

Molecular analysis of circulating tumor cells in prostate cancer: moving toward a liquid biopsy and personalized medicine

Edwin M. Posadas, MD FACP
Medical Director, Urologic Oncology Program
Samuel Oschin Comprehensive Cancer Institute
Cedars-Sinai Medical Center

February 10, 2014



CEDARS-SINAI

LEADING THE QUEST

cedars-sinai.edu

Prostate cancer is a significant health problem

Estimated New Cases*

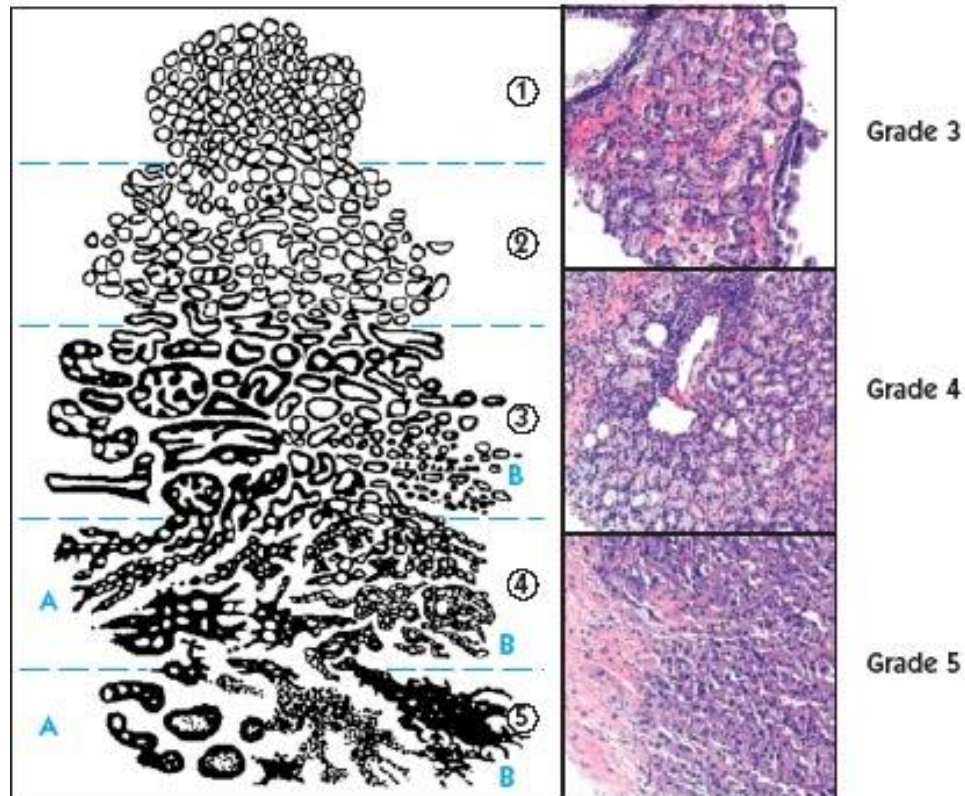
Estimated Deaths

Prostate	233,000	27%
Lung & bronchus	116,000	14%
Colorectum	71,830	8%
Urinary bladder	56,390	7%
Melanoma of the skin	43,890	5%
Kidney & renal pelvis	39,140	5%
Non-Hodgkin lymphoma	38,270	4%
Oral cavity & pharynx	30,220	4%
Leukemia	30,100	4%
Liver & intrahepatic bile duct	24,600	3%
All Sites	855,220	100%

Lung & bronchus	86,930	28%
Prostate	29,480	10%
Colorectum	26,270	8%
Pancreas	20,170	7%
Liver & intrahepatic bile duct	15,870	5%
Leukemia	14,040	5%
Esophagus	12,450	4%
Urinary bladder	11,170	4%
Non-Hodgkin lymphoma	10,470	3%
Kidney & renal pelvis	8,900	3%
All Sites	310,010	100%

Our PATHOLOGIC description of prostate cancer has NOT evolved

FIGURE 1. Gleason Grading System Diagram



Prostate cancer is classified relative to therapy: Clinical states model (2000)

