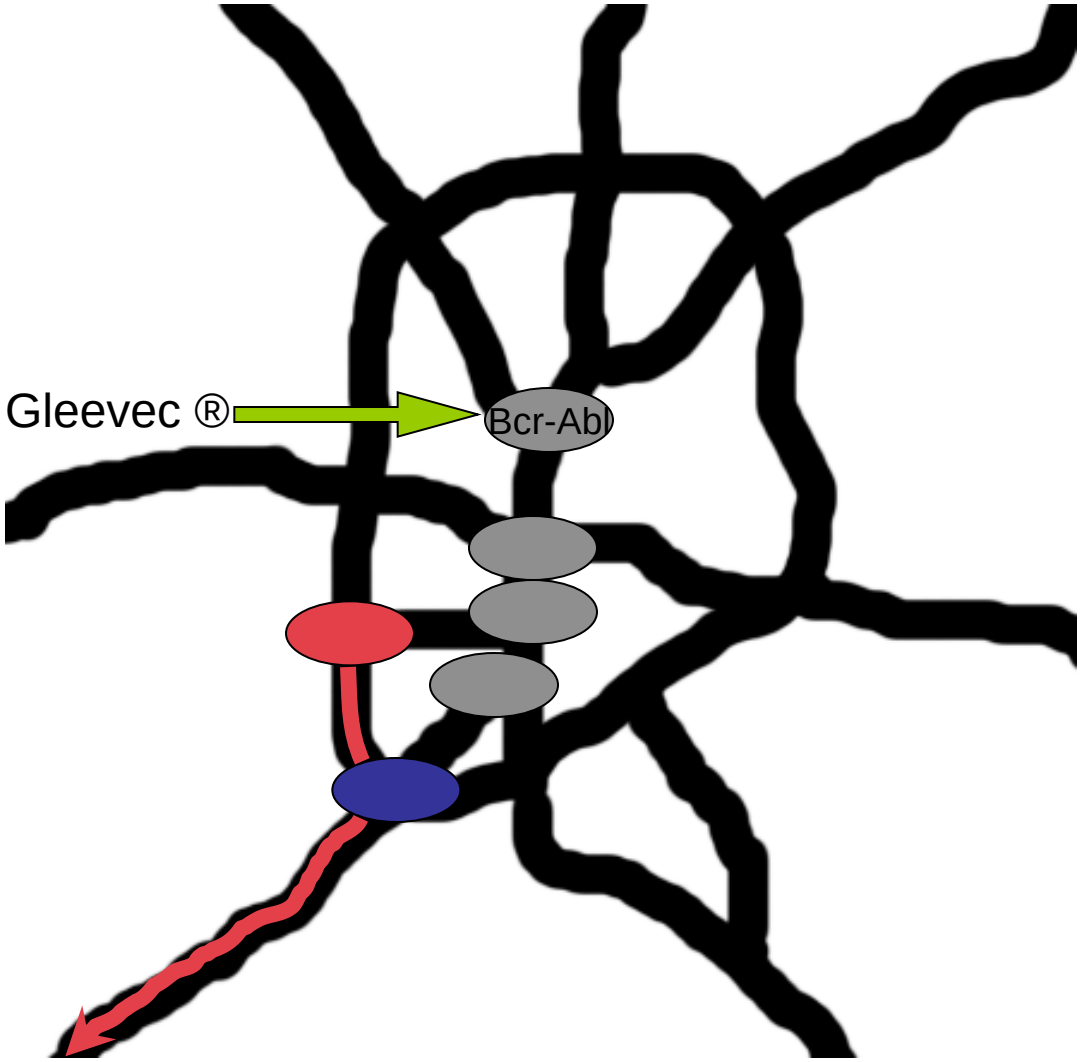
Cell division



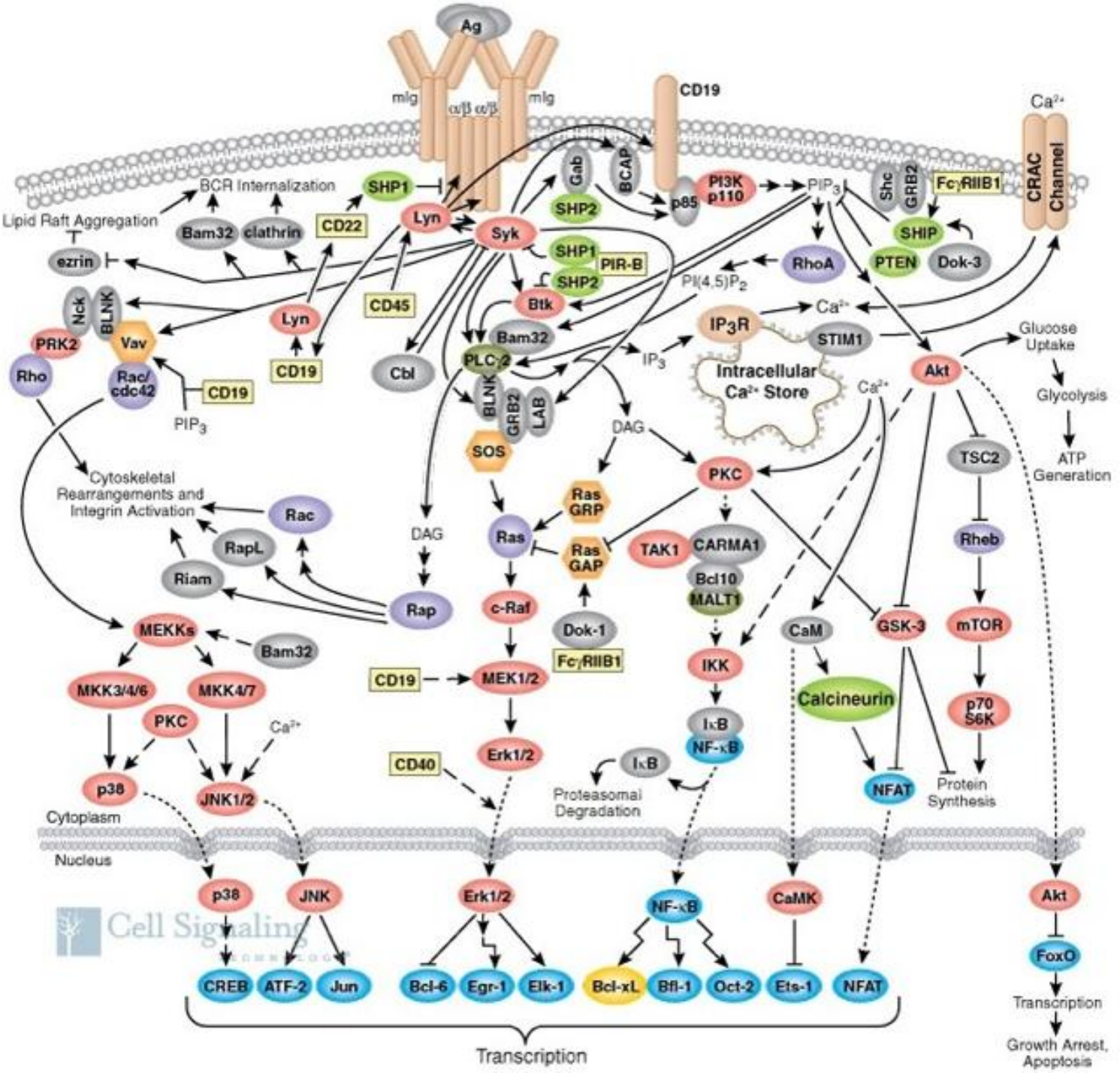
Cell division



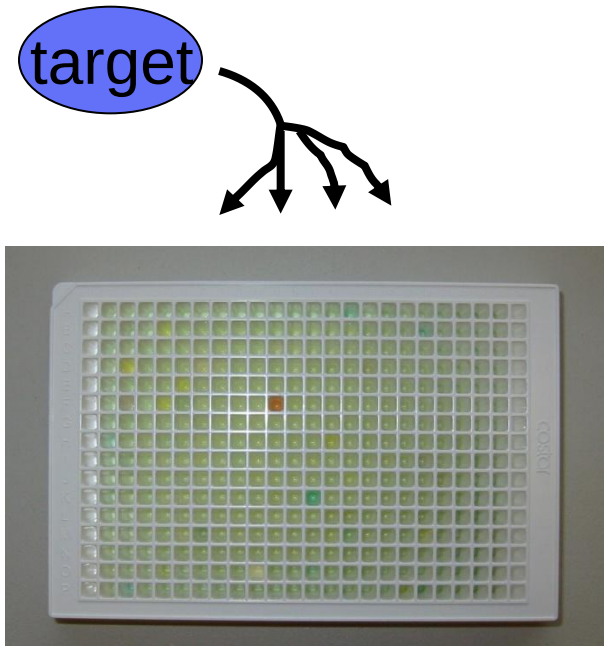
Cell division



Cell division


Ag
mIg
α/β ω/β
mIg
CD19
Ca2+
CRAC Channel
BCR Internalization
Lipid Raft Aggregation
SHP1
Gab
BCAP
PI3K p110
p85
PIP3
Shc
GRB2
FcγRIIB1
Bam32
clathrin
CD22
Lyn
Syk
SHP2
SHIP
ezrin
SHP1
PIR-B
SHP2
RhoA
PTEN
Dok-3
PI(4,5)P2
Nck
BLNK
Btk
Ca2+
PRK2
Vav
Lyn
CD45
Bam32
IP3R
STIM1
Glucose Uptake
Rho
Rac/ cdc42
CD19
CD19
Cbl
PLC-γ2
IP3
Intracellular Ca2+ Store
Akt
Glycolysis
PIP3
BLNK
GRB2
LAB
DAG
Ca2+
SOS
PKC
TSC2
ATP Generation
Cytoskeletal Rearrangements and Integrin Activation
Rac
Ras GRP
Ras
