Drug Repurposing And Reducing Cancer Incidence in Li Fraumeni Syndrome?

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George Pantziarka TP53 Trust

Cancer Risk in LFS

- LFS is associated with a germline mutation in TP53 (around 70% of patients)
- Cumulative cancer incidence 50% by age 31 years among females and 46 years among males
- Nearly 100% by age 70 years for both sexes
- Approximately 49% of those with a first cancer develop one or more cancers after a median of 10 years
- Risk management strategies revolve around active surveillance protocols and risk-reducing mastectomy

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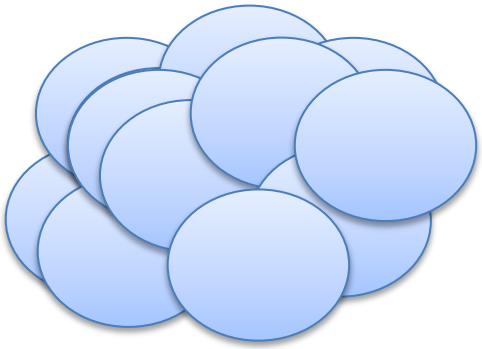
What is TP53?

NIH U.S. NATIONAL LIBRARY OF MEDICINE

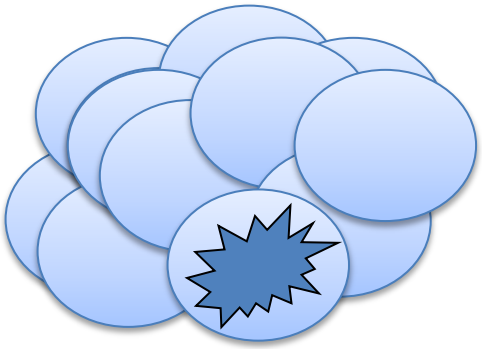
Genetics Home Reference

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… In people with Li-Fraumeni-like Syndrome there is often a mutation in another gene that is related to TP53

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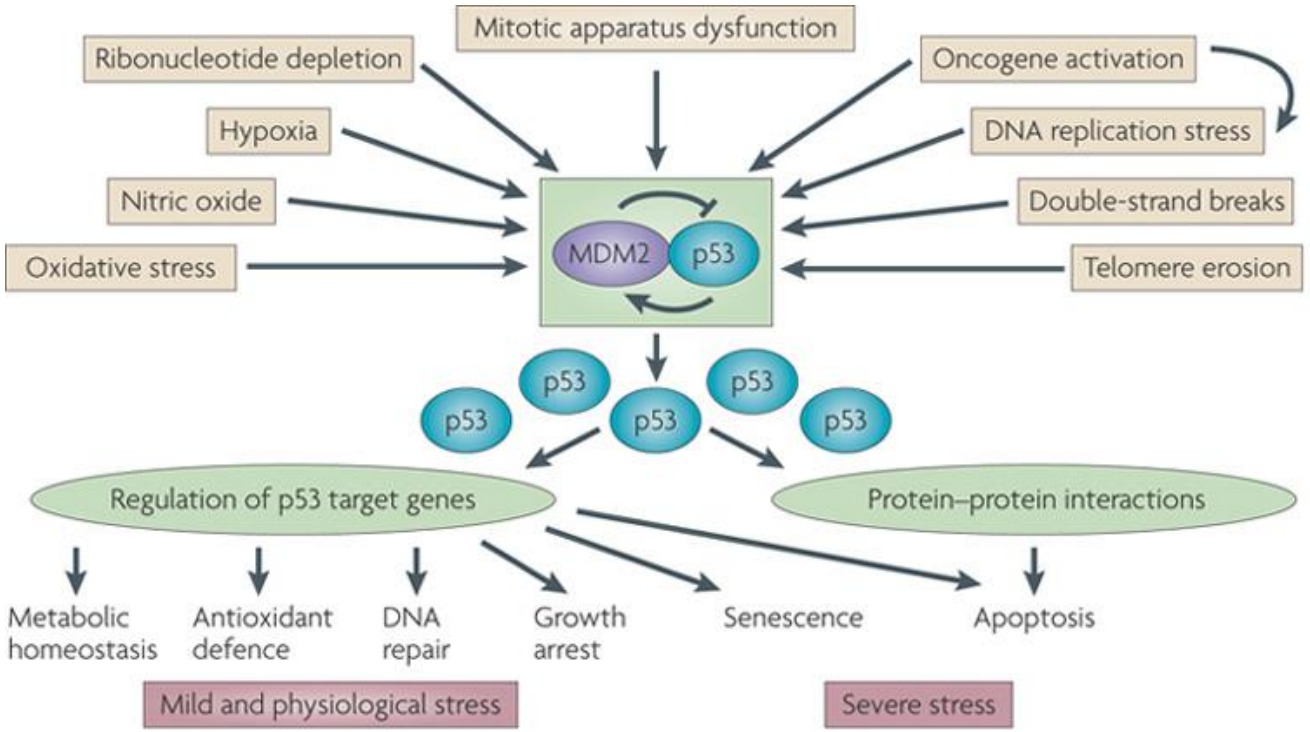
More than a tumour suppressor



