Prostate Cancer Management in the Modern Era

Michael E. Cox, PhD
Dept. Urologic Sciences, University of British Columbia
The Prostate Centre at Vancouver General Hospital
Disclosure

I am part of a multidisciplinary research team at the Vancouver Prostate Centre dedicated to translating knowledge gained from laboratory science into clinical practice.

DISCOVERY & VALIDATION ⇒ FUNCTION ⇒ HUMAN TESTING

Tumour Bioprofiling

MicroArray Facility
- mRNA Profiling
- Protein Profiling
- SNP Profiling
- Gene function arrays

Molecular Pathology
- Tissue Microarrays
- Molecular Imaging

Functional Genomics
- Gene Function
- Animal Models
- Signal Transduction
- Metastases

Proof-of-Principle

Therapeutic Development
- Drug delivery, pK
- Pharmacology & Toxicology
- Pharmacogenomics
- GLP

Translational Trials
- Clinical Trials Unit

I am a co-discoverer, and will discuss investigational use, of compounds covered by: Cherkasov A, Rennie PS, Cox ME, Hsing MMK, Butler MS, Roshan-Moniri M. HUMAN ETS-RELATED GENE (ERG) COMPOUNDS AS THERAPEUTICS AND METHODS FOR THEIR USE. US Provisional Patent.
Acknowledgements

**UBC & Vancouver Prostate Centre**
- Paul Rennie
- Artem Cherkasov
- Emma Guns
- YZ Wang
- Lawrence McIntosh
- Ladan Fazli
- *Jacob Gordon*
- Ankur Midha
- Hans Adomat

**FHCRC**
- Janet Stanford
- Beatrice Knudsen
- Pete Nelson
- Michael Hsing
- *Mani Moniri*
- Miriam Butler
- Desmond Lau
- Sam Lawn
- Yubin Guo
- Daiana Becker-Santos
- Manju Sharma
- Mitali Pandey
- Elaine Vickers
- *Mazyar Ghaffari*
- Manuel Altamirano-Dimas
- Melanie Lehman

*The Terry Fox Research Institute*
- L’Institut de recherche Terry Fox
- The Canadian Cancer Society
- Société canadienne du cancer
- CIHR
- IRSC
- Prostate Cancer Canada
- Pacific Northwest Prostate Cancer SPORE
- Roman M. Babicki Fellowship in Medical Research
### Canadian Cancer Rates by Site

#### Incidence

<table>
<thead>
<tr>
<th>Males</th>
<th>102,900 New cases</th>
<th>Females</th>
<th>99,500 New cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>21,600 21.0%</td>
<td>Breast</td>
<td>25,700 25.8%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>14.1%</td>
<td>Lung and bronchus</td>
<td>14.1%</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>14.0%</td>
<td>Colorectal</td>
<td>11.7%</td>
</tr>
<tr>
<td>Bladder</td>
<td>6.4%</td>
<td>Body of uterus and uterus NOS</td>
<td>6.6%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4.3%</td>
<td>Thyroid</td>
<td>5.3%</td>
</tr>
<tr>
<td>Kidney and renal pelvis</td>
<td>4.0%</td>
<td>Non-Hodgkin lymphoma</td>
<td>3.6%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3.6%</td>
<td>Melanoma</td>
<td>3.1%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3.4%</td>
<td>Oral</td>
<td>3.1%</td>
</tr>
<tr>
<td>Oral</td>
<td>3.1%</td>
<td>Pancreas</td>
<td>2.6%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2.5%</td>
<td>Leukemia</td>
<td>2.4%</td>
</tr>
<tr>
<td>Stomach</td>
<td>2.1%</td>
<td>Kidney and renal pelvis</td>
<td>2.3%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>1.7%</td>
<td>Bladder</td>
<td>2.1%</td>
</tr>
<tr>
<td>Liver</td>
<td>1.7%</td>
<td>Cervix</td>
<td>1.5%</td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>1.7%</td>
<td>Oral</td>
<td>1.5%</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1.6%</td>
<td>Stomach</td>
<td>1.3%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1.5%</td>
<td>Brain/CNS</td>
<td>1.3%</td>
</tr>
<tr>
<td>Testis</td>
<td>1.1%</td>
<td>Multiple myeloma</td>
<td>1.2%</td>
</tr>
<tr>
<td>Larynx</td>
<td>0.9%</td>
<td>Liver</td>
<td>0.6%</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>0.5%</td>
<td>Esophagus</td>
<td>0.5%</td>
</tr>
<tr>
<td>Breast</td>
<td>0.2%</td>
<td>Hodgkin lymphoma</td>
<td>0.5%</td>
</tr>
<tr>
<td>All other cancers</td>
<td>10.7%</td>
<td>Larynx</td>
<td>0.2%</td>
</tr>
<tr>
<td>All other cancers</td>
<td>8.9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Mortality

