



Innovations in bladder cancer research.

David J. McConkey, PhD
Departments of Urology and
Cancer Biology

THE UNIVERSITY OF TEXAS

MDAnderson
Cancer Center

Making Cancer History®

Current basic science priorities

- Define the role of cancer stem cells in disease initiation, progression, metastasis, and therapeutic resistance
- Identify the somatic mutations that function as “drivers” of disease progression (TCGA)
- Explore the role of single nucleotide polymorphisms (SNPs) in inter-individual variations in cancer risk and therapeutic response
- Define the extent of intra and inter-tumoral heterogeneity and its impact on cancer biology

Common mutations in bladder cancer

- **FGFR3**
- **P53**
- **Rb**
- **Ras**
- **PIK3CA**
- **PTEN**
- **Chromatin modifying enzymes**

FGFR3, *HRAS*, *KRAS*, *NRAS* and *PIK3CA* Mutations in Bladder Cancer and Their Potential as Biomarkers for Surveillance and Therapy

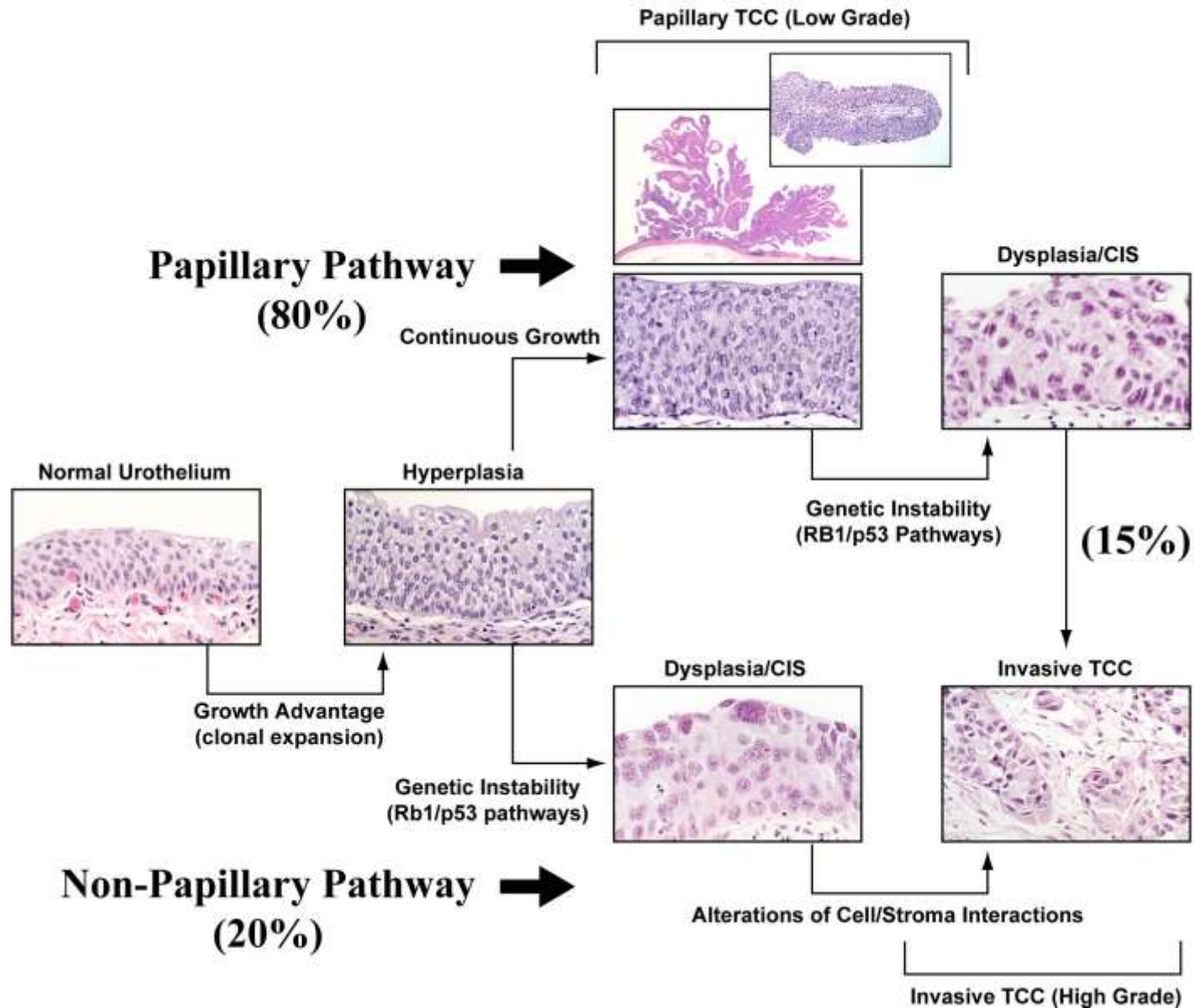
Lucie C. Kompier¹, Irene Lurkin¹, Madelon N. M. van der Aa¹, Bas W. G. van Rhijn², Theo H. van der Kwast³, Ellen C. Zwarthoff^{1*}

