Research areas in the WEHI Healthy Development and Ageing Theme – around Healthy Ageing, particularly PD and dementia

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@MelanieBahlo

Centenary Institute Healthy Ageing Symposium

Melanie Bahlo, August 17th, 2022

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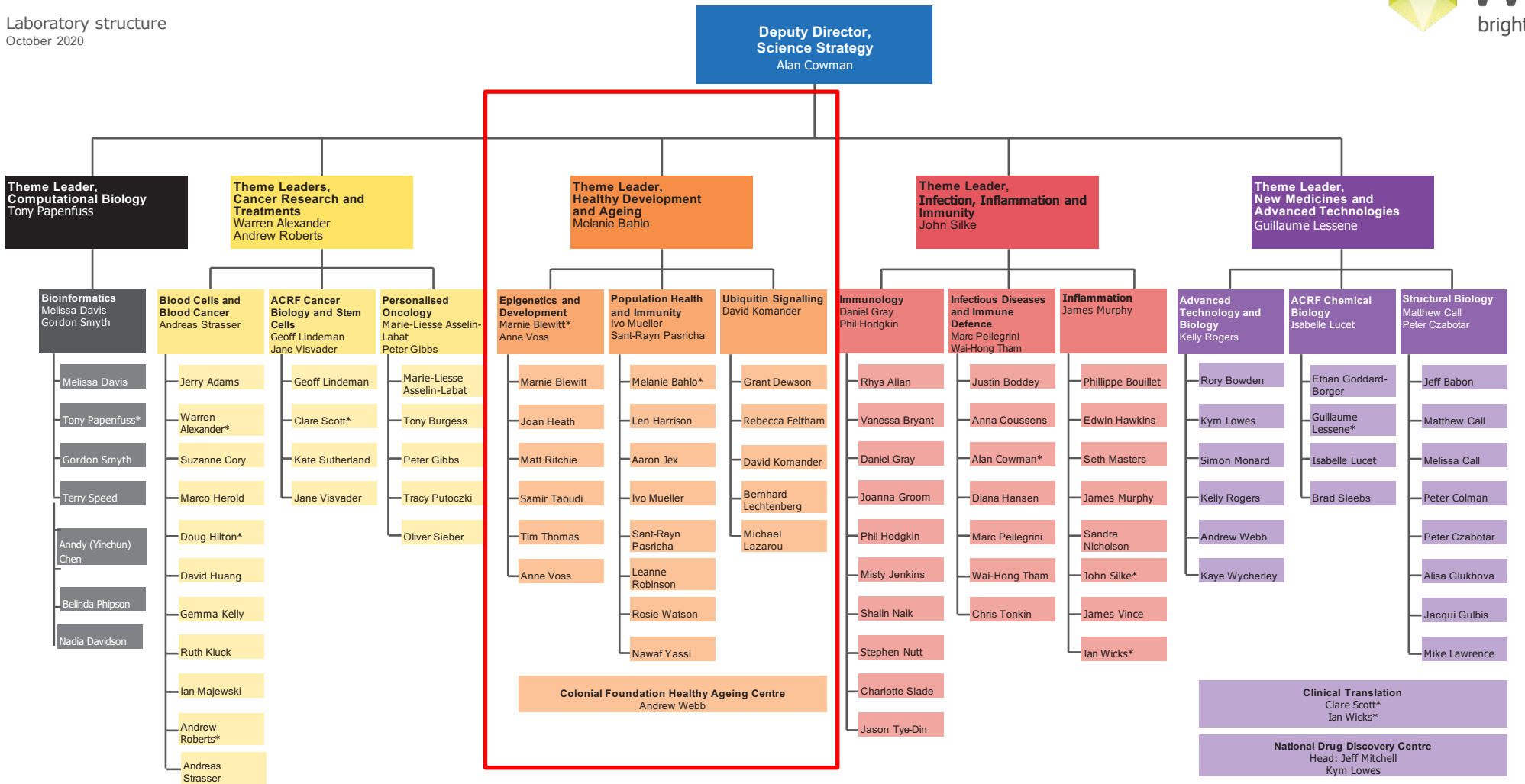
Laboratory structure

October 2020



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Scientific structure
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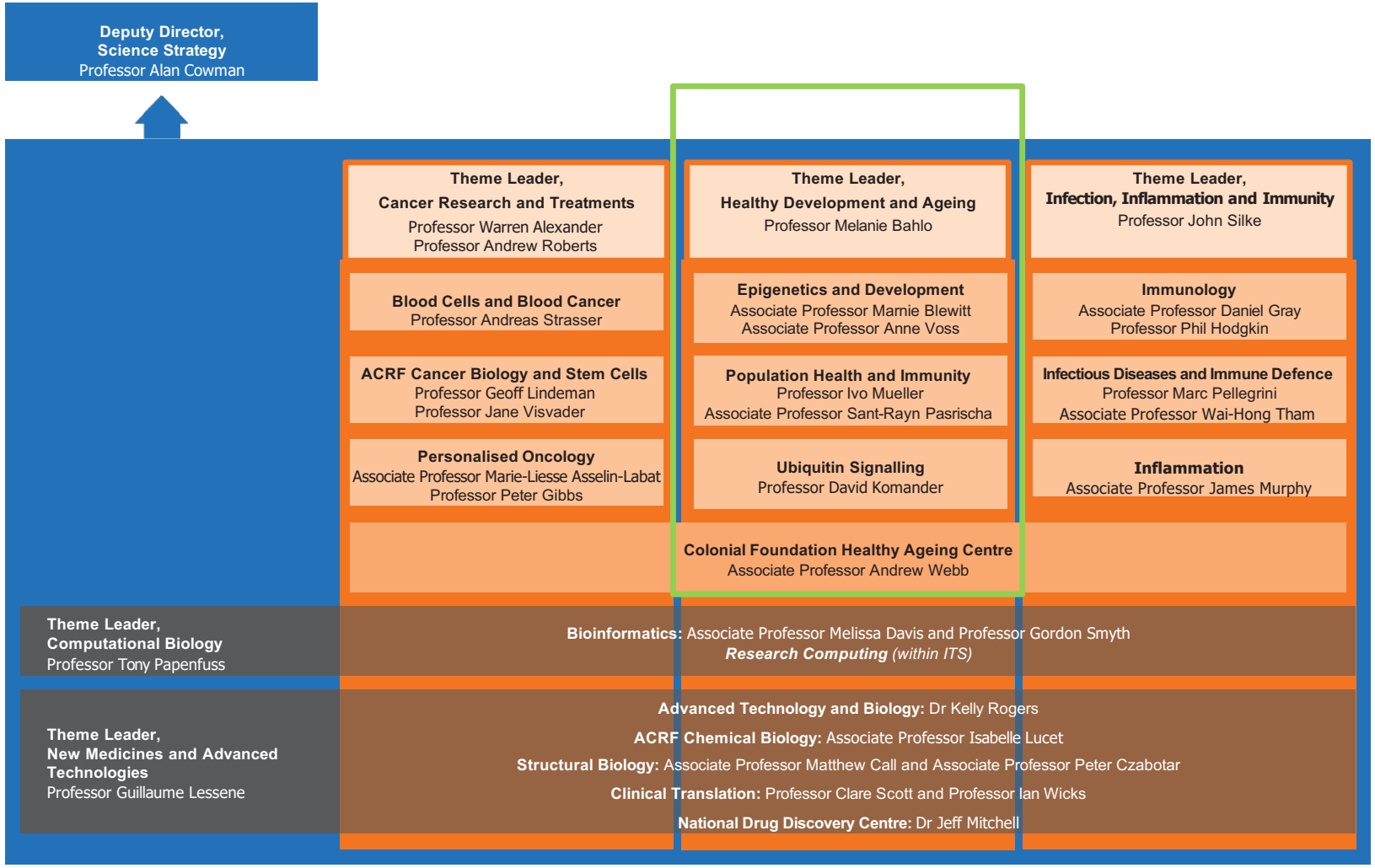


WEHI Strategic Plan 2019-203 (and beyond)

Knowledge and health

Focus and collaboration to better understand the biomedical world

Our overarching goal remains unchanged: to be an institute that makes major discoveries which deepen the understanding of the biomedical world, shape the global direction of research, and improve disease prevention, diagnosis and treatment. Achieving this goal requires focus on our key research questions; multi-disciplinarity; vibrant local, national and global relationships; outward-looking strategic leadership; and innovation through the use of advanced new technologies and methods.

Focus on a defined set of challenges in human health

We will build on our five-decade commitment to tackling infectious diseases, immune disorders and inflammation, and cancer. We will both strengthen and enrich our research through the establishment of three biomedical themes - Cancer Research and Treatments; Infection, Inflammation and Immunity; and Healthy Development and Ageing. The establishment of these themes will ensure we have critical mass to undertake ambitious discovery research and address health priority goals, and that our translational links are robust enough to effectively take our discoveries to the clinic to improve health.

Healthy Development and Ageing is a new area of focus for the Institute and responds to the increasing burden of chronic and degenerative diseases in Australia. We will apply a distinctive approach to this area that will take advantage of the Institute's existing expertise in understanding the molecular basis of development, health and disease, our track record of developing new medicines, and our translational links to Melbourne Health and within the Parkville Precinct. The area will rely on the collaborative culture of the Institute to build bridges across themes) and will be bolstered by strategic recruitment.

We have a responsibility to improve the health outcomes for Aboriginal and Torres Strait Islander Peoples. We will contribute to closing the gap in life expectancy by collaborating with Aboriginal and Torres Strait Islander communities and researchers whose strengths align with our areas of research including chronic diseases, cancer and ageing. We will provide Aboriginal and Torres Strait Islander researchers with access to expertise and technology at the Institute. We will support our researchers to contribute to this national priority by fostering their active engagement in a way that respects Aboriginal and Torres Strait Islander communities.

