New Paradigms in Personalized Medicine and Drug Discovery for Cancer

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Cancer of the Bladder

The Clinical Challenge of Metastatic Disease

Overall Survival of 405 patients with T4b or N2-3 or M1 urothelial carcinoma randomized to Gem-Cis or MVAC


Metastatic disease = Death
Visceral Metastasis curable only in ~5-7%

Needs

Individualize “personalize” therapy
Better drugs / drug combinations
Challenges of Individualized cancer therapy

- We have prognostic markers of outcome
- We don’t have predictive biomarkers of treatment response in majority of tumors
  - Could our single drugs or drug combinations that cure 5-10% of patients, if applied to specific patient subsets, this result in improved cure rates?

Cancer → Treatment → Treatment Response Biomarkers → Tumor Sample → Chemotherapy Regimens

- MVAC
- GC
- GT

In aggregate Cures Likely >10%

Optimized Regimen Selection
Challenges of Drug Discovery

5,000 - 10,000

Compound Success Rate in Drug Discovery

Screened

250

Enter preclinical testing

5

Enter clinical testing

1

Approved by FDA

~$880 million / successful drug

Time—12 years!
Drug Discovery and Clinical Medicine
Common Problem—The “Tumor-Drug Disconnect”

**NCI-60 Cell Panel**

**Human Cell Lines**
- Leukemia (6)
- Melanoma (7)
- Breast (8)
- Ovarian (6)
- CNS (6)
- Lung (9)
- Prostate (2)
- Colon (7)
- Kidney (8).

**HTS Drugs Screening (eg. NCI)**
- >100,000 chemical compounds
- Results of 45K are available publicly

**Clinical Practice**

**Poor Predictability of Drug Action in Patients**
Classic Solution to the “Tumor-Drug Disconnect” does not help efficiency of drug discovery!

Discovery (2-10 Years)

Preclinical Testing
- Laboratory and animal testing
  - Phase I: Determine safety and dosage
  - Phase II: Efficacy and side effects

Phase III: Adverse reactions to long-term use

FDA Review/Approval

Additional Post-market Testing

Biomarker Development

Clinical use with Response Biomarker

Tumor Sample Taken

3 Drug Chemotherapy Regimen “ABC”

Responders

Non Responders

Biomarker Development

Treatment Response Biomarkers

Clinical Use of ABC

Selection of patients that respond to ABC

$$$$$$ and 1-2 yrs!

Limited utility
Comprehensive solution to the “Tumor-Drug Disconnect”
Addressing both Drug Discovery and Individualized Therapy

Inspiration…. The Rosetta Stone

Hieroglyphic: script for important / religious documents

Demotic Egyptian: common script of Egypt

Greek: language of the rulers of Egypt

Idea…. 

NCI-60 Panel Cell Lines

Gene expression profile

Patient Bladder Tumor
The Idea: COXEN “CO-eXpression ExtrapolatioN”
Uses in Drug Discovery and Individualized Therapy

NCI-60 Cell Line Panel

Expression Profiling

IC50 for 45,345 Compounds

Human Bladder Cancer Cell Lines

COCO

Bladder Cancer patient samples

Gene Expression Model (GEM) for each TestCompound

GEM Score Evaluation on Bladder Cancer patient tissues or cells

COXEN Score for each drug across all patients

COXEN Score for each patient for specific drug

Drug Discovery

Individualized Therapy
The Idea: COXEN “CO-eXpression Extrapolation”
Uses in Drug Discovery and Individualized Therapy

**Discovery (2-10 Years)**
- Preclinical Testing
  - Laboratory and animal testing
  - Phase I: Determine safety and dosage
  - Phase II: Efficacy and side effects
  - Phase III: Adverse reactions to long-term use

**FDA Review/Approval**
- Additional Post-market Testing
- Biomarker Development

**Clinical use with Response Biomarker**
COXEN Applied to Individualized Therapy

COXEN provides treatment response biomarkers without the need for tissue from patients treated with chemotherapy regimens!