¹ Department of Pathology, Erasmus MC, Rotterdam, The Netherlands, ² Department of Urology, University Health Network, Toronto General Hospital, Toronto, Canada, ³ Department of Laboratory Medicine and Pathobiology, University Health Network, Toronto General Hospital, Toronto, Canada

Frequent mutations of chromatin remodeling genes in transitional cell carcinoma of the bladder

Yaoting Gui^{1,12}, Guangwu Guo^{2,12}, Yi Huang^{1,12}, Xueda Hu^{2,12}, Aifa Tang^{1,3,12}, Shengjie Gao², Renhua Wu², Chao Chen², Xianxin Li¹, Liang Zhou¹, Minghui He², Zesong Li^{1,3}, Xiaojuan Sun³, Wenlong Jia², Jinnong Chen², Shangming Yang², Fangjian Zhou⁴, Xiaokun Zhao⁵, Shengqing Wan², Rui Ye², Chaozhao Liang⁶, Zhisheng Liu², Peide Huang², Chunxiao Liu⁷, Hui Jiang², Yong Wang¹, Hancheng Zheng², Liang Sun¹, Xingwang Liu², Zhimao Jiang¹, Dafei Feng², Jing Chen¹, Song Wu¹, Jing Zou², Zhongfu Zhang¹, Ruilin Yang¹, Jun Zhao¹, Congjie Xu¹, Weihua Yin¹, Zhichen Guan¹, Jiongqian Ye¹, Hong Zhang¹, Jingxiang Li², Karsten Kristiansen^{2,8}, Michael L Nickerson⁹, Dan Theodorescu^{10,11}, Yingrui Li², Xiuqing Zhang², Songgang Li², Jian Wang², Huanming Yang², Jun Wang^{2,8} & Zhiming Cai^{1,3}

Dual Track Concept of Bladder Carcinogenesis



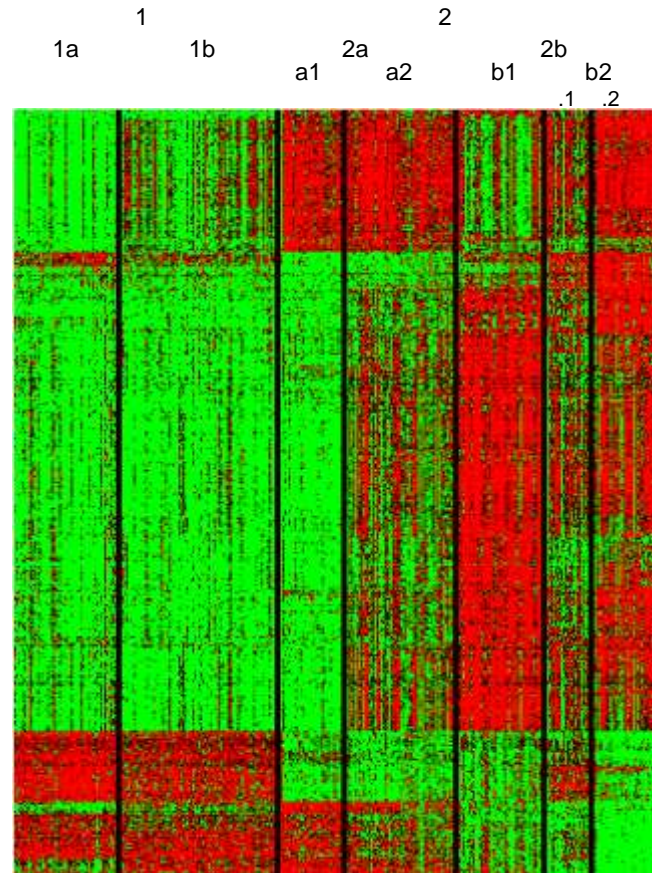
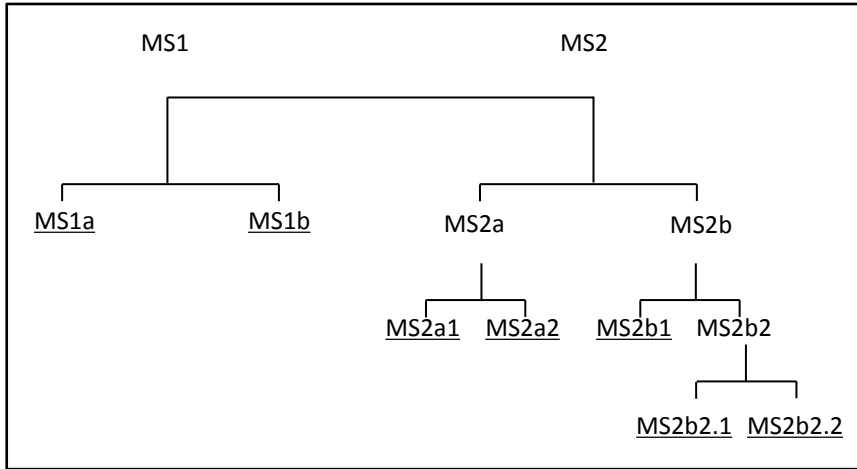