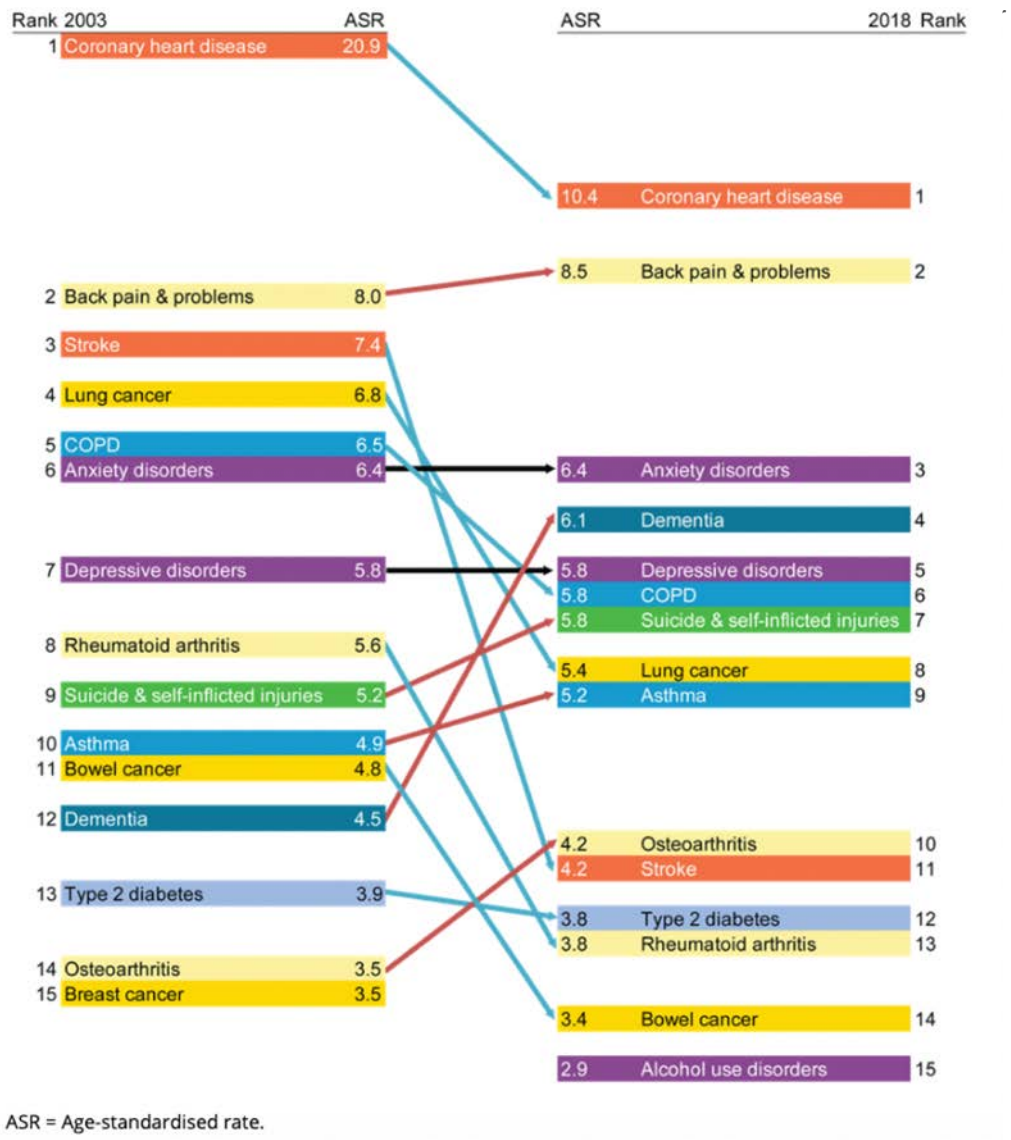
The detection of early transitions to disease states to enable timely personalised, innovative and accessible diagnosis is now possible with current technology. However, there is no platform or facility to translate the existing scientific knowledge and technology into cutting-edge diagnostics. To achieve this, we will establish a new research program in partnership with Melbourne Health and the Colonial Foundation that will bring together clinicians, pathologists and researchers, using the latest in '-omics' technology to create a 'wellness' model for ageing Australians.

Figure 2: Leading underlying causes of death in Australia, by age group, 2018–2020

Age group (years)	Rank 1st	2nd	3rd	4th	5th
Under 1	Perinatal and congenital conditions	Other ill-defined causes	Sudden infant death syndrome	Accidental threats to breathing	Selected metabolic disorders
1–14	Land transport accidents	Perinatal and congenital conditions	Brain cancer	Other ill-defined causes	Suicide
15–24	Suicide	Land transport accidents	Accidental poisoning	Other ill-defined causes	Assault
25–44	Suicide	Accidental poisoning	Land transport accidents	Coronary heart disease	Other ill-defined causes
45–64	Coronary heart disease	Lung cancer	Suicide	Colorectal cancer	Breast cancer
65–74	Lung cancer	Coronary heart disease	Chronic obstructive pulmonary disease	Colorectal cancer	Cerebrovascular disease
75–84					
85 and over					

Why work on Dementia?

Figure 4: Change in disease ranking and age-standardised DALY rate (per 1,000 population), 2003 and 2018



ASR = Age-standardised rate.

From “Australia’s health 2022: topic summaries” (AIHW)

Healthy Ageing @ WEHI: working up a program in dementia

- Program development driven by strengths in:
  - Specific molecular pathways
  - platforms/technical expertise
  - clinical interests

- Led to a focus on PD and the development of the WEHI Parkinson's Disease Research Centre
  - How did we get there?
    - Introduction to the WEHI laboratories involved
  - Plans

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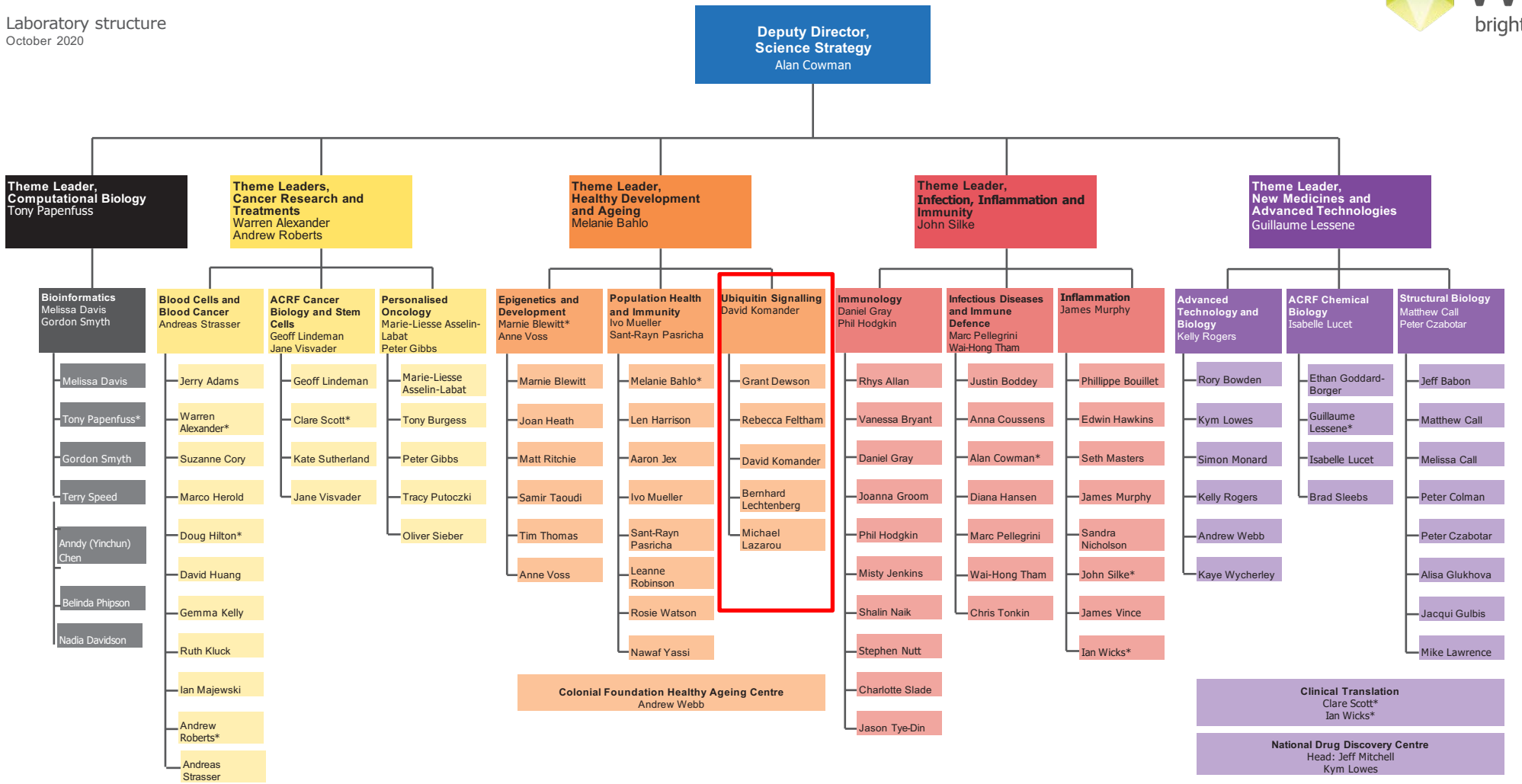