*Adapted from HI Scher, Urology
2000*

Urology / Radiation Oncology

Medical Oncology

Localized

Rising PSA

Clinical
Metastases,
Non-
Castrate

Clinical
Metastases,
Castrate

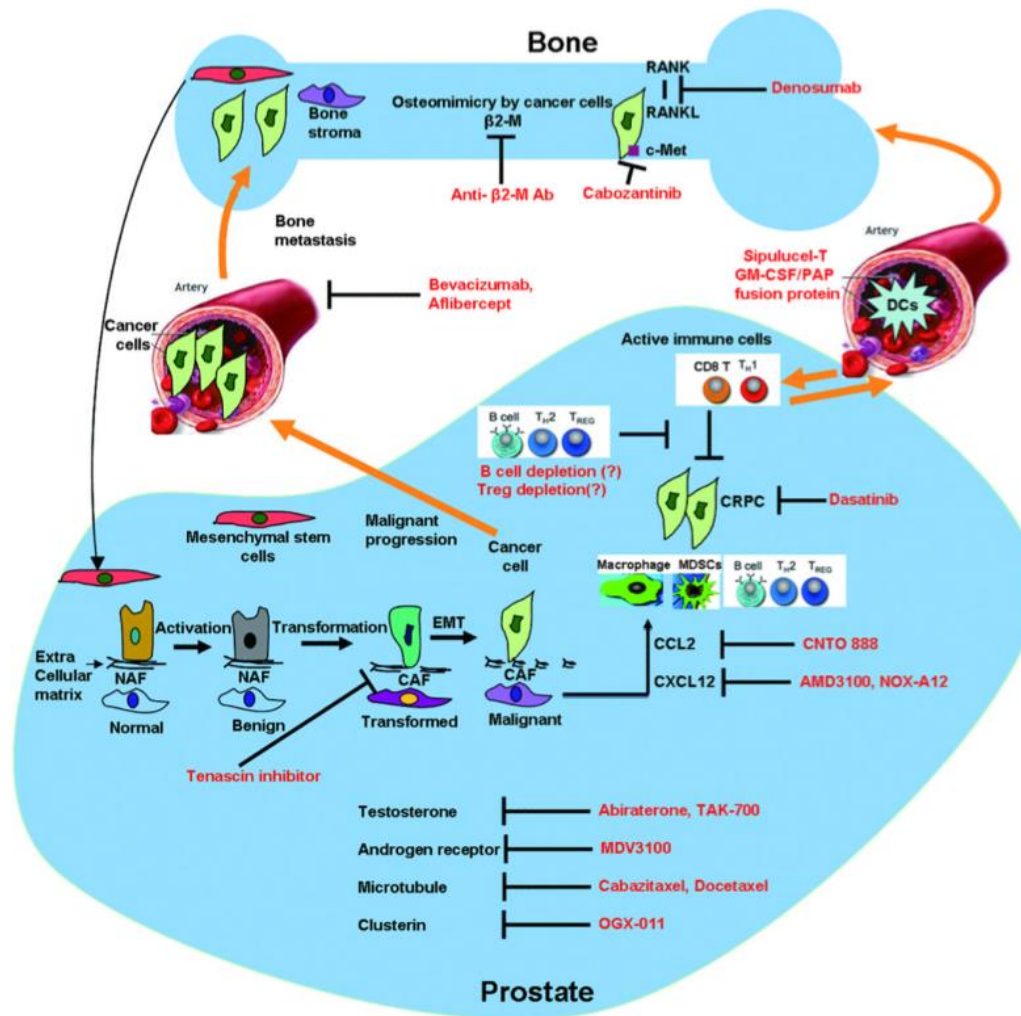
Death from prostate cancer



CEDARS-SINAI

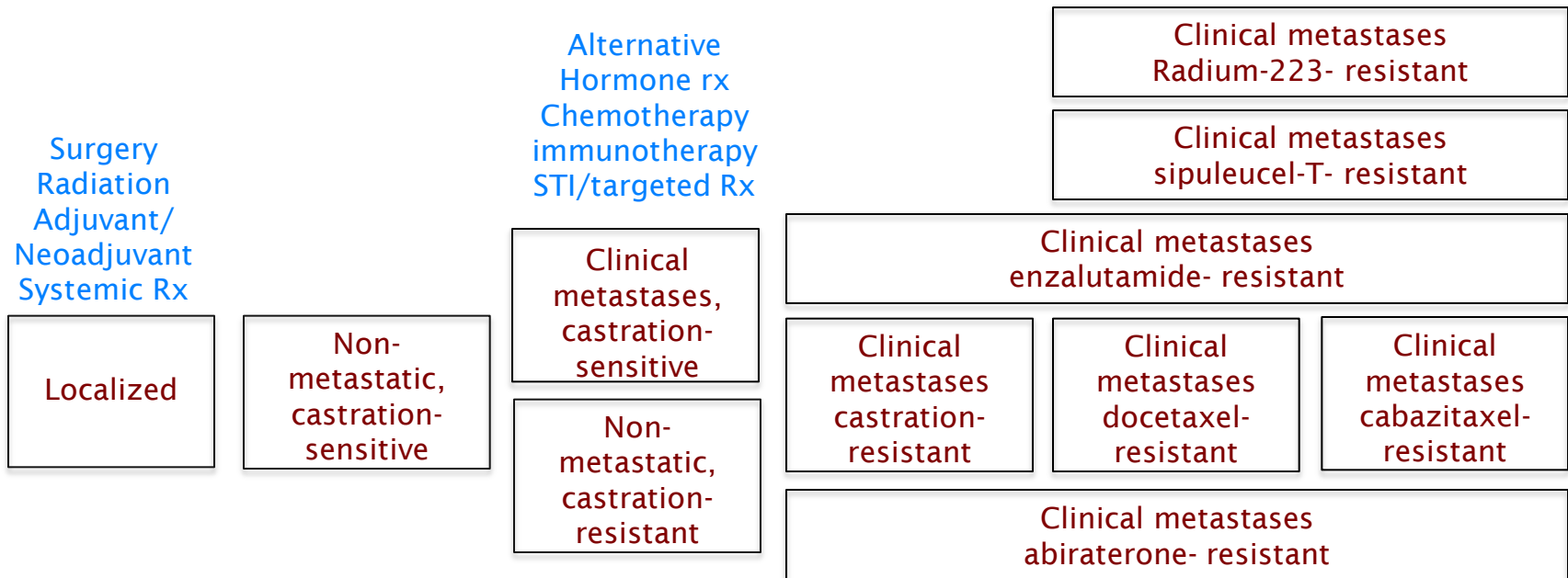
UROLOGIC ONCOLOGY PROGRAM

New targets and approaches in prostate cancer



M Gururajan, E Posadas, L Chung. Trans Androl 2012

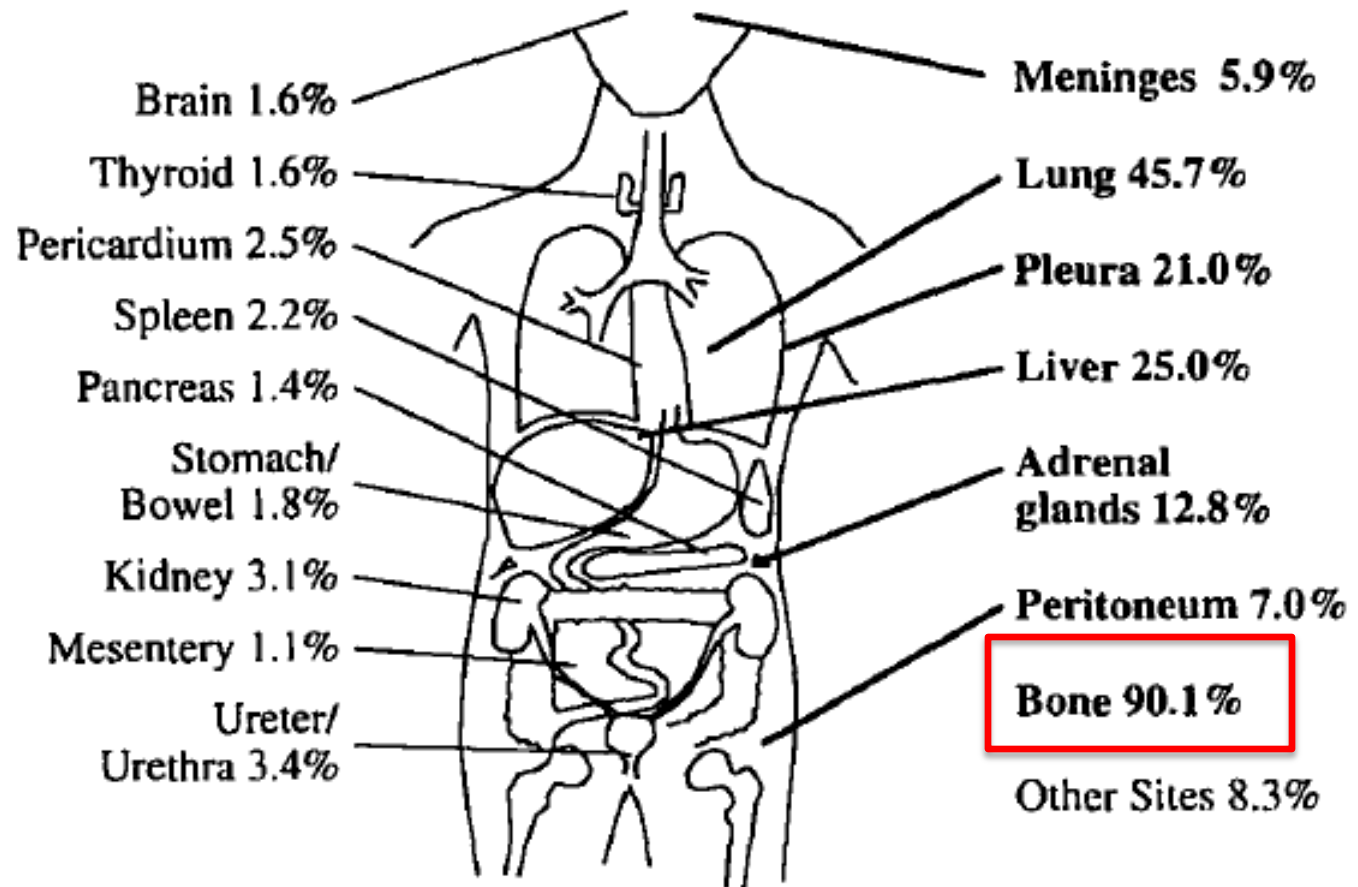
Prostate cancer is STILL classified by therapy: Clinical states model (2014)



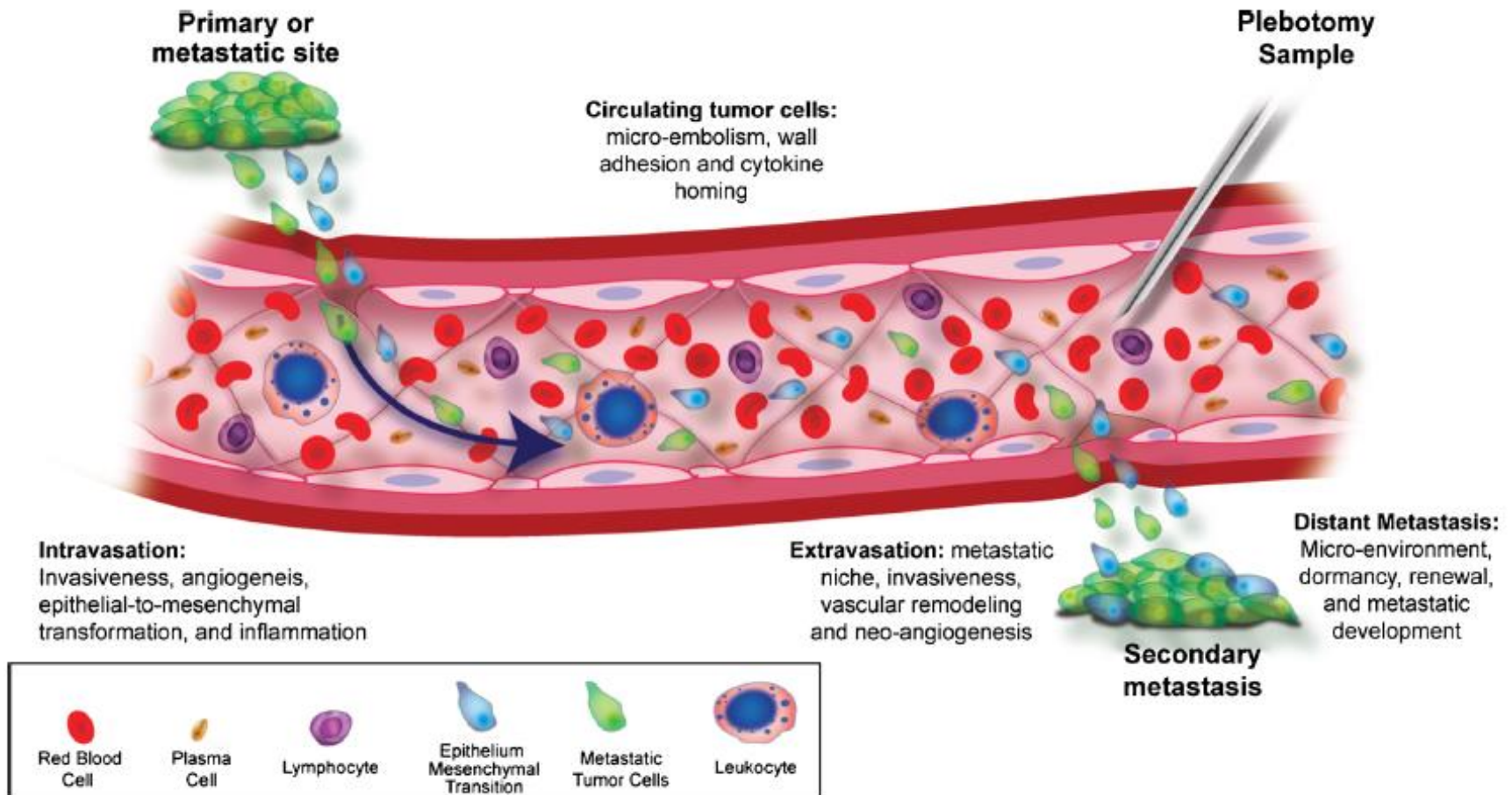
Death from prostate cancer



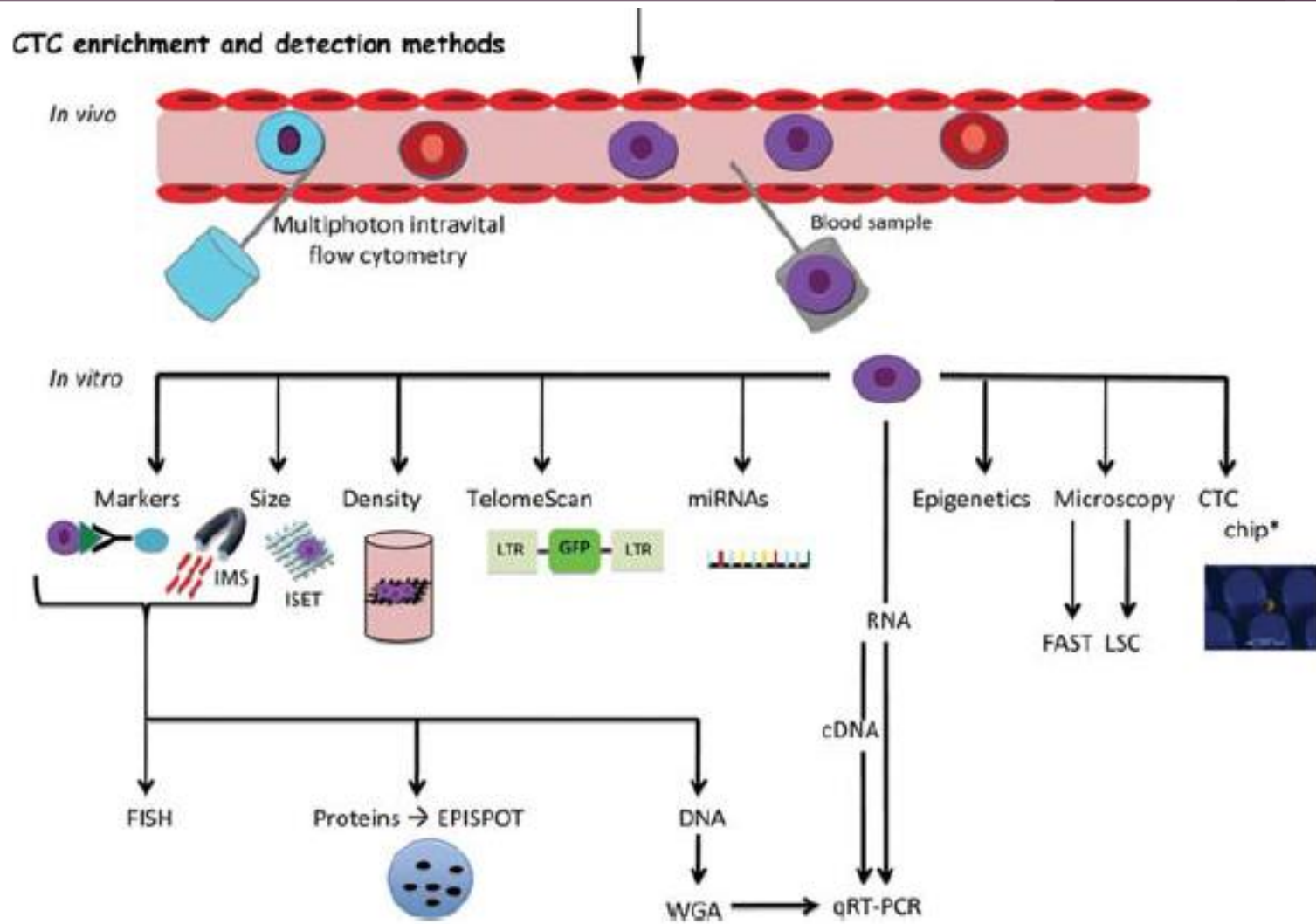
Tissue is difficult to obtain in prostate cancer



