Translating Research

Professor Martin Delatycki

Medical Director, Victorian Clinical Genetics Services

Co-Director, Bruce Lefroy Centre, Murdoch Children's Research Institute

Translational research

- Term first used in late 1990s which is surprising given how much of a buzz word it now is

- “NIH stands for the National Institutes of Health, not the National Institutes of Biomedical Research, or the National Institutes of Basic Biomedical Research.” Alan Schechter

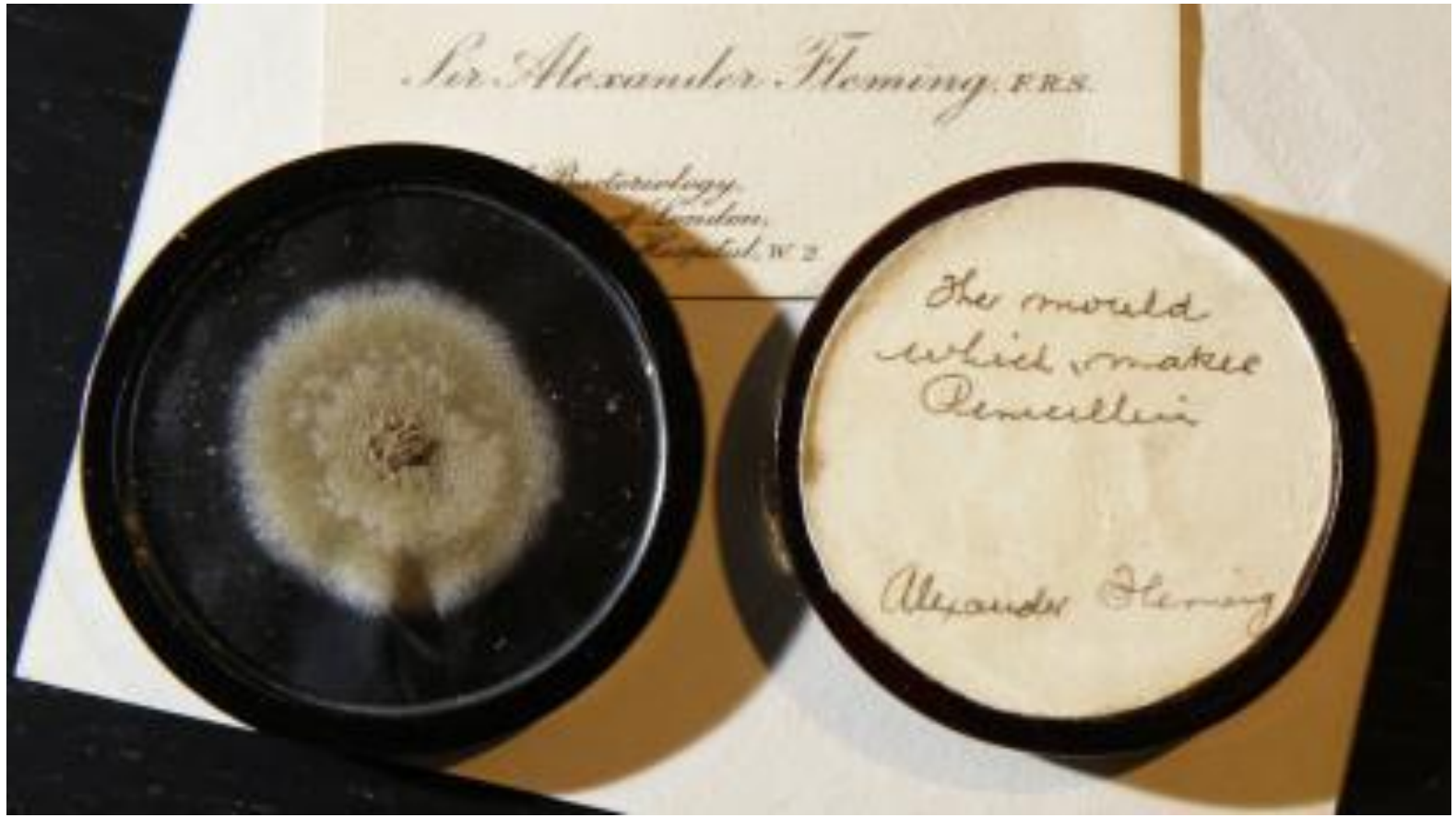
Definitions

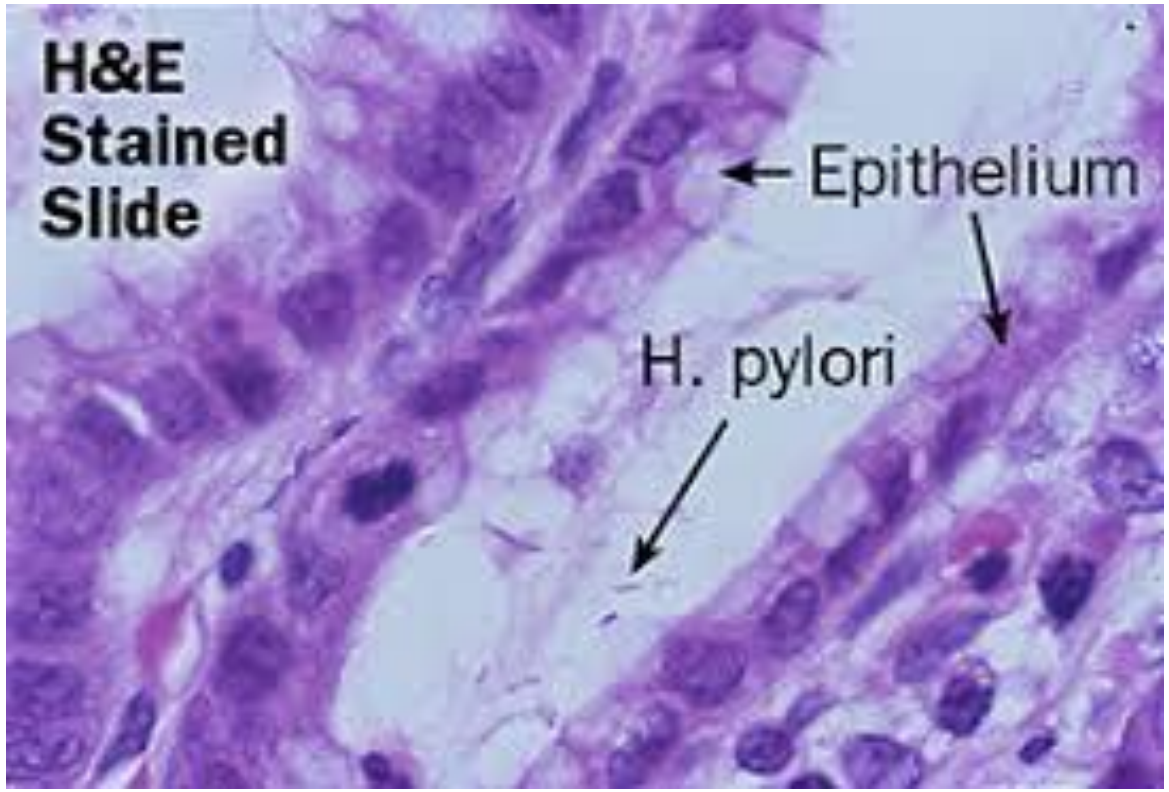
- **Research translation** is the process whereby knowledge is passed anywhere along the translational pathway i.e. research findings are translated into practice, policy or further research (Davidson, 2011).

- **Translational research** is research that looks at how best to translate research into practice and/or policy e.g. research that addresses particular gaps in translation (Davidson, 2011).

The four phases of translational research

- T1- the translation of basic research into a potential clinical application.
- T2- efficacy studies, in which new interventions are trialled under optimal conditions.
- T3- effectiveness studies, where promising phase 2 interventions are trialled in ‘real world’ settings.
- T4- impact studies, which examine the impact of a new intervention/guideline at a population level.


Sir Alexander Fleming, F.R.S.
The mould which makes Penicillin
Alexander Fleming


H&E
Stained
Slide
Epithelium