- Uses *in vitro* data
- Can develop biomarkers for any drug combinations within days with minimal effort!

Diagram:
- Discovery (2-10 Years)
- Preclinical Testing
  - Laboratory and animal testing
  - Phase I: Determine safety and dosage
  - Phase II: Efficacy and side effects
- Phase III: Adverse reactions to long-term use
- FDA Review/Approval
- Additional Post-market Testing
- Biomarker Development
- Clinical use with Response Biomarker

Years:
- 0
- 2
- 4
- 6
- 8
- 10
- 12
- 14
- 16
Can COXEN predict effectiveness of cisplatin and paclitaxel in Bladder cancer cells?

Cisplatin (GI50) and Paclitaxel (GI50)

- **Cisplatin normalized log(GI50) & MiPP prediction scores**
  - **Sensitive log(GI50):** (p-value = 0.016)
  - **Sensitive: Actual GI50**
  - **Resistant: Actual GI50**

- **Paclitaxel normalized log(GI50) & MiPP prediction scores**
  - **Sensitive log(GI50):** (p-value = 0.006)
  - **Sensitive: Actual GI50**
  - **Resistant: Actual GI50**

**BLA-40 Cell line**

- **umuc9**
- **X253jp**
- **silt4p3**
- **X253jbv**
- **umuc14**
- **cm7833**
- **fl3p10**
- **ku7**
- **umuc3**
- **umuc3e**
- **rt4**
- **cri7193**
- **cri2169**
- **ht1197**
- **X575a**
- **cubill**
- **mghu3**
- **jon**
- **kk47**
- **bc16.1**

**BLA-40 Cell line**

- **htb9**
- **cri2742**
- **umuc2**
- **ku7**
- **X253jbv**
- **scaber**
- **umuc6**
- **umuc1**
- **X253jp**
- **vmcub1**
- **jon**
- **cubill**
- **cri7193**
- **j82**
- **psi**
- **bc16.1**
- **ht1197**
- **rt4**
- **kk47**
- **umuc1**

- **Standardized log(GI50)**
- **Standardized COXEN Score**

**…..No bladder cell lines were on NCI60 panel**
But WAIT!....most human cancers treated with combination chemotherapy

- Can COXEN predict effectiveness of known chemotherapeutic drug combinations in bladder cancer cell lines?
- Can COXEN predict treatment responses of known drug combinations in bladder cancer patients?
Can COXEN Predict Combination Chemotherapy Responses?

- **Approach**
  - Use 40 bladder cancer cell lines (BLA-40)
  - Evaluate common “doublet” drug combinations used in patients

Validation of COXEN predictions on BLA-40

- **COXEN Scores** of:
  - cisplatin + gemcitabine
  - cisplatin + paclitaxel
  - gemcitabine + paclitaxel

In vitro evaluation of combinations in BLA-40 cells

**IC50**
Results: COXEN predicts effectiveness of combination therapy in bladder cancer cells?
Can COXEN Predict Combination Chemotherapy Response in bladder cancer patients?

Reference Set (Used for Model Development)
- MSKCC (N=105) and UVA (N=58)
- Tissues profiled prior to undergoing TURBT or cystectomy
- No follow up information used
- Pathological Information:

<table>
<thead>
<tr>
<th>Stage</th>
<th>UVA (N=58)</th>
<th>MSKCC (N=105)</th>
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<tbody>
<tr>
<td>T0</td>
<td>5 (8)</td>
<td>3 (3)</td>
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<td>Tis, G3</td>
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</tr>
<tr>
<td>Ta, G1</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Ta, G2</td>
<td>10 (17)</td>
<td>2 (2)</td>
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<tr>
<td>Ta, G3</td>
<td>19 (33)</td>
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<tr>
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<td>3 (5)</td>
<td>13 (12)</td>
</tr>
<tr>
<td>T1, G3</td>
<td>3 (5)</td>
<td>12 (11)</td>
</tr>
<tr>
<td>T2, G2</td>
<td>1 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>T2, G3</td>
<td>3 (5)</td>
<td>10 (10)</td>
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<td>T3, G2</td>
<td></td>
<td>4 (4)</td>
</tr>
<tr>
<td>T3, G3</td>
<td>3 (5)</td>
<td>48 (46)</td>
</tr>
<tr>
<td>T4, G2</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>T4, G3</td>
<td>4 (7)</td>
<td>11 (10)</td>
</tr>
</tbody>
</table>
Can COXEN Predict Combination Chemotherapy Response in bladder cancer patients?

