LFS – Always primed for cancer?

George Pantziarka TP53 Trust

Pan Pantziarka

Background

- The George Pantziarka TP53 Trust (www.tp53.org.uk) – was founded following the death of my son in April 2011
- Scientist working with the Anticancer Fund (www.anticancerfund.org) – primarily looking at drug repurposing in oncology
- Have also published two scientific papers on LFS – and this talk is based on that work

July 28 1993 – April 25 2011

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Anticancer Fund

What is TP53?

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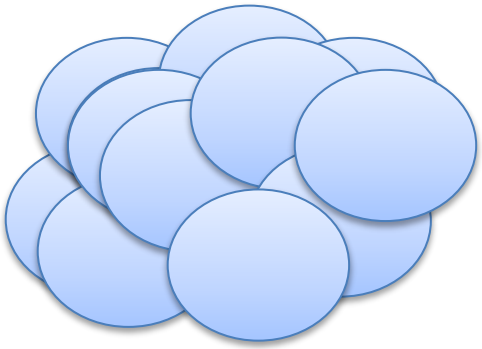
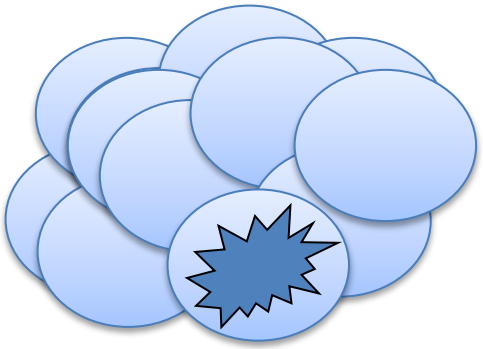
Genetics Home Reference

The guardian of the genome

The *TP53* gene provides instructions for making a protein called tumor protein p53 (or p53). This protein acts as a tumor suppressor, which means that it regulates cell division by keeping cells from growing and dividing too fast or in an uncontrolled way.



Healthy cells



A cell suffers DNA damage….

p53 kicks in and zaps damaged cell….

(Most) People with Li Fraumeni Syndrome have a mutated TP53 gene – they have no natural anti-cancer defences… Lifetime risk of cancer is around 90%.

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But...

More than just a tumour suppressor

Chronic inflammation and oxidative stress

Immune Dysregulation

TP53

Angiogenesis

Metabolic Reprogramming

Tissue-specific factors

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Primed for cancer: Li Fraumeni Syndrome and the pre-cancerous niche

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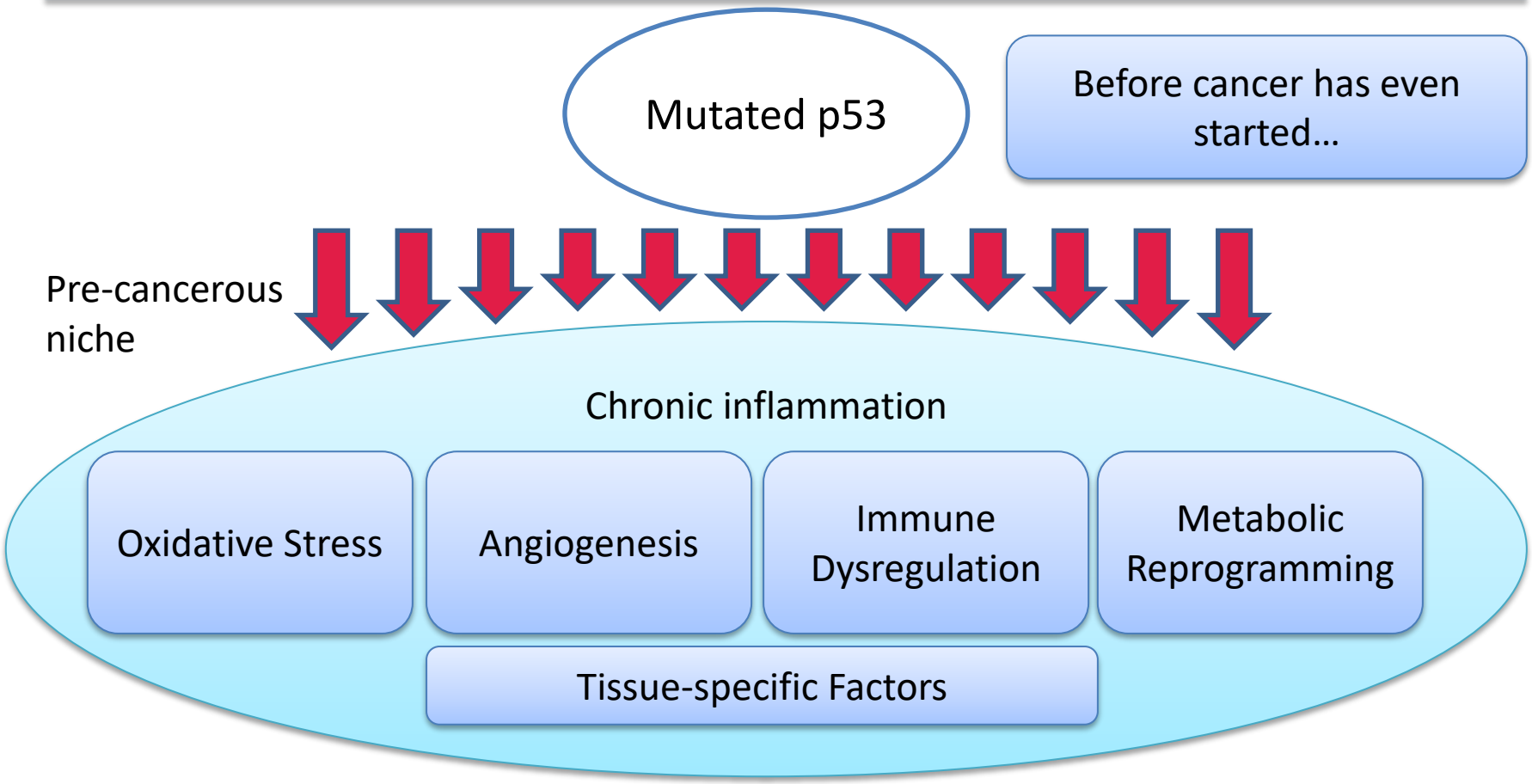
The pre-cancerous niche