H. pylori

A personal journey of clinical research and translation

- Clinical geneticist

- Clinician researcher
  - Neurogenetic disorders- Friedreich ataxia
  - Genetic screening- reproductive and personal risk

- Involved in T1-T4 translational research (although until I prepared this talk, I didn’t know I did this!)

Identify a clinical question and answer it

- See an issue in patients seen
- Design a study to answer and then translate the findings into clinical practice

Example of T1/2 translational research

Friedreich ataxia

- 1 in 30,000

- Previously healthy people become unsteady (ataxia)
- Average age of onset 15 years
- Reduced lifespan
- Cardiomyopathy, diabetes, scoliosis, affects speech, swallowing, hearing

Research philosophy

- To study all aspects of morbidity and to develop interventions to manage these that are evidence based

- Developed collaborations with people who are experts in those areas- cardiology, physiotherapy, occupational therapy, speech therapy, audiology, neuroimaging, neuro-otology, sleep, sex….

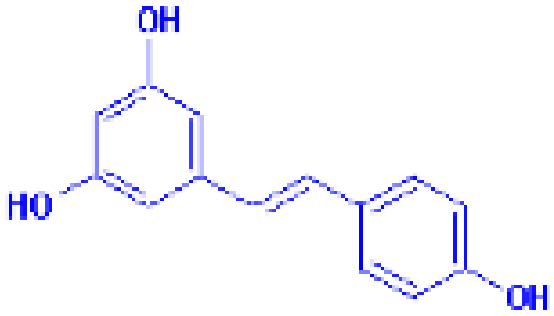
- A basic science program running in parallel to identify therapies and to test these in clinical trials

An open-label clinical pilot study of resveratrol as a treatment for Friedreich ataxia

E Yiu, G Tai, R Peverill, K Lee, K Croft, T Mori, B Scheiber-Mojdehkar, B Sturm, M Praschberger, A Vogel, G Rance, S Stephenson, P Lockhart, J Sarsero, C Stockley, M Evans-Galea, M Ryan, L Corben, M Delatycki