TAK1
CARMA1
Rheb
RapL
DAG
Ras GAP
Bcl10
MALT1
Riam
Rap
c-Raf
Dok-1
FcγRIIB1
CaM
GSK-3
mTOR
MEKKs
Bam32
CD19
MEK1/2
IKK
MKK3/4/6
MKK4/7
Calcineurin
p70 S6K
PKC
Ca2+
IκB
NF-κB
p38
JNK1/2
CD40
Erk1/2
IκB
Proteasomal Degradation
NFAT
Protein Synthesis
Cytoplasm
Nucleus
p38
JNK
Erk1/2
NF-κB
CaMK
Akt
FoxO
Transcription
Growth Arrest, Apoptosis
CREB
ATF-2
Jun
Bcl-6
Egr-1
Elk-1
Bcl-xL
Bfl-1
Oct-2
Ets-1
NFAT
Transcription

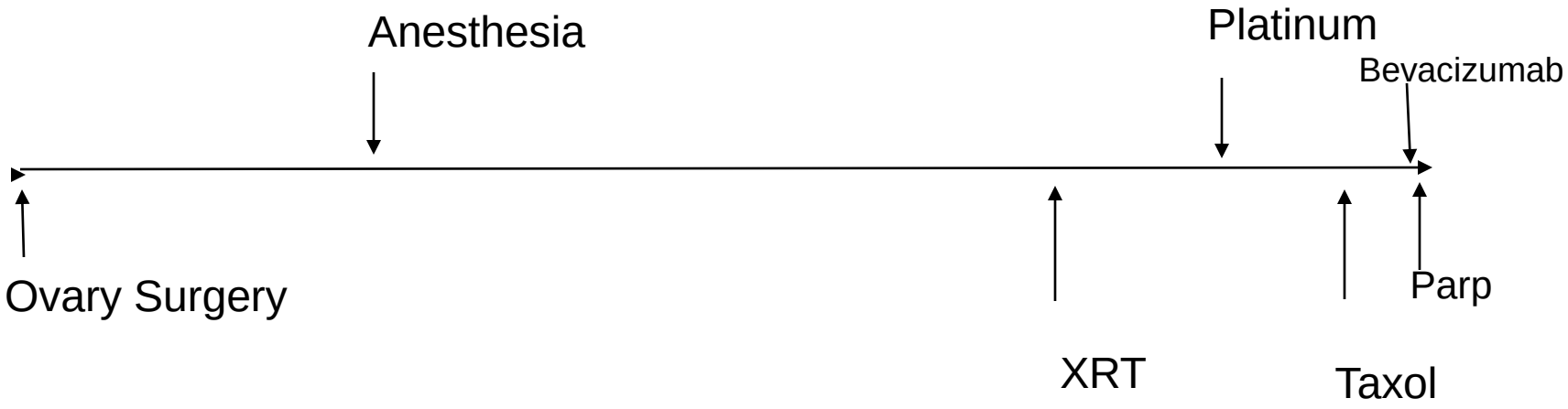
Moving from targets to therapies



Events in History

- 100,000 BC-Homo Sapiens
- December 24, 1809 Ephraim McDowell
- October 1846-Ether Anesthesia
- 1950's Radioactive Gold and Cobalt for ovary cancer
- 1953-Structure of DNA
- 1960's single agent chlorambucil and cyclophosphamide
- 1976 Cisplatin in ovarian cancer
- 1989 Taxol in ovarian cancer
- 1994 BRCA-Identified
- 1995 BRCA-2 Identified
- 2001 Report of Sequencing Human Genome
- 2005-Bevacizumab in ovarian cancer
- 2009-Parp inhibitors in ovarian cancer

Timeline


Anesthesia
Platinum
Bevacizumab
Ovary Surgery
XRT
Taxol
Parp

Did You Know

Why is Translational Research Hard?

- Requirements
  - Trained scientists and clinical investigators working as teams
  - Patients willing to participate
  - Funding
  - Often additional regulatory work and regulations
  - Some ideas are not yet ready to translate


FOX CHASE CANCER CENTER
West Building