The Clinico-Genomics of Localized Prostate Cancer: Moving Beyond the Bench

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Disclosures

• I have no relevant disclosures
The Problem of Heterogeneity

Low/Fav. Intermediate Risk
- 80% of all cases
- 7% failing w/in 3 years
- 20,000 cases/year
- 1,400 rapid failures

PROGNOSTIC BIOMARKERS TO INFORM TREATMENT INTENSIFICATION/DEINTENSIFICATION

Pollard et al, 2017
The Last 20 Years: Physical Precision

The Next 20 Years: UNDERSTANDING OF PERSONAL GENETICS (Biological Precision)
Molecular Subtypes...

333 primary prostate cancers

- mutations
- copy-number alterations
- miRNA expression
- DNA methylation
- microRNA expression
- protein expression

molecular subtypes

Dal Pra et al, CCR, 2013

TCGA, 2015

Minner et al, CCR, 2013
CPC-GENE: An Outcomes-Driven ICGC Program

INTERMEDIATE RISK PC

**IGRT Cohort (Radiotherapy)**
- 150 cases
- 150 specimens
- Mostly matched blood
- O₂ measurements
- 10-year median follow-up

**Central Pathology**
- 2-3 Pathologists
- >70% tumour cellularity
- Gleason concordance

**RP Cohort (Surgery)**
- 300 cases
- 350 specimens
- Matched blood
- 8-year median follow-up

**Multiple national TMAs**

**WGS Methylation**
- H3K27Ac
- RNA-Seq
- Proteomics

**OUTCOME!**

All patients reconsented
What Did We Find?

- 477 tumor whole-exomes (coding SNVs)
- 200 whole-genomes (coding/non-coding SNVs, SVs)
- 250 tumor SNP arrays (CNAs)
- 90 RNA microarrays
- 104 DNA methylation arrays
Localized PC is Highly Heterogeneous

Fraser et al, Nature, 2017
Very Few Driver SNVs

<10% recurrence

Fraser et al, Nature, 2017
Novel Structural Variation

Fraser et al., Nature, 2017
Does Any of This Matter?

40 Driver Features

- Clinical T stage
- ACTL6B hyper-methylation
- TCERG1L hypomethylation
- Chr7:61 Mbp translocation
- ATM SNV
- MYC amplification

Fraser et al, Nature, 2017
Tumours Are Not Static...

Spatial genomic heterogeneity within localized, multifocal

ALSO CONSIDER TEMPORAL EVOLUTION

Creative Commons, 2014
Tumour Evolution and Clinical Outcome

Espiritu et al, Cell, 2018
The Localized-Metastatic Axis

Hypothesis: Drivers of aggressive localized PC will be enriched in metastatic disease

CPC-GENE
631 Localized PC
*Fraser et al, Nature, 2017*
*Espiritu et al, Cell, 2018*

SU2C
101 mCRPC
*Quigley et al, Cell, 2018*

72 Driver Genes

113 Driver Aberrations
(31 CNA, 49 SNV, 33 SV)

3,386 Total Driver Aberrations
Driver Enrichment in PC

Fraser et al, 2019 (under review)
Identifying Potential Prognostic Aberrations

- **47/113** Enriched in mCRPC
- **14/47** ≥5% Localized
- **3/14** Associated with 30-month BCR

**Graphical Representation:**
- **MYC Amplification**
- **CHD1 Deletion**
- **ZNRF3 Deletion**

**Statistical Information:**
- Time to BCR:
  - > 30 months
  - ≤ 30 months
- HR = 8.34 (4.10, 17.0)
- P = 4.94 × 10⁻³

**Proportion of Patients**
ZNRF3: A WNT Pathway Inhibitor

- Lost in 11% of localized PC
- Associated with WNT activation
ZNRF3 Deletion is Associated With Poor Prognosis
ZNRF3 Deletion is Associated With Poor Prognosis

TCGA (n = 486)

- ZNRF3 Status
  - Neutral
  - Deletion
- HR = 2.42 (1.44, 4.05)
- P = 8.42 × 10^{-4}

MSKCC (n = 174)

- ZNRF3 Status
  - Neutral
  - Deletion
- HR = 2.28 (1.07, 4.84)
- P = 0.032
Interactions Between Prognostic Biomarkers

Fraser 6-Feature Clinico-Genomic Signature

Percentage Genome Alteration
Summary

• Localized PC genomes are highly heterogeneous within and between patient groups
• Multi-modal genomic/epigenomic indices can identify *clinically-important* subgroups
• Comparative genomics identifies rare drivers in localized disease that portend poor outcomes (tumour evolution!)
• What about the germline?
  – It matters. A lot. I’m around all day to chat...
How Do We Translate?

• GOAL: Prevent progression to metastatic disease
• Intensify or deintensify based on *individual* genomic risk profiles
• Test should be:
  – Accurate
  – Cheap*
  – Applicable across the risk spectrum
  – Capable of simultaneously capturing multiple analytes

* - Cost ≠ value. “Death is cheap.”
What Will The Test Look Like?