**Validation Sets**
- Studies with clinical response to therapy and gene profiling information
- NCI60-Drug sensitivity information on panel available
- Completely independent from Training/COXEN model derivation

- **Als (Denmark)** *(Clin Cancer Res 2007;4407 13(15):4407)*
  - Treatment MVAC (N=16) or GC (N=14)
  - M0 or M+ patients, no other therapy
  - Outcome: Overall survival

- **Takata (Japan)** *(Clin Cancer Res 2005;11(7): 2625)*
  - Neoadjuvant MVAC (N=45) followed by surgery or XRT
  - Outcome: Tumor size reduction/Downstaging, Overall survival
COXEN prediction of treatment outcome in patients treated with MVAC or GC

Als (Denmark) (Clin Cancer Res 2007;4407 13(15):4407)
Treatment MVAC (N=16) or GC (N=14)

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>N(%)</th>
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<tr>
<td>Follow-up for patients at risk (mo)</td>
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</tr>
<tr>
<td>Median (range)</td>
<td>81.8 (56.7-98.0)</td>
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<tr>
<td>Age (y)</td>
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<tr>
<td>Median (range)</td>
<td>61.5 (49-74)</td>
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<tr>
<td>Sex</td>
<td></td>
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<td>Male</td>
<td>24 (80)</td>
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<tr>
<td>Female</td>
<td>6 (20)</td>
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<tr>
<td>PS (ECOG)</td>
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<tr>
<td>0-1</td>
<td>27 (90)</td>
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<tr>
<td>&gt;2</td>
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<tr>
<td>Hemoglobin</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>15 (50)</td>
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<tr>
<td>Low</td>
<td>15 (50)</td>
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<tr>
<td>P-alkaline phosphatase</td>
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<tr>
<td>Normal</td>
<td>22 (74)</td>
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<tr>
<td>Elevated[dagger]</td>
<td>8 (26)</td>
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<tr>
<td>Stage</td>
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</tr>
<tr>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>T4b, N2-3</td>
<td>15 (50)</td>
</tr>
<tr>
<td>M1</td>
<td></td>
</tr>
<tr>
<td>Extra pelvic lymph node</td>
<td>6 (20)</td>
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<tr>
<td>Visceral organs</td>
<td>9 (30)</td>
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</table>

Overall Survival

Time (months)

Proportion Surviving
COXEN prediction of treatment outcome in patients using combination drug GEM for MVAC or GC

MSKCC & UVA

COXEN

Gene Expression Model

Evaluation of Model on Cells or Tumors (PCR)

NCI-60 Panel
  Cisplatin
  Gemcitabine
  Methotrexate
  Doxorubicin
  Vinblastine

MVAC (N=16)

Survival Time (Months)

p = 0.039

GC (N=14)

Survival Time (Months)

p = 0.030
COXEN prediction of treatment outcome in patients treated with neoadjuvant MVAC

Takata (Japan) (*Clin Cancer Res 2005;11(7): 2625*)
Neoadjuvant MVAC (N=45)

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>N(%)</th>
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<tbody>
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<td>Follow-up for patients (mo)</td>
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<tr>
<td>Median (range)</td>
<td>27 (2-56)</td>
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<tr>
<td>Age (y)</td>
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</tr>
<tr>
<td>Median (range)</td>
<td>67 (53-77)</td>
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<td>Sex</td>
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<tr>
<td>Male</td>
<td>33 (73)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (27)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>T2a, N0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>T2b, N0</td>
<td>8 (18)</td>
</tr>
<tr>
<td>T2b, N2</td>
<td>1 (2)</td>
</tr>
<tr>
<td>T3a, N0</td>
<td>5 (11)</td>
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<tr>
<td>T3b, N0</td>
<td>30 (67)</td>
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</table>