Circulating tumor cells (CTCs)- easily accessible prostate cancer cells

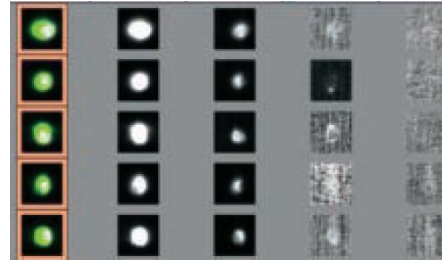
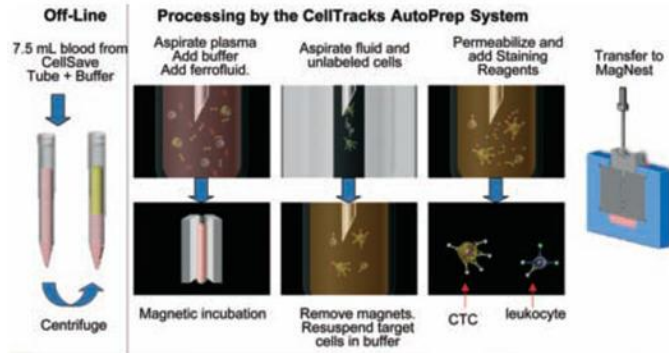


CTC Technologies

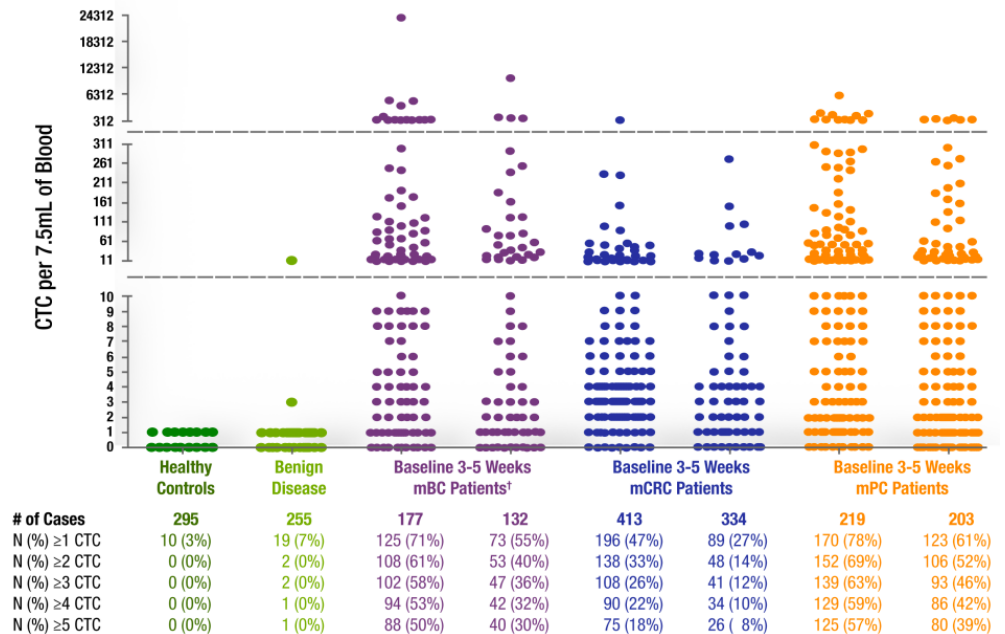


N. Gerges et al., *Br Med Bull.* 2010;94:49-64.

CTC Technologies: CellSearch (Janssen Diagnostics, LLC)

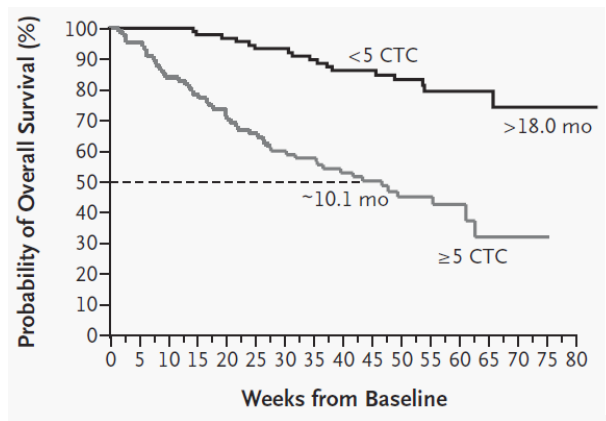


Frequency of CTCs in Healthy Controls vs Patients with Metastatic Breast (mBC), Colorectal (mCRC), and Prostate* (mPC) Cancers²



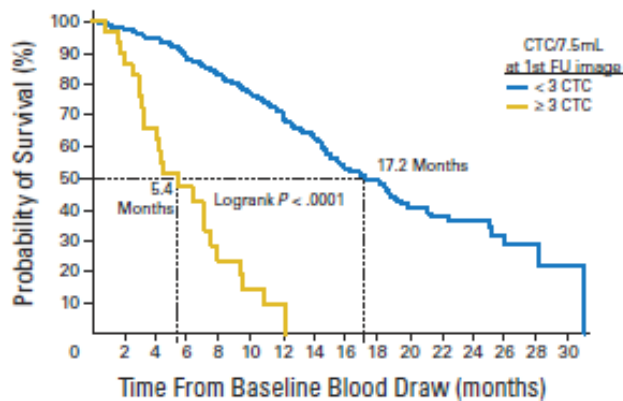
CTCs as a prognostic tool

Breast cancer



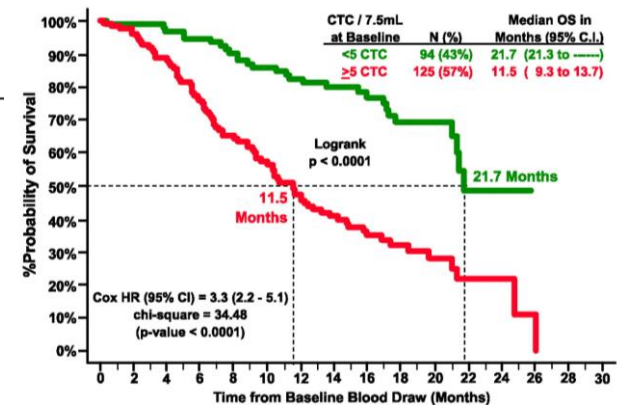
Cristofanilli, M.
et al., *N Eng J Med* 2004

Colon cancer



Cohen, SJ. et al.,
J Clin Oncol 2008

Prostate cancer



de Bono, JS. et al., *Clin Cancer Res* 2008

Beyond Enumeration of CTCs



CEDARS-SINAI

LEADING THE QUEST

cedars-sinai.edu

Could CTCs serve as a liquid biopsy?

RESEARCH BRIEF

Androgen Receptor Signaling in Circulating Tumor Cells as a Marker of Hormonally Responsive Prostate Cancer

David T. Miyamoto^{1,3}, Richard J. Lee^{1,4}, Shannon L. Stott^{2,5}, David T. Ting^{1,4}, Ben S. Wittner¹, Matthew Ulman¹, Malgorzata E. Smas¹, Jenna B. Lord¹, Brian W. Brannigan¹, Julie Trautwein¹, Neil H. Bander⁷, Chin-Lee Wu⁶, Lecia V. Sequist^{1,4}, Matthew R. Smith^{1,4}, Sridhar Ramaswamy^{1,4}, Mehmet Toner^{2,5}, Shyamala Maheswaran^{1,5}, and Daniel A. Haber^{1,4,8}