Levine AJ and Oren M (2009) **The first 30 years of p53: growing ever more complex**. *Nature Reviews Cancer*, **9**(10), pp. 749–758.

As our understanding of p53 has expanded – and continues to expand – it is time to integrate this into our picture cancer formation in LFS.

- Metabolic Reprogramming
- Immune Dysregulation
- Tissue-specific factors
- Angiogenesis
- Chronic inflammation and oxidative stress

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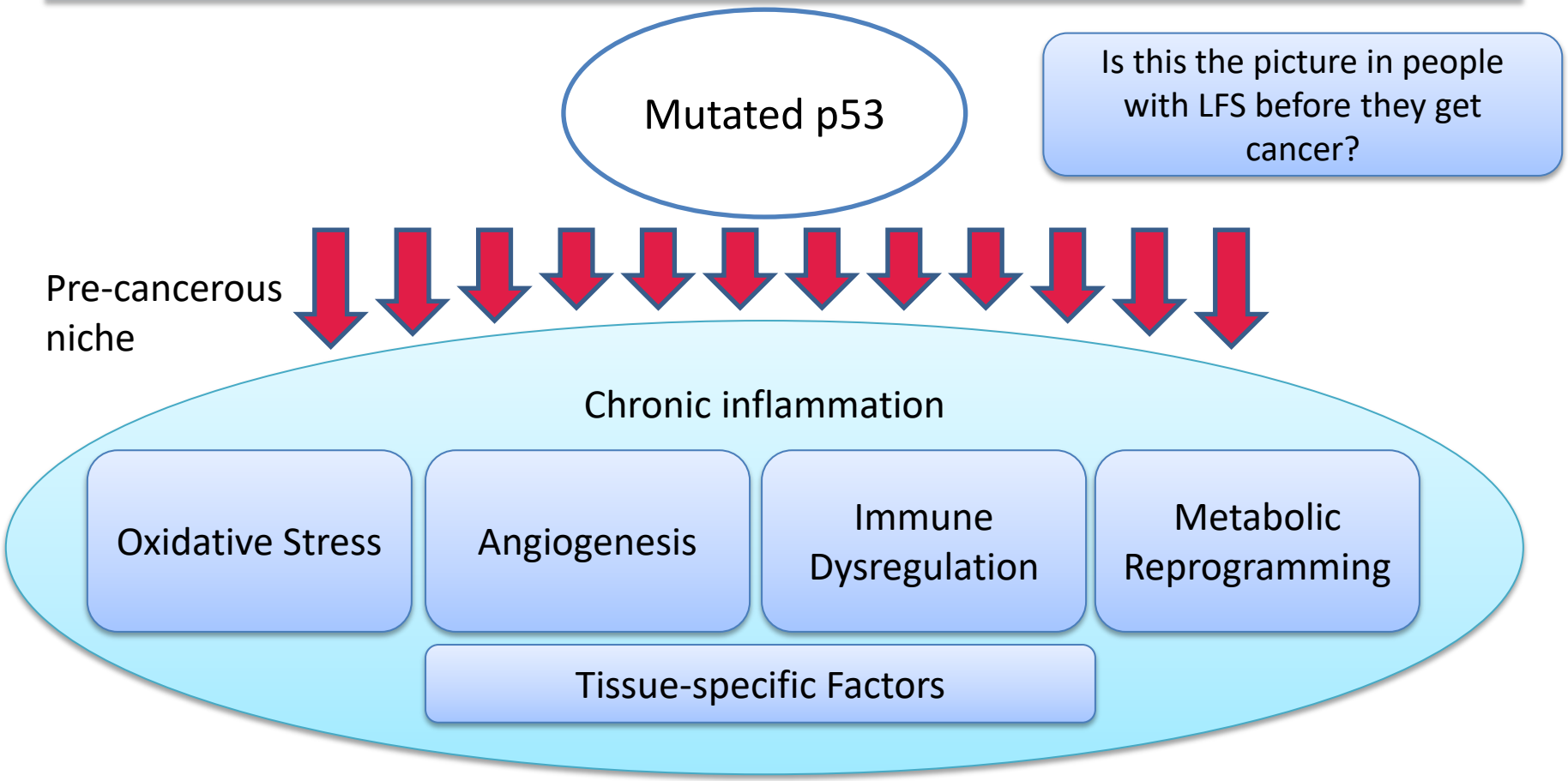
The pre-cancerous niche