LUND
UNIVERSITY

Molecular subtypes of bladder cancer

Mattias Högländ

1a. Defining molecular subtypes



500 ANOVA top

NCI WORKSHOP

NOVEL NEOADJUVANT THERAPY FOR BLADDER CANCER

AGENDA

MONDAY, SEPTEMBER 19TH FROM 8:00 AM – 6:45 PM ET
TUESDAY, SEPTEMBER 20TH FROM 7:30 AM – 1:15 PM ET

GAITHERSBURG MARRIOTT WASHINGTONIAN CENTER
9751 WASHINGTONIAN BLVD
GAITHERSBURG, MD

ROOM: SALONS EFG (FOR MAIN SESSION)

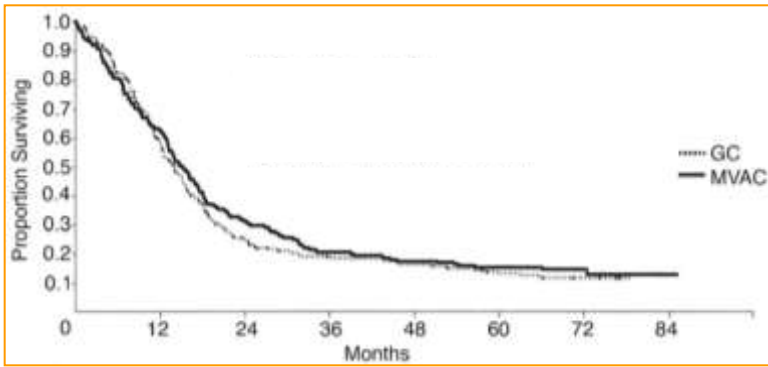
Session 1: Candidate biomarkers (McConkey and Theodorescu)