- Whole genome sequencing is (probably) not the answer
- Storage and analysis overhead is huge!
- Identify relevant regions of the genome (NOT exomes) and go DEEP!

<table>
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<th>Mutation Type</th>
<th>Mutation Number</th>
<th>Size/Mutation (bp)</th>
<th>Cost (1x)</th>
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<td>Non-coding SNVs</td>
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<tr>
<td>CNAs</td>
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<td>Mitochondrial Genome</td>
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<td>16,569</td>
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<tr>
<td><strong>TOTAL</strong></td>
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<td><strong>42,616,569</strong></td>
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**Design/Validation (In Progress)**

- 10 T/N Pairs
- 2 x 500x Seq
- In silico Validation
- Optimize Loci and Coverage

**Prospective Testing**

- Routine Informed Consenting
- DNA Extraction (Core Biopsies)
- Panel Sequencing (500x Target)
- Data Analysis (<2 weeks)
A Model for Genomics-Driven Clinical Trials

Fraser, JTGG, 2018
An Iterative Process

- Biomarker discovery
- Retrospective validation
- Assay design
- Prospective evaluation
- Regulatory approval
Acknowledgements

The 573 families (...and counting) who have trusted us with their tissues and private medical information – during the most difficult period of their lives.

NONE of this would be possible without them.
A Short Digression on BCR...

- PPV for 10-yr mets = 27%
- What about ‘time to BCR’?
The Germline

- Germline *BRCA2* mutations are associated with very poor clinical outcomes
  - 5yr OS ~60%
BRCA2-Associated Prostate Cancer

**Figure 1** | The genomics of BRCA2-mutant prostate cancer.

(a) Percent genome altered (PGA) and number of SNVs, GRs and CNAs per tumour sample is shown. GRs are stratified by type: orange—deletions (Del), green—inversions (Inv), purple—duplications (Dup), yellow—translocations (Ctx). Y-axis values for CNAs and GRs are in log10-scale. Box plots compare the number of events observed in BRCA2-mutant specimens versus sporadic PCa samples split into two groups by age. Y-axis values are the same as in the adjacent bar plot. Whiskers indicate the maximum and minimum values, the box outline indicates the third and first quartile and the bar indicates the mean. Multiple foci from the same patient are indicated in the same patient covariate colour, where sample type colour indicates IC in blue, IDC in yellow and a mix of IDC and IC in green. Unavailable data is indicated by grey background.

(b) Per gene copy-number profiles of 18 prostate tumour specimens from 14 germline BRCA2-mutation carriers, including 4 patients with multifocal disease. Red indicates gain; blue indicates loss. Rows represent specimens and columns represent genes. Top plots show frequency of each gene per group (BRCA2, n = 14; sporadic PCa arising in individuals 50 years of age or younger, n = 7; sporadic PCa arising in individuals older than 50 years of age, n = 276) and the q-value shown is from a two-sided proportion test comparing BRCA2-mutant and all sporadic PCa samples. Genes are ordered by genomic co-ordinates per chromosome. Multiple foci from the same patient are indicated in the same patient covariate colour, where sample type colour indicates IC in blue, IDC in yellow and a mix of IDC and IC in green.

(c) Key prostate cancer driver genes that are mutated at elevated proportions in BRCA2-mutant PCa relative to sporadic PCa. Columns are patients, rows are genes, a black square indicates a CNA. Bar plots to the right show the frequency of each gene in the three groups (BRCA2, n = 14; sporadic PCa arising in individuals 50 years of age or younger, n = 7; sporadic PCa arising in individuals older than 50 years of age, n = 276).

Robinson et al, Cell, 2015
Taylor, Fraser, Boutros, Bristow, Nat Comms, 2017
BRCA2-Mutant Cancers: Ludicrous Mode

Fraser, Taylor, Boutros, Bristow, Nat Comms, 2017
Can We Do This for Sporadic Tumours?

Discovery:
- 230 intermediate-risk prostate cancer genomes
- ~ 560,000 SNPs (LD pruned)
- 34 somatic events
  - Copy Number Aberrations
  - Coding and Non-coding SNVs
  - Genomic Rearrangements
  - Methylation

Fraser et al. Nature 2017
Consider *PTEN* Deletions

Houlahan *et al.* Nature Genetics, in press
Or ETS Fusions (TMPRSS2:ERG)

Houlahan et al. Nature Genetics, in press
Hundreds of Germline-Somatic Interactions

Houlahan et al. Nature Genetics, in press
Consider A Driving (and Prognostic!) Methylation Event

TCERG1L-5’

Houlahan et al. Nature Genetics, in press
Allele-Specific Expression Differences

Houlahan *et al.* Nature Genetics, in press
Brastianos et al, under review
Rouette, Fraser, Boutros, Nat Gen (under review)
Rouette, Fraser, Boutros, Nat Gen (under review)