Androgen Receptor Signaling



IN THE SPOTLIGHT

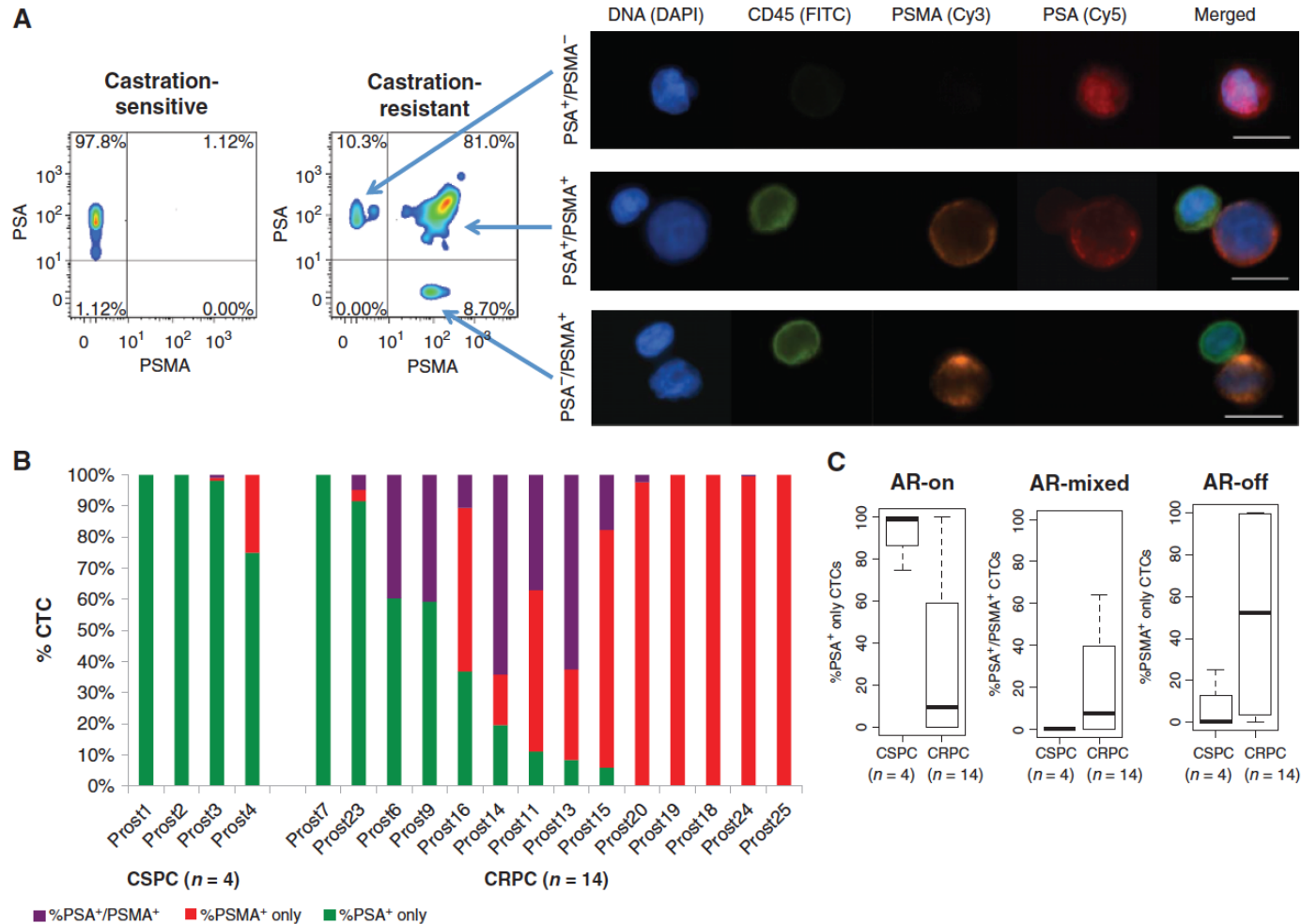
The Potential of Circulating Tumor Cells as a Liquid Biopsy to Guide Therapy in Prostate Cancer

Klaus Pantel¹ and Catherine Alix-Panabières^{2,3,4}

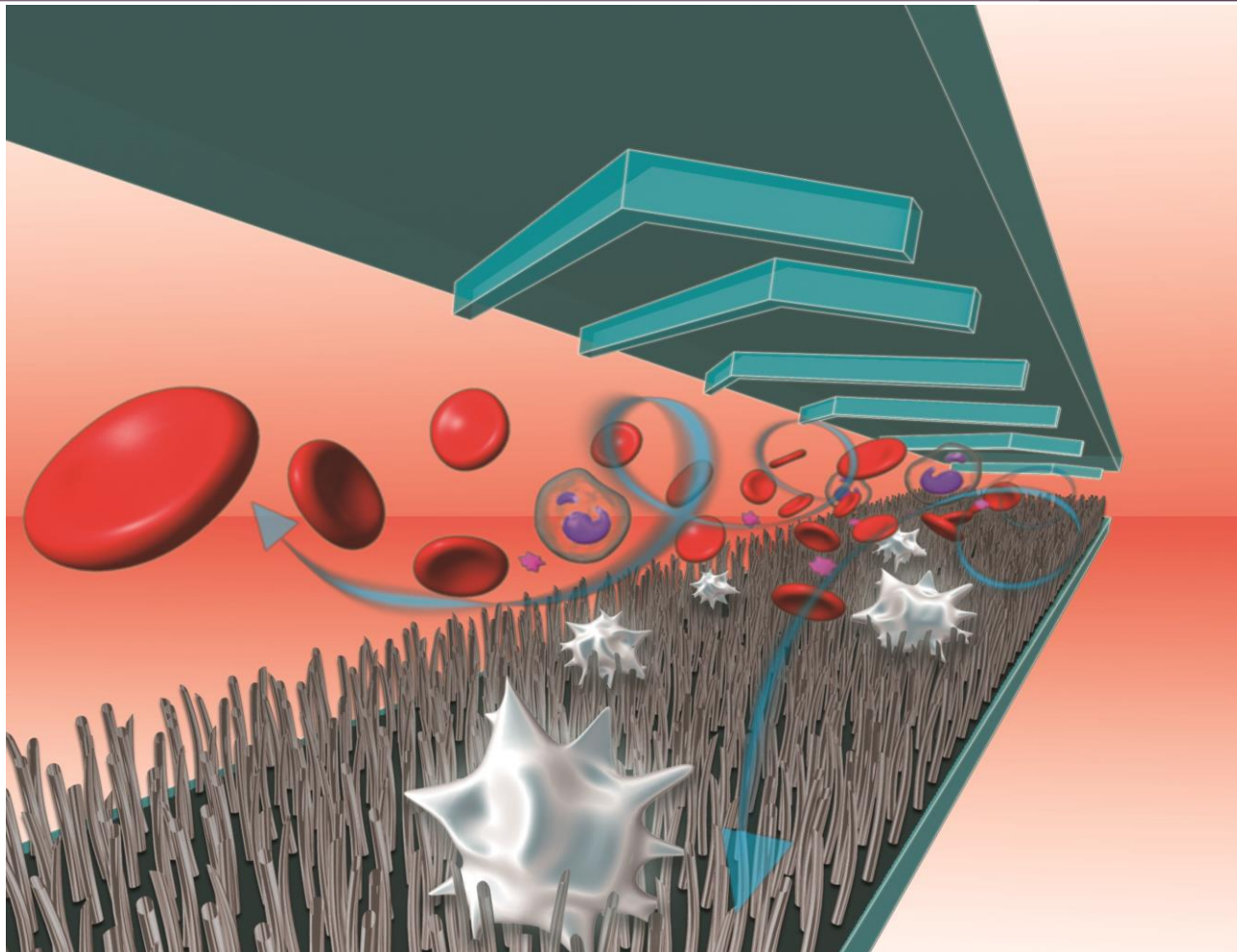
Summary: Miyamoto and colleagues present data that prostate-specific antigen/prostate-specific membrane antigen (PSA/PSMA)-based measurements of androgen receptor (AR) signaling in circulating tumor cells (CTC) enable real-time quantitative monitoring of intratumoral AR signaling. This finding indicates that measuring AR signaling within CTCs may help to guide therapy in metastatic prostate cancer and highlights the use of CTCs as liquid biopsy. *Cancer Discov*; 2(11): 974-5. ©2012 AACR.

Commentary on Miyamoto et al., p. 995 (6).

PSA/PSMA expression of CTCs relates to castration sensitivity



NanoVelcro CTC isolation technology

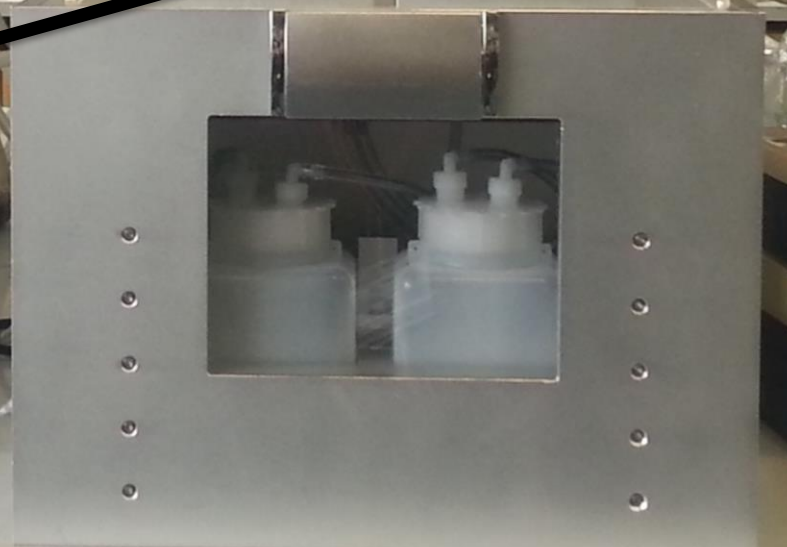
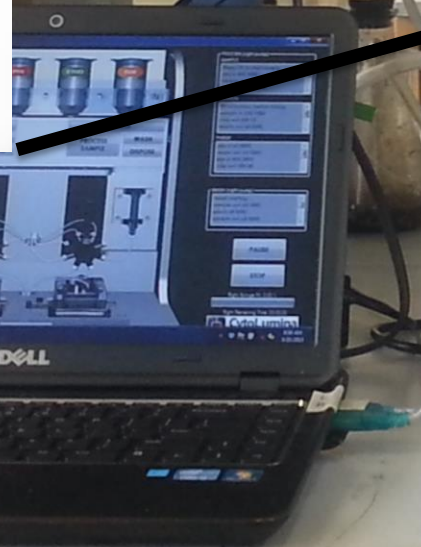
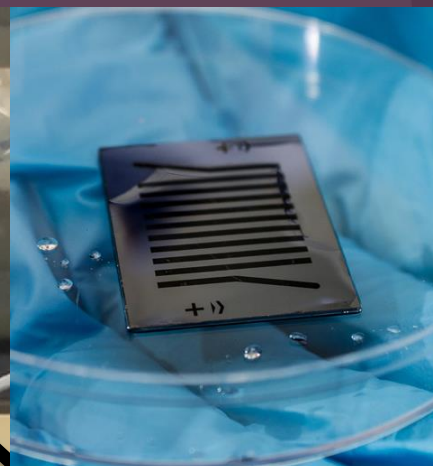
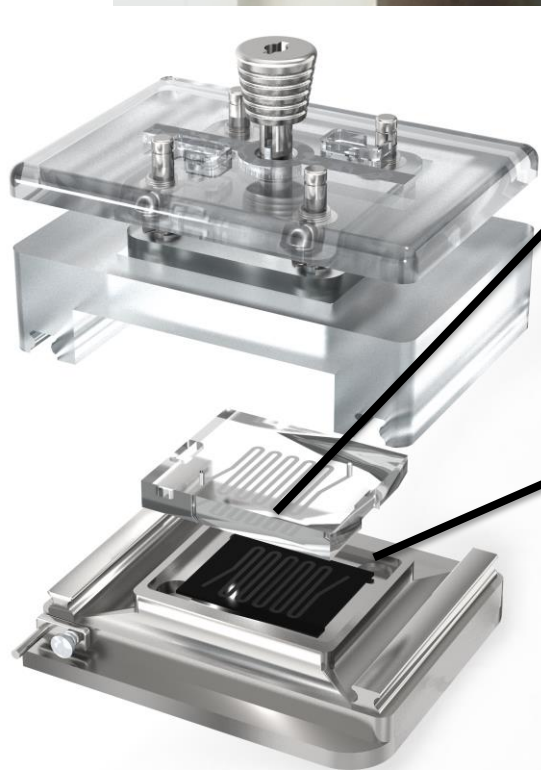