Novel targets and intermediate endpoints

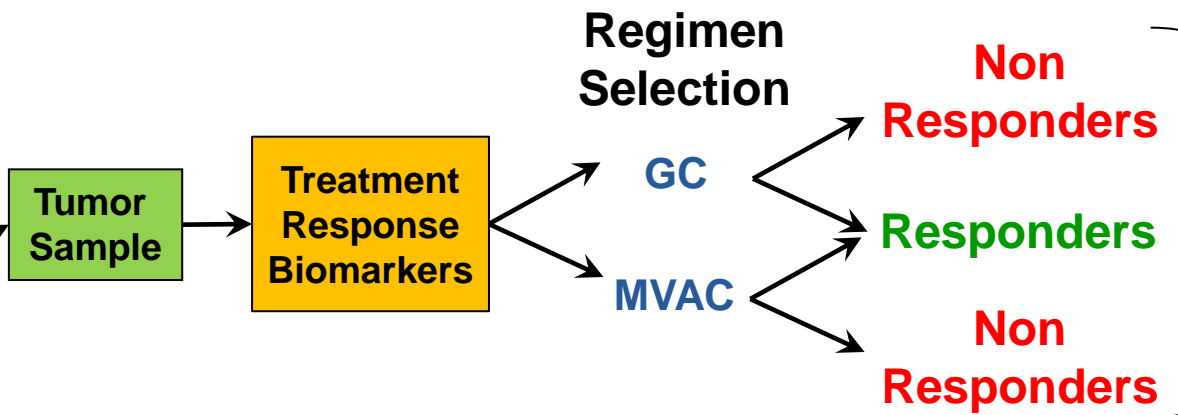
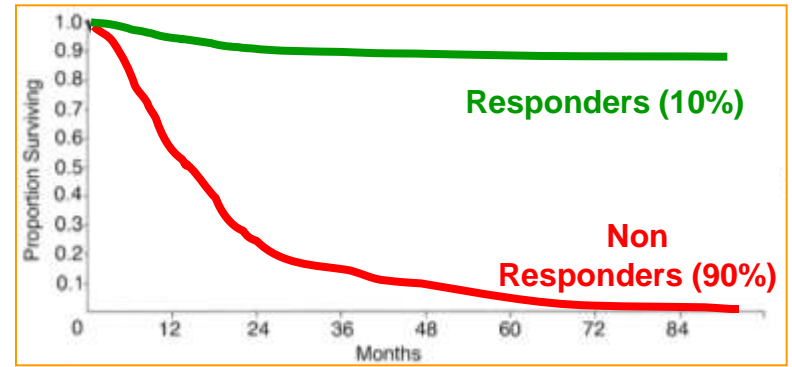
- Stem cells (Cordon-Cardo, Berman, Chan)
- CTCs (Darren Davis, Apocell, Inc.)
- “Druggable” mutations (Knowles, Davies)
- Whole genome/whole organ analyses(Czerniak)
- SNPs (Bajorin)
- Statistical Methodologies (Lisa McShane)
- SWOG COXeN TRIAL: Theodorescu

Individualized Bladder Cancer Therapy

The Current Reality



The Dream



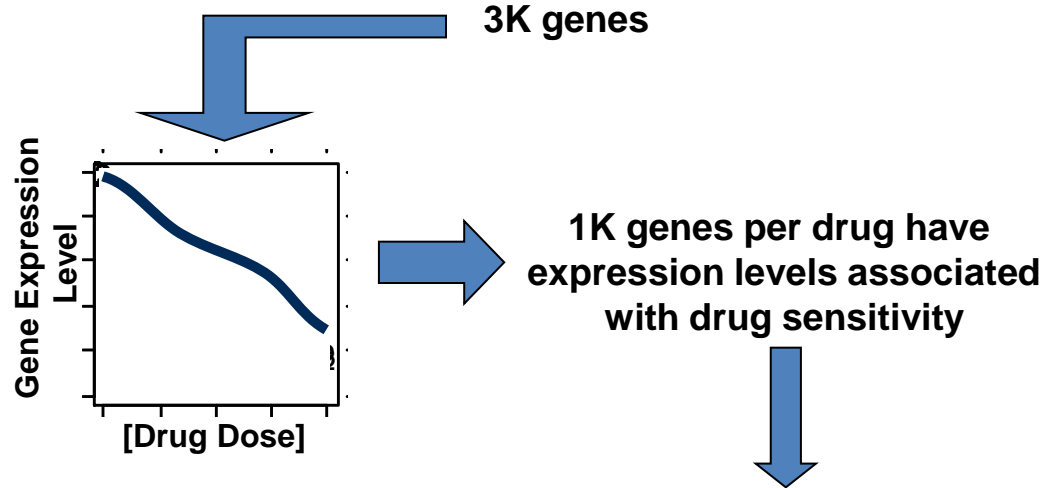
COXEN “CO-eXpression Extrapolation”

“How it Works”