<table>
<thead>
<tr>
<th>Males</th>
<th>41,700 Deaths</th>
<th>Females</th>
<th>37,100 Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung and bronchus</td>
<td>26.1%</td>
<td>Lung and bronchus</td>
<td>26.4%</td>
</tr>
<tr>
<td>Prostate</td>
<td>9.6%</td>
<td>Prostate</td>
<td>13.2%</td>
</tr>
<tr>
<td>Breast</td>
<td>4,900</td>
<td>Breast</td>
<td>4,900</td>
</tr>
<tr>
<td>Pancreas</td>
<td>5.8%</td>
<td>Pancreas</td>
<td>6.5%</td>
</tr>
<tr>
<td>Bladder</td>
<td>4.0%</td>
<td>Bladder</td>
<td>4.0%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4.0%</td>
<td>Leukemia</td>
<td>3.2%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>3.8%</td>
<td>Esophagus</td>
<td>3.2%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3.6%</td>
<td>Non-Hodgkin lymphoma</td>
<td>3.6%</td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>3.1%</td>
<td>Brain/CNS</td>
<td>3.1%</td>
</tr>
<tr>
<td>Stomach</td>
<td>3.0%</td>
<td>Stomach</td>
<td>2.7%</td>
</tr>
<tr>
<td>Kidney and renal pelvis</td>
<td>2.9%</td>
<td>Kidney and renal pelvis</td>
<td>1.8%</td>
</tr>
<tr>
<td>Liver*</td>
<td>2.2%</td>
<td>Liver*</td>
<td>1.7%</td>
</tr>
<tr>
<td>Oral</td>
<td>2.0%</td>
<td>Oral</td>
<td>1.1%</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1.9%</td>
<td>Multiple myeloma</td>
<td>1.9%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1.8%</td>
<td>Melanoma</td>
<td>1.2%</td>
</tr>
<tr>
<td>Larynx</td>
<td>0.8%</td>
<td>Larynx</td>
<td>0.2%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.2%</td>
<td>Thyroid</td>
<td>0.3%</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>0.2%</td>
<td>Hodgkin lymphoma</td>
<td>0.1%</td>
</tr>
<tr>
<td>Breast</td>
<td>0.1%</td>
<td>Breast</td>
<td>0.1%</td>
</tr>
<tr>
<td>Testis</td>
<td>0.1%</td>
<td>Testis</td>
<td>0.1%</td>
</tr>
<tr>
<td>All other cancers</td>
<td>12.7%</td>
<td>All other cancers</td>
<td>12.1%</td>
</tr>
</tbody>
</table>

---

*Canadian Cancer Statistics 2016*
Male Cancer Incidence & Mortality Rates 1987-2016

Canadian Cancer Statistics 2016

1 in 8

PSA Screening

>40%
still 1 in 27
Prostate Cancer Development & Progression

- Normal Prostate
- Histological Cancer
- Local Disease
- Metastatic Disease

Image by Seward Hung ©1998
Prostate Cancer Symptoms

- Need to urinate frequently, especially at night
- Difficulty starting or holding back urination
- Weak or interrupted urine
- Painful or burning urination
- Erectile difficulties
- Painful ejaculation
- Blood in urine or semen
- Frequent pain or stiffness in the lower back, hips, or upper thighs

symptoms not typically helpful!
Early Detection Saves Lives!!

Suspicious DRE &/or Elevated PSA

Prostate Biopsy

PROSTATE SELF-EXAMINATION
CANADIAN CANCER SOCIETY

PCA3.org
<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Small, uniform glands with minimal nuclear changes</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Medium-sized acini, still separated by stroma but more closely arranged.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>The most common finding in prostate cancer biopsies. Marked variation in glandular size and organization, infiltration of stromal and neighboring tissues.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Markedly atypical cells with extensive infiltration into surrounding tissues.</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Sheets of undifferentiated cancer cells.</td>
</tr>
</tbody>
</table>