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In the wider population chronic inflammation is associated with cancer incidence.

Evidence?

What do we know from people with LFS *before* they get cancer?

- People with LFS have higher background levels of oxidative stress compared to family members without a TP53 mutation
- Cells from people with LFS secrete a higher amount of a chemical called VEGF – a key driver of angiogenesis
- A key marker for 'reverse Warburg' cellular metabolism is reduced cav-1 levels this finding has been confirmed in people with LFS compared to non-affected family members
- An analysis of breast cancer in women with LFS found that 84% of invasive tumours were hormone responsive, with a majority of these also being positive for Her2/neu, this is higher than for a comparable non-LFS population (driven by p53/PGE2)

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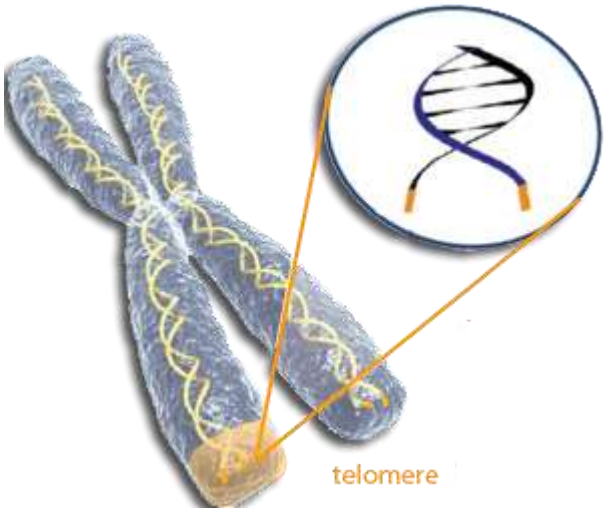
And



Telomeres cap the ends of chromosomes – when they go you get DNA damage

- Telomere length in blood cells of people with TP53 mutations is **shorter** than that of non-TP53 individuals
- For people with LFS the **shorter** their telomeres the **earlier** they get cancer
- **Chromosome instability** is a common trait of fibroblast cells from Li-Fraumeni families
- This means we have pockets of **abnormal** cells in patients with LFS before they get cancer