Crump Institute
Molecular Imaging

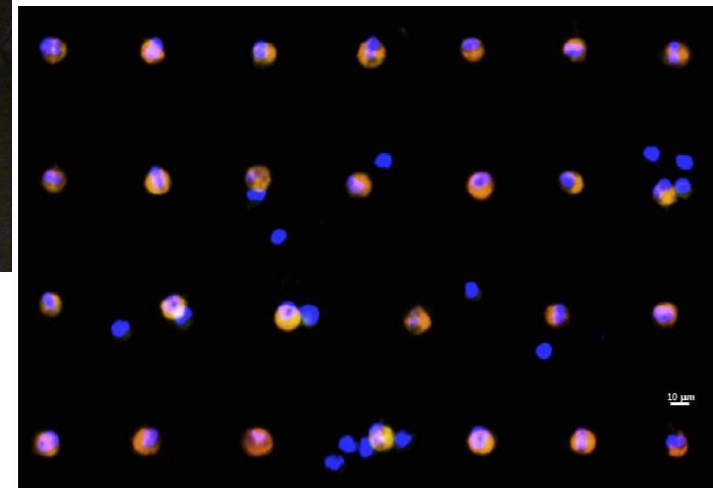
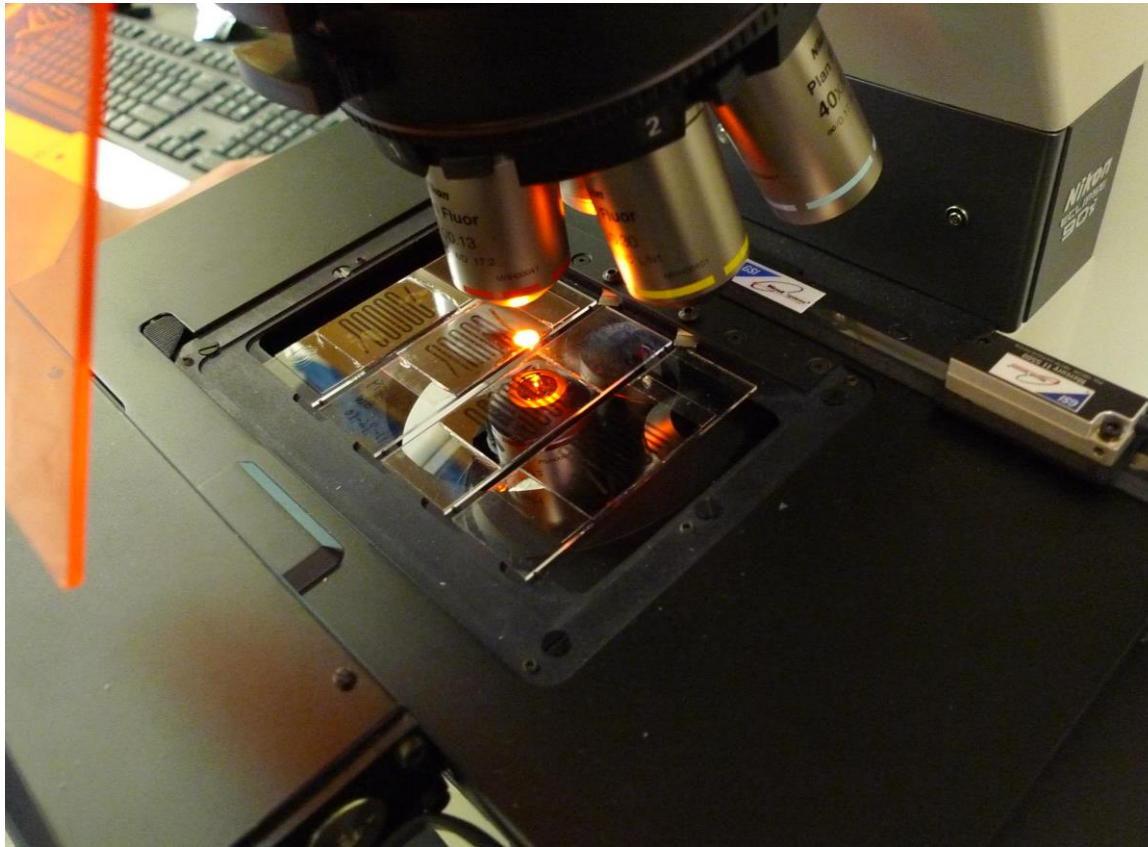