Overall Survival

![Overall Survival Graph](image)
COXEN prediction of treatment outcome in patients treated with neoadjuvant MVAC

MSKCC & UVA

NCI-60 Panel

Gene Expression Model

Evaluation of Model on Cells or Tumors (PCR)

Takata (Japan)

Tumor Size Reduction vs. COXEN Score

Downstaging vs. COXEN Score

Downstaging defined as ≤pT1 or ≤T1 after two courses of MVAC
**Conclusion:**

- COXEN Score thresholding can provide patient cohorts more (A) or less (B) likely to respond to therapy depending on clinical requirements.
Coxen prediction of treatment with neoadjuvant MVAC
Coxen GEM vs. Conventional GEM prediction

**MSKCC & UVA**

- NCI-60 Panel
- Tumor Sample Taken
- MVAC Drugs
- COXEN
- N=87

**Takata (Japan)**

- Tumor Sample Taken
- MVAC Chemotherapy treatment
- Biomarker Development
- COXEN GEM
- N=18

**Evaluation of Model on Test Sets**

- **A**: Takata (Japan) N=45
  - Predicted Responders (32)
  - Predicted Nonresponders (13)
  - P = 0.00474
  - Months: 0 1 2 22 43 64 86 07 2
- **B**: Als (Denmark) N=14
  - Predicted Responders (4)
  - Predicted Nonresponders (10)
  - P = 0.0198
  - Months: 0 1 2 22 43 64 86 07 2 96
- **C**: Takata (Japan) N=45
  - Predicted Responders (27)
  - Predicted Nonresponders (18)
  - P = 0.00117
  - Months: 0 1 2 22 43 64 86 07 2
- **D**: Takata (Japan) N=27
  - Predicted Responders (4)
  - Predicted Nonresponders (10)
  - P = 0.0198
  - Months: 0 1 2 22 43 64 86 07 2 96
- **E**: Takata (Japan) N=27
  - Predicted Responders (20)
  - Predicted Nonresponders (7)
  - P = 0.0527
  - Months: 0 1 2 22 43 64 86 07 2 96
- **F**: Als (Denmark) N=14
  - Predicted Responders (7)
  - Predicted Nonresponders (7)
  - P = 0.73
  - Months: 0 1 2 22 43 64 86 07 2 96
- **G**: Als (Denmark) N=14
  - Predicted Responders (7)
  - Predicted Nonresponders (7)
  - P = 0.0777
  - Months: 0 1 2 22 43 64 86 07 2 96
Can COXEN predict clinical outcome in other cancer types beyond bladder cancer?
Can COXEN Algorithm Predict Combination Chemotherapy Responses in patients?

- **Studies**
  - **Data Search**
    - Collect studies with clinical response to therapy and gene profiling information (same criteria as single drug breast trials)
    - Drug sensitivity information on NCI60 panel
  - **Breast cancer: 5 studies**
    - Patients with stage I-III breast cancer
    - Adj Tam or Neoadjuvant Docetaxel single agent
    - Neoadjuvant paclitaxel and fluorouracil-doxorubicin-cyclophosphamide (T/FAC), Overall survival
    - Outcome: Pathological response
  - **Ovarian: 2 studies**
    - Carbo-Paclitaxel or Cisplatin Chemotherapy
    - Outcome: Overall survival
- **Analysis:** Similar to that shown for BLA-40 combination chemotherapy but instead of in vitro validation, we would validate our predictions by the clinical outcome
Validation: Can COXEN predict patient treatment outcome in breast cancer clinical trials?

Primary tumor response to neoadjuvant docetaxel (DOC-24)

Survival following adjuvant tamoxifen (TAM-60)

- Responder: Tumor size
- Sensitive: COXEN Prediction
- Non-responder: Tumor size
- Non-responder: COXEN Prediction

(p-value = 0.033)

(p-value = 0.021)
Validation: Can COXEN Algorithm Predict T/F Responses in breast cancer patients?
Validation: Can COXEN Algorithm Predict Clinical Responses in Ovarian cancer patients?

