Muscle Invasive Urothelial Cancer
April 2018
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Emeritus
Director, UC Davis Comprehensive Cancer Center
Associate Dean for Cancer Programs, UC Davis School of Medicine
Distinguished Professor, Department of Urology
Codman-Radke Chair in Cancer Research
Invasive TCC $\geq$ T2

- 25% of initial tumors
- 8% of all tumors
- 85% of TCC deaths
- 40-50% Response to chemotherapy

Improving Survival
- Clinical Trials
- Evidence based medicine
- Standard of care

DSS No improvement in 25 Years
Curative Intent Therapy for MIUC
28,691 Patients; 04-08 NCDB

<table>
<thead>
<tr>
<th>Age</th>
<th>Cystectomy</th>
<th>RADS</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50</td>
<td>62%</td>
<td>2%</td>
<td>15%</td>
</tr>
<tr>
<td>51-60</td>
<td>58%</td>
<td>2%</td>
<td>17%</td>
</tr>
<tr>
<td>61-70</td>
<td>56%</td>
<td>3%</td>
<td>19%</td>
</tr>
<tr>
<td>71-80</td>
<td>45%</td>
<td>5%</td>
<td>25%</td>
</tr>
<tr>
<td>81-90</td>
<td>22%</td>
<td>8%</td>
<td>36%</td>
</tr>
</tbody>
</table>

(2% NCT)

(Gray J.P EUR GRO 63 823 2013)
Muscle Invasive Urothelial Cancer
Most Effective Therapy

- Neoadjuvant Chemotherapy
- Radical Cystectomy
- Pelvic Lymph Node Dissection
Radical Cystectomy has Been Part of Urologic Training for 50 years
So, How Well is it Performed?
### Extent of Node Dissection SWOG8710

<table>
<thead>
<tr>
<th>Extent</th>
<th>5YSR</th>
<th>LR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (9%)</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Limited (33%)</td>
<td>46%</td>
<td>25%</td>
</tr>
<tr>
<td>Standard (54%)</td>
<td>54%</td>
<td>6%</td>
</tr>
</tbody>
</table>

- Low Volume Surgeons: 38% (*P=0.001*)
- High Volume Surgeons: 77%

*Local Recurrence

---

Herr. HW et al.; JCO; 22 (14) 27, 8, 1-9 04
• Clinicians must perform a bilateral pelvic LND at the time of any surgery with curative intent (Grade B)

• When performing bilateral pelvic LND, clinicians should remove, at a minimum, the external and internal iliac and obturator lymph nodes (standard lymphadenectomy). (Clinical Principle)
Outcome in Node Positive Patients

- Number of lymph nodes removed
  - Important in both node negative and node positive patients
- Number of positive lymph nodes
- Percent of nodes involved with cancer
  - Lymph node density
- Pathologic stage of the primary tumor
- New TNM staging recommends > 12 nodes as minimum standard
Rationale for Extended PLND

- Standard LND includes external/internal iliac and obturator lymph nodes
  - Identifies $\geq 95\%$ of N1; skip metastases rare [2.2%]

- Extended LND includes pre-sacral, CI and distal aorta/IVC nodes
  - increases node yield by 34-40%
  - 36-43% of P3,P4N+ have node metastasis above CI bifurcation
Schema – SWOG S1011

T2+LVI, T3, T4a Radical Cystectomy

Standard PLND
External/internal iliac, obturator nodes

Extended LND
Standard + CI, pre sacral, distal IVC and aorta

N+ Adjuvant Chemotherapy

Sample size 564 patients
Powered to detect 10% improvement in 3 yr DFS from 55-65%
Comparison LEA and SWOG

<table>
<thead>
<tr>
<th></th>
<th>LEA</th>
<th>S-1011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility</td>
<td>T1-T4a</td>
<td>T2-T4a</td>
</tr>
<tr>
<td>Neoadjuvant chemo</td>
<td>Not allowed (14% adjuvant)</td>
<td>Allowed (56%)</td>
</tr>
<tr>
<td>Planned randomized</td>
<td>400</td>
<td>564</td>
</tr>
<tr>
<td>Registered (n)</td>
<td>438</td>
<td>659</td>
</tr>
<tr>
<td>Randomized (n)</td>
<td>433</td>
<td>620</td>
</tr>
<tr>
<td>Drop out/ineligible</td>
<td>71 (16.4%)</td>
<td>Assume 10% ineligible</td>
</tr>
<tr>
<td>ITT</td>
<td>362</td>
<td>Estimate 576</td>
</tr>
<tr>
<td>LND control</td>
<td>Limited</td>
<td>Standard</td>
</tr>
<tr>
<td>ePLND</td>
<td>IMA</td>
<td>Aorta bifurcation-&gt;IMA</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>RFS at 5 years</td>
<td>PFS at 3 years</td>
</tr>
<tr>
<td>Effect size</td>
<td>15% 50-&gt;65%</td>
<td>10% improvement (55-&gt;65%)</td>
</tr>
<tr>
<td>Power</td>
<td>90%</td>
<td>85%</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.80 (final result)</td>
<td>0.72</td>
</tr>
</tbody>
</table>
Problem: Reduce Morality