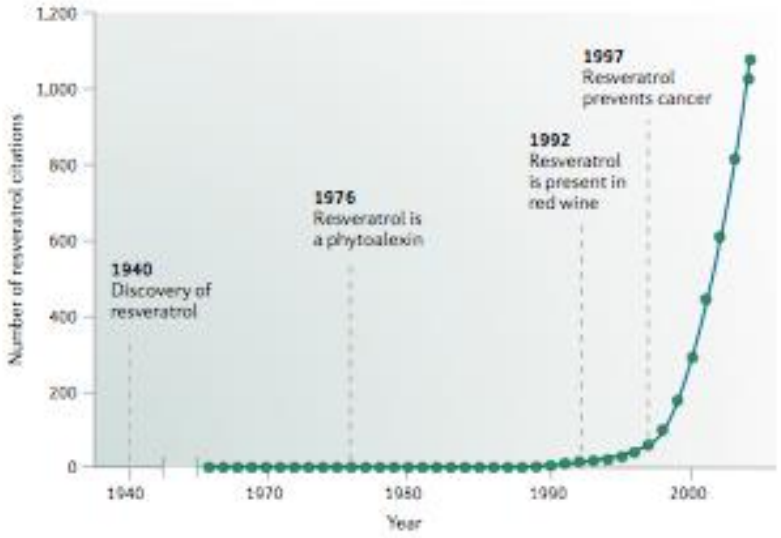
Resveratrol

- Dietary polyphenol found in grapes, red wine, berries and nuts.



Resveratrol

- Multiple and complex molecular targets yet to be fully elucidated



- Postulated effects:
  - Neuroprotective
  - Antioxidant
  - Anti–cancer
  - Anti–diabetic
  - Cardioprotective
  - Prolong lifespan in mice…..

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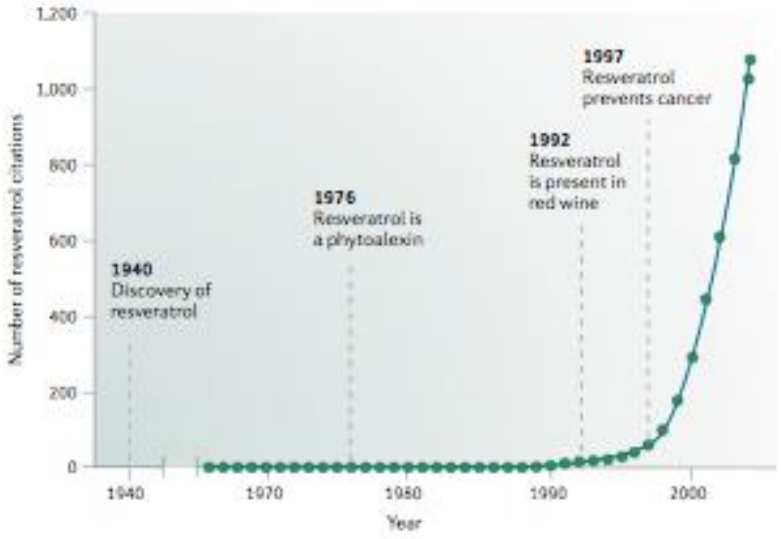

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  - Neuroprotective
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  - Prolong lifespan in mice…..

Rationale for study

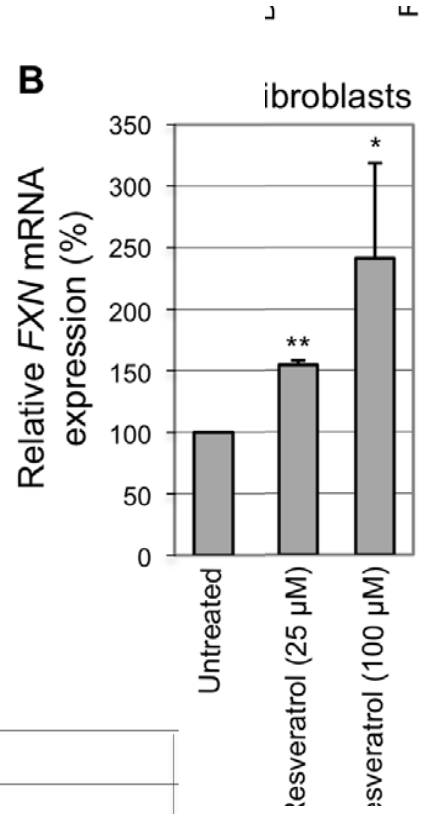
OPEN ACCESS Freely available online

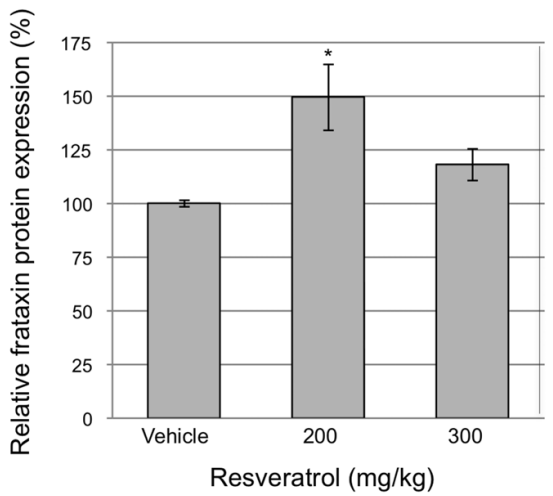
PLOS ONE

Pharmacological Screening Using an *FXN-EGFP* Cellular Genomic Reporter Assay for the Therapy of Friedreich Ataxia