CEDARS-SINAI

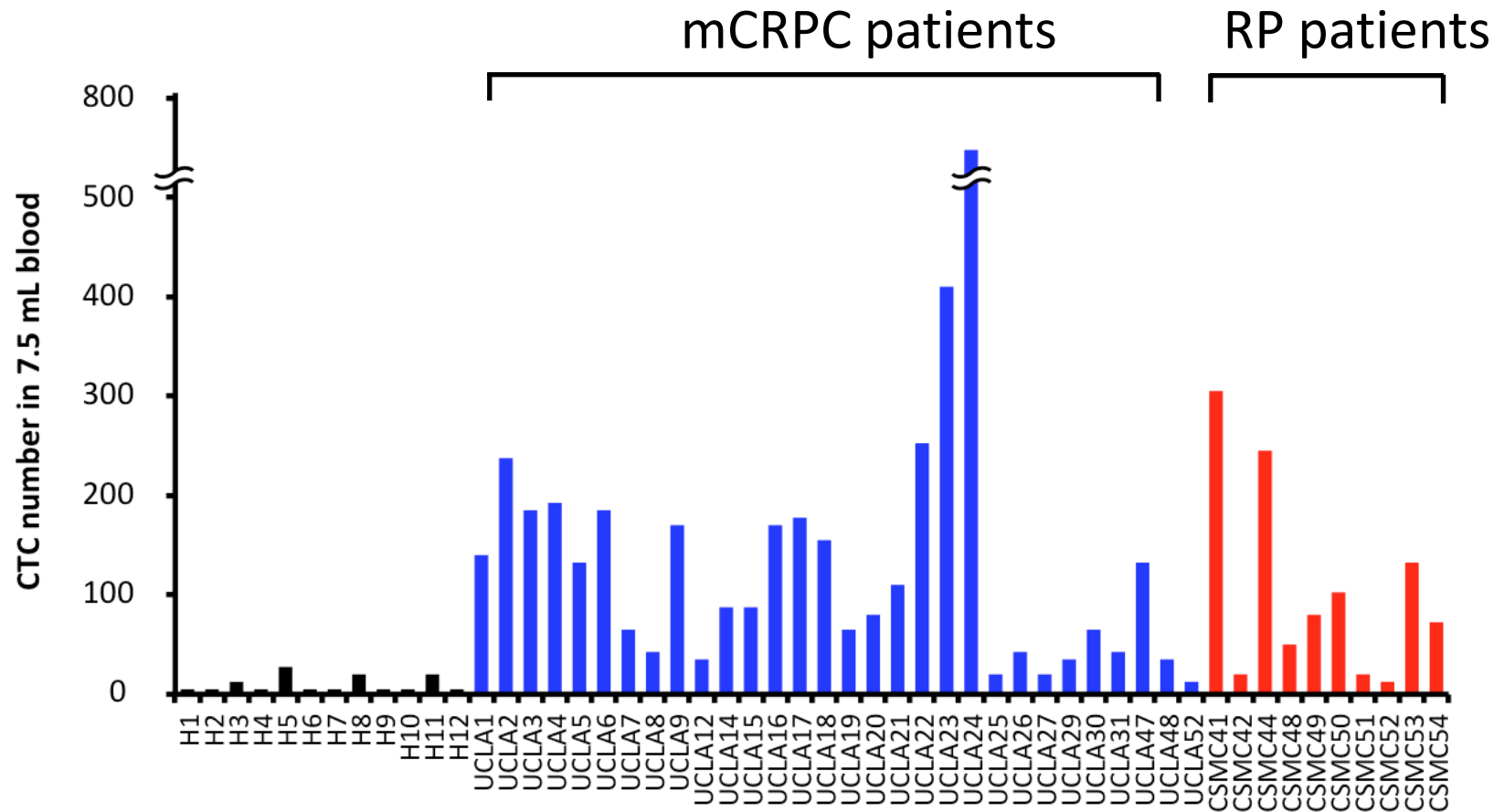
UROLOGIC ONCOLOGY PROGRAM



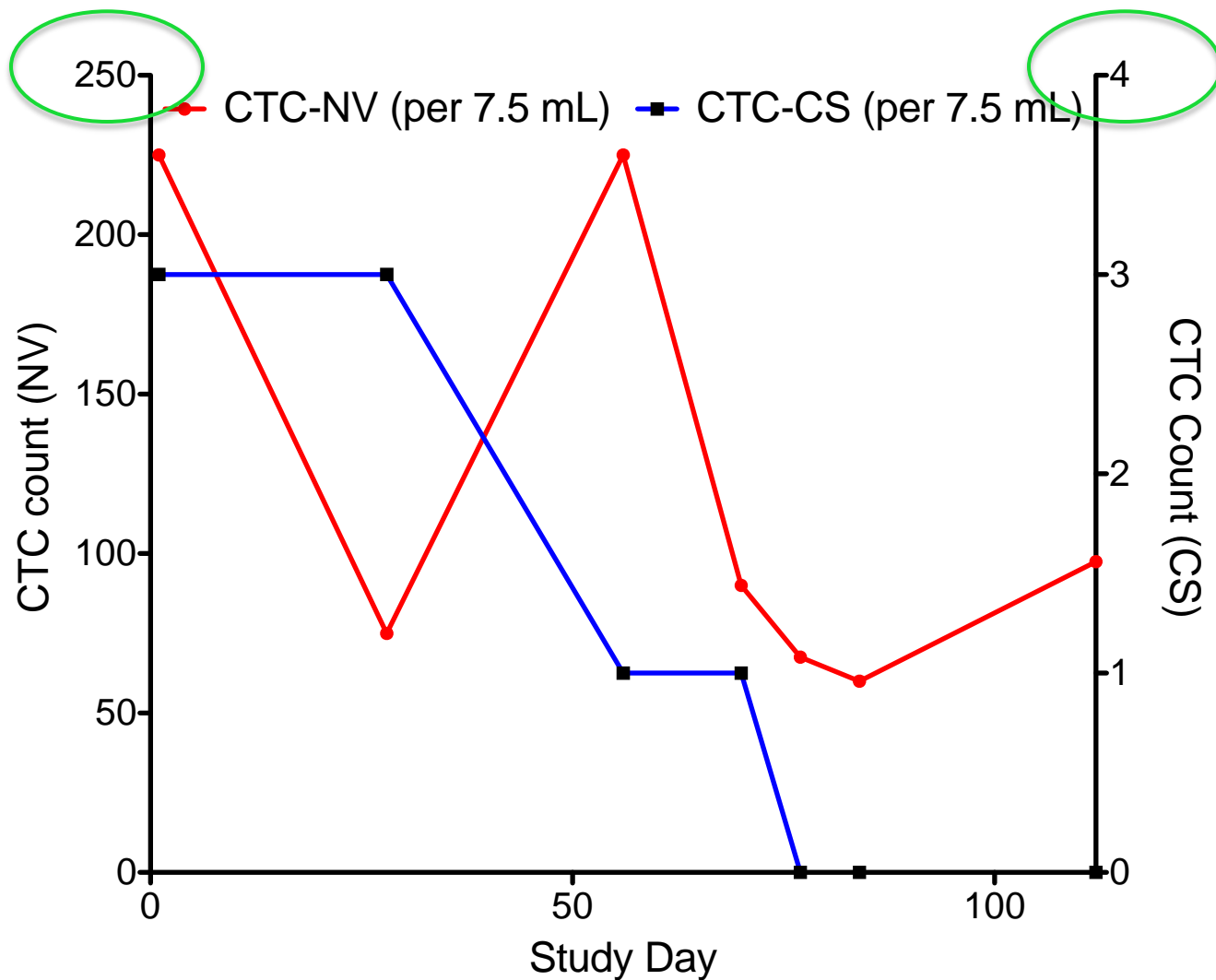
Automatic microscopic scanning for CTCs



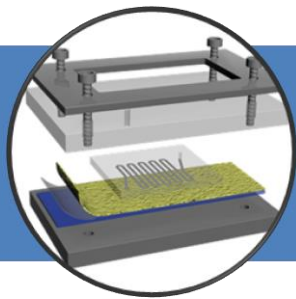
NanoVelcro chip for enumeration in localized PCa patients



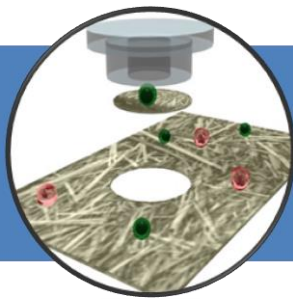
NanoVelcro (NV) vs. CellSearch (CS): advanced mCRPC



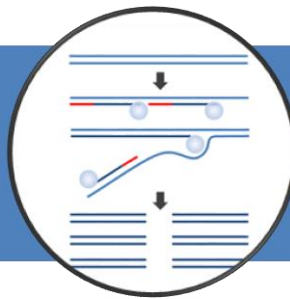
Next generation sequencing in CTCs



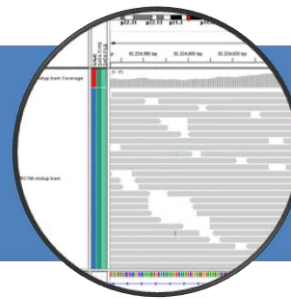
Polymer-NanoVelcro
CTC Chip



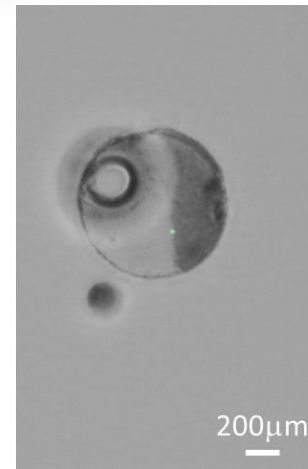
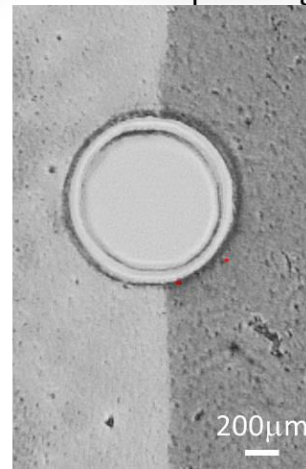
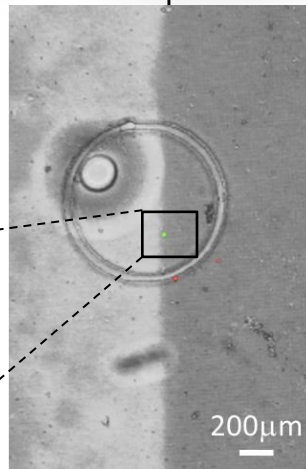
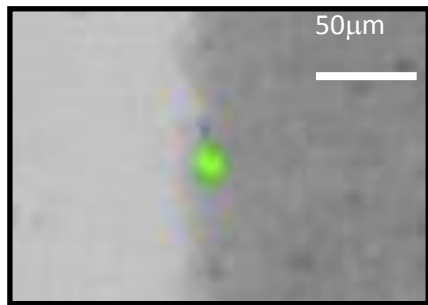
Laser Capture
Microdissection



Multiple Displacement
Amplification



Whole Genome
Sequencing



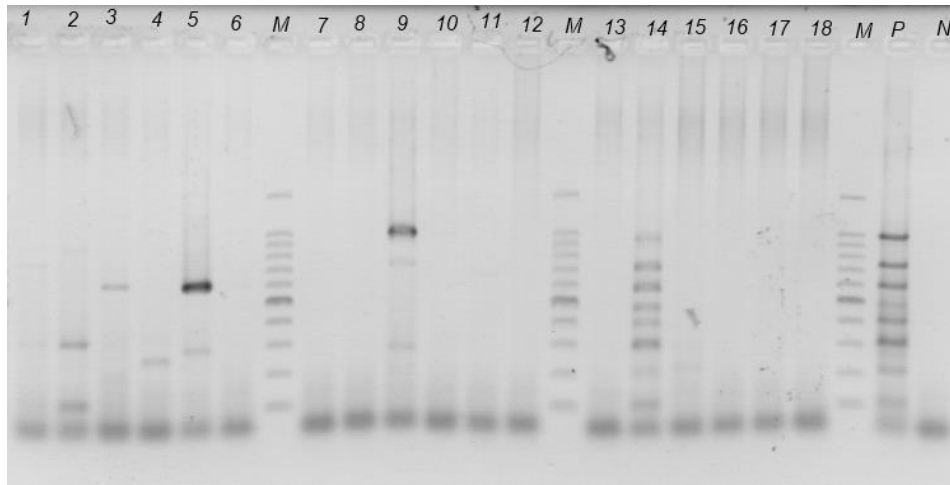
华大基因
BGI



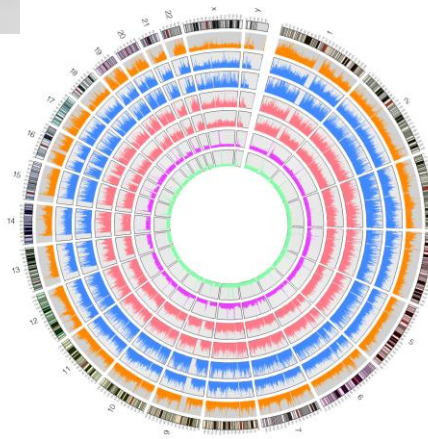
CEDARS-SINAI

UROLOGIC ONCOLOGY PROGRAM

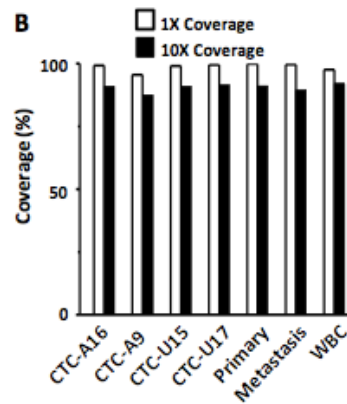
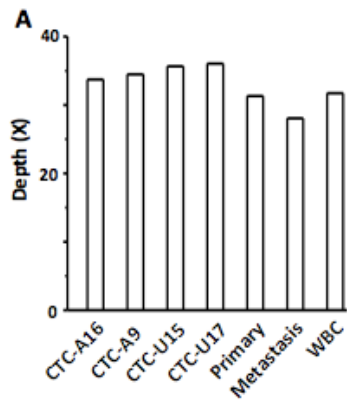
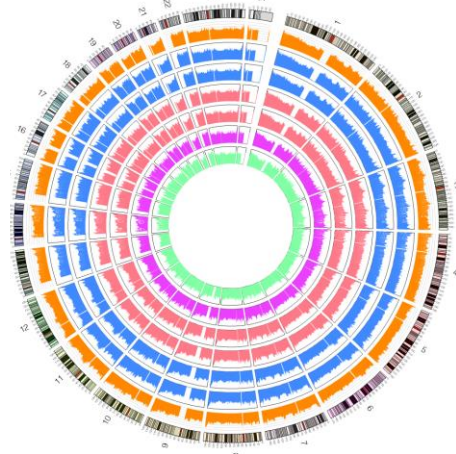
DNA extraction and sequencing quality assessment