Step 1:
Co-Regulation

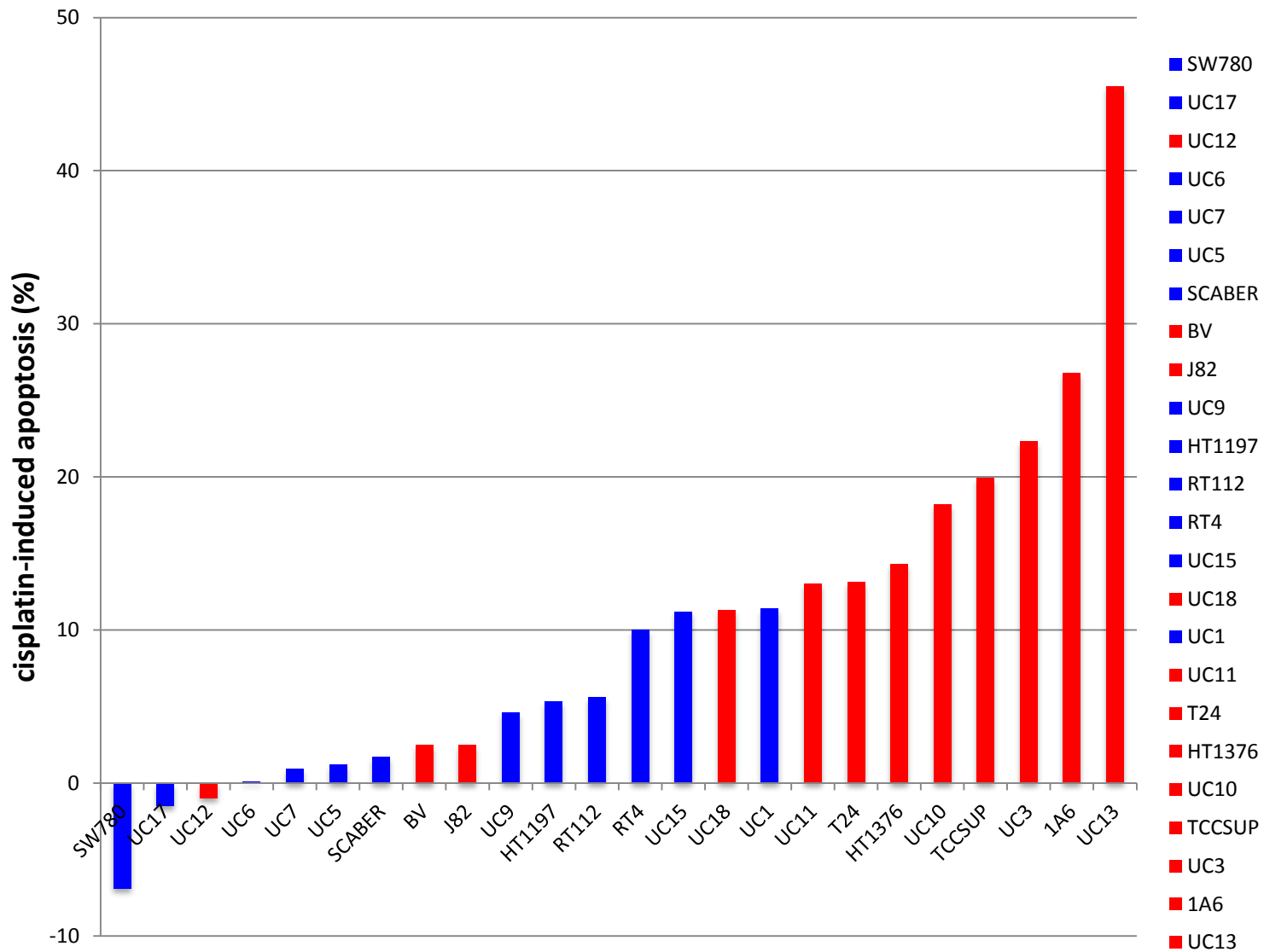


Step 2: Correlation with drug sensitivity



Step 3: Construction of Gene Expression Model (GEM) for each Test Compound

Smallest number genes that when combined offer best correlation of expression with drug sensitivity