Lingli Li[1,2], Lucille Voullaire[1], Chiranjeevi Sandi[5], Mark A. Pook[5], Panos A. Ioannou[1,39†], Martin B. Delatycki[2,3,49], Joseph P. Sarsero[1,2,3*9]

- Resveratrol increases levels of frataxin *in vitro* and *in vivo*
- Resveratrol is postulated to have antioxidant and neuroprotective properties





Results - Participants

- 27 participants enrolled
  - 3 participants did not complete the study
- 24 participants completed the study

Characteristic	1 g daily (n=12)	5 g daily (n=12)
Age, years, mean (SD)	34.9 (12.7)	39.2 (7.7)
Age at onset, years, mean (SD)	15.6 (6.1)	19.7 (7.7)
GAA1 repeat length, mean (SD)	624 (171)	568 (212)
Male, number (%)	7 (58.3)	9 (75.0)
Baseline FARS score, mean (SD)	98.5 (27.2)	91.6 (25.8)

Abbreviations: FARS – Friedreich ataxia rating scale; GAA_1 – repeat length of the shorter GAA allele

Results – Clinical data

Resveratrol dose	1 g daily (n=12)		5 g daily (n=12)	
Outcome measure	**Difference Mean (95% CI)**	**p-value**	**Difference Mean (95% CI)**	**p-value**
Total FARS score	-2.7 (-6.8, 1.4)	0.17	-3.4 (-6.6, -0.3)	**0.04**
Total ICARS score	-0.3 (-3.2, 2.6)	0.80	-1.9 (-3.1, -0.8)	**0.004**
Total SARA score	-0.3 (-1.8, 1.3)	0.73	-1.0 (-2.1, 0.1)	0.08
Phoneme score	1.3 (-2.3, 4.9)	0.45	4.6 (1.0, 8.2)	**0.02**
Mean pause length	-0.005 (-0.03, 0.02)	0.60	-0.011 (-0.018, -0.004)	**0.006**

FARS - Friedreich Ataxia Rating Scale; ICARS – International Cooperative Ataxia Rating Scale; SARA – Scale for the Assessment and Rating of Ataxia; FACS – Freidreich Ataxia Composite Score; Phoneme score – percentage phonemes correct in 50 word speech perception test in background noise; Mean pause length – total pause duration / number of pauses, in seconds for 'days of the week' speech task

Randomised placebo controlled trial

- Funded by NHMRC
- Melbourne, Perth, Brisbane
- Double blind, placebo controlled, cross over
- 6 months resveratrol, 6 months placebo with one month washout in between
- Tests of neurological function, heart function before, 6 months and 13 months

Do not try this at home!

- 1g resveratrol = ~200 bottles of red wine
- 5g resveratrol = ~1000 bottles of red wine

To ensure results are translated…….

- Produce guidelines!

Corben *et al. Orphanet Journal of Rare Diseases* (2014) 9:184
DOI 10.1186/s13023-014-0184-7

ORPHANET JOURNAL OF RARE DISEASES

REVIEW Open Access

Consensus clinical management guidelines for Friedreich ataxia

Louise A Corben[1,2], David Lynch[3,4,5], Massimo Pandolfo[6], Jörg B Schulz[7], Martin B Delatycki[1,8,9*] and On behalf of the Clinical Management Guidelines Writing Group

Abstract

Friedreich ataxia (FRDA), a multisystem autosomal recessive condition, is the most common inherited ataxia in Caucasians, affecting approximately 1 in 29,000 individuals. The hallmark clinical features of FRDA include progressive afferent and cerebellar ataxia, dysarthria, impaired vibration sense and proprioception, absent tendon reflexes in lower limbs, pyramidal weakness, scoliosis, foot deformity and cardiomyopathy. Despite significant progress in the search for disease modifying agents, the chronic progressive nature of FRDA continues to have a profound impact on the health and well-being of people with FRDA. At present there is no proven treatment that can slow the progression or eventual outcome of this life-shortening condition. Thirty-nine expert clinicians located in Europe, Australia, Canada and USA critically appraised the published evidence related to FRDA clinical care and provided this evidence in a concise manner. Where no published data specific to FRDA existed, recommendations were based on data related to similar conditions and/or expert consensus. There were 146 recommendations developed to ensure best practice in the delivery of health services to people with FRDA. Sixty-two percent of recommendations are based on expert opinion or good practice indicating the paucity of high-level quality clinical studies in this area. Whilst the development of these guidelines provides a critical first step in the provision of appropriate clinical care for people with FRDA, it also highlights the urgency of undertaking high-quality clinical studies that will ensure the delivery of optimum clinical management and intervention for people with FRDA.