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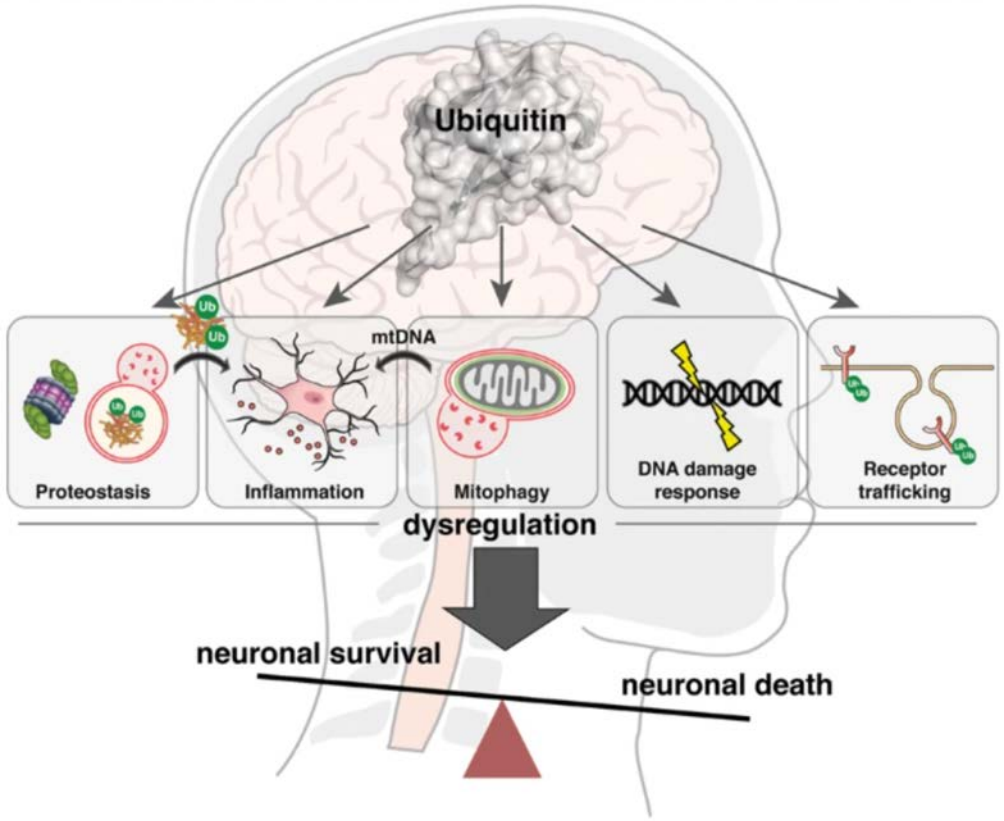
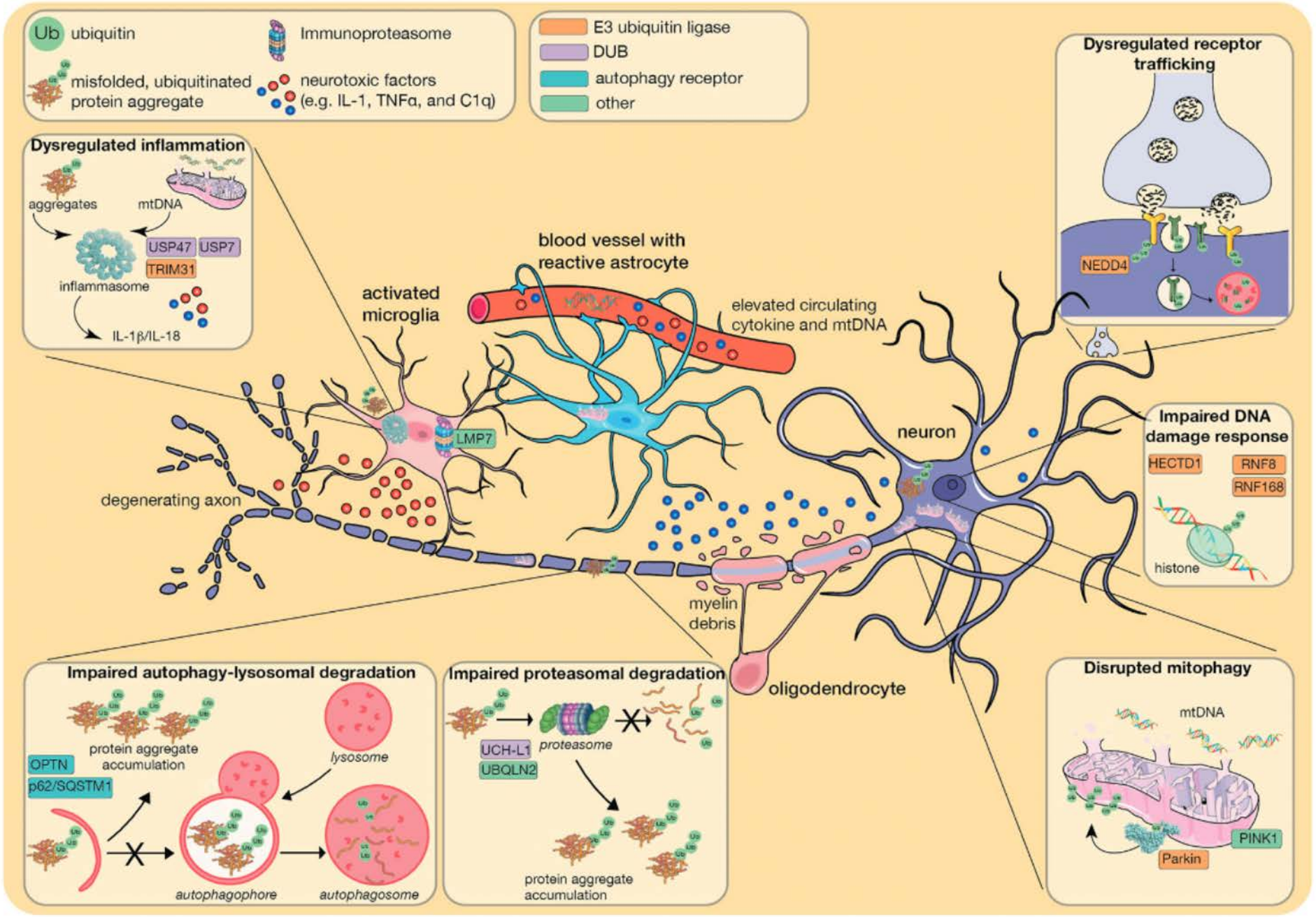
Ubiquitin Signalling



Schmidt et al 2021, Cell Death and Differentiation

- Ubiquitin Signalling (US) is an important biological mechanism to maintain neuronal homeostasis (proteostasis)
- Genetic mutations and risk alleles found in neurodegenerative diseases including AD, **PD**, HD, ALS/MND are associated with proteins involved in the ubiquitin–proteasome system (UPS) and the autophagy–lysosomal system, two major protein degradation pathways



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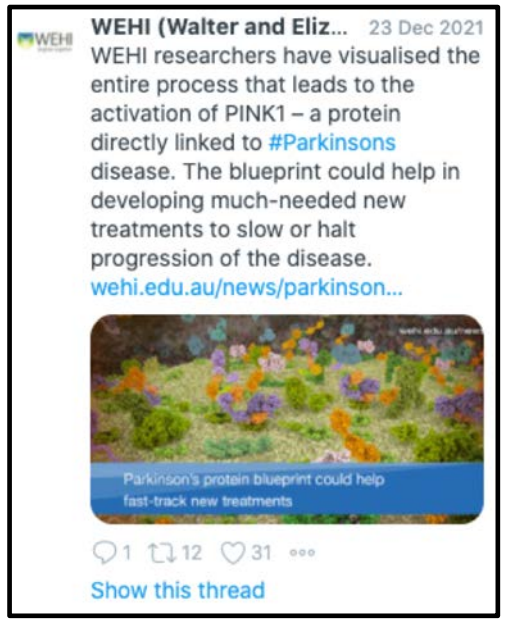

Gan et al, Nature 2021

Schmidt et al 2021, Cell Death and Differentiation

US dysregulation is a key driver of (Early Onset) Parkinson's Disease

Review of PD genetics ('monogenic' causes)

Blauwendraat et al, Lancet Neurology, 2019

	Mutation	Note	Year of discovery	Proposed disease mechanism	Inheritance	Frequency	Nominated by GWAS	Multiple independent families reported*	Functional evidence†	Negative reports published‡	Confidence as actual PD gene§
SNCA	Missense or multiplication	Often with dementia	1997, 2003	Gain of function or overexpression	Dominant	Very rare	Yes	++	++	+	Very high
PRKN	Missense or loss of function	Often early onset	1998	Loss of function	Recessive	Rare	No	++	++	+	Very high
UCHL1	Missense	..	1998	Loss of function?	Dominant	Unclear	No	–	+	––	Low
PARK7	Missense	Often early onset	2003	Loss of function	Recessive	Very rare	No	++	++	+	Very high
LRRK2	Missense	..	2004	Gain of function	Dominant	Common	Yes	++	++	+	Very high
PINK1	Missense or loss of function	Often early onset	2004	Loss of function	Recessive	Rare	No	++	++	+	Very high
POLG	Missense or loss of function	Atypical PD	2004	Loss of function?	Dominant	Rare	No	++	+	+	High
HTRA2	Missense	..	2005	Unclear	Dominant	Unclear	No	–	+	––	Low
ATP13A2	Missense or loss of function	Atypical PD	2006	Loss of function	Recessive	Very rare	No	++	++	+	Very high
FBXO7	Missense	Often early onset	2008	Loss of function	Recessive	Very rare	No	++	++	+	Very high
GIGYF2	Missense	..	2008	Unclear	Dominant	Unclear	No	+	+	––	Low
GBA	Missense or loss of function	..	2009	Likely loss of function	Dominant (incomplete penetrance)	Common	Yes	++	++	+	Very high
PLA2G6	Missense or loss of function	Often early onset	2009	Loss of function	Recessive	Rare	No	++	++	+	Very high
EIF4G1	Missense	..	2011	Unclear	Dominant	Unclear	No	–	+	––	Low
VPS35	Missense	..	2011	Loss of function	Dominant	Very rare	No	++	+	+	Very high
DNAJC6	Missense or loss of function	Often early onset	2012	Loss of function	Recessive	Very rare	No	++	+	+	High
SYNJ1	Missense or loss of function	Often atypical PD	2013	Loss of function	Recessive	Very rare	No	++	+	+	High
DNAJC13	Missense	Same family as *TMEM230*	2014	Unclear	Dominant	Unclear	No	+	+	–	Low
TMEM230	Missense	Same family as *DNAJC13*	2016	Loss of function?	Dominant	Unclear	No	–	+	–	Low
VPS13C	Missense or loss of function	..	2016	Loss of function	Recessive	Rare	Yes	++	+	+	High
LRP10	Missense or loss of function	..	2018	Loss of function?	Dominant	Unclear	No	–	+	––	Low