Pantziarka P (2015) **Primed for cancer: Li Fraumeni Syndrome and the pre-cancerous niche.** *Ecancermedicalscience*, **9**, p. 541.

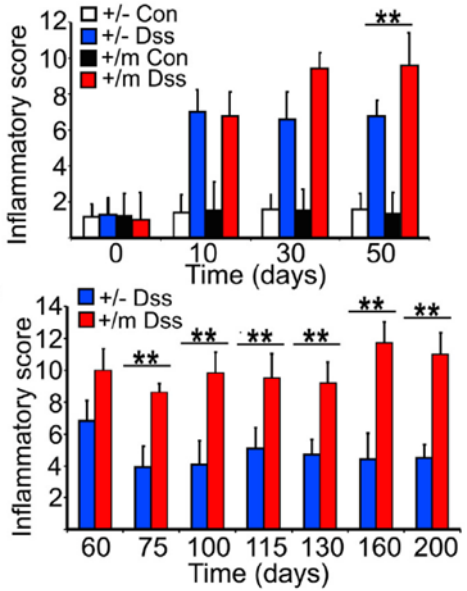
In the wider population chronic inflammation is associated with increased cancer incidence.

Chronic inflammation/Oxidative Stress

Mutant p53 (R175H,-R273H, and D281G) shown to *induce* NF-κB (a major driver of inflammation)

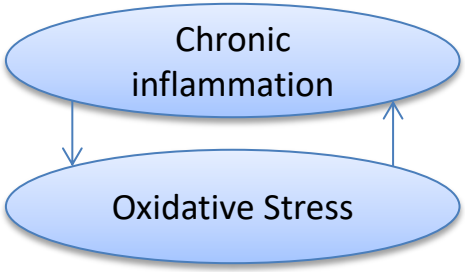
Scian MJ et al. (2005) **Tumor-derived p53 mutants induce NF-kappaB2 gene expression.** *Molecular and cellular biology*, **25**(22), pp. 10097–110.

Chronic inflammation is well-characterised as a driver of cancer formation, cancer progression and metastasis. The key question for the pre-cancerous niche hypothesis is whether mutant p53 initiates the cascade…



LFS-type mice (R273H) showed prolonged NF-κB activation and signs of chronic colonic inflammation on DSS treatment. Treatment with NSAID sulindac inhibited carcinogenesis.

