Drug Repurposing And Reducing Cancer Incidence in Li Fraumeni Syndrome?

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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
What is TP53?

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

The pre-cancerous niche

Mutated p53

Is this the picture in people with LFS before they get cancer?

Pre-cancerous niche

Chronic inflammation

Oxidative Stress

Angiogenesis

Immune Dysregulation

Metabolic Reprogramming

Tissue-specific Factors

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

Chronic inflammation/Oxidative Stress

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...

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


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


Data from LFS patients show high basal levels of oxidative stress

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.

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?
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).
Drug repurposing

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

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

Changing the environment for cancer formation

- Metabolic Reprogramming
  - Metformin
  - Pioglitazone
  - L-Arginine
  - L-Glutamine
  - Calcitriol

- Immune Dysregulation
  - Cimetidine
  - Omeprazole
  - Propranolol
  - Fluvastatin

- Tissue-specific factors
  - Propranolol
  - Fluvastatin
  - Mebendazole
  - Aspirin
  - Naproxen or Sulindac

- Angiogenesis

- Chronic inflammation and oxidative stress

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


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 precancerous niche.
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.

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).

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

Multiple relevant mechanisms of action...
- Mitochondrial respiration
- Gluconeogenesis
- AMPK
- mTOR
- Immunological
- Anti-angiogenic
- Anti-inflammatory

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.

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.

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.

Multiple relevant mechanisms of action...
- COX1/COX2/PGE2/NF-kB
- Platelet aggregation
- mTOR
- c-Myc
- Immunological
- Anti-angiogenic
- Anti-inflammatory

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. 


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).


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.

Where next?

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!