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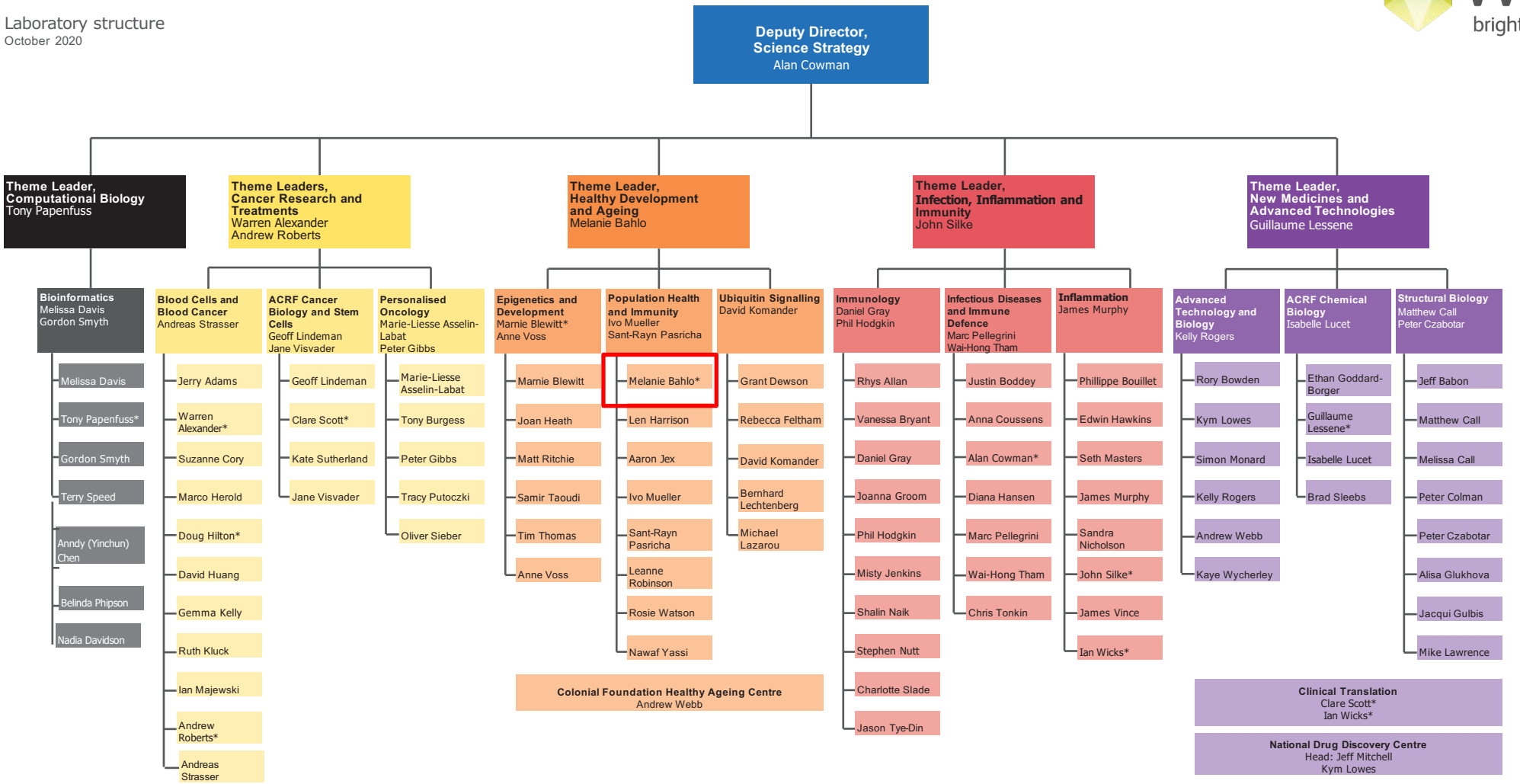

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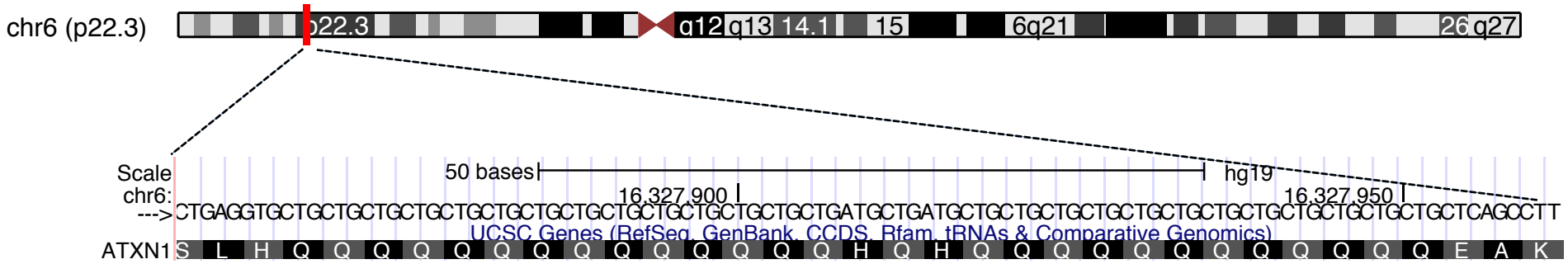
Bahlo Lab Interests – Healthy Ageing

- Statistical Genetics and Bioinformatics Lab (Dry lab)
- **Overall Goal:** Identification of genetic risk factors for neurological and retinal disorders
  - **rare and common variants**
- **Diseases:** epilepsy, ataxia, dementia/PD, AMD, MacTel (only lab working on retinal disorders at WEHI, collaborate with Eye and Ear Hospital, Melbourne)
- **Biological mechanisms of interest:** RNA editing, **repeat expansions**, interplay between rare and common disease variants, causation analysis with Mendelian Randomisation (mainly with metabolites)
- Extensive users of UK Biobank (500K individuals). Some projects underway:
  - Repeat expansion analysis
  - Retinal imaging GWAS
  - Collaborative work to interrogate this data with specific hypothesis in addition to our biological mechanisms of interest (Pasricha lab, Blewitt lab)

Repeat Expansion Disorders: *e x p a n d e d* short tandem repeats

- Short Tandem repeats can expand to breach thresholds where they become pathogenic
  - ➠ repeat expansion disorders
- Cause ~50 known human disorders as expansions e.g. Huntington's Disease, many SCAs
- Pathogenic molecular mechanisms vary considerably, **more research needed**
- Overrepresented in neurological disorders. Longevity, slow turn over of neurons
- **Example:** SCA1 caused by coding CAG (Q = glutamine) expansion in *ATXN1*
  - Normal 6–38, affected 40–81



Human Genome Reference = $(CAG)_{12}$

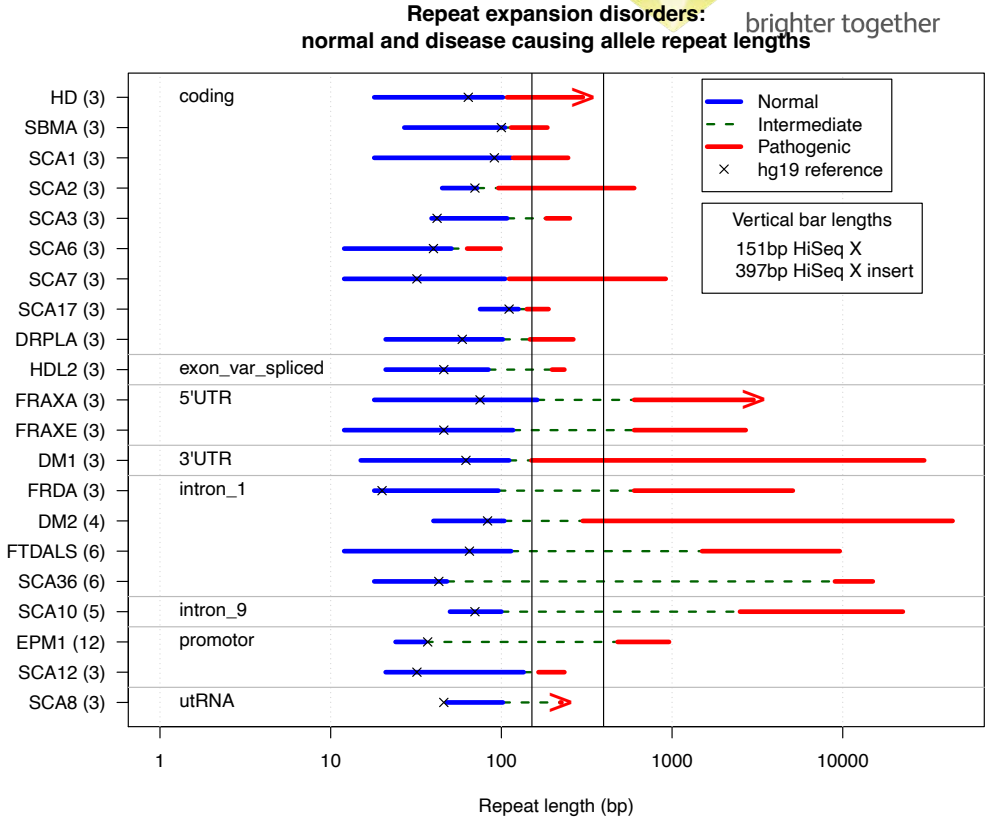
Bioinformatic methods can detect repeat expansions with standard WES/WGS