Cooks T et al. (2013) **Mutant p53 prolongs NF-κB activation and promotes chronic inflammation and inflammation-associated colorectal cancer.** *Cancer cell*, **23**(5), pp. 634–46.



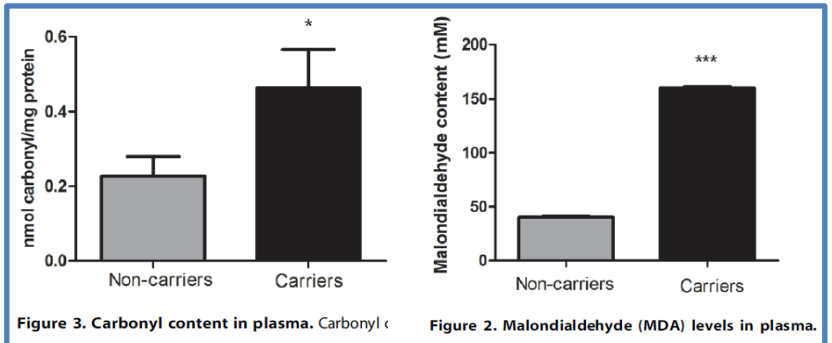


Figure 3. Carbonyl content in plasma. Carbonyl

Figure 2. Malondialdehyde (MDA) levels in plasma.

Data from LFS patients show high basal levels of oxidative stress

Macedo GS et al. (2012) **Increased Oxidative Damage in Carriers of the Germline TP53 p.R337H Mutation**. *PLoS ONE*, **7**(10), p. e47010.

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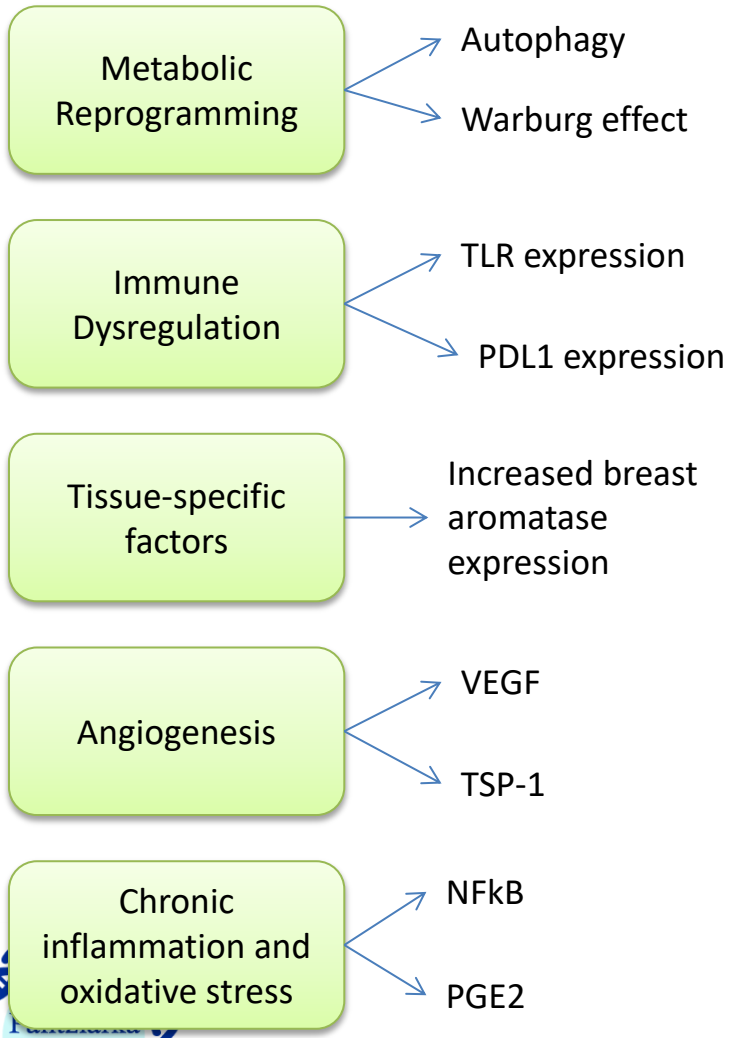
The LFS host environment