- 80% of deaths from 20% of patients
  (with muscle invasive disease)
- Chemotherapy before surgery:
  - 40% PT0, 85% 5 year survival
  - 60% RD, 45% 5 year survival

...yet, no improvement in survival in the last 30 years
<table>
<thead>
<tr>
<th>Stage</th>
<th>Contemporary (After 1985)</th>
<th>Historical (Before 1985)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT2</td>
<td>67%</td>
<td>60%</td>
</tr>
<tr>
<td>PT3</td>
<td>35%</td>
<td>33%</td>
</tr>
</tbody>
</table>
Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer.

- 8710 Only 5% survival benefit
- Statistically true clinically not relevant to the patient
- 50% of patients benefitted from neoadjuvant chemotherapy
- Only ≈ 50% of patients are eligible
- Since 2003 gone from 5% adoption to 40%
A Sequential Treatment Approach to Myoinvasive Urothelial Cancer

- A Phase II Southwest Oncology Group Trial (S0219) of Neoadjuvant Paclitaxel, Carboplatin, and Gemcitabine (PCG) Followed by a TUR
- If cT0 patient’s choice cystectomy or active surveillance

Ralph de Vere White, Primo N. Lara, Jr., Bryan Goldman, Cathy Tangen, David C. Smith, David Wood, Maha Hussain, E. David Crawford

University of California Davis Cancer Center, SWOG Statistical Center, University of Michigan, and University of Colorado
34 Patients cT0 at Post NAC TUR

- 10 Patients Chose to Undergo Cystectomy
- 6 of 10 Patients (60%) were > PT2

de Vere White RW, J Urol 2009
UCD Sequential Approach TUR after NAC

- 55 Patients 31 (56%) cT0
  - 3/31 (10%) Died of Urothelial Cancer

  de Vere White RW, J Urol 2009

P(c) To After NAC

- SWOG 8710 38% (PTO)
- Milken (MDA) 40% (PTO)
- HERR (MDA) 54% (PTO)
## UCD Sequential Approach Update

### 60 Patients MIBC NAC Followed by TUR
**Median Follow-Up 60 Months**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Overall Survival</th>
<th>Cancer-Specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients (60 Patients)</td>
<td>65%</td>
<td>73%</td>
</tr>
<tr>
<td>&gt;cT0 Following NAC – Immediate Cystectomy (27 Patients)</td>
<td>51%</td>
<td>53%</td>
</tr>
<tr>
<td>cT0 Following NAC – No Recurrence or Cystectomies (17 Patients)</td>
<td>83%</td>
<td>100%</td>
</tr>
<tr>
<td>cT0 Following NAC – +Recurrence (15 Patients)</td>
<td>66%</td>
<td>73%</td>
</tr>
</tbody>
</table>

Survival Local Regional Disease 38% (2017)
# Therapy for Muscle Invasive Bladder Cancer Meta-Analysis (2018)

<table>
<thead>
<tr>
<th>Trimodality (TMT)</th>
<th>RC +/- NAC (3.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,402 PT’s</td>
<td>26,891 PT’s</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>10 Year Survival Rates</strong></td>
<td></td>
</tr>
<tr>
<td>OS 31%</td>
<td>35% (+4%)</td>
</tr>
<tr>
<td>DSS 51%</td>
<td>58% (+7%)</td>
</tr>
<tr>
<td>T2 DSS 69%</td>
<td>79% (+10%)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5 Year OS RC 49%</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RC+NAC 61% (+12%)</td>
</tr>
<tr>
<td><strong>5 Year Survival Rates</strong></td>
<td></td>
</tr>
<tr>
<td>TMT</td>
<td>TMT+NAC</td>
</tr>
<tr>
<td>OS 50%</td>
<td>58% (+8%)</td>
</tr>
<tr>
<td>DSS 62%</td>
<td>72% (+10%)</td>
</tr>
</tbody>
</table>

(Fahmy, J URO ONC 36(2018) 43-53)
How to increase adoption of Neoadjuvant Chemotherapy

- Can we identify the patients that will respond to cisplatin?
  - Micro dosing studies
- Can we identify new successful therapies?
  - Patient derived xenographs [PDX]
  - Microfluidic chambers
Response vs resistance to platinum chemotherapy

- DNA damage is the critical step in platinum-induced cell death.
- Chemo sensitivity can be identified by measuring drug-induced DNA damage.