Keywords: Friedreich ataxia, Clinical, Guidelines, Evidence, Recommendations

Example of T3 translational research

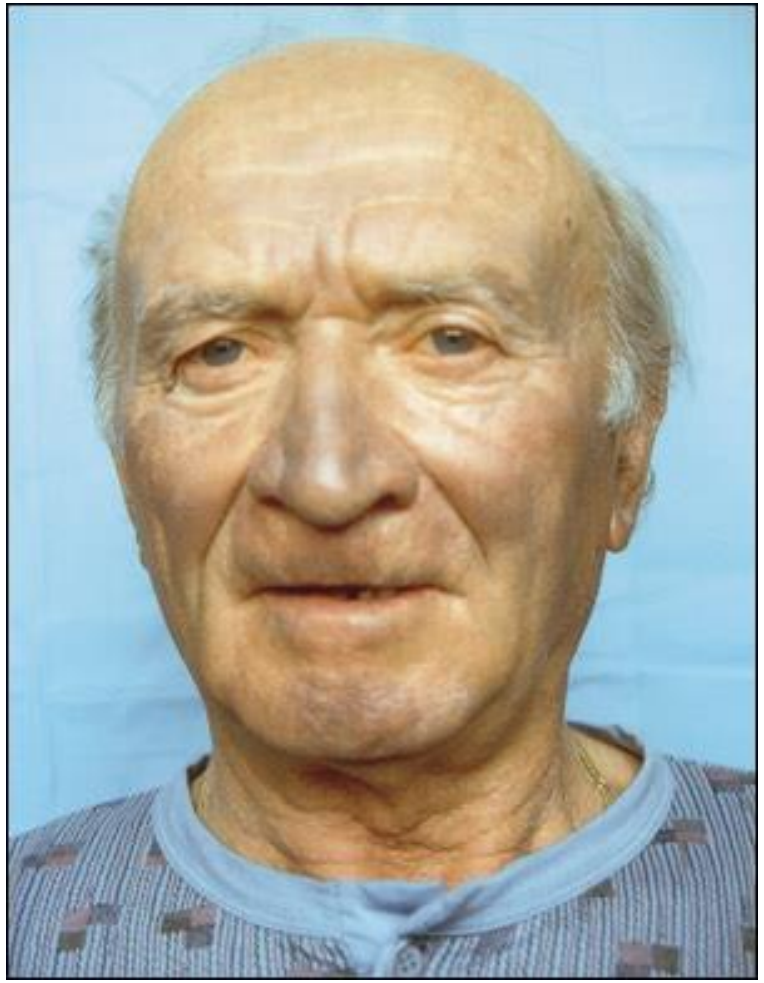
Genetic screening

- Screening for reproductive risk- cystic fibrosis, diseases common in the Jewish community

- Screening for health risk in the individual- haemochromatosis, BRCA screening in the Jewish community

Haemochromatosis

- The most common genetic condition among Caucasians
- 1 in 200 at genetic risk
- Iron overload- untreated can result in liver cirrhosis, cardiomyopathy, diabetes, arthritis, fatigue
- Preventable by blood donation



Who to treat?

- Iron overload identified by high serum ferritin (SF)
- Normal is ~20-300µg/L
- Those with SF>1000µg/L are at increased risk of cirrhosis so no doubt require treatment