- Increased levels of oxidative stress in people with LFS
- LFS fibroblasts increased levels of VEGF
- LFS fibroblasts have shortened telomeres
- Decreased level of cav-1 (metabolic marker)
- Increased oxidative metabolism
- Higher levels of hormone responsive breast cancer

Currently no studies of general health in people with LFS have been carried out. Do they have more or less inflammatory illness, infections, diabetes, rheumatism etc?

More research is required to understand whether people with LFS have the same range of health conditions as the general population

Pantziarka P (2015) **Primed for cancer: Li Fraumeni Syndrome and the pre-cancerous niche.** *Ecancermedicalscience*, **9**, p. 541.

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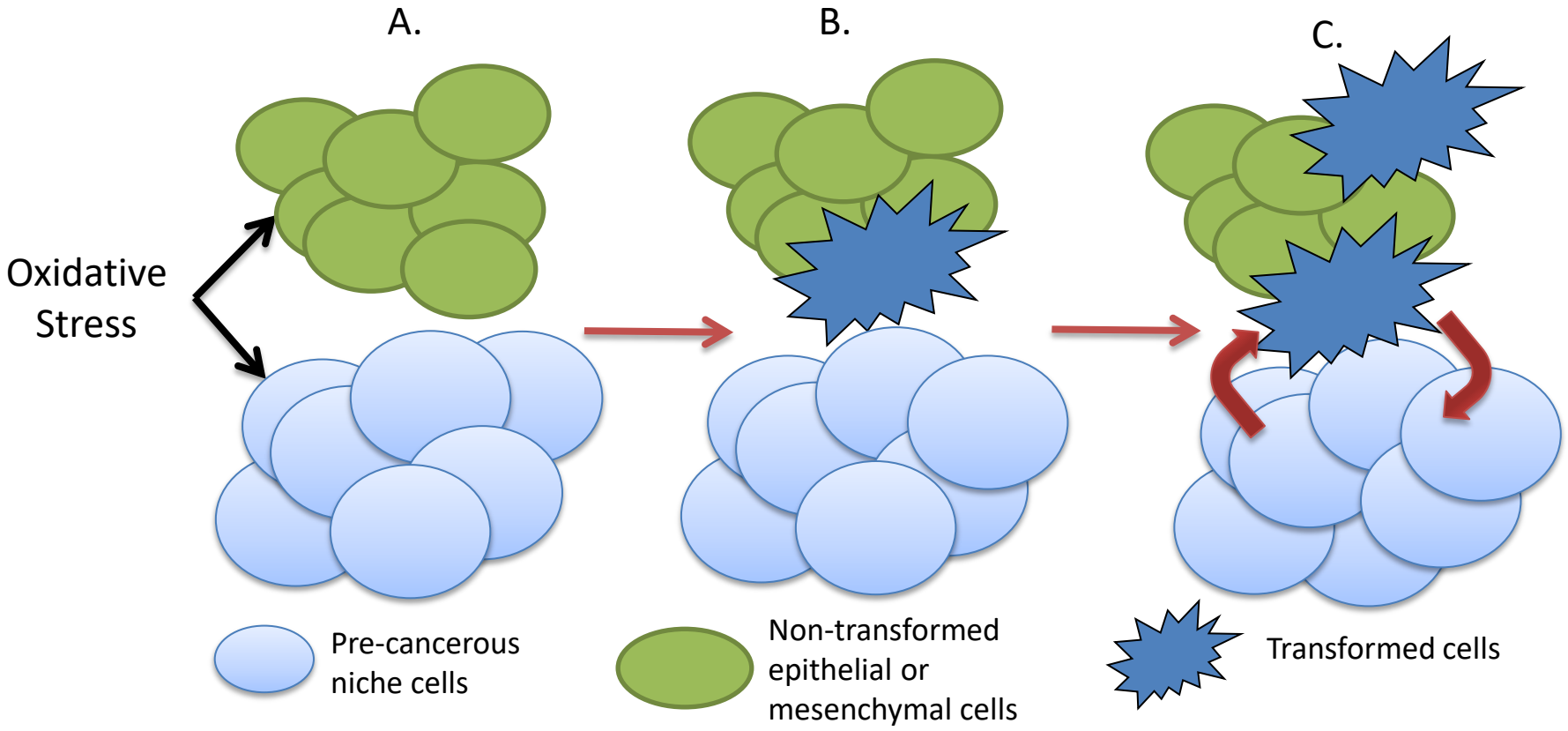
Is this how cancer forms in LFS?



