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Conflicts of interest

No financial conflict of interest to disclose.

I will be discussing research for which provisional patent applications have been filed on which I am listed inventor.

- U.S. Patent 63/010,327: Forecasting individual patient response to radiotherapy with a dynamic carrying capacity model (provisional)
Quantitative Personalized Oncology

@EnderlingLab

**Mission:** To integrate quantitative modeling into oncology decision making

**Vision:** Optimal adaptive cancer therapy for each patient

**Strategy:**
- understand clinical needs
- foster synergistic collaborations
- build calibrated and validated mathematical models of cancer dynamics that provide
  - dynamic biomarkers *and*
  - actionable triggers for treatment personalization
Treatment pipeline

Enderling et al., Trends In Cancer, 2019
Quantitative Personalized Oncology

Preclinical studies

- in vitro
- in vivo

Historic clinical data

Mathematical model

- develop
- calibrate
- validate

Virtual patient

Patient-specific clinical data

Aherne et al. (Enderling), Oral Oncol, 2020
..our ability to predict the future is severely limited by the complexity of the equations...

Stephen Hawking
Predictive modeling standard

- Identify putative biomarker
- Develop mechanistic model
- Calibrate model with existing data
- Validate model with untrained data
- Evaluate predictive performance for known treatment
- Simulate and predict unknown treatment

- “A climate computer model is not trusted unless it can predict the past.”
- “Any proposed set of statistics is not considered to be of any value unless it can be used to show outcomes of a past [baseball] season”.

Prostate Cancer

1 in 41 men will die from PCa

1 in 9 men diagnosed with PCa

Hormone Therapy

Abiraterone/Enzalutamide

Abiraterone/Enzalutamide

Tumor burden
# Prostate Architecture

<table>
<thead>
<tr>
<th>BASAL COMPARTMENT</th>
<th>SECRETORY COMPARTMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stem</td>
<td>Transit Amplifying</td>
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- **Prostate in Castrate**
- **Prostate in Intact**

**Androgen Independent** | **Androgen Dependent**

*Isaacs & Coffey, Prostate, 1989*
Prostate Cancer stem cells are treatment resistant

ADT: androgen deprivation therapy - chemical castration

mouse tissues

human tissues

Lee et al., J. Mol. Cell Biol., 2013
• Does a PCaSC model fit clinical data?
• Can early treatment response predict outcomes?
• Can the model predict alternative treatment that would improve outcomes?
Intermittent Hormone Therapy

Final Results of the Canadian Prospective Phase II Trial of Intermittent Androgen Suppression for Men in Biochemical Recurrence after Radiotherapy for Locally Advanced Prostate Cancer

Clinical Parameters

Nicholas Bruchovsky, MD, PhD
Laurence Klotz, MD
Juanita Crook, MD
Shawn Malone, MD
Charles Ludgate, MD
W. James Morris, MD
Martin E. Gleave, MD
S. Larry Goldenberg, MD

BACKGROUND. This prospective Phase II study was undertaken to evaluate intermittent androgen suppression as a form of therapy in men with localized prostate cancer who failed after they received external beam irradiation.

METHODS. Patients who demonstrated a rising serum prostate-specific antigen (PSA) level after they received radiotherapy and who were without evidence of distant metastasis were accepted into the study. Treatment in each cycle consisted of cyproterone acetate given as lead-in therapy for 4 weeks, followed by a combination of leuprolide acetate and cyproterone acetate, which ended after a total of 36 weeks.


- 103 patients with intermittent ADT
- PSA measurements every four weeks
Prostate specific antigen (PSA) dynamics during ADT

Four no more: The ‘PSA cutoff era’ is over

Prostate-specific antigen (PSA) testing has been mired in controversy throughout the short time it has been a clinical tool for detecting prostate cancer. During the first decade after it was approved for prostate cancer screening, the dogma prevailed that the upper limit of normal was 4.0 μg/L. Healthy patients with values above this cutoff were believed to be at risk of prostate cancer and were usually advised to undergo biopsy. Patients with levels below this threshold were told they had normal readings and were reassured that they did not have prostate cancer.

An individual patient’s PSA value is only part of the equation. Other risk factors need to be considered, such as his age, race, family history, findings on digital rectal examination, prostate size, results of earlier prostate biopsies, percent free PSA ratio, and whether he takes a 5-alpha reductase inhibitor. Moreover, PSA levels in men who have undergone treatment for prostate cancer are completely independent of the reference ranges in widespread laboratory use, making such references and thresholds even more meaningless in this setting.
5 parameters \( \left( p_s, \lambda, \rho, \alpha, \varphi \right) \) that we can tune to fit the model PSA dynamics to clinical PSA dynamics.
Intermittent Androgen Deprivation

Final Results of the Canadian Prospective Phase II Trial of Intermittent Androgen Suppression for Men in Biochemical Recurrence after Radiotherapy for Locally Advanced Prostate Cancer