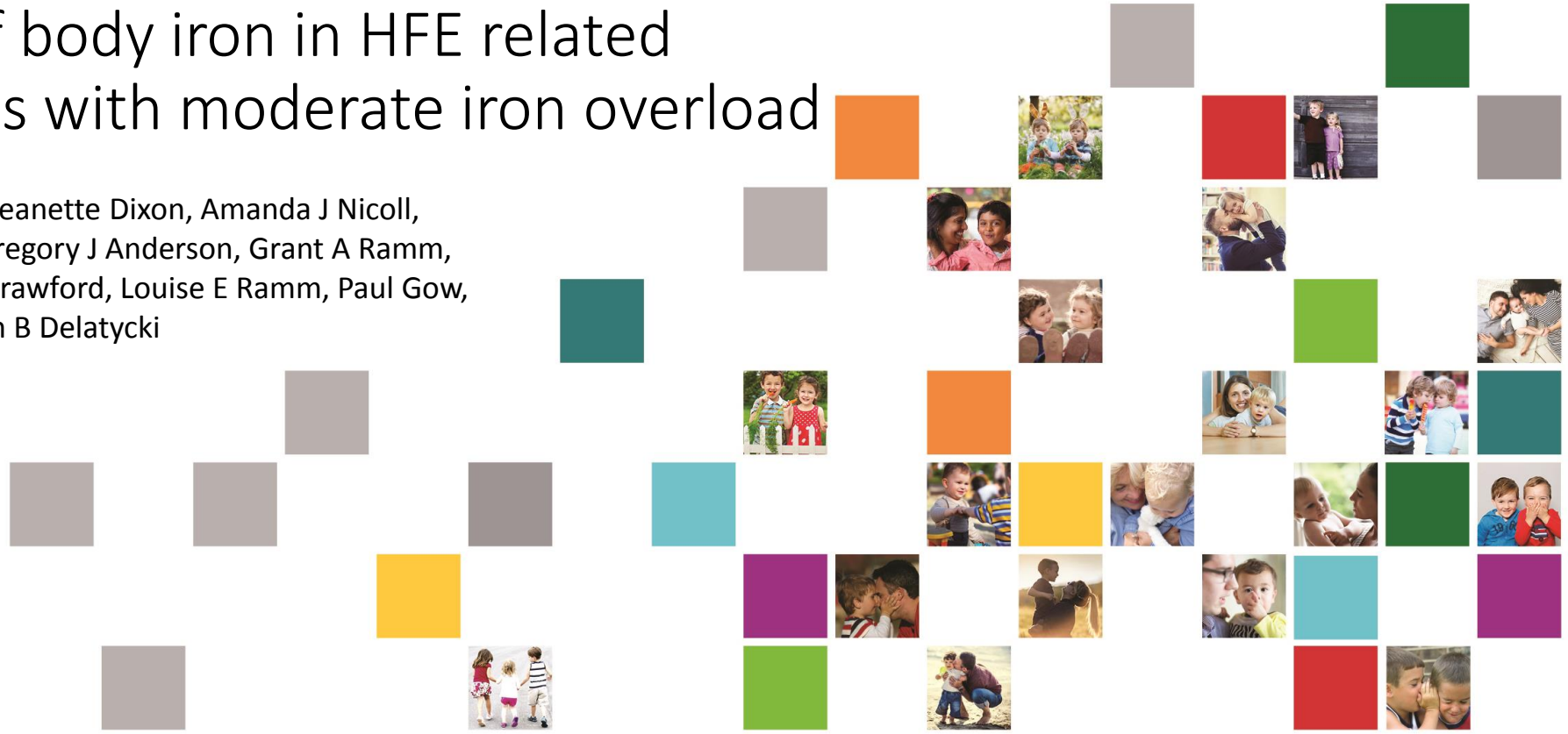
Do people with HH and SF >300μg/L but less than 1000μg/L need treatment?

- >1 million people in each of US and Europe and >85,000 Australians have or will get SF> 300μg/L but < 1000μg/L due to p.C282Y homozygosity or p.C282Y/p.H63D

- Increasing number of commentators advising not to treat HH if SF less than 1000μg/L

A randomized patient-blinded study of true versus sham reduction of body iron in HFE related haemochromatosis with moderate iron overload

Sim Y Ong, Lyle C Gurrin, Lara Dolling, Jeanette Dixon, Amanda J Nicoll, Michelle Wolthuizen, Erica M Wood, Gregory J Anderson, Grant A Ramm, Katrina J Allen, John K Olynyk, Darrell Crawford, Louise E Ramm, Paul Gow, Simon Durant, Lawrie W Powell, Martin B Delatycki

