A Darwinian Eye View of Cancer
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8 million cases/year

-50% 'developed' countries

-50% 'less developed' countries

Breast
Prostate
Colon
Skin
Liver
Cervix
Naso-pharynx
Oesophagus

Migration impact

99% adult versus 1% childhood/young adults

Epithelial carcinomas
\[ \text{‘Developmental’ cancers (in utero initiation)} \]

Extended latencies (years/decades)

Multiple genetic events; Genetic instability

Intractable
Curable

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Risk of cancer

- Malignant adult cancer: 1 in 3 (→ 80 yrs)
- Malignant paediatric cancer: 1 in 800 (→ 15 yrs)
- Benign tumours
  - Adult: ubiquitous
  - Children: common

Man versus beast?

Cancer: the very basics

![Tumour and Cancer](image)

- Localised growth of cells
- Normal architecture/function
- Mutant clone of cell

Benign

- Disseminated, disorganised growth
- Loss of function
- Multiple mutations in clone

Malignant

Cancer cell biology

- Territorial expansion of a mutant clone
- Hijack of vital tissue functions
- Step-wise acquisition of mutations and single cell adaptation/selection through bottlenecks

= The proximate cause
DNA-damaging ‘exposures’
Sequential mutations (~1-3% genome)
in stem cells

Cancer roulette

Genetics
Diet
Modulators of risk

DNA-damaging ‘exposures’
Sequential mutations

‘Nothing in biology makes sense except in the light of evolution’

Theodosius Dobzhansky, 1973
"No biological problem is solved until both the proximate and the evolutionary causation has been elucidated. Furthermore, the study of evolutionary causation is as legitimate a part of biology as is the study of the usually physico-chemical proximate causes."

E. Mayr, 1982, *The Growth of Biological Thought*

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**Darwinian medicine**

- Applying the concepts of evolutionary biology to the problems of medicine
- Discovering why, as a species (and as individuals) we are vulnerable to common (chronic) diseases
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Darwinian medicine

‘Design’ by natural selection inevitably involves compromises, limitations and trade-offs. Under some circumstances, these can result in malfunction and disease.

Limitations of evolutionary adaptation by natural selection

1. Lack of perfection in evolutionary engineering - just selects from the best available
2. Evolutionary adaptation has ‘no eyes to the future’ (G. Williams)
3. Natural selection will happen
4. The only fitness test of ‘natural selectability’ in evolution is - survival and reproductive success

= Lack of intelligent design!

Evolutionary medicine and cancer

1. Lack of perfection in evolutionary engineering
   ➞ Design limitations and flaws
   ➞ Trade-offs
   ✤ ‘Risky' DNA, ‘risky' cells, ‘risky’ physiological processes and ‘risky’ people
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Design limitations/trade-offs

- DNA sequence fidelity/break repair: Mutation/recombination; Error-prone (NHEJ)
- Embryo engineering: Phenotypic plasticity, invasiveness, DNA damage
- Oxidative metabolism and inflammation: Mutagenic
- Angiogenic responses to anoxia/wound healing: Tumour rescue; Migration routes
- Stem cells: Clonal escape

Stem cells - a good idea?

- 'Invented - 450-500 myr
- Retain protozoan propensity for self-replication: socially regulated
- Adaptation
  - Developmental plasticity -> complex embryo engineering
  - Tissue resilience -> regeneration, longevity

Programmed stem cell behaviour and cancer risk

- Internal, signal circuitry controls
- Networked intercellular signals
- Architectural constraints
- Sensitivity to p53-dependent senescence

Stem cells

- Quiescent
- Transient cycling
- Apoptosis
- Differentiation

Stop
Go
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Programmed stem cell behaviour and cancer risk

- DNA damage
- Regenerative stress
- Quiescent
- Persistent cycling
- Apoptosis
- Differentiation

- Telomerase, proliferative longevity or immortality
- Migratory, barrier-breaching functions

Evolutionary medicine and cancer

2. Genetic diversity, increased numbers and competition/stress always result in selection

Survival of the fittest

Evolution of robust cancer cells

Clonal evolution of a cancer

Bottlenecks/selective pressure

Mutations 1 2+ 3+ 4+ 21
But not that simple

- Complex non-linear dynamics
  - Variation in population structure, pace, number/sequence of genetic events
  - +/- accelerated by genetic instability
- Reciprocal interactions between cancer cells and microenvironmental stroma
- Evolutionary steps driven by mutations in rare, clonogenic stem cells

Implications of the Darwinian development of cancer clones

- Most tumours never emerge through the bottlenecks:
  - Cancer is commonly initiated but promotion to full malignancy is rare (- promotion factors are critical)
- Cells emerging through all bottlenecks are robust and genetically diverse:
  - Likelihood of drug resistance
  - Early intervention beneficial
  - Tackle microenvironment/angiogenesis (Darwinian by-pass)
- Each cancer clone has a unique evolutionary trajectory
  - Tailoring treatment to genotype/phenotype of tumour

Evolutionary medicine and cancer

3. Evolutionary adaptation has 'no eyes to the future'

- Mismatches between genes/environments
- Stone age genetics versus exotic "modern" lifestyles
  - Cancer risk ↑
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#### 'Adaptive' feature

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<th>Behavioral mismatch</th>
<th>Cancer</th>
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#### Logic of breast cancer risk

- Oestrogens ↓
  - Persistent proliferative stress to stem cells

- Early pregnancy
- Breast feeding
- Diet/exercise

- Levels of oestrogens
- # cycles
- Net signal strength

- Genetics

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<td>Immune system programming: infection</td>
<td>'Hygienic' infancy</td>
<td>Childhood leukemia</td>
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<tr>
<td>anticipated/required</td>
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Evolutionary medicine and cancer

4. The only evolutionary logic is to increase survival/reproductive fitness

→ Post-reproductive longevity is a luxury

- Ageing health problems are immune to natural selection (P. Medawar)
- Ageing bodies decay in efficiency trade-offs/"disposable soma"
  (T. Kirkwood)

Ageing and cancer

~90% is 'post-reproductive' (50+ years)

- Deficient defences
  - DNA repair
  - Anti-oxidation
  - Immunity

- Limited stem cell pools?
  - Proliferative stress?

- Time for chronic exposures to promote cancer clones,
  i.e. exacerbates all other evolutionary design/mismatch problems
The cancer prescription

- The paradox: we all have 'risky' genes and cells: we are not engineered to perfection!
- We are not 'engineered' at all!
- Our socially diverse and exotic lifestyles are mismatched with our genetic programming which evolved as an adaptation to very different lifestyles
- Lifestyle genotoxic exposures can be chronic or persistent (decades)
- The (second) paradox: we live longer - more time for accidents to happen!

Risk + time = chance
Accidents will happen