Repeat Expansion Detection Tools

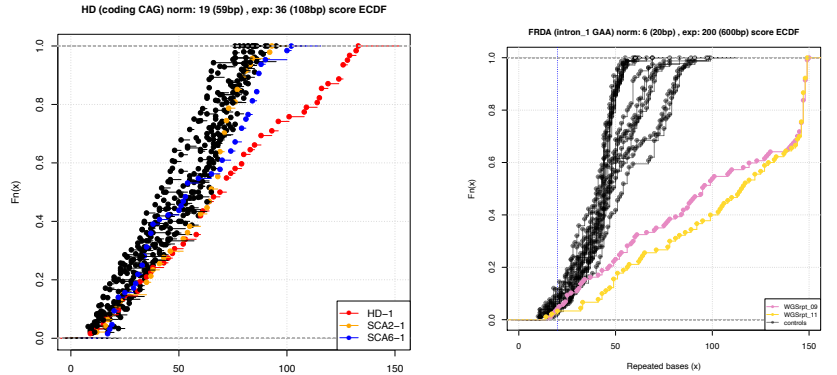
- Expansion Hunter (Dolzhenko et al, Genome Res 2017)
- **exSTRa (Tankard et al, AJHG 2018)**
- **ExpansionHunterDN (Dolzhenko, Bennett et al, Genome Biol 2020)**

- *Ibanez et al, Lancet Neurol. 2022*
- *"Detecting repeat expansions using short read data for clinical use" Bennett et al, 2022 (Chapter 2 in "Genomic Structural Variants in Nervous System Disorders" ed C Proukakis)*

- Not yet standard in clinical genomics analysis pipelines



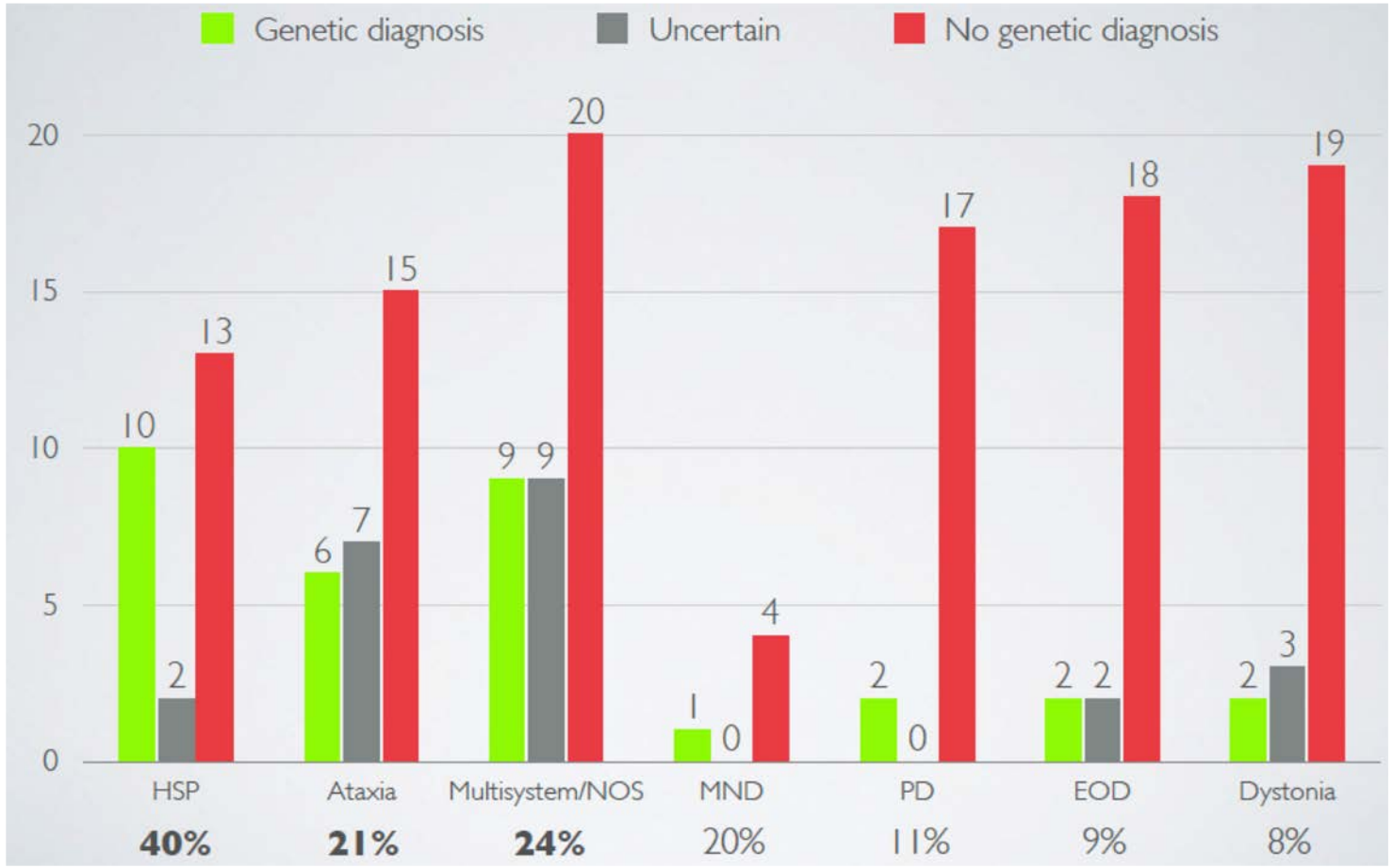
from Rick Tankard, PhD thesis, 2018



MGHA Adult Neurology Flagship (2019-2020)

CIs: Berkovic, Velakoulis, Kwan, Leventer, Delatycki, Bahlo, Fahey

- 160 patients recruited & analysed with WES data (using gene panel approach)



RMH, Austin, Alfred

Eratne et al, J Neurol Sci 2021

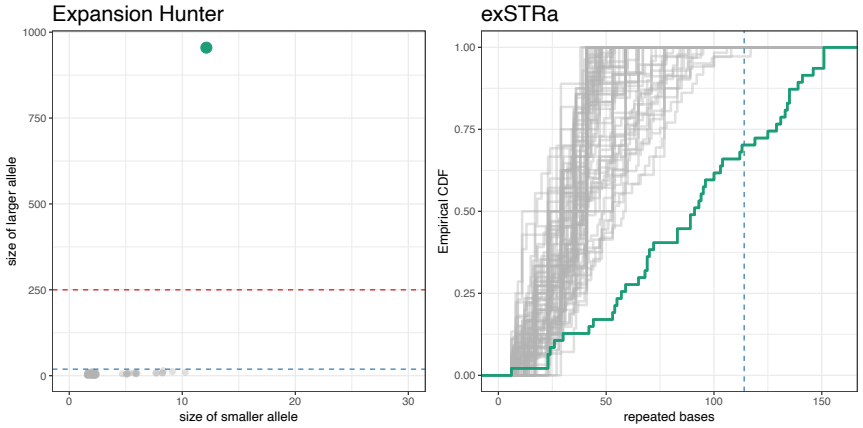
Example: Genetic Re-diagnosis with WES + bioinformatic approach

- Re-analysed MGHA WES data with bioinformatic repeat expansion detection pipeline (Haloom Rafehi)
- Detection of HD repeat expansion for one of the ataxia patients
- Validated by VCGS using RP-PCR (39 repeats, >37 considered pathogenic)
- HD masquerading as ataxia. Has been previously reported (*Rodriguez-Quiroga BMJ Reports, 2013*)
- Solved puzzling symptoms, family took up genetic testing

Repeat Expansions contribute substantially to disease burden in rare and complex neurological disorders*

- Fragile X RE – causes 50% of all monogenic X-linked ID and autism

- C9orf72 RE causes ALS/MND/LGD & FTD
  - 1 in 10 ALS patients
  - 1 in 10 FTD patients
  - differential diagnosis for HD, **PD & other diseases**