GC Content



Regional Depth



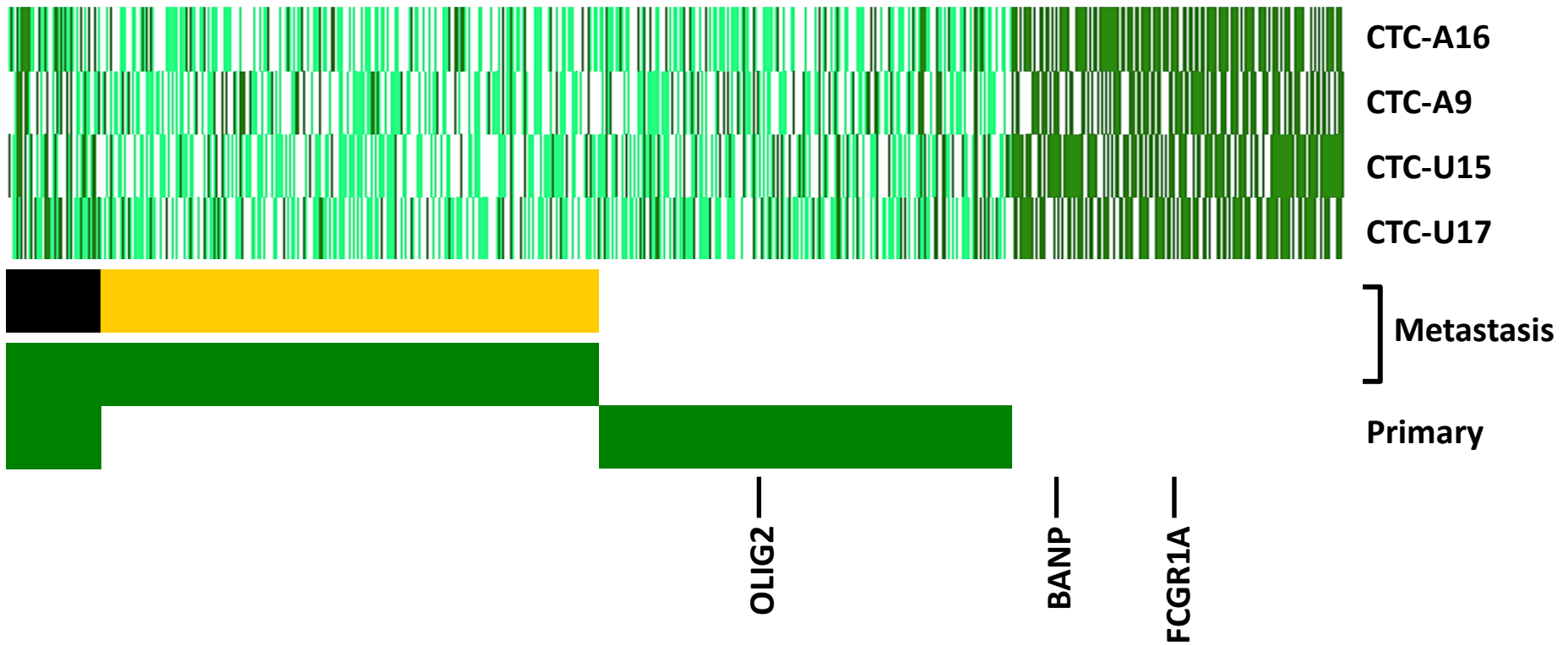
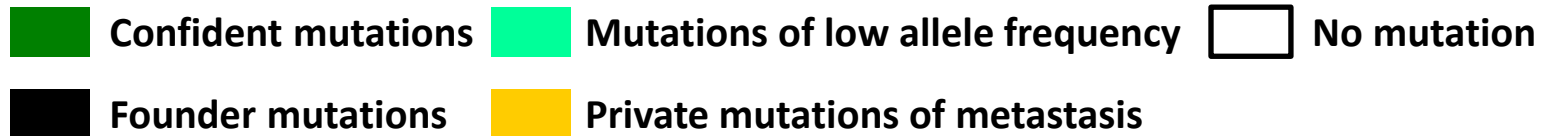
华大基因
BGI



CEDARS-SINAI

UROLOGIC ONCOLOGY PROGRAM

CTC genomic alteration landscape



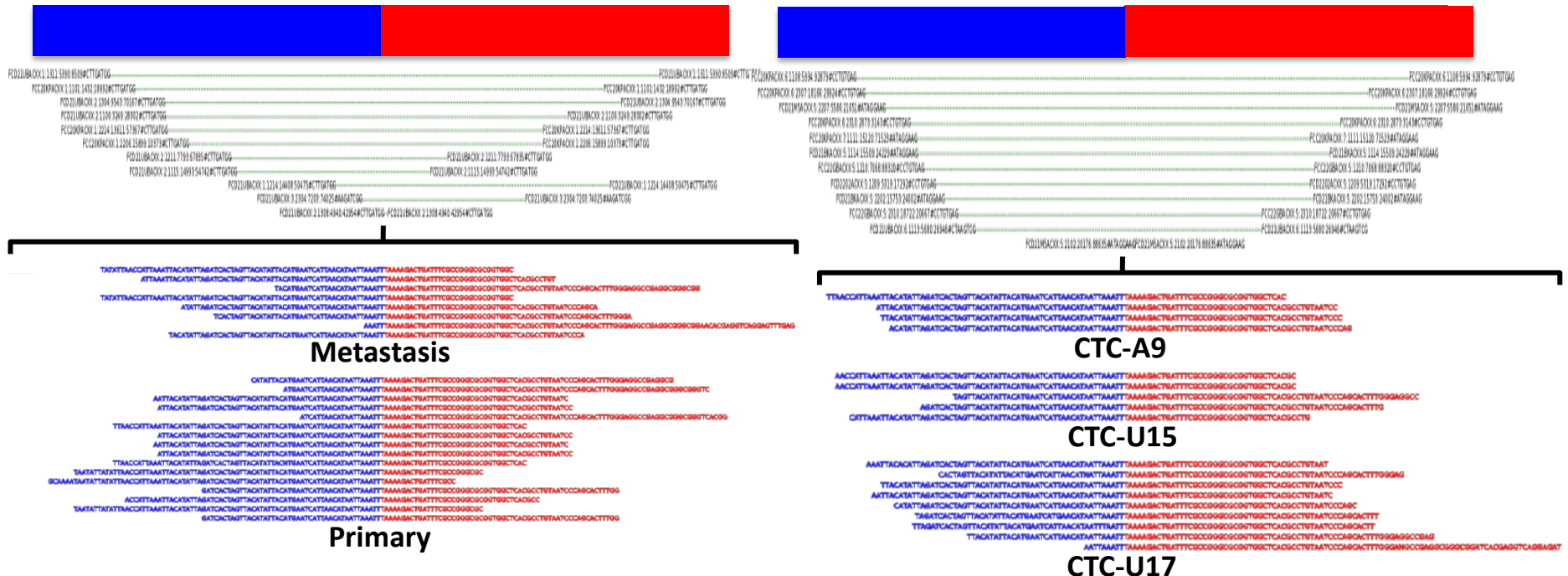
Shared rearrangements between primary, metastasis, and CTCs