**Chemotherapy**
- Metabolism
- Cellular uptake and efflux
- Intracellular Inactivation
- DNA damage

**Cell cycle arrest**
- DNA repair
- Cell death (chemosensitive)
- Cell survival (chemoresistant)

**DNA repair**

**Steps detected by MS**

**Measured by AMS**

DNA repair in cells

Diadducts

Repaired DNA

Pt

$\text{H}_3\text{N}$

$\text{NH}_3$

$\text{HOOC}^*$

$\text{HOOC}$

Lawrence Livermore National Laboratory
Human cancer cell lines exposed for 4h to 1 mM or 100 mM carboplatin

Therapeutic Dose

DNA damage (per 100M DNA bases)

18 nude mice injected with A549 (lung cancer) tumor cells and treated with carboplatin
Tumor-specific survival after chemotherapeutic treatment of NSG PDX mice bearing four different bladder cancer xenografts.

**A** BL0269 Survival

- Control
- Cisplatin
- Gemcitabine
- Gem/Cis

(Day 1 = treatment initiation)

**B** BL0293 Survival

- Control
- Cisplatin
- Gemcitabine
- Gem/Cis

(Day 1 = treatment initiation)

**C** BL0440 Survival

- Control
- Cisplatin
- Gemcitabine
- Gem/Cis

(Day 1 = treatment initiation)

**D** BL0645 Survival

- Control
- Cisplatin
- Gemcitabine
- Gem/Cis

(Day 1 = treatment initiation)
<table>
<thead>
<tr>
<th></th>
<th>BL0269</th>
<th>BL0293</th>
<th>BL0440</th>
<th>BL0645</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD45+</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
</tr>
<tr>
<td>Response To:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIS</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>R</td>
</tr>
<tr>
<td>GEM</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>R</td>
</tr>
<tr>
<td>Median Survival in Days:</td>
<td>39</td>
<td>28</td>
<td>64</td>
<td>-</td>
</tr>
<tr>
<td>Adduct, Positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARB</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>GEM</td>
<td>—</td>
<td>+x4</td>
<td>+x6</td>
<td>—</td>
</tr>
<tr>
<td>Synergy</td>
<td>No</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>
Correlation of microdose-induced $[^{14}\text{C}]$ carboplatin-DNA monoadducts in PBMC with tumor response to subsequent full-dose chemotherapy [In Patients]

![Graph A: PBMC DNA Adducts vs. 24 h](image)

![Graph B: Tumor DNA Adducts vs. 24 h](image)

- **PBMC DNA Adducts/10^8 nt**
  - 0.0
  - 0.3
  - 0.6
  - 0.9
  - 1.2

- **Tumor DNA Adducts/10^8 nt**
  - 0
  - 10
  - 20
  - 30
  - 40
  - 50
The average risk of urethral recurrence reported in multiple contemporary cystectomy series is 10%, ranging from 4% to 17% overall. It poses diagnostic and therapeutic challenges.

No definitive treatment guidelines exist to date. Whether or not surveillance should occur at defined intervals versus evaluation only at onset of symptoms is not clear.
# Urethral Recurrence after R.C Meta-Analysis

6,189 PT’s (14 Articles)

<table>
<thead>
<tr>
<th>Overall R.R</th>
<th>4.4% (1.3%-13.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Effect On RR</td>
<td></td>
</tr>
<tr>
<td>CIS/Prostatic Stroma or urethral involvement</td>
<td></td>
</tr>
<tr>
<td>Type of Diversion</td>
<td>Recurrence Rate</td>
</tr>
<tr>
<td>Orthotopic (42%)</td>
<td>RR 2.2%</td>
</tr>
<tr>
<td>Non Orthotopic</td>
<td>RR 5.5%</td>
</tr>
<tr>
<td>No information on urethral margin status</td>
<td></td>
</tr>
</tbody>
</table>

(Fahmy O URU ONC 36(2018) 54-59)
5 FDA Approved immune Checkpoint inhibitors

All for platinum Refractory Disease
  – 2 for 1st Line Therapy

3 Metastatic Settings
  – Chemotherapy Naïve
  – Cisplatin ineligible
  – Progression after platinum

4 Large Trial,
  – Combination ICI’s v. chemotherapy
POST PLATINUM: PEMBROLIZUMAB (KEYTRUDA) KEYNOTE 45
Data cutoff: May 19, 2017.