(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

Can we alter the host environment to inhibit aspects of this process?

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Drugs for cancer prevention

Drugs for cancer prevention should impact p53 function directly or via changes to *the pre-cancerous niche*

Ideal characteristics of candidate drugs

- Good tolerability – need to be designed for chronic (regular) use
- Low toxicity – particularly need to know if they cause cell damage (i.e. increase the risk of cancer)
- Well characterised – existence of extensive human data an advantage compared to newly designed drugs
- Low cost – small patient population
- Known mechanisms of action
- Evidence of anti-cancer activity (from test tube, animals and human data)

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Drug repurposing

Repurposing is the use of a licensed drug for a new medical indication

Speed up development lifecycle

User-friendly

Examples:

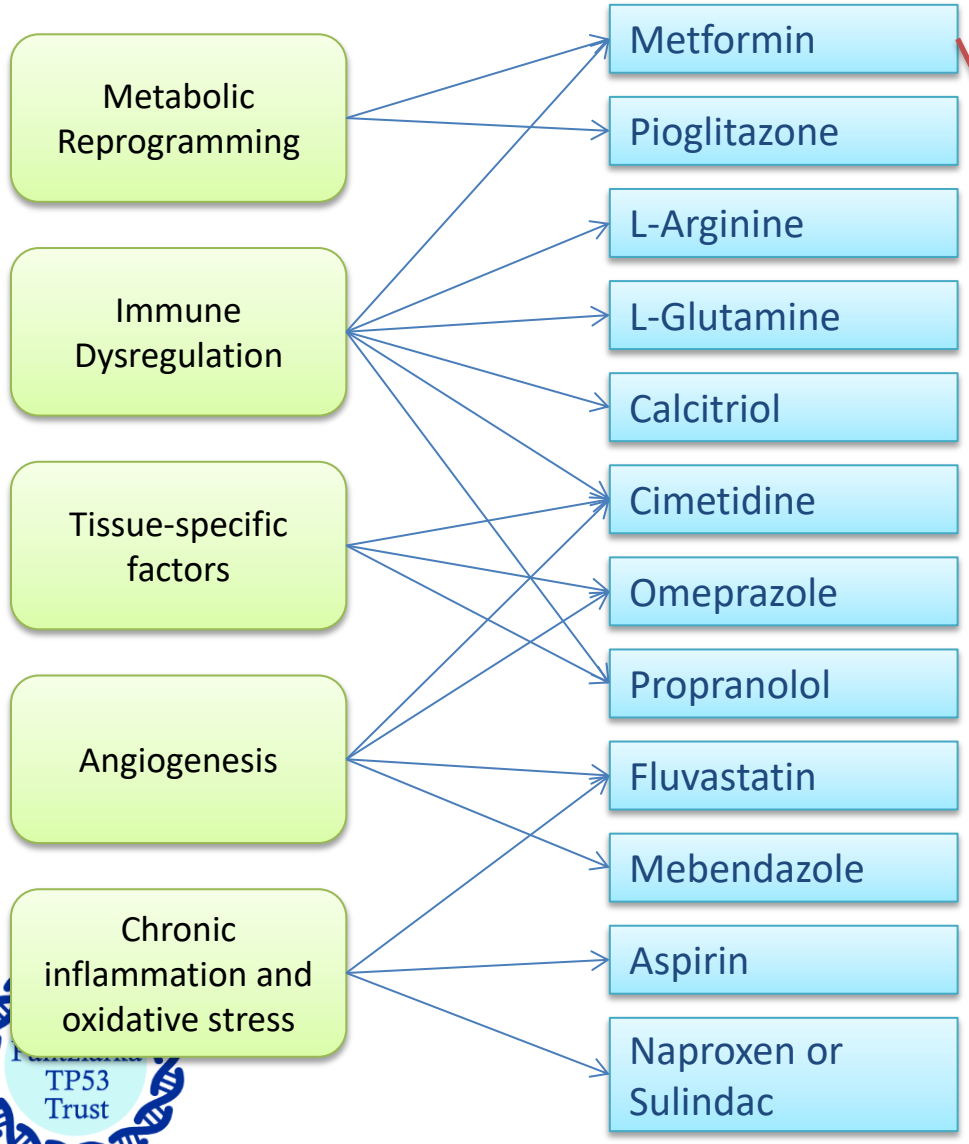
- Sildenafil (viagra) – Angina > Erectile dysfunction, pulmonary hypertension
- Duloxetine – Anti-depressant > Diabetic neuropathy
- Methotrexate – Cancer > Rheumatoid arthritis
- Propranolol – Blood pressure > Infantile hemangioma