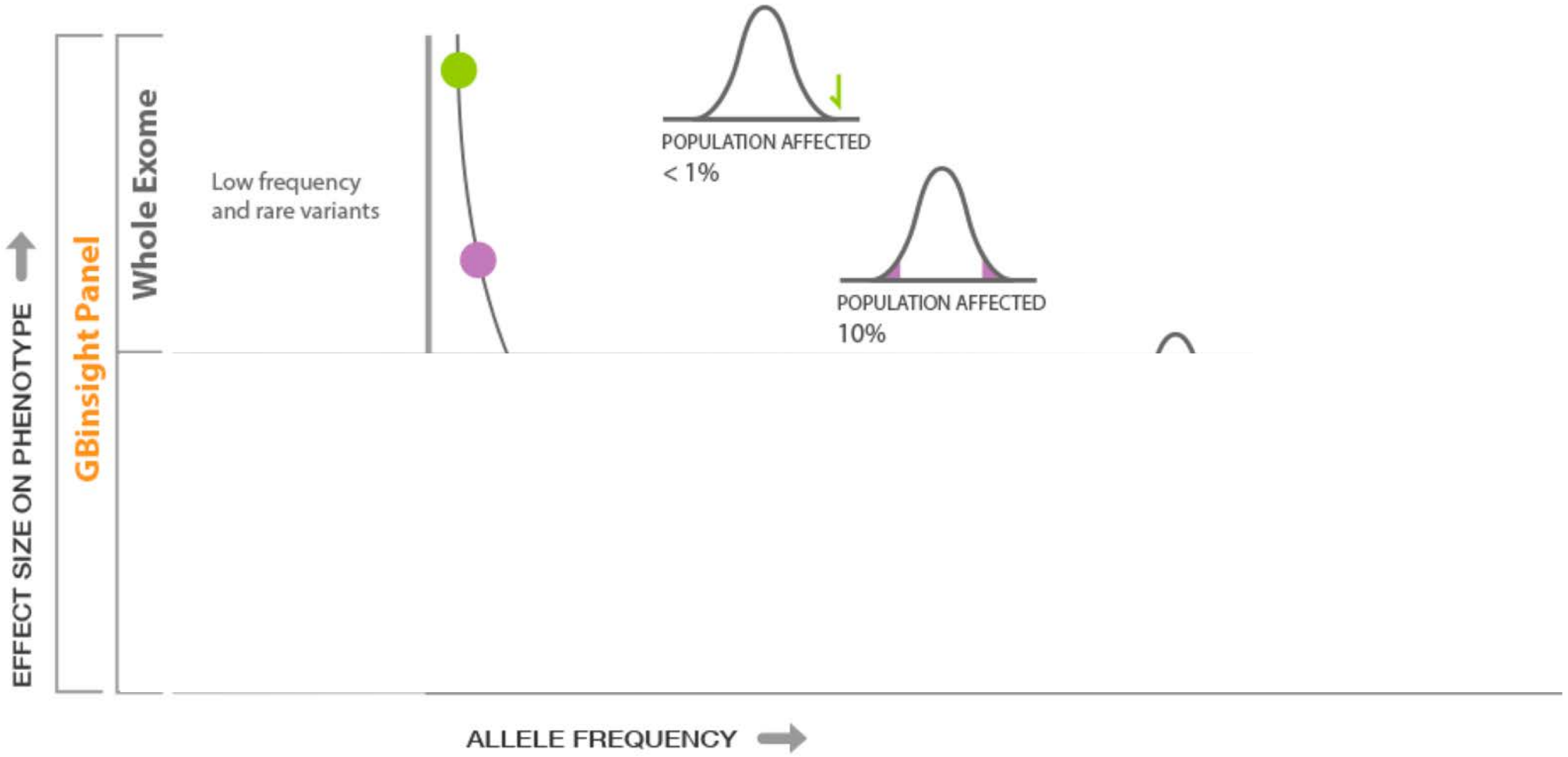


- HD (~1,800 Australians affected, ~6,000 carriers)

- Michael J Fox Foundation APP021399 “Investigating the role of repeat expansions and mitochondrial dysfunction in Parkinson’s disease” Bahlo M, Bennett M, Wang L, Dewson G, Watson R, Cooper A. (2022-2023)

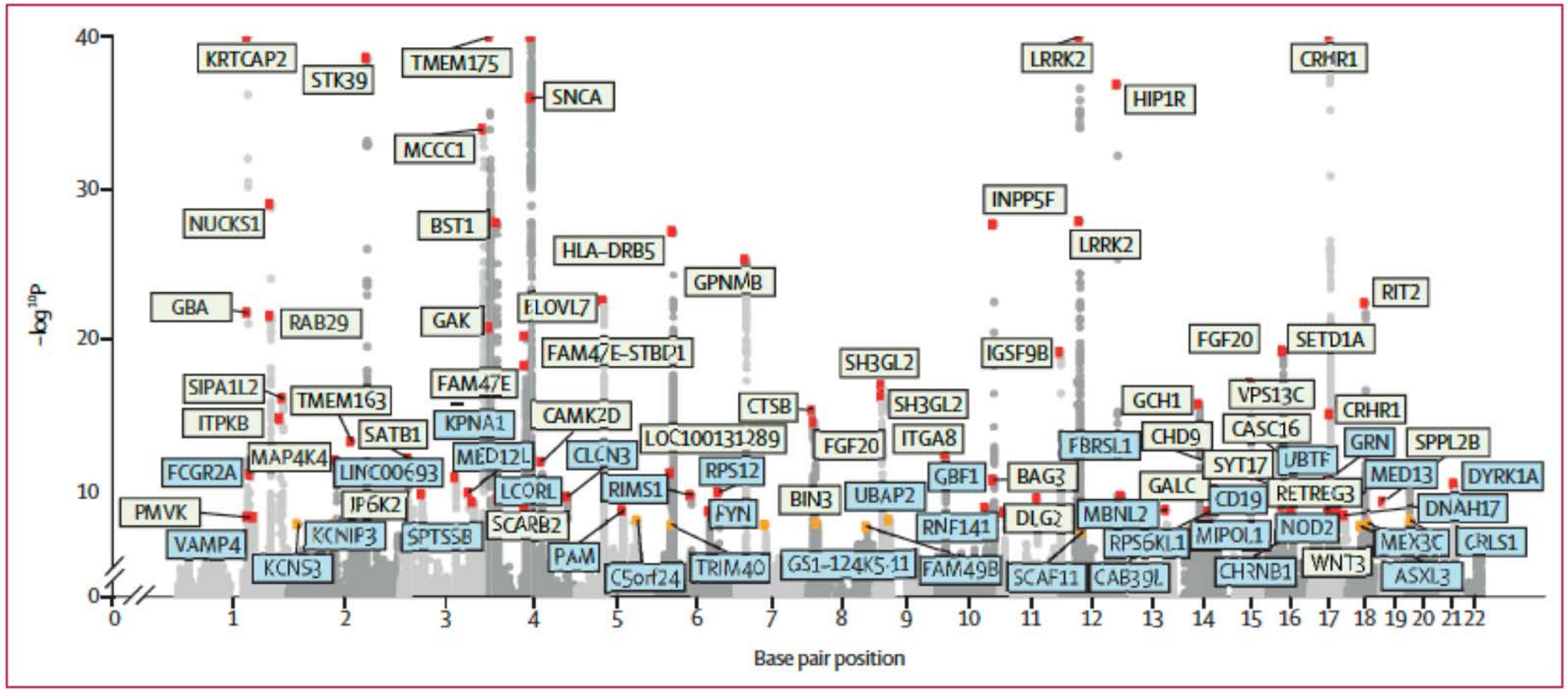
*underestimate!

Individual rare SNPs cause rare diseases. One SNP has a *huge* detrimental effect



https://www.gbhealthwatch.com/gbinsight/images/chart-common-rare-variants.png

2019 PD GWAS: 37,688 cases, 18,618 UK biobank proxy-cases, 1.4 million controls



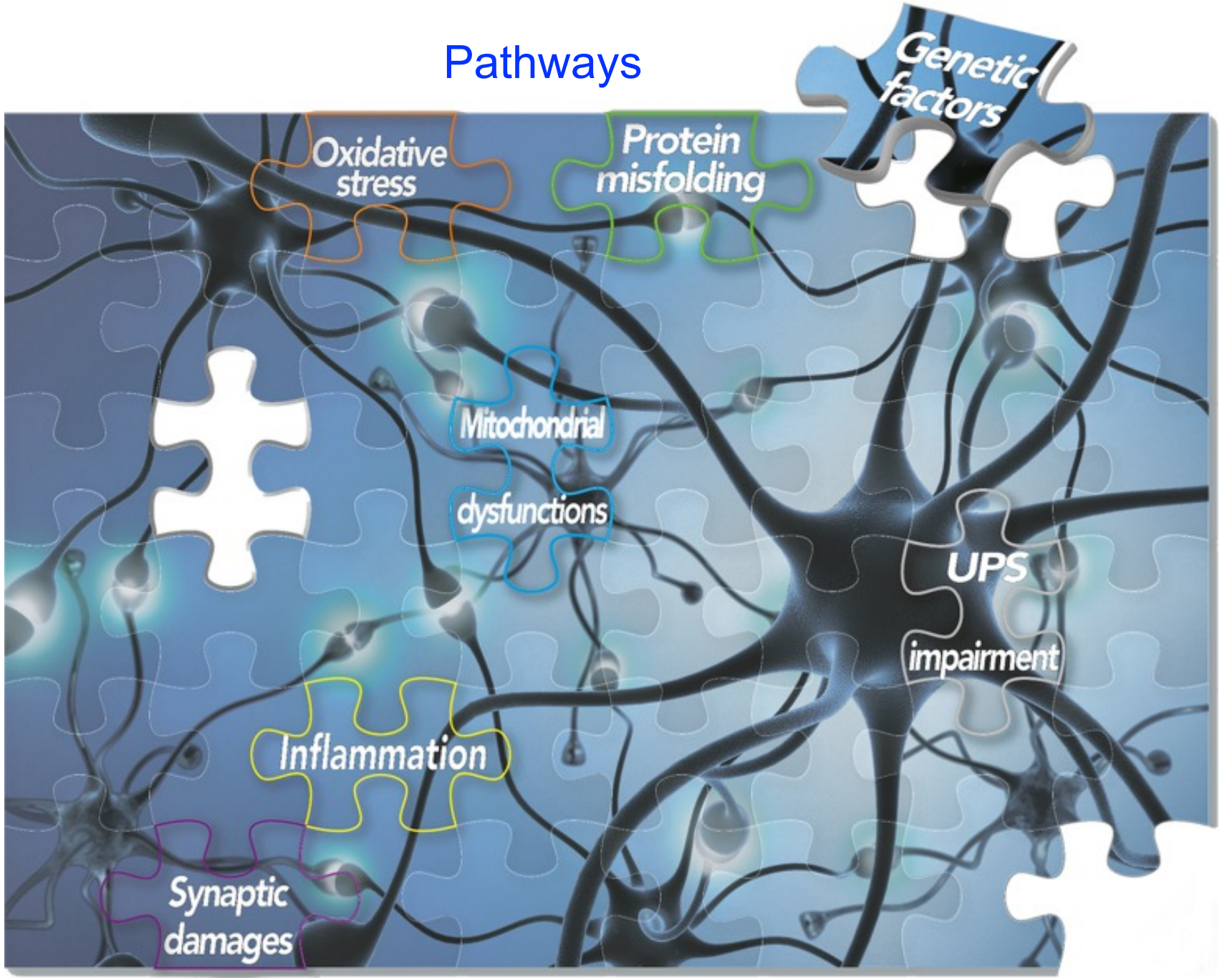
Nalls et al, Lancet Neurology, 2019. Ten loci with more than one signal