- N=85 advanced-stage serous ovarian cancers
- Treated with neoadjuvant platinum-based chemotherapy

- N=119 advanced-stage serous ovarian cancers
- Treated with platinum-based chemotherapy

P-VALUE = 0.002

P-VALUE < 0.001
Conclusion

- COXEN offers predictive ability for:
  - Known single and combination chemotherapeutic drugs in bladder cancer cell lines
  - Treatment responses of known single and combination drugs in bladder cancer patients.
  - Clinical outcomes for several major cancer types (breast, bladder and ovarian)
  - Clinical outcomes prediction similar (better?) than conventional (using patients) GEM derivation
COXEN can discover new drugs for bladder cancer that have a high probability of working in patients.

- Uses *in vitro* data
- Can identify drugs with high likelihood of success in patients weeks after initial synthesis with minimal cost!
COXEN in drug discovery
Computational screening of 45,000 compounds

NCI-60 Panel
Expression Profiling
IC50 for 45K Compounds

Human Bladder Cancer Cells
N=40 (BLA-40)

Drug Leads

Human Bladder Cancer Tissues
COXEN in drug discovery

Screening results

Compound Library (N=45,678)

COXEN Screening

N=858 Compounds Effective in Bladder Cancer

COXEN Score

Rank: 1

234 Cisplatinum
234 Carboplatin
5FU/ Pemetrexed
Adriamycin
Gemcitabine
Paclitaxel
Methotrexate
Vinblastine

Drugs Currently Used in Bladder Cancer

233 Compounds better than Cisplatin in Bladder Cancer
Identification of 115 novel putative anticancer compounds for human bladder cancer with COXEN SCORES > 90

Top candidate: NSC 637993

Validation of NSC 637993 potency on BLA-40

COXEN Scores of NSC 637993 activity in the BLA-40

In vitro evaluation of NSC 637993 activity in BLA-40 cells
Validation of new drug effectiveness in human bladder cancer cells

NSC 637993

40 human bladder cancer cell lines (BLA-40)

Log base 10 of molar concentration of NSC 637993
Specificity (for bladder cancer) of 637993

- Breast
- Leukemia
- Ovarian
- CNS
- Melanoma
- Prostate
- Colon
- NSLC
- Renal

Sensitive cell lines at dose concentration $10^{-6}$
NSC 637993 and C1311

- **NSC 637993 (CID 367849)**
  - No data in vivo or patients
  - Dead end?
  - Discussions with DTP staff led to chemists in Poland who described an entire family of compounds...

- **C1311 (CID 132127)**
  - Analog of NSC 637993
  - Top hit in COXEN screen
  - Member of imidazoacridinone anticancer drug family
  - Structure is closely related to mitoxantrone and losoxantrone
  - Orally bioavailable
  - Effective in **xenograft models** of breast and colon cancer
  - In **Phase 2 trials in breast and colon cancer and IBD, MS**
NSC 637993 and C1311

In vitro effect of C1311 on human bladder cancer cells

In vivo attainable concentration

Drug Concentration (μM)

Percent Cell Number at 48 hrs vs. No drug

C1311

NSC637993

HT1197
253J-BV
KU7
UMUC6
253J-P
UMUC3
T24T
**Conclusion:** COXEN can discover new drugs for bladder cancer

**But WAIT!**......are not most human cancers treated with **combination** chemotherapy?

- **Question:** What do we need to figure out how to use new drugs in rational combinations?

