Mapping what drives cancer &
taking the guesswork out of chemotherapy

Prof Sean Grimmond
• Understanding the molecular basis of cancer

• Using Genomics to map out what drives each cancer type

• The International Cancer Genome Consortium

• Using cancer atlases to find the Achilles’ Heel in cancers, one patient at a time
APGI-2057:
DNA: The cell’s computer hard drive
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- 3,000,000,000,000 bases
- 23 chromosomes
- 30,000 genes
- 1,000s of gene networks

- 3,000,000,000 bits of data
- 23 partitions to the drive
- 30,000 files
- 1,000s of programs
Tempting fate with your computer ....

- Change code
- Rearrange code
- Delete files
- Move files
- Make extra copies
- Join files...
Tempting fate with your cell’s hard drive….

- Change code
- Rearrange code
- Delete genes
- Move genes
- Make extra copies
- Join genes…
Cancer arises due to accumulated damage to DNA:

- Mutagens, radiation, inflammation
- Random DNA damage

Diagram:

- Relax DNA repair
- Over-ride built in senescence
- Acquire a continuous growth signal
- Turn off “internal suicide” system

Diagram shows the progression from normal cells to malignant cells through successive mutations.
Decoding a Cancer Genomes

1. Create 2 heaps of 320,000 copies of a 24 jigsaw puzzles (2,000,000 double sided jigsaw puzzles - all of the same sort of picture)....

2. Randomly sample 1,000,000,000 pieces from each pile.

3. Match the pieces back using the pictures on the boxes despite 50,000,000 pieces looking identical to 1000s locations on the main picture and 20,000,000 pieces having random printing errors.

4. Find the 30 pieces with deliberate changes in some of the “tumour” puzzle only....
Genomics Revolution

Human Genome Project:

International effort
US$2 billion

Wolfson Wohl Cancer Centre: £5000
Monday-Sunday.

2015: WWCRC @£1500
Monday-Wednesday
ICGC Goal:

• To obtain a comprehensive description of all genomic changes in 50 different tumor types and/or subtypes which are of clinical and societal importance across the globe.

• 500 tumours per tumour type/subtype
Currently committed: 37 projects, >17,000 patients.
Cancer is Complex
A New Vision for Clinical and Translational Cancer Research

“We can no longer think of cancer as one disease. Even something like lung cancer could be hundreds of distinct cancers, each defined by specific molecular characteristics requiring different treatment approaches. This makes research more challenging, but the payoff for patients will be enormous.”

MICHAEL P. LINK, MD, PRESIDENT OF ASCO
A New Model for Therapeutic Development

OLD MODEL: Treatment is determined by a tumor’s location in the body, without regard to the molecular characteristics of the patient or the tumor.

NEW MODEL: Treatment is determined by key molecular “hubs” that must be targeted within the cells, and is only administered to patients whose tumors are found to have those hubs – potentially without regard to the tumor’s location in the body.
Genome Directed Oncology

Molecular Phenotyping for all candidate targets
Are there therapeutic targets for PDAC?

1. DNA damage repair defect: 10%**
2. RNF43 mutation: 8%*
3. RNA processing defects: 8%*
4. ROBO- SLIT-SRGAP mutation: 7%*
5. ATM mutation: 6%**
6. SMARCA4 defects: 5%
7. RICTOR mutations: 3%**
8. HER2 Amplification: 3%**
9. MET Amplification: 2%**
10. KRAS wildtype**: 5%**
11.

Chang et al, 2014
Exceptional PDAC responder:

**ICGC_0006**
UNSTABLE / SOMATIC BRCA2 Biallelic
BRCA signature Rank 14
Complete radiological & CA19.9 response

- SURGERY
- RECUR
- PLATINUM THERAPY
- ADJUVANT GEMCITABINE

CA 19.9 (U/mL)

MONTHS

Upper Limit of normal

ALIVE
Patient Cancer Genome Report: APGI-1992

Somatic simple mutations
- ABCC9
- ADAMTS20
- AMAC1L2
- B3GALT4
- BLID
- BRCC3
- C3orf62
- C11orf94
- CACNA1C
- CAPN11
- CENPE
- COLEC11
- CTCF
- FRMD6
- GPR137B
- IQCH
- KIR3DX1
- KLKB1
- LEMD2
- PIK3CD
- PXDN
- RPA1
- SIGLECP3
- SLC26A5
- TIMELESS
- ZNF432
- ZNF132

Genes affected by Inter-chromosomal translocations
- FGFR1 (bi-allelic)
- LYPD6B
- NRXN3
- SFTPB
- TNPO1
- TP53BP2
- ZNF468

Genes affected by intra-chromosomal breakpoint
- 133 genes

Expressed Fusion transcript
- ATE1 – KLRAQ1

Differential Methylation & Expression
- 1800 genes

Preclinical models?
- Xenograft
- Cell Line
• Recent advances in Genome science are making it possible to determine the molecular basis of a patient’s cancer.

• International efforts to build large cancer genome atlases that stands to become the foundations for cancer research for the next decade.

• These technological advances are starting to provide tangible clinical benefit (cancer surveillance, and improving treatment selection).