Progressive Myoclonus Epilepsies (all recessive)
SCARB2 *(Berkovic et al, 2008, AJHG)*
GRN *(Smith et al, 2011, AJHG)*
GBA (Gaucher Disease)

Work with Berkovic Lab & Karen Oliver

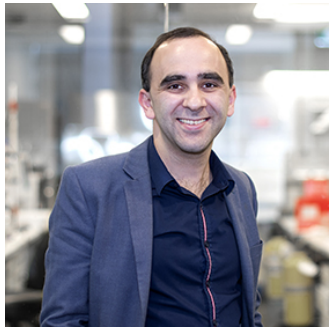
La Cognata, Hum Genet, 2017

Pathways



Watson/Yassi Dementia Lab @WEHI

- Rosie Watson (Geriatrician)
  - Dementia with Lewy Body (Lewy Body Dementia + PD with dementia)
  - Leads the **CO**m**B**ining memantine **A**nd cholinesterase inhibitors in **L**ewy body dementia treatment **T**rial (**COBALT**) NHMRC funded



- Nawaf Yassi (Neurologist)
  - Vascular and Alzheimer's Dementia
- Biomarker testing
  - SAMOA platform

Colonial Foundation Centre for Healthy Ageing

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The Royal Melbourne Hospital

Led by Andrew Webb (head of WEHI proteomics)

Our goals

Stage 1: Discover biomarkers

We are generating proteomic and metabolic data to identify a biomarker or panel of biomarkers that could be used to detect and diagnose dementia.

Stage 2: Develop assays for emerging biomarkers

The centre is developing immunoassays for ultrasensitive detection of blood biomarkers for dementia.

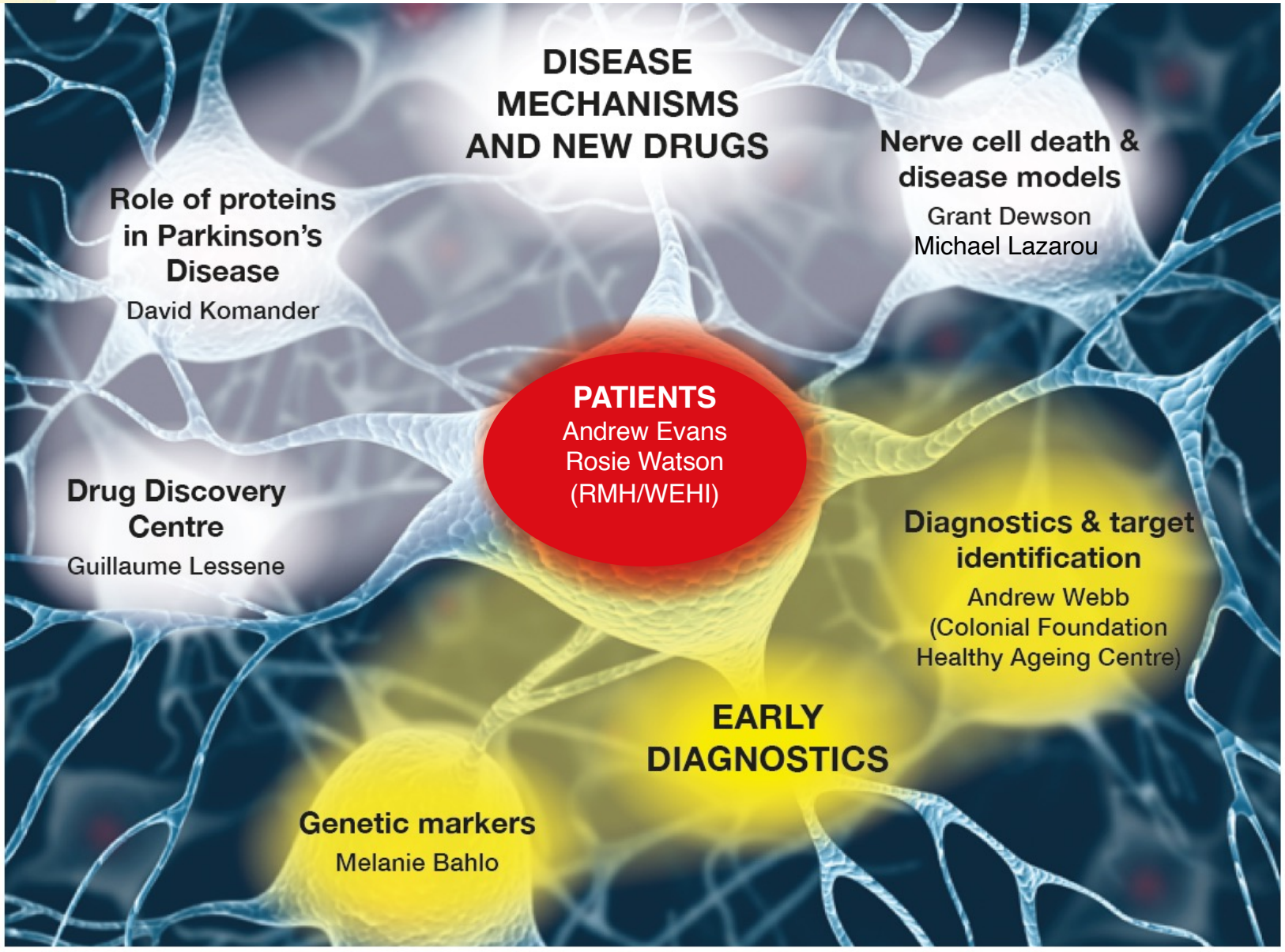
Stage 3: Implement tests in pathology labs

We are addressing the challenges of implementing powerful mass spectrometry-based tools for diagnostics, to produce an accredited pathology test for the early detection of dementia.

Stage 4: Conduct patient data-driven research

We are investigating Parkinson's disease biomarkers and optimising tools for biomarker discovery.

WEHI Parkinson's Disease Research Centre



Grant Dewson slide

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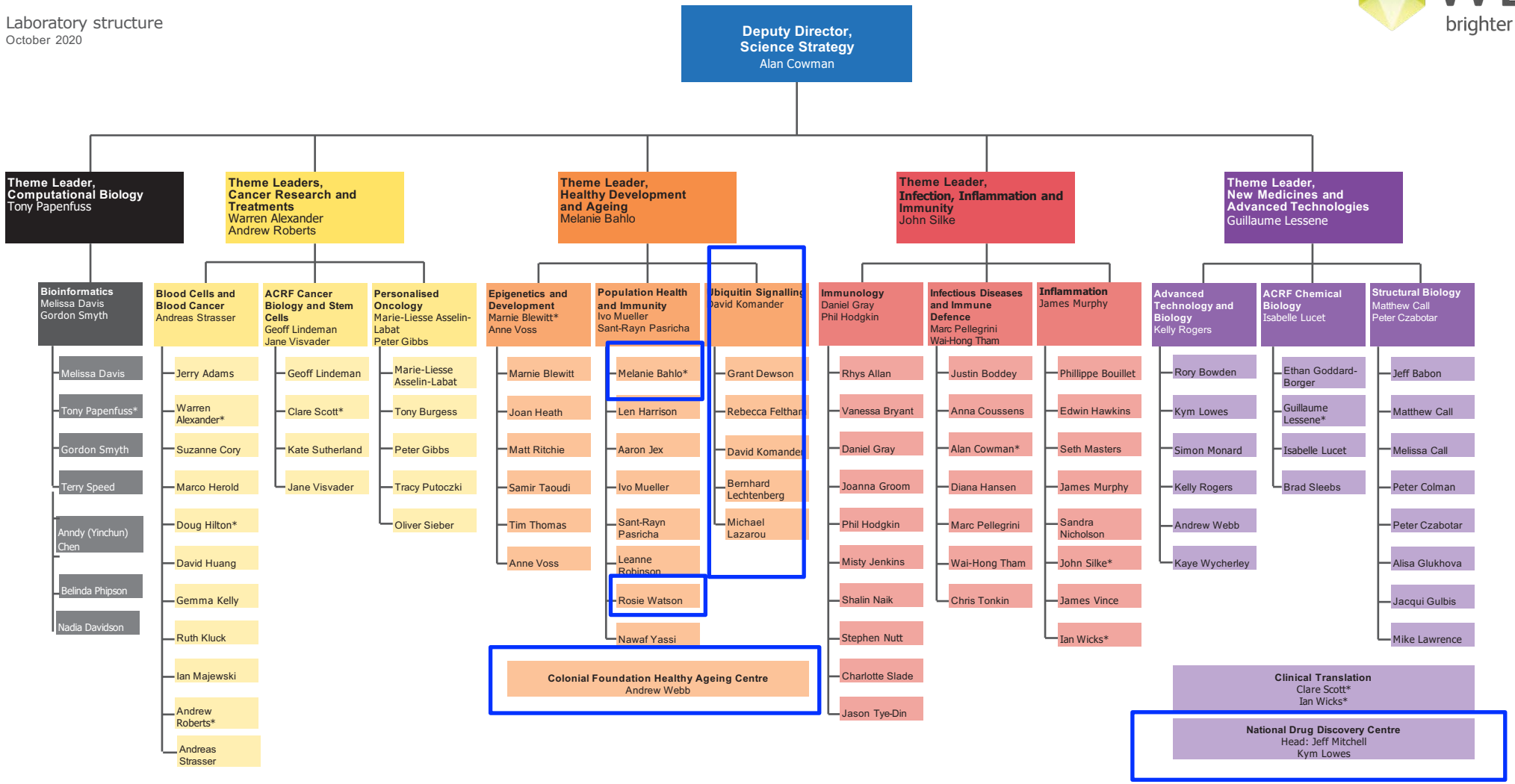