- **Answer:** We need to know their mechanism of action and molecular target!
Mechanism of action of new drug

Concept of Synthetic Lethality

<table>
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<th>Mutation</th>
<th>Phenotype</th>
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<tbody>
<tr>
<td>Gene A</td>
<td>Alive</td>
</tr>
<tr>
<td>Gene B</td>
<td>Alive</td>
</tr>
<tr>
<td>Gene A &amp; B</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Use of Synthetic Lethality to Define Drug Mechanism of Action

<table>
<thead>
<tr>
<th>Mutation in Gene A</th>
<th>Phenotype</th>
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</thead>
<tbody>
<tr>
<td>Addition of Drug 1</td>
<td>Alive</td>
</tr>
<tr>
<td>Gene A and Drug 1</td>
<td>Dead</td>
</tr>
</tbody>
</table>

A and B act redundantly or in parallel pathway

A and Drug 1 act redundantly or in parallel pathway
Exploring the Mode-of-Action of bioactive compounds by Chemical-Gene Genetic Profiling and SGA in Yeast.

Nature Methods, 2006, 3, 601-605

Yeast is in low abundance

Yeast is in normal abundance
Validating the Yeast Mode-of-Action of in human bladder cancer xenografts

![Graph showing tumor volume over weeks for different treatments and cell lines.](image-url)

- **No Drugs**
- **C1311[C]**
- **Taxol[T]**
- **C+T**

**T24T** and **UMUC3** cell lines are shown with tumor volume (mm³) on the y-axis and weeks from subcutaneous inoculation on the x-axis. Statistically significant differences are indicated by * (p < 0.05) and ** (p < 0.01).**
Plans for the 115 COXEN hits in bladder

115 Drug Leads

**Human Bladder Cancer Cell Panel (BLA-40)**

**IC50 for Lead Compounds**

**B**

**Yeast Mutant panel**

**Chemical Genomic Profiling and SGA**

**Rational combinations**

**Clinical Trials**

**Best Novel Agents**

**Xenograft response for Lead Compounds**

**ADME / Tox**
Conclusion

**COXEN Biomarkers**

- Predicted clinical outcomes in patients in 4 cancer types
- Discovered new drugs in bladder cancer
- Predictions are equivalent to patient developed biomarker panels
- Prediction for targeted agents are superior to target analysis readouts

...and can do all this from **ONLY IN VITRO DATA**
“Personalized Therapy”: Match patient’s tumor with drug treatment

- COXEN applied to patient tissue removed at surgery
- COXEN provides recommendations for:
  - Best FDA approved chemotherapy drugs and targeted agents
  - Best drug combination regimen:
    - Established combinations: GC, MVAC etc…
    - Novel combinations with FDA approved agents

Discovery of new compounds (and Drug Rescue) for most cancer types

- By virtue of the algorithm design:
  - Discovered drugs should be effective in patients
  - Improve compound attrition rate in clinical trials
- Significantly reduced discovery timelines
Clinical Applications
Personalized Therapy

Applications
Neoadjuvant
Adjuvant
Metastatic

Pre Tx Tumor Harvest

RNA Extraction

Sample Profiling

Gene Expression Model (GEM) Score Calculation

MVAC Score
- Responder
  - MVAC Therapy Option
- Non Responder
  - Is patient a GC Therapy Responder?
    - Yes
      - Empiric MVAC or GC Selection or Clinical Investigations (i.e. COXEN “Miniscreen”)
    - No

GC Score
- Responder
  - GC Therapy Option
- Non Responder
  - Is patient a MVAC Therapy Responder?
    - Yes
      - Empiric MVAC or GC Selection or Clinical Investigations (i.e. COXEN “Miniscreen”)
    - No
Novel Trial Designs: 2 Birds 1 Stone
Personalized Therapy + New Drugs Evaluation

Stratification Factors
KPS: good (> 70) v poor (70)
TNM staging: M0 v M1
Alk. phos. group: normal v high
Disease: measurable v nonmeasurable
Number of sites: ≤3 v > 3
Visceral metastasis: no v yes

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- **Theodorescu Lab**
  - Paul Williams PhD
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  - Chris Moskaluk

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  - Mark Conaway

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  - Stuart Berr

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  - John Karpovich
Thank you to my PMH/OCI teachers and mentors
Liberty is to the collective body, what health is to every individual body……..*Without health no pleasure can be tasted by man*……..without liberty, no happiness can be enjoyed by society.

*Thomas Jefferson*

*Founder University of Virginia*