**Gleason Score** = most frequent grade + 2\(^{nd}\) most frequent grade
# A Contemporary Prostate Cancer Grading System

<table>
<thead>
<tr>
<th>Gleason Patterns</th>
<th>Gleason Score</th>
<th>Grade Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3 distinct, discrete, individual glands</td>
<td>≤6</td>
<td>I</td>
</tr>
<tr>
<td>4 fused, cribriform, or poorly-formed glands, or glomerular</td>
<td>3+4=7</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>4+3=7</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>4+4=8</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>3+5=8</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>5+3=8</td>
<td>III</td>
</tr>
<tr>
<td>5 comedo necrosis, cords, sheets, solid nests, single cells</td>
<td>4+5=9</td>
<td>V</td>
</tr>
<tr>
<td></td>
<td>5+4=9</td>
<td>V</td>
</tr>
<tr>
<td></td>
<td>5+5=10</td>
<td>V</td>
</tr>
</tbody>
</table>
High cure rates in low-intermediate risk diseases, but ~20% of men will progress.
"The ctDNA stuff is all for advanced disease. Local disease, especially patients on surveillance, have such low amounts of tumour that is not turning over that we wouldn’t detect anything at this time with our platforms." KC.
• **Cell free DNA (cfDNA) and circulating tumour DNA (ctDNA)**
  - cfDNA: DNA found freely in the circulation
  - Higher cfDNA concentration in cancer patients vs. healthy controls
  - ctDNA can constitute <1% - 90% of total cfDNA

• **Genomic changes in ctDNA are detectable in mCRPC patients**
  - CN gains/losses, mutations, rearrangements
Androgens Control Prostate Development

Andrew V. Schally
Nobel Prize 1977

Locke J. MSc Thesis 2009
Androgens: Mechanism of Action

Feldman & Feldman, Nat Rev Cancer, 2001

Nicholas Bruchovsky
Androgens Regulate Prostate Cancer

Established the androgen pathway as the 1st credentialized therapeutic target in prostate cancer

Charles B. Huggins
Nobel Prize, 1966
Androgen Pathway Targeting

LHRH Analogues

Surgical Castration

Steroid Synthesis Inhibition

Anti-androgens
Prostate Cancer: Managing Castration Resistance

AR continues to play a pivotal role in maintaining the castration-resistant phenotype.

Chen et al., Lancet Oncol. 2009; Hofland et al., Cancer Res. 2010
CRPC Immuno-Oncology

Sipuleucel-T
Monocytes enriched from patient's leukocytes
- Culture
- Activation of antigen-presenting cells
- Antigen processing
- Infused into patient

Ipilimumab
- Tumour antigen
- Activated antigen-presenting cell
- CTLA4
- CTLA4-specific antibody
- T cell stimulation
- Tumour-specific T cell
- Tumour lysis

PROSTVAC-VF
Vaccine product expressing PSA and costimulatory molecules
- Infection and necrosis of epithelial cells
- PSA
- Debris
- Tumour lysis

GVAX
Irradiated prostate cancer cells expressing GM-CSF
- Recruitment and activation of antigen-presenting cells
- Tumour lysis

Yap, Nat. Reviews Drug Discovery, 2016
First human therapy with $^{177}$Lu-labeled PSMA617

**Imaging**

- **$^{68}$Ga-11-HBED-CC**
  - December 13
  - 3.3 GBq
  - $^{177}$Lu-617
  - 03.02.14
  - PSA level 14
  - 4.0 GBq
  - $^{177}$Lu-617
  - 05.05.14
  - PSA level 38
  - Imaging
  - $^{68}$Ga-11-HBED-CC
  - July 14
  - PSA level 8

```
  PSA [µg/L]

  40  30  20  10  0

  8

  3.3 GBq

  4.0 GBq
```

Afshar-Oromieh, Kratochwil et al., Department of Nuclear Medicine, University Hospital Heidelberg
Mechanisms of CRPC Progression

From Quinn 2013: ^1^Heinlein, Endocr Rev. 2004; ^2^Hu, Expert Rev Endocrinol Metab. 2010
Cholesterol is the critical testosterone precursor.
Cholesterol levels are elevated in PCa bone metastases.

Expression of cholesterol regulatory factors are increased in PCa bone metastasis.

Androgen receptor promotes cholesterol influx and synthesis.
Cholesterol Synthesis: Mevalonate Pathway

Tobert, Nat Rev Drug Discov, 2003
Simvastatin Delays CRPC and Reduces Intratumoral Steroidogenesis

Gordon et al., Prostate Cancer and Prostatic Dis. 2016
Statins inhibit growth of PCa models

Recent well-designed epidemiologic reports indicate that statins decreased risk of advanced PCa.

*PSA decline similar for ABI and ENZA patients on and off statins, but statin using ABI patients had greater PSA decline and tended to have improved progression-free survival

Clinical trials could assess the potential use of statins in combination with MAB to prevent prostate cancer progression

*Chehrouri et al., unpublished
Scavenger Receptor Class B Type I (SR-BI)

- Ubiquitous, but concentrated in hepatic and steroidogenic tissues (adrenals, testes)

- Expression is increased PCa vs normal prostatic epithelium

- Imports cholesterol from lipoproteins (HDL, LDL, VLDL)

Inhibiting Cholesterol Import & Synthesis as part of MAB to Manage CRPC Progression

Gordon et al, 2015 (unpublished)
Molecular Taxonomy of Primary PCa

333 primary prostate cancers

- mutations
- copy-number alterations
- mRNA expression fusions
- DNA methylation
- microRNA expression
- protein expression

molecular subtypes

Percent of tumors

DNA hypermethylation

AR pathway activity

DNA repair defects

PI3K/RAS/RAF pathway alterations

Olaparib-FDA Breakthrough Therapy Designation for CRPC

A) BRCA1 or BRCA2, ATM

Responding cohort

ATM other

Other

Non-responding cohort

B) A family history of breast or ovarian cancer?