Clinical Parameters

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S. Larry Goldenberg

Cancer

107(2), 389-395, 2006

Number of patients: 70
Total data points: 3,101
Avg. data points / patient: 43

Training Set
Test Set
Model training

A. Patient 029 (Continuous Responder)

- PSA (µg/L)
- Days

B. Patient 101 (Resistant in 4th Cycle)

- PSA (µg/L)
- Days

Brady-Nicholls et al., Nat. Commun. 2020
Model training

Identify putative biomarker

Develop mechanistic model

Calibrate model with existing data

Validate model with untrained data

Evaluate predictive performance for known treatment

Simulate and predict unknown treatment

Brady-Nicholls et al., Nat. Commun. 2020
Simultaneous model training

A. Patient 029 (Continuous Responder)

- PSA (μg/L)
- PCaSC
- Days

B. Patient 101 (Resistant in 4th Cycle)

- PSA (μg/L)
- PCaSC
- Days

C. Simulated PSA vs Measured PSA

- $R^2 = 0.74$

D. Self-Renewal Rate, $\rho_s$

- Resp.
- Resist.

E. ADT Cytotoxicity, $\alpha$

- Resp.
- Resist.

Brady-Nicholls et al., Nat. Commun. 2020

Identify putative biomarker
Develop mechanistic model
Calibrate model with existing data
Validate model with untrained data
Evaluate predictive performance for known treatment
Simulate and predict unknown treatment
Model validation

(a) Patient 091 (Continuous Responder)

PSA (µg/L)

Data
Model (P)

Days

0
500
1000
1500

Slowly increasing

(b) Patient 033 (Resistant in 3rd Cycle)

PSA (µg/L)

Days

0
200
400
600
800

Rapidly increasing

(c) Simulated PSA vs Measured PSA

$R^2 = 0.63$

(d) Self-Renewal, $P_s$

ADT Cytotoxicity, $z$

Brady-Nicholls et al., Nat. Commun. 2020
Research Questions

- Does a PCaSC model fit the data?
- Can early treatment response predict outcomes?
- Can the model predict alternative treatment that would improve outcomes?
‘Hurricane prediction model’

A

2nd Cycle Response Prediction

\[ P(\Omega) = 0.02 < \kappa_2 \]

Responsive

Responding to T_x (98%)

B

3rd Cycle Response Prediction

\[ P(\Omega) = 0.097 < \kappa_3 \]

Responsive

Responding to T_x (90.3%)

Patient 017 (Cont. Responder)

Patient 054 (Resistant in 3rd Cycle)

\[ P(\Omega) = 0.235 < \kappa_2 \]

Responsive

PSA increasing during T_x (23.5%)

Responding to T_x (76.5%)

\[ P(\Omega) = 0.466 > \kappa_3 \]

Resistant

PSA increasing during T_x (46.6%)

91% Predictive Power!
Research Questions

• Does a PCaSC model fit the data?

• Can early treatment response predict outcomes?

• Can the model predict alternative treatment that would improve outcomes?
Should we give concurrent chemotherapy early (castration naive) or late (castration resistant)?
Added Docetaxel improves outcomes
Trend toward early DOC for castration naive pts

Brady-Nicholls et al., Nat. Commun. 2020
Can we predict who’d benefit from added chemo?
Early Docetaxel benefits patients with higher PCaSC self-renewal rates

Brady-Nicholls et al., Nat. Commun. 2020
Research Questions

• Does a PCaSC model fit the data?
• Can early treatment response predict outcomes?
• Can the model predict alternative treatment that would improve outcomes?
Summary

- evaluated PSA dynamics as dynamic biomarker

- PCaSC mathematical model of ADT response/resistance

- trained for PCa patient cohort and individual patients

- validated on untrained data set

- predict response to given therapy with 91% accuracy

- makes testable predictions of alternative treatment protocols
Collaborators

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Dr. Tian Zhang, Duke
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Dr. Jingsong Zhang

Dr. Robert Gatenby

U.S. Patent 62/944,804 (provisional)
Reality check

• All models are wrong - some are useful [George Box]

• As simple as possible (given sparse data), but not simpler than necessary [Albert Einstein]

• Model can only proof ideas wrong, but never right (plausible at best)

• Many models may explain data equally well, but may predict different outcomes

• VALIDATION VALIDATION VALIDATION !
• Quantitative approaches will **not** replace the oncologist!

• The oncologist who uses quantitative approaches **may** replace the oncologist who does not.
Funding

Active

1 U01 CA244100-01 (Enderling/SPT)
1 R21 CA234787-01A1 (Enderling/RG)
1 U54 CA193489-01 (Gatenby, EOC)

Completed

Miles for Moffitt
DeBartolo Personalized Medicine (x2)
ACS-IRG
IMO workshop (x3)
CoE Evolutionary Therapy
PhD program in Mathematical Oncology

http://moffitt.org/CancerPhd/IMO

- Competitive stipends
- Full tuition coverage
- Full benefits
- Small class sizes

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