Oncology?

- Thalidomide – leprosy > multiple myeloma
- ATRA – acne (topical application) > promyelocytic leukemia
- Zoledronate – osteoporosis > bone metastases

Pantziarka P, Bouche G, Meheus L, Sukhatme V and Sukhatme VP (2014) **The Repurposing Drugs in Oncology (ReDO) Project.** *Ecancermedicalscience*, **8**, p. 442.

Changing the environment for cancer formation



Has been studied in LFS patients in the US – primary outcome was safety/tolerability. Also showed decreased mitochondrial activity.

Wang P et al. (2017) Inhibiting mitochondrial respiration prevents cancer in a mouse model of Li-Fraumeni syndrome. *JCI, 127(1), pp. 132–136.*

These are all repurposed drugs/agents with strong evidence of anticancer activity and designed for chronic administration. They are all low cost and safe medications. Mechanisms of action are related to one or more facets of the pre-cancerous niche.

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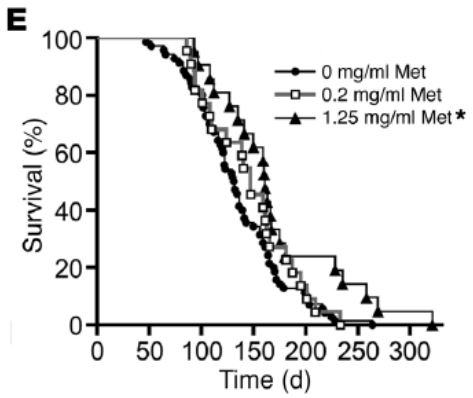
Metformin

In addition to clinical investigation as a cancer treatment (adjuvant and neo-adjuvant), there is interest in the use of metformin as a cancer prevention drug in breast, colon, lung, oral and other cancers.

Data from numerous animal models shows that metformin can reduce cancer incidence – though concerns about the doses of metformin used in some studies.

Results from a Phase III RCT in non-diabetic patients with previous polypectomy showed that one year of *low dose metformin* reduced prevalence and number of metachronous adenomas or polyps. (PMID: 26947328).

The anti-diabetic drug Metformin is subject of intense investigation in the world of oncology. Currently over 80 open clinical trials in a range of cancers types.