YES

Saliva or blood sample identify germline BRCA1 or BRCA2 mutation

Fresh Tumour Biopsy

Isolate DNA from verified cancer

Identify somatic BRCA1, BRCA2 or ATM mutation

Mutation

No mutation

PARP inhibitor treatment

100% responding (3/3)

90% responding (9/10)

No treatment

12% responding (4/36)

Helleday, Ann Oncol., 2016; Mateo, NEJM, 2015
Targeting ERG to Manage Disease Progression

Why target ERG

- ERG gene fusion in ~45% of PCa patients.
- ERG expression is associated with high Gleason score, advanced tumor stage, metastasis, and shorter survival times.
- ERG promotes metastasis through:
  - Cell migration and invasion,
  - Epithelial-to-Mesenchymal transition,
  - ILK activation and AMOT expression,
  - Epigenetic reprogramming towards a stem cell-like phenotype.
- Persistent ERG expression occurs in mCRPC due to self-promoting expression of wild type ERG and to loss of SPOP.
- ERG status is linked to increased taxane resistance risk.
- No approved ETS-targeted therapeutics are available.

**Hypothesis:** Targeting ERG can disrupt PCa metastatic potential by suppressing ETS-driven angiogenesis, migration, and invasion.
How to target ERG-ETS domain

- ERG DNA-binding (ETS) domain
- Virtual atomic probes
- DNA

Top 0.01% 3M molecules

Docking score

Purchasable chemical space

- Molecular docking
- Medicinal Chemistry
- Chemical Similarity
- Molecular Dynamics
- Structure Activity Relationship

Lower score is better

Butler et al., Oncotarget 2017
VPC-18005 Binding Perturbs ERG-ETS Amino Acids

NMR Spectroscopy

Saturation Transfer Difference Spectroscopy

Butler et al., Oncotarget 2017
VPC-18005 Suppresses ERG Transcriptional Activity

Endoglin EBD-Luc Reporter Assay

ERG Target Gene Expression

Recombinant ERG-ETS EMSA

Butler et al., Oncotarget 2017
VPC-18005 Suppresses Metastatic Potential of ERG PCa Cells

Butler et al., Oncotarget 2017
Clinical Challenges and Opportunities

Clinical Challenges:
Major unmet need for systemic anti-metastatic treatments. Identifying appropriate combinatorial therapeutic opportunities.

Clinical Opportunities:
Neoadjuvant treatment of ERG-positive, low burden disease. Non- or low-metastatic CRPC in combination with ARPIs, to maximize ERG suppression. In combination with chemotherapy, as ERG expressing tumors exhibit increased resistance.

VPC-18005 Development Summary

The small molecule ERG antagonist, VPC-18005:
Directly binds to the ETS DNA binding domain of the ERG protein
Inhibits transcriptional activity and migration capacity of cells
Reduces metastasis in cell and animal models

Clinical Challenges and Opportunities

Clinical Challenges:
Major unmet need for systemic anti-metastatic treatments. Identifying appropriate combinatorial therapeutic opportunities.

Clinical Opportunities:
Neoadjuvant treatment of ERG-positive, low burden disease. Non- or low-metastatic CRPC in combination with ARPIs, to maximize ERG suppression. In combination with chemotherapy, as ERG expressing tumors exhibit increased resistance.

VPC-18005 Development Summary

The small molecule ERG antagonist, VPC-18005:
Directly binds to the ETS DNA binding domain of the ERG protein
Inhibits transcriptional activity and migration capacity of cells
Reduces metastasis in cell and animal models

Clinical Challenges and Opportunities

Clinical Challenges:
Major unmet need for systemic anti-metastatic treatments. Identifying appropriate combinatorial therapeutic opportunities.

Clinical Opportunities:
Neoadjuvant treatment of ERG-positive, low burden disease. Non- or low-metastatic CRPC in combination with ARPIs, to maximize ERG suppression. In combination with chemotherapy, as ERG expressing tumors exhibit increased resistance.
PCFBC has awarded > $1M since 2003 supporting basic researchers and their trainees, patient wellness/knowledge programs such as the Prostate Cancer Supportive Care Program, Centre for Integrated Healing/Inspire Health, and Nurse practitioners in the lower mainland and Victoria.