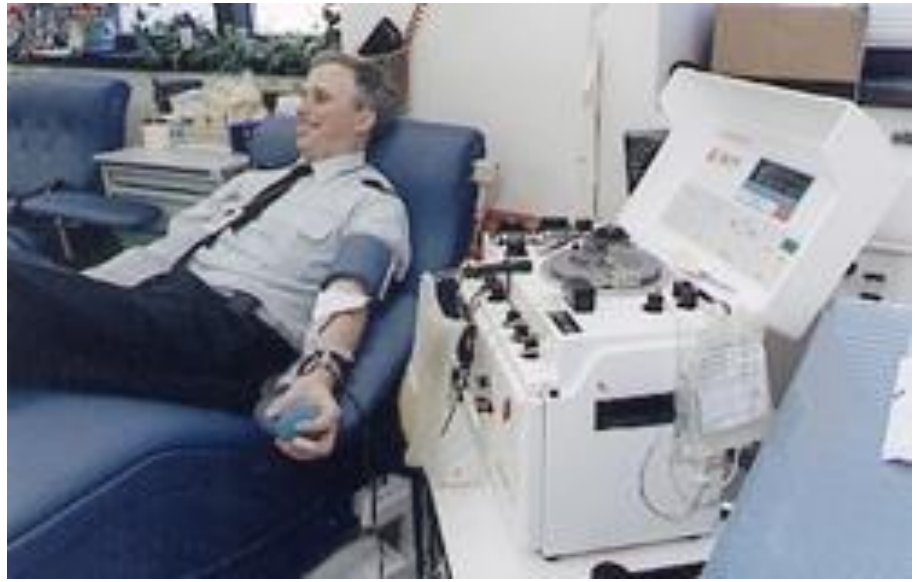


Study Aim

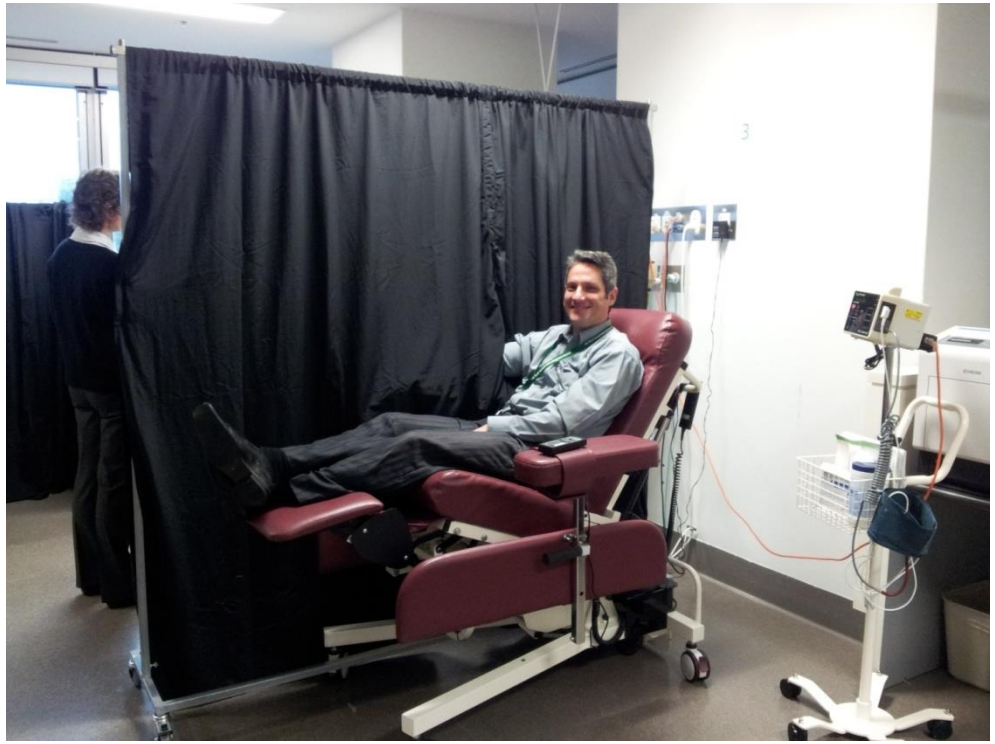
- To undertake a randomised patient-blinded trial of erythrocytapheresis compared to sham erythrocytapheresis (using plasmapheresis) in individuals who have serum ferritin (SF) > 300μg/L but <1000μg/L (defined here as moderate iron overload) due to HFE p.C282Y homozygosity and to compare the prevalence of symptoms and objective markers of disease in the two treatment arms

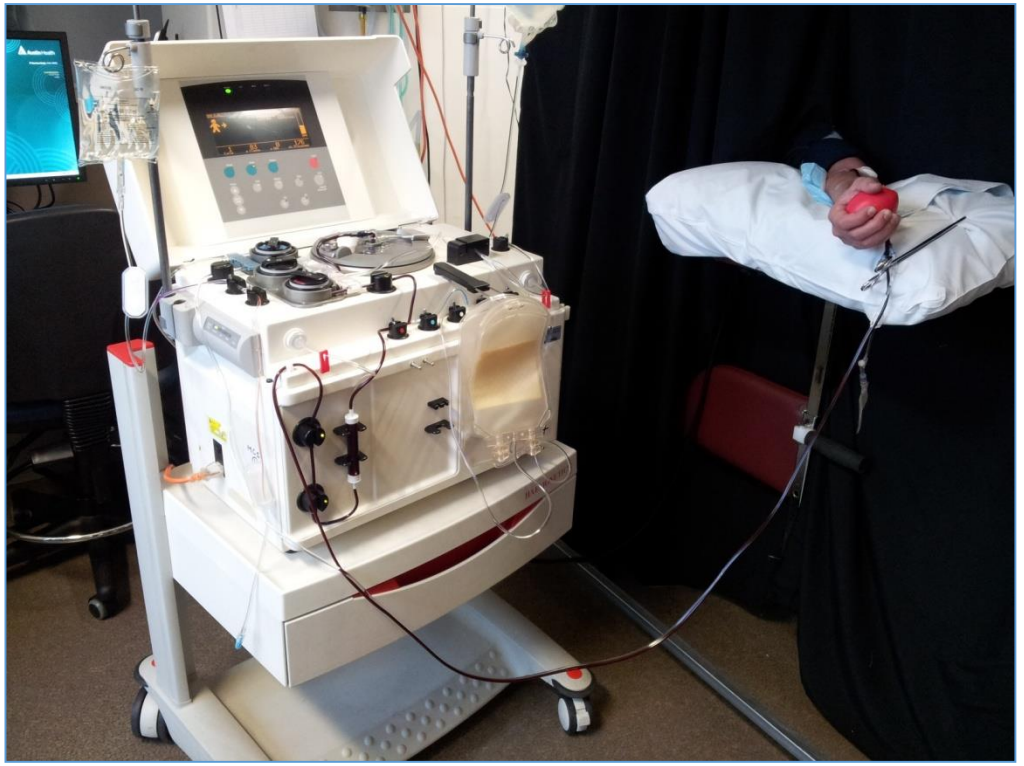
Erythrocytapheresis

- Blood removed
- Spun
- RBCs discarded
- Plasma returned to subject
- Plasmapheresis- opposite
- One treatment removes ~3x RBCs cf venesection
- Reduced hypovolaemia SE cf venesection because of saline replacement
- Anticoagulant can cause SE due to ↓ Ca^{++} (citrate reaction)