Based on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 mo).

One-sided $P$ value based on stratified log-rank test.
12m Overall Survival: Urothelial Cancer Post-Platinum (as of November 2017)

- Atezolizumab (ImVigor 211, Powles et al, JCO 2017) 39%
- Avelumab (Apolo et al, JCO 2017) 54%
- Durvalumab (ENRICHED, Powles et al, JAMA Onc 2017) 55%
- Nivolumab (Sharma et al, Lancet Onc 2017) 43.9%
- Pembrolizumab (Bellmunt et al, NEJM 2017)

Historical Control w Chemo ~ 26%
Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>HR (95% CI)\textsuperscript{a}</th>
<th>(P\textsuperscript{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>191</td>
<td>0.70 (0.57-0.86)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>209</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Based on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 mo).

\textsuperscript{b}One-sided \(P\) value based on stratified log-rank test.

Data cutoff: May 19, 2017.

R. de Wit et al. ESMO 2017
Use of PDXs to Improve Survival for Patients with Urothelial Cancer

Ralph de Vere White, M.D.
Emeritus
Director, UC Davis Comprehensive Cancer Center
Associate Dean for Cancer Programs, UC Davis School of Medicine
Distinguished Professor, Department of Urology
Codman-Radke Chair in Cancer Research
Most cancers have **MANY** genetic changes

Only one or a few are **molecular drivers** critical for tumorigenesis.
- 12% response for patients with matched targeted therapy

Targeted therapy against passenger mutations does not affect cancer cells.

Current computational biology cannot distinguish driver mutations from passenger ones

How can we identify driver mutations in cancer?
Each Cancer Harbors Many Genetic Alterations

Urothelial carcinoma

B

Non-synonymous mutations per tumor
(median +/- one quartile)

A

Glioblastoma (14)
Medulloblastoma (8)
Rhabdoid cancer (4)
Neuroblastoma (12)
Acute lymphocytic leukemia (11)

Glioblastoma (35)
Non-Hodgkin lymphoma (74)
Breast cancer (33)
Hepatocellular cancer (39)
Pancreatic cancer (45)

Head and neck cancer (66)
Lung cancer (non-small cell) (147)
Lung cancer (small cell) (163)
Esophageal adenocarcinoma (57)
Esophageal squamous cell carcinoma (79)
Gastric cancer (53)
Colorectal cancer (66)
Ovarian cancer (42)
Endometrial cancer (49)
Prostate cancer (41)
Melanoma (135)

Colorectal (LSLCO)
Lung (NSCLCO)
Melanoma
Esophageal (ECCO)
Non-Hodgkin lymphoma
Gastrointestinal
Endometrial (endometrioid)
Pancreatic adenocarcinoma
Ovarian (high-grade serous)
Prostate
Hepatocellular
Glial tumors
Breast
Endometrial (serous)

Lung (never smoked NSCLCO)
Chronic lymphocytic leukemia
Acute myeloid leukemia
Glioblastoma
Neuroblastoma
Acute lymphoblastic leukemia
Medulloblastoma
Rhabdoid
PDXs for Precision Medicine
Characterization of PDXs

Fidelity of morphology
Conservation of genetic aberrations (92-97%)
Patient-Derived Xenografts (PDXs) for Precision Medicine

- Cancer Patients
- Tumor Specimens
  - Deep sequencing
  - Target selection
  - Target validation
  - Efficacy screening in PDXs
  - Precision medicine
- PDX in NSG mice
Two Different Patient Bladder Cancers
Same Molecular Driver, Same Treatment

but have different responses to EphB4 inhibition

A - BL0293
(no neoadjuvant therapy)

B - BL0645
(failed neoadjuvant therapy)

PDX: BL0293

Tumor size (ratio) vs. Time points post injection (Days)

(IHC by Salma Siddiqui; IF by Parkash Gill)