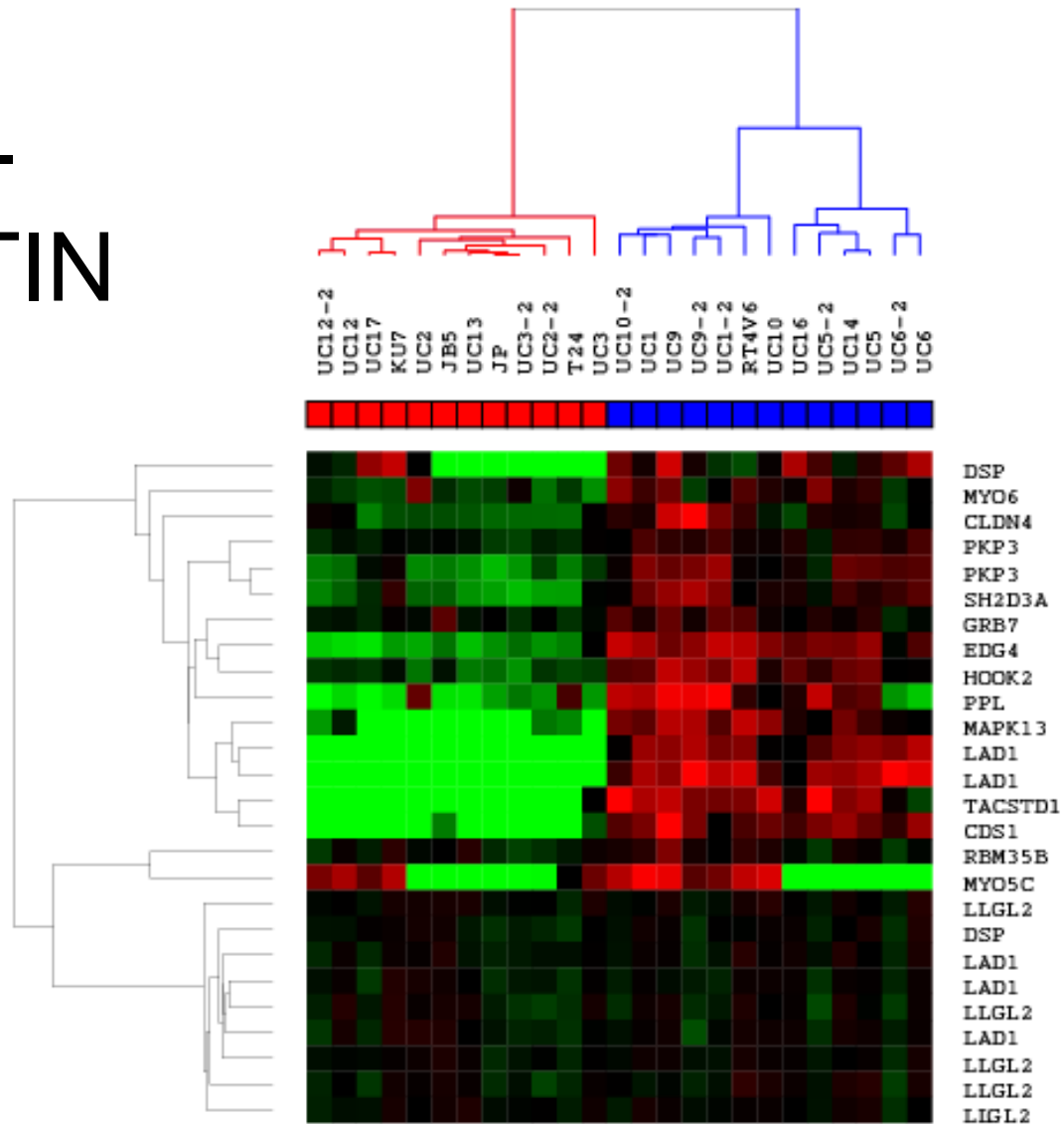


Blue: "epithelial"

Red: "mesenchymal"

(HT1376, UC10 and 1A6 have characteristics of both)