Data from mouse model of LFS shows metformin increases overall survival. Data from LFS patient shows similar decrease in mitochondrial respiration

Wang P et al. (2017) **Inhibiting mitochondrial respiration prevents cancer in a mouse model of Li-Fraumeni syndrome.** *The Journal of clinical investigation*, **127**(1), pp. 132–136.

Multiple relevant mechanisms of action…

- Mitochondrial respiration
- Gluconeogenesis
- AMPK
- mTOR
- Immunological
- Anti-angiogenic
- Anti-inflammatory

Aspirin

In addition to clinical investigation as a cancer treatment (adjuvant and neo-adjuvant), there is interest in the use of aspirin as an agent to reduce recurrence rates as well as in primary cancer prevention.

Of particular interest has been the use of aspirin in cancer predisposition syndromes (Lynch syndrome and FAP). CAPP2 was a double-blind RCT of aspirin vs placebo in people with Lynch Syndrome. Study conclusion was that 600 mg aspirin per day for a mean of 25 months substantially reduced cancer incidence after 55·7 months in carriers of hereditary colorectal cancer (PMID: 22036019).

Follow-up study (CAPP3) is looking at alternative doses of aspirin.

Aspirin has been extensively studied as an anti-cancer agent – with significant clinical trial activity in a wide range of cancers. Currently just under 40 trials in progress

No direct data on activity of aspirin from in vivo LFS models or from LFS patients. However, in vitro evidence shows that aspirin stabilises mutant p53 (R273H) at normal aspirin dosing

Ai G et al. (2015) **Aspirin acetylates wild type and mutant p53 in colon cancer cells: identification of aspirin acetylated sites on recombinant p53.** *Tumour biology*.

Multiple relevant mechanisms of action…

- COX1/COX2/PGE2/NF-kB
- Platelet aggregation
- mTOR
- c-Myc
- Immunological
- Anti-angiogenic
- Anti-inflammatory

Other approaches?

Data from animal models…

Reactivating p53: Data presented at AACR 2017 showed that ReACp53, (an experimental p53 reactivating drug), reduced cancer incidence in a mouse model of LFS (R172H mutation). LFS mice administered the peptide twice weekly showed a 38% improvement in OS.

Soragni A et al (2017) **Targeted tumor prevention in Li-Fraumeni syndrome.** *LB-169 , AACR 2017.*

Rapamycin: p53 KO (+/-) mice administered rapamycin (an mTOR inhibitor) showed reduced tumour incidence and increased overall survival (by 28% in young mice, 10% in older).

Komarova E et al. (2012) **Rapamycin extends lifespan and delays tumorigenesis in heterozygous p53+/- mice.** *Aging*, **4**(10), pp. 709–14.

Diet: p53 KO (+/-) adult mice on calorie restricted (60% of calories compared to normal diet) or 1 day/week fasting showed increased overall longevity compared to unrestricted diet. CR or fasting mice had reduced body weight and reduced IGF1 and leptin levels.

Berrigan D et al (2002) **Adult-onset calorie restriction and fasting delay spontaneous tumorigenesis in p53-deficient mice.** *Carcinogenesis*, 23(5), pp. 817–22.

Where next?

- Metformin
- Pioglitazone
- L-Arginine
- L-Glutamine
- Calcitriol
- Cimetidine
- Omeprazole
- Propranolol
- Fluvastatin
- Mebendazole
- Aspirin
- Naproxen or Sulindac

We don't know how these drugs act on mutant p53

Need to assess effects in pre-clinical studies

Need to test with a range of different LFS cells

The George Pantziarka TP53 Trust will work with Jean-Christophe Bourdon and the p53 lab at Dundee University to answer these questions.

Cells from LFS volunteers in the UK (hopefully some of you!) will be tested in the lab to see how they respond to treatment with each of these drugs.

This data can then be used to assess which drugs should be considered for further investigation – possibly leading to clinical trial

This research will be funded by the Trust – which means we need to start fund-raising to make this happen!

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