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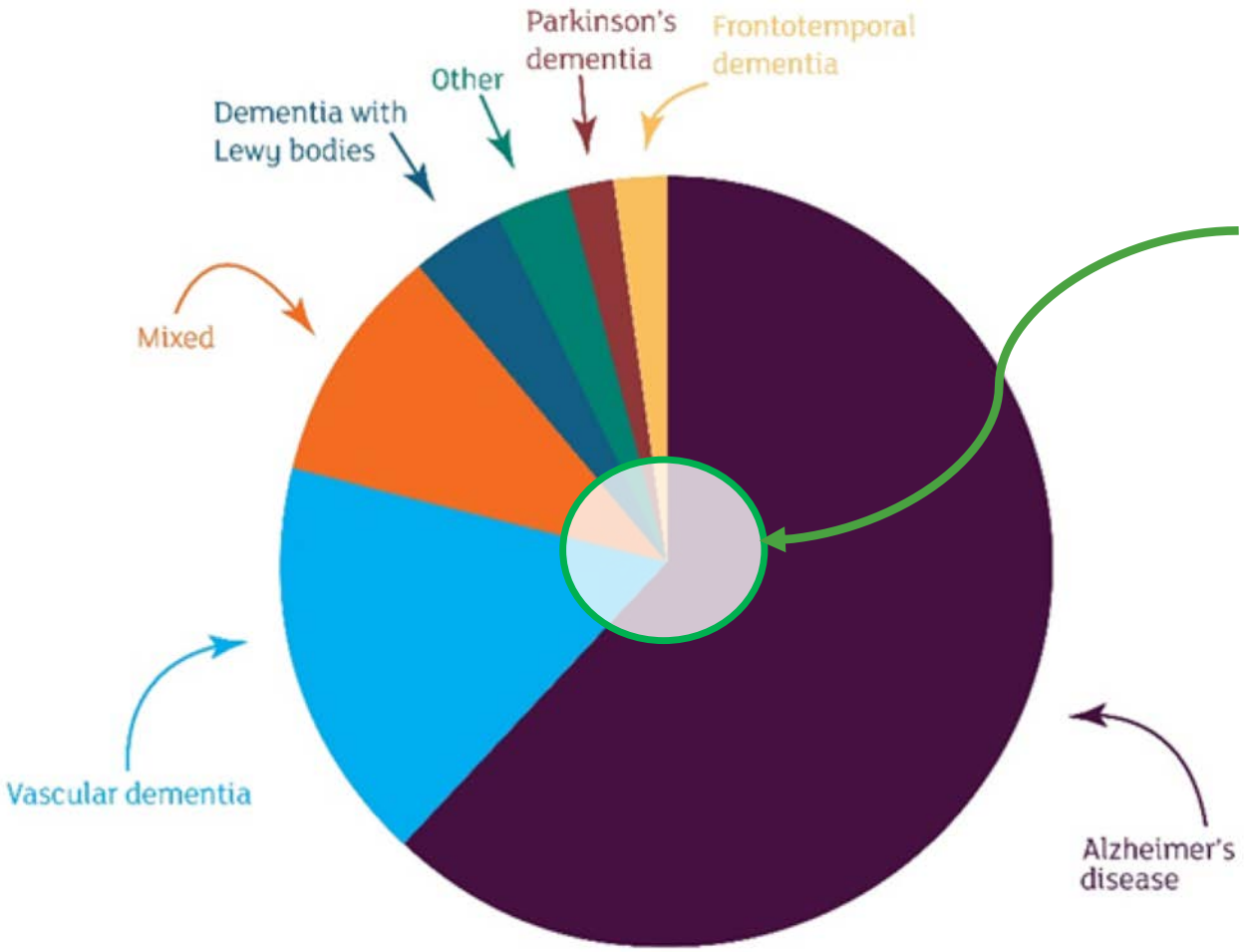
WEHI PD Research Centre

Dementia is not one, but many diseases (over 100!)



Early onset dementia (<65 yrs) *-includes early onset PD*

https://www.alzheimersresearchuk.org/blog/dementia-with-lewy-bodies-explained/

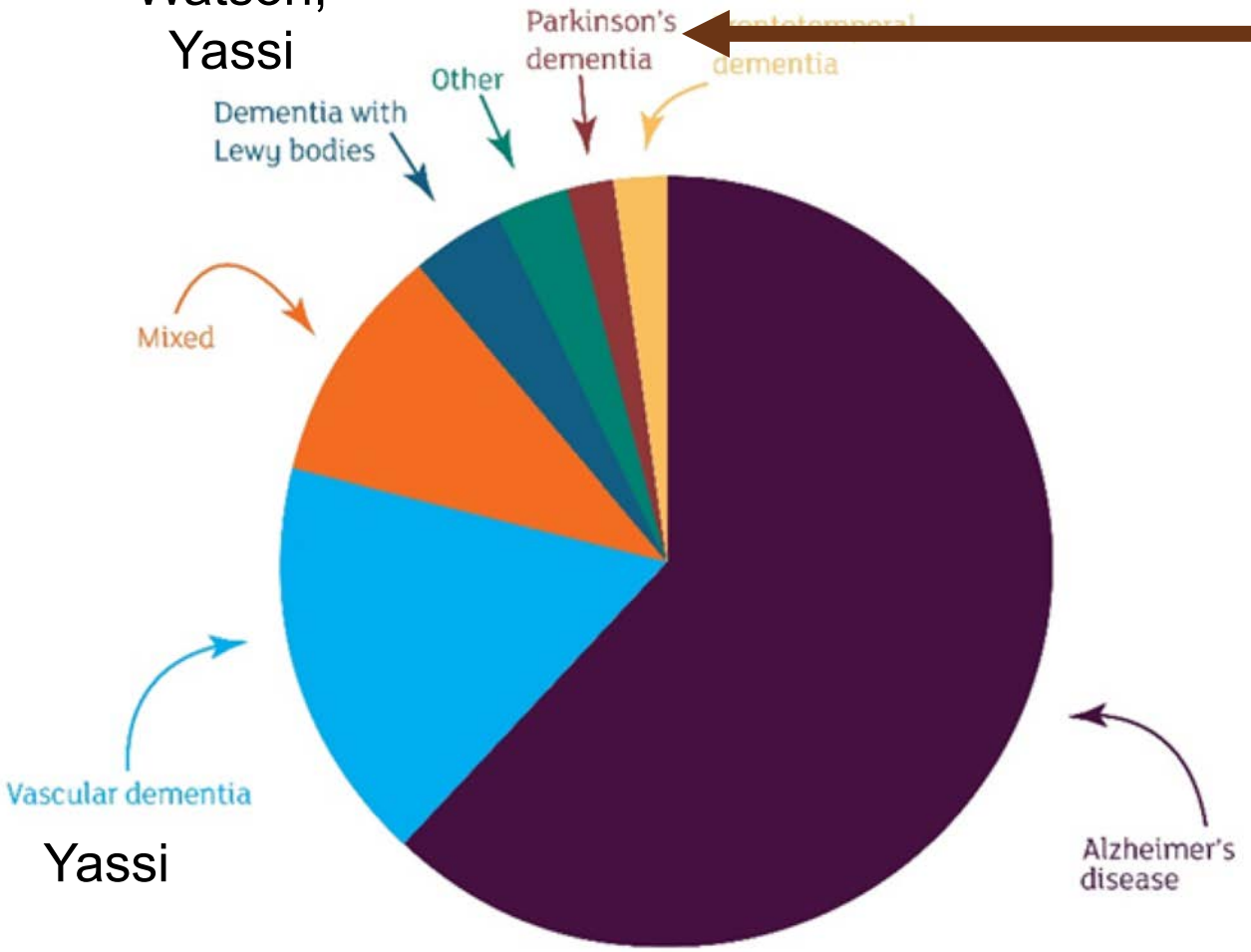
Current WEHI labs working on dementia, mapped to dementia subtypes

Komander
Dewson
Watson
Lazarou
Bahlo
Webb
Lessene

Parkinson's Disease Research Centre

Watson,
Yassi

Webb
Bahlo
Lessene



Yassi

https://www.alzheimersresearchuk.org/blog/dementia-with-lewy-bodies-explained/

Recent WEHI dementia achievements at WEHI

- ***Late 2021**: Recruitment of A/Prof Michael Lazarou to the Ubiquitin Signalling Division
  - Further strengthening PD work on mitophagy/PINK1/Parkin axis
- **Nov 2021:** Nawaf Yassi NHMRC Clinical + Dementia focused EL2 Fellowship award for 2022-2026 (vascular dementia)
- ***Dec 2021:** Nature publication led by David Komander on PINK1 structure
- **Feb 2022:** $1M Felton bequest award – providing genomics support for WEHI dementia work (2022-2027)
  - Provides a platform to engage additional clinical collaborators across Melbourne – **close collaboration with the RMH**
    - **COBALT** study participants WGS
- ***August 2022:**
  - Successful MJFF PD genomic analysis (Bahlo/Dewson/Watson/Cooper (Garvan))

*** = PD focused**

Increasing research impact from PD to dementia more broadly @WEHI

- Parkinson's Disease RC @ WEHI has 'taken root' but we want to work more broadly in the dementias in a similar way to the PDRC

What's needed?

- Increase in dementia clinician-scientists working in dementia alongside WEHI basic researchers
- Increase collaborations with healthy ageing focused institutes (Howard Florey, Centenary)
- Improving WEHI's ability to do human focused research
  - 2021: Launch of the WEHI Human Research Hub
- Continue to develop platforms to integrate our 'omics data assets with clinical data