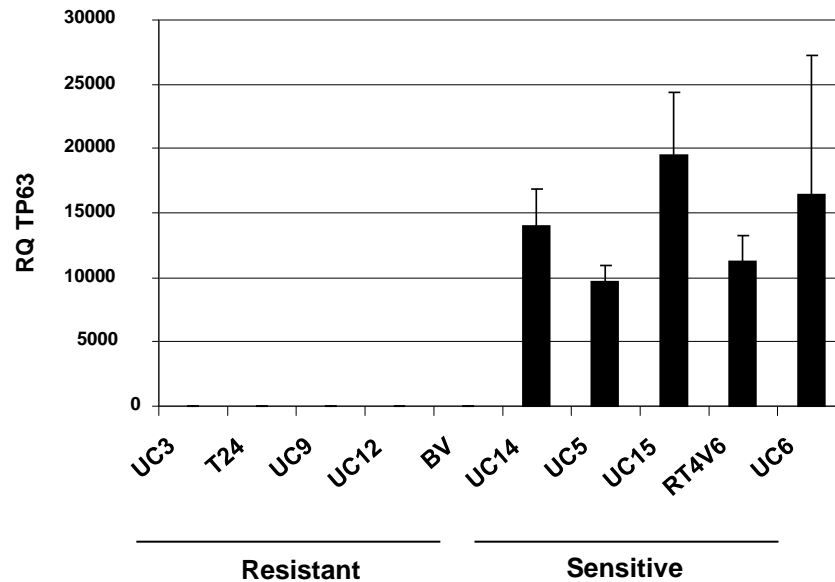
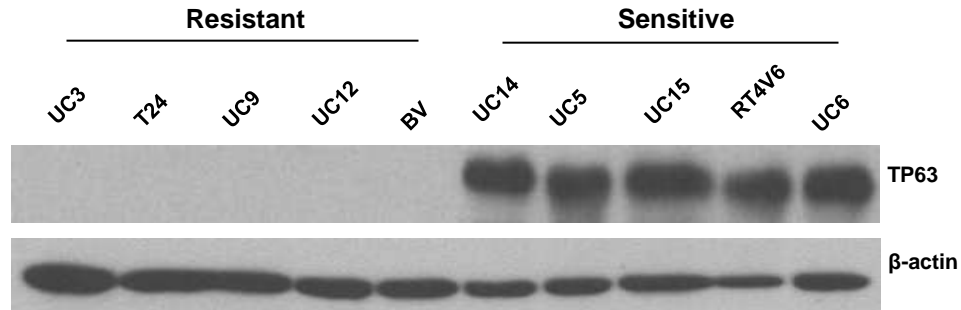
COXEN gene list- CISPLATIN



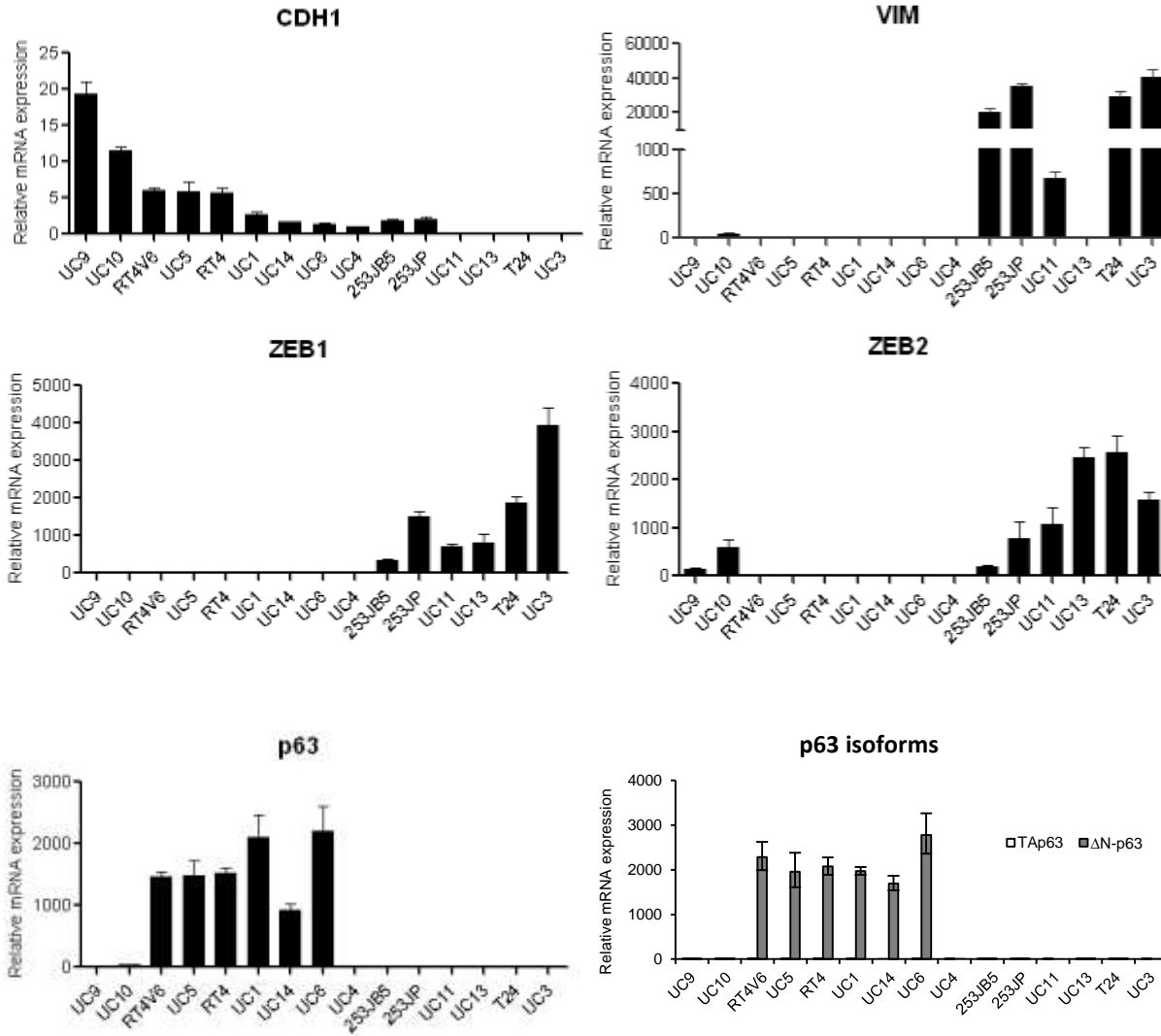
AZD4877 (an anti-mitotic)