Intergenic region

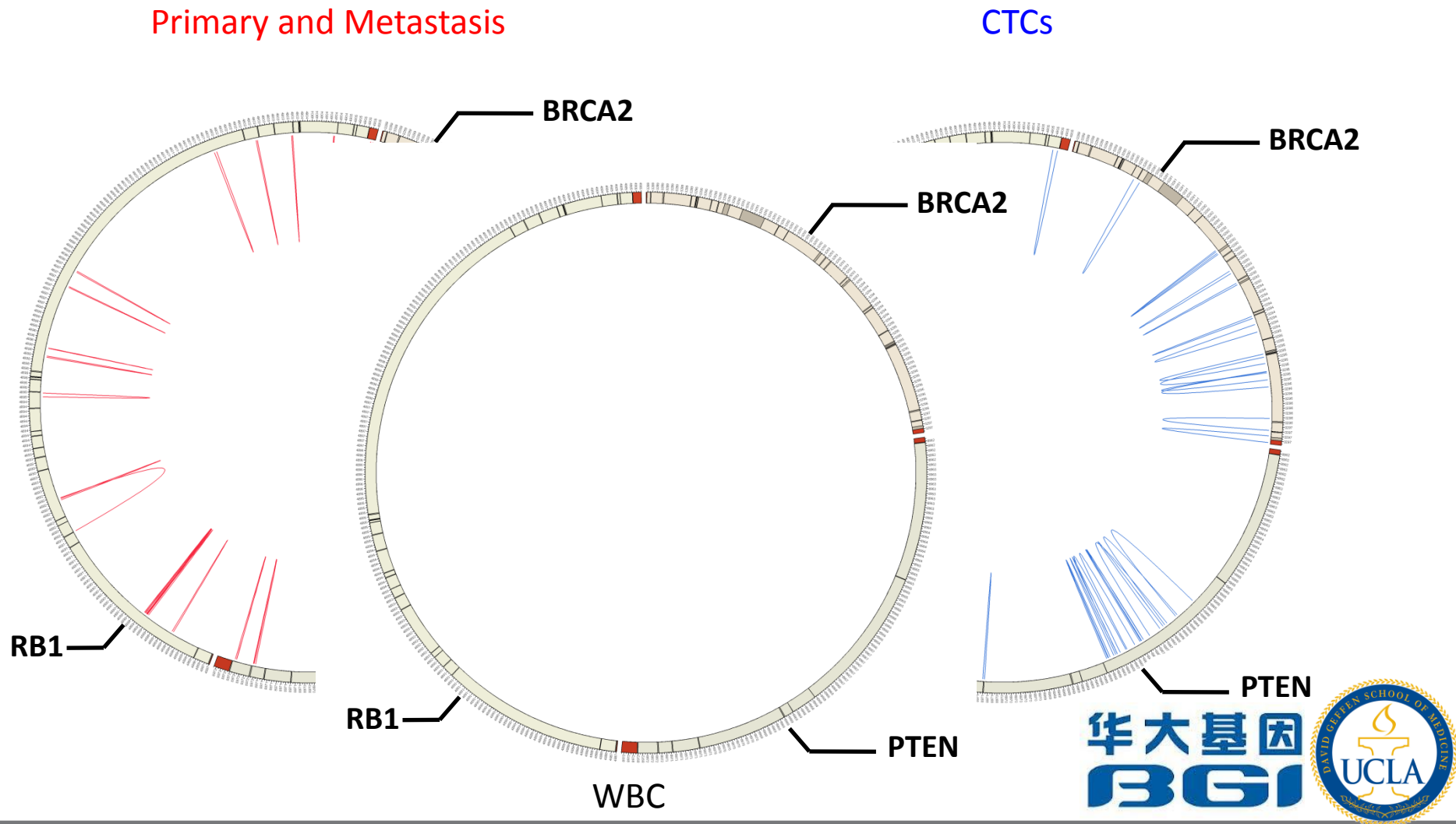
TMEM207

Intergenic region

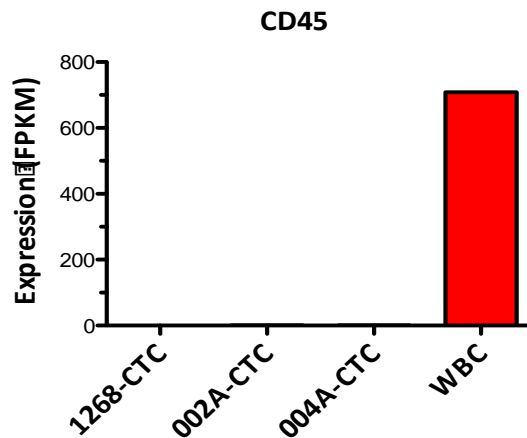
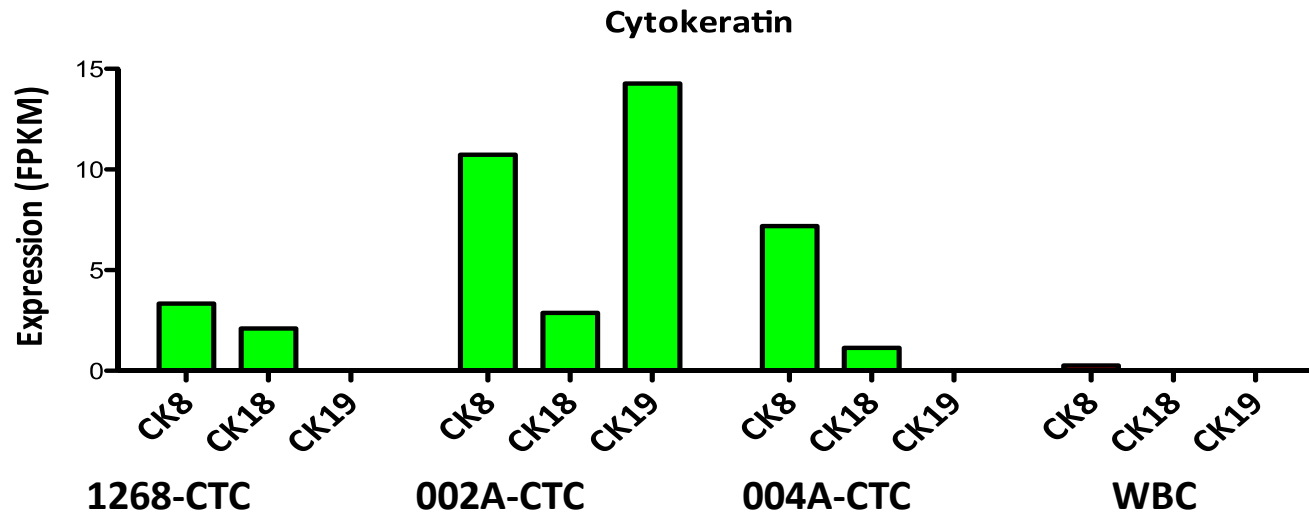
TMEM207



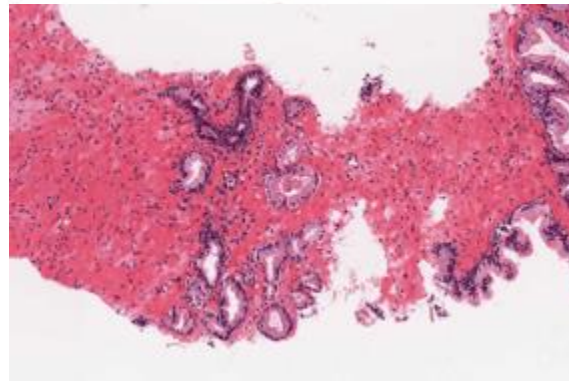
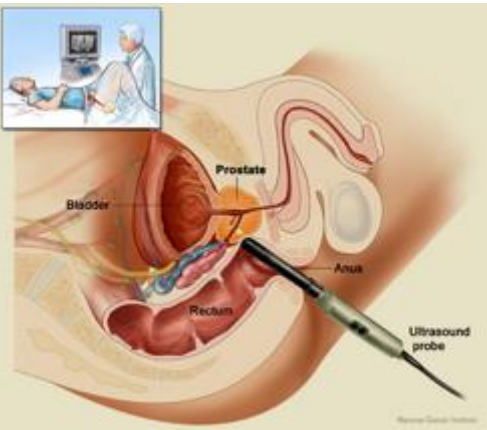
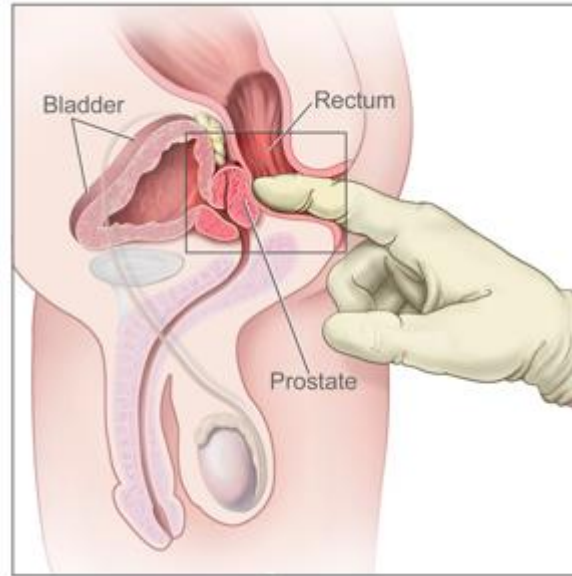
Structural variations in cancer-related genes: tumors and CTCs



RNA assessment from CTCs-qPCR



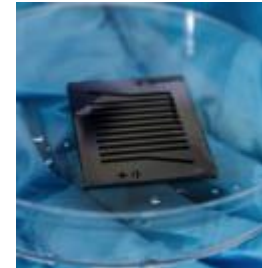
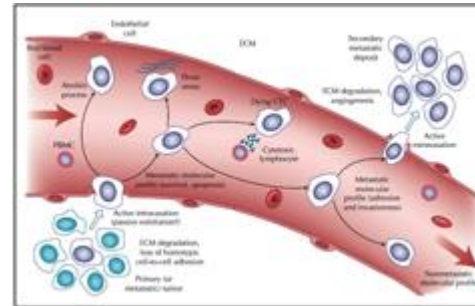
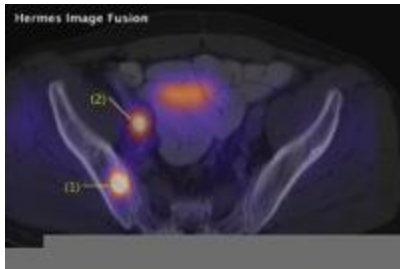
Prostate cancer detection and evaluation in 2014 has not evolved significantly



- Prostate cancer is only pathologically characterized at diagnosis
- The only characterizations used are morphologic (Gleason score) and clinic- NO MOLECULAR FEATURES
- Current experimental approaches involve painful tissue extractions such as bone marrow biopsies

Modernizing personalized medicine using circulating tumor cells

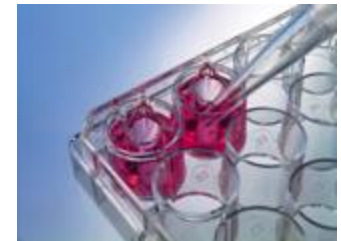
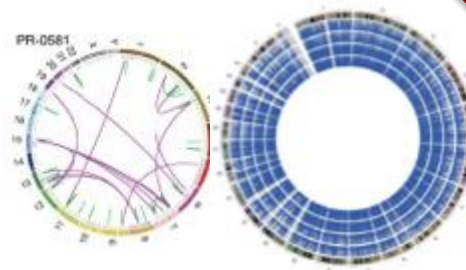
Detect (Relevant)
Disease



CTC
"Liquid"
Biopsy



Molecular
Analysis



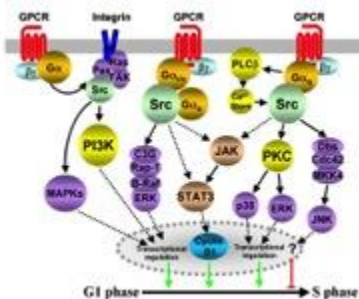
Ex vivo
modeling



Risk
stratification
& molecular
tumor board



Systemic
Therapy



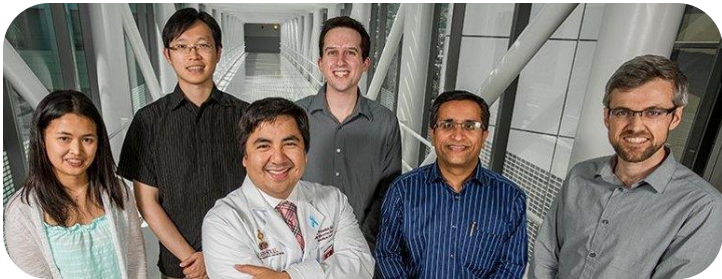
CEDARS-SINAI

UROLOGIC ONCOLOGY PROGRAM

Thank you

Posadas Lab

Murali Gururajan, PhD
Yi-Tsung "John" Lu, MD
Margarit Sievert, MS
Challen Lu, MS
Jake Licherterman
Andrew Hallum



Hsian-Rong Tseng, PhD (UCLA)

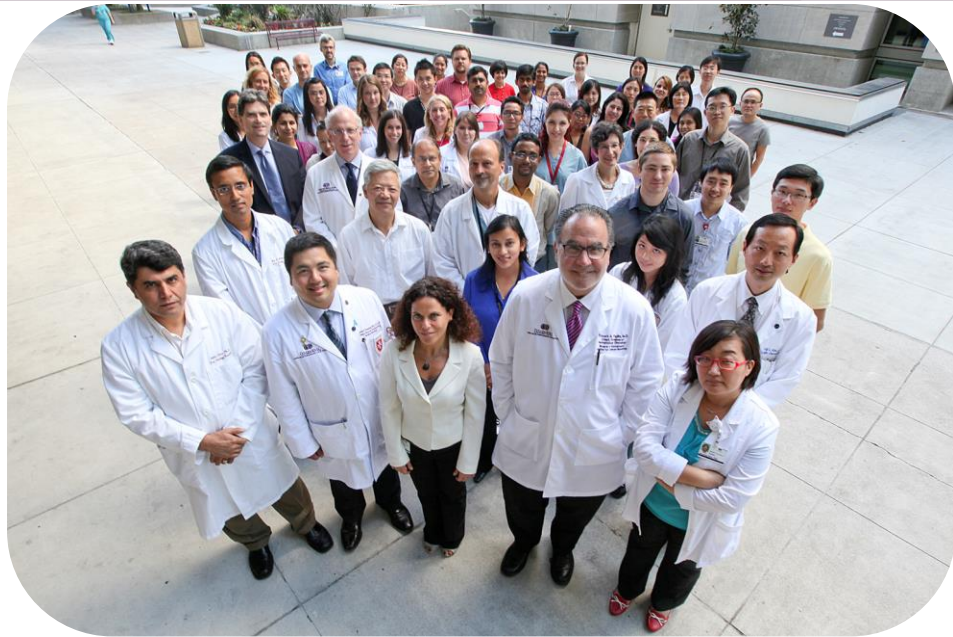
Bo Li, PhD

Leland W K Chung, PhD (CSMC)

Ruoxiang Wang, PhD
Haiyen Zhua, PhD

CSMC UOP Research Team

Amy Oppenheim
Jessica Hamman
Nancy Moldawer, RN, MSN
James MacDonald, RN, MSN



Edwin M. Posadas, MD FACP KM: 310-423-7600 Edwin.Posadas@csmc.edu

SDG



CEDARS-SINAI

UROLOGIC ONCOLOGY PROGRAM