*50 mg/kg, B.W.
PDX Platform in Precision Medicine
Drug Screening: Chemotherapy

BL0269 Tumor Response

BL0293 Tumor Response

BL0382 Tumor Response

BL0479 Tumor Response

BL0440 Tumor Response

BL0515 Tumor Response

Group 1 - Vehicle
Group 2 - Cisplatin
Group 3 - Gemcitabine
Group 4 - Cisplatin & Gem
### Targeted Therapy Matched with Genetic Alterations
**BL0293**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>BGJ398</th>
<th>sEphB4-HSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (days)</td>
<td>9.5</td>
<td>18.5</td>
<td>16.7</td>
</tr>
<tr>
<td>P value</td>
<td>N/A</td>
<td>2.61 X 10^-6</td>
<td>3.17 X 10^-5</td>
</tr>
</tbody>
</table>

#### BL0293

- **ERBB2**
  - Protein: +
  - mRNA: 19.2033
- **ERBB3**
  - Protein: Negative
  - mRNA: 0.43993
- **FGFR3**
  - Protein: ++
  - mRNA: 0.19273
- **Src**
  - Protein: -
  - mRNA: 7.88632
- **EphB4**
  - Mouse: Positive
  - Human: Positive

#### Diagram:
- **PDX: BL0293**
  - Drug treatment (Days)
  - Tumor Ratio
  - Biopsy
  - Deep sequencing
  - Computational biology
  - Target selection
  - Efficacy test
  - Re-transplant and expansion in mice

#### Efficacy test
- Drugs to overcome secondary resistance

---

**Vehicle**
- **BGJ398 (FGFR3 inhibitor)**
- **EphB4-HSA**
- **BGJ398/EphB4-HSA**
PDXs for Precision Medicine

Studying resistance mechanisms

**PDX: BL0293**

- **Vehicle**
- **FGFR3 inhibitor**

<table>
<thead>
<tr>
<th>Drug treatment (Days)</th>
<th>pErk</th>
<th>pAKT</th>
<th>tAKT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Re-transplant and expansion

**FGFR3I-resistant BL0293**

- **Vehicle**
- **FGFR3 inhibitor**
- **Sorafenib**
- **PIK3CA inhibitor**

**Molecular Targets**

- FGFR3, EGFR, HER2, EphB4, etc.
- RAS
- RAF
- MEK
- PYK2
- JAK
- PI3K
- AKT
- PIK3CAI
Rodent Eye as a Non-invasive Window for Understanding Cancer NanoRx

“EyePod”: label-free OCT, confocal, adaptive optics

Non-invasive, real-time monitoring of tumor growth, neovasculature development, nanoparticle distribution and tumor response.
PDX – Bladder Cancer

PDX (Bladder Cancer) after 14 Days of culture in microchambers

**Anti-Pan**

**Cytokeratin**

**Vimentin**

**DAPI**

PDX ID# BL0808

Passage# 2

Microchambers (µC):

- Biocompatible
- Optically transparent
- Excellent oxygen transport
- Accumulation of endogenous factors
- Enhancement of autocrine and paracrine signals
- Long-term function maintenance of difficult-to-culture cells (ex. Primary hepatocytes and mESC (mouse Embryonic Stem Cells))

Cell Input/ Media reservoirs (500 µl)

Cell culture µC (1 µl)

PDMS

Glass slide
# Urothelial Cancer Initiative Membership

**Clinicians - Urology**
- M. DallEra
- R. de Vere White
- C. Evans
- E. Kurzrock
- S. Yap

**Hem/Onc**
- P. Lara
- K. Lam
- F. Meyers
- C. Pan
- H. Zhang

**Rad/Onc:**
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**Pathology:**
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- S. Jiang
- S. Miyamoto
- S. Osborn
- T. Scharadin
- S. Steward
- C. Tepper
- H. Zhang
- M. Zimmerman
- Luis Carvajal-Carmona

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- C. Slupsky

**Biochem**
- C. Lebrilla

**Vet School**
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- S. Frazier
- M. Kent
- M. Lairmore
- C. Palm
- C. Rodriguez

**California Northstate Univ College of Pharmacy**
- R. Vinall

**JAX West**
- E. Liu
- S. Airhart
- C. Bult
- Jeff C. Huang
- Karoline Palucka
- J. Wagner
- James Keck

**Admin**
- S. Soares
- M. Bradnam
- D. Robles

**LLNL**
- B. Buchholz
- M. Malfatti
- K. Turteltaub

*Bladder Cancer Dream Team: UC Davis, UCSF, UCLA and USC*