- Inhibits the mitotic kinesin Eg5
- Arrests cells in mitosis (like taxol)
- Astra-Zeneca: activity in preclinical models of human bladder cancer

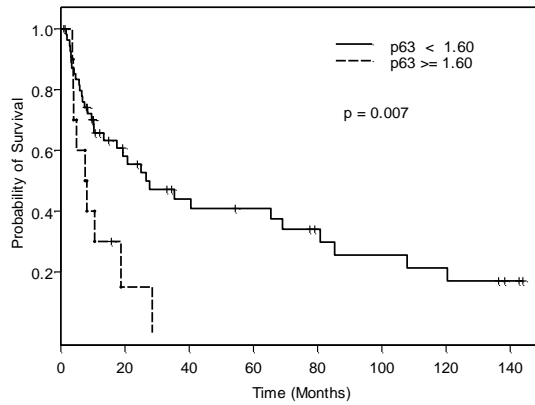
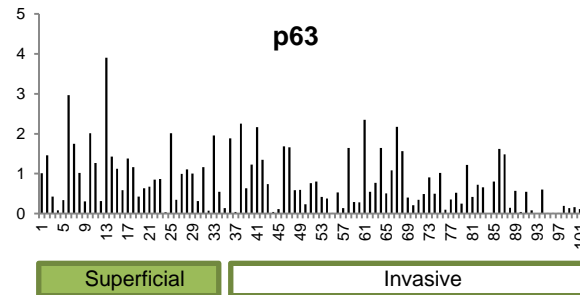
p63 and sensitivity to AZD4877



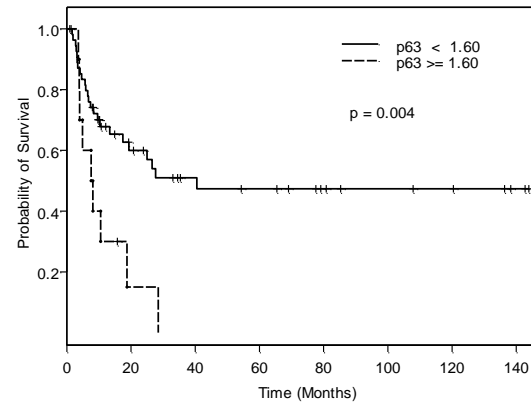
p63 expression and EMT



$\Delta Np63$ is associated with adverse outcome



Disease-free



Overall

Conclusions

- Our understanding of bladder cancer biology is increasing rapidly, largely through collaborative (“team science”) efforts
- This knowledge has important implications for prognostication and treatment
- *Clinical trials are playing an essential role in using these new insights to radically change disease management*

Key Contributors

**MD Anderson SPORE in Bladder Cancer
(NIH/NCI)**

**Southwest Oncology Group (SWOG) GU
Subcommittee**

**BCAN's Bladder Cancer Research
Network**

National Cancer Institute

Email: dmcconke@mdanderson.org