Blinding





Modified Fatigue Impact Scale

	N	ΔControl	ΔTreatment	Adjusted Mean Difference	p-value
MFIS Total	93	-1.35 (1.74)	-6.82 (1.61)	-6.25 (2.46)	**0.01**
MFIS: Cognitive	94	-0.80 (0.83)	-3.90 (0.78)	-3.60 (1.16)	**<0.01**
MFIS: Physical	93	-0.60 (0.89)	-2.34 (0.83)	-1.93 (1.29)	0.14
MFIS: Psychosocial	94	-0.07 (0.23)	-0.58 (0.22)	-0.54 (0.33)	0.10

How successful was blinding?

"Do you think your iron level was reduced?"

	Control (n=44)	Treatment (n=50)	p-value
Yes	10 (22.7%)	10 (20%)	0.603
No	6 (13.6%)	9 (18%)	
Not sure	28 (63.6%)	29 (58%)	
Missing	0 (0%)	2 (4%)	

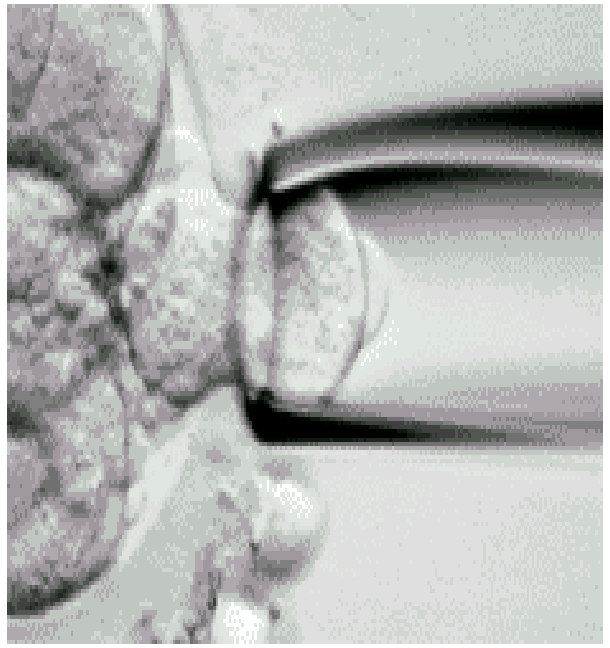
Translate into clinical care

- Clinical guidelines now recommend that all with the genetic predisposition to haemochromatosis and elevated body iron as defined by a raised SF have treatment to reduce SF into the normal range

Example of T4 translational research

Reproductive screening

- Testing for 12 *CFTR* mutations began in 2005
- Screening for fragile X syndrome and spinal muscular atrophy added in 2012
- Now can screen for 100s of conditions
- Couples at increased risk can take steps to avoid having a child with that condition
  - Test an established pregnancy
  - Test embryos produced by IVF



Mackenzie's Mission

Professor Martin Delatycki
Professor Edwin Kirk
Professor Nigel Laing

Why Mackenzie's Mission?

- Mackenzie Casella died at 7 months from spinal muscular atrophy in 2017
- Her parents, Rachael and Jonny Casella, asked the question why they didn't know they were carriers
- They discovered carrier screening for SMA was possible and available in Victoria
- They lobbied the Federal Government to introduce carrier screening for the whole of Australia
- They met with Health Minister Greg Hunt

Mackenzie's Mission

- $20 million from Medical Research Future Fund
- Medical research into how best to offer carrier screening

Proposed Aims

- To screen 10,000 couples for carrier status for ~1500 autosomal and X-linked recessive conditions pre or early in pregnancy

- To research the following outcomes:
  - Uptake
  - Carrier frequencies for genes on the screening panel
  - Incidence of high risk carrier couples
  - Reproductive decisions made by carrier couples
  - Psychosocial outcomes
  - Health economics
  - Implementation research
  - Ethical research

Project timeline

- Phase 1- 2019- set up program
- Phase 2- 2020- screening in Victoria, NSW, WA (4000 couples)
- Phase 3- 2021- other states and territories added (6000 couples)
- Aim to submit an application to MSAC to seek funding recommendation to Government for a nationwide program

Research

- Health economics- Paul Scuffham
- Ethics- Ainsley Newson
- Implementation research- Jeffrey Braithwaite
- Psychosocial/ epidemiology- Martin Delatycki

Translational research

- Will inform a submission to MSAC to (hopefully) recommend that the Government introduces a funded screening program

Thank you