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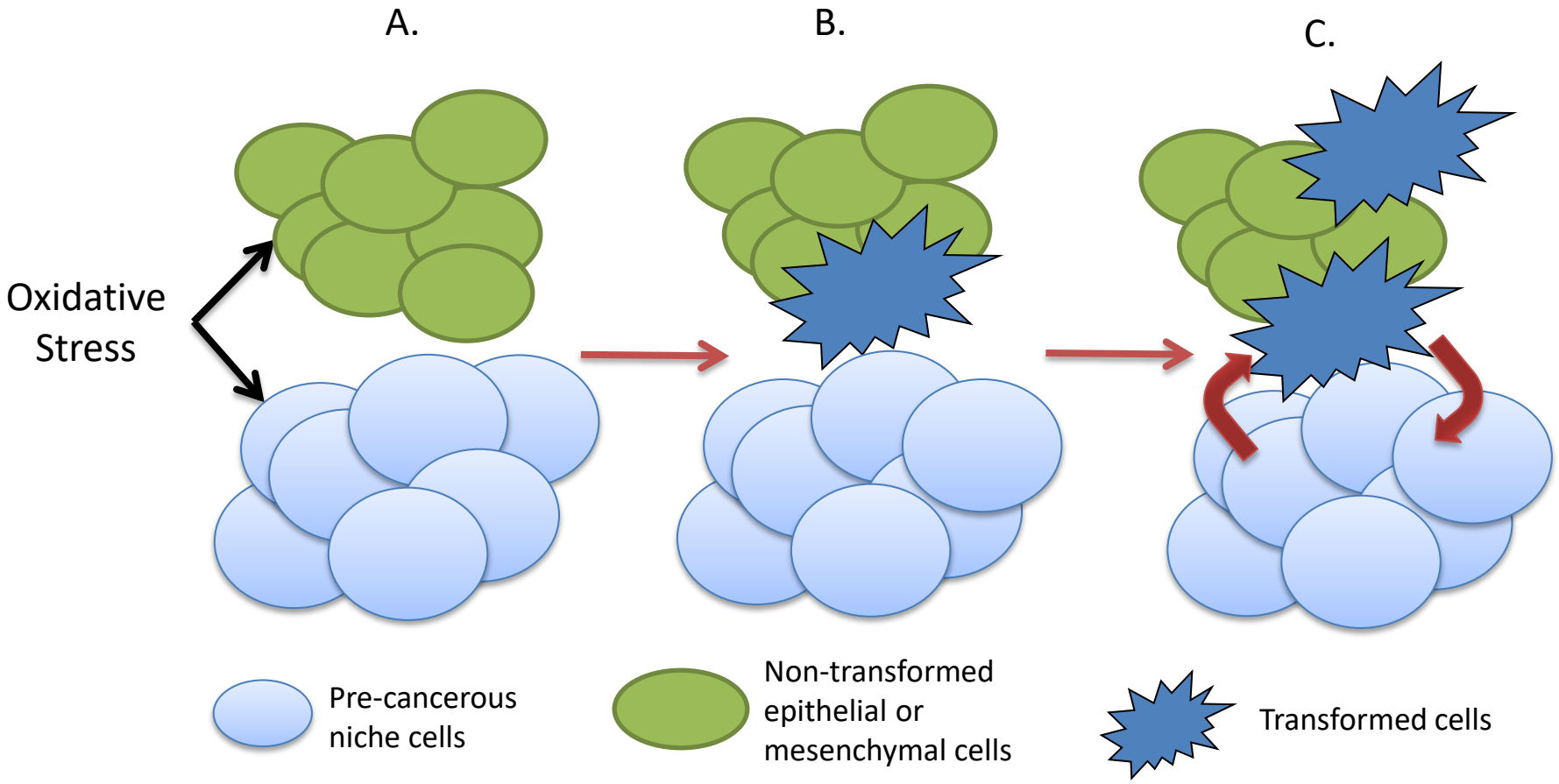
What does this mean?



(A). Cells heterozygous for TP53 and with shortened telomeres undergo telomere attrition in response to oxidative stress. (B). Telomere crisis may lead to loss of heterozygosity and malignant transformation. (C). Malignant cells in contact with chronically inflamed pre-cancerous niches proliferate and initiate tumour growth

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Conclusions?

- TP53 has multiple additional effects over and above classical tumour suppressor functions
- People with LFS have high levels of oxidative stress, shorter telomere lengths etc – even when they don't have cancer
- Mutated p53 is associated with the formation of pre-cancerous niches – places in the body that are supportive of cancer
- Once cancer is initiated then it can take off because of the supportive niche…

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Is it all bad news?

- Gene therapy is a long way off – no current way to permanently fix mutated TP53
- Early days in drugs to tackle the tumour suppressor action of p53
- But we do have drugs that can tackle some of the drivers of the pre-cancerous niche…
  - Metformin…
  - Aspirin…
  - Anti-inflammatories…

This may be a way to *decrease* the risk of cancer developing in people with LFS

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Where next?

- More research needed to confirm the ‘pre-cancerous niche’ idea
- Animal studies to test different drugs for reducing cancer incidence in LFS
- Need to consider life-style and other factors…
  - Diet
  - Stress-reduction
  - Exercise

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Questions?

Thanks for your time…

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