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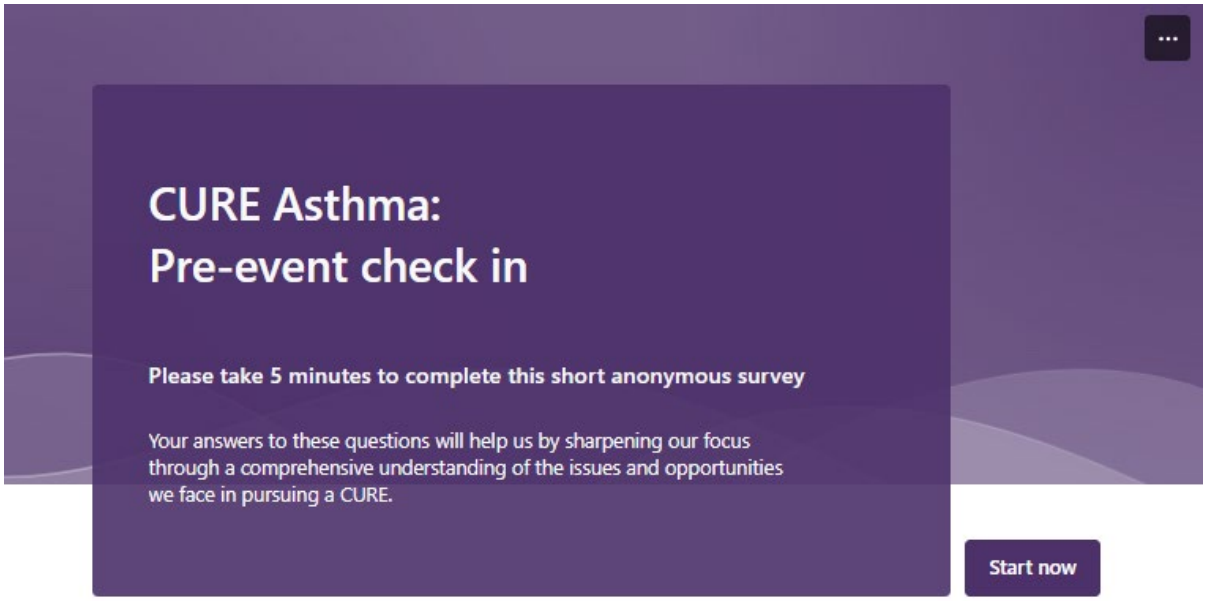
CURE Asthma Symposium Agenda

SESSION	FOCUS	LEADER/S
Event MCs: Professor Vanessa McDonald and Assoc Professor John Blakey		
10.00-10.30	Welcome to the University of Melbourne Acknowledgement of Country Welcome from Asthma Australia Introduction to CURE asthma	Professor Jenny Wilkinson-Berka James Wright Professor Gary Anderson
10.30-10.50	What is the clinical problem?	Professor Christine Jenkins Professor Sarath Ranganathan
10.50-11.15	Definitions: CURE vs remission	Professor Peter Gibson
11.15-12.15	Asthma > COPD: treatable trajectories across the life course Keynote address + panel Q&A	Professor Shyamali Dharmage Panel: Profs Shyamali Dharmage, Guy Marks, Alan James, Gary Anderson, Jo Douglass, Michael Menden
Group photo and lunch		
12.45-14.15	Early life airway injury, disease susceptibility and sequelae Keynote address and breakout group discussion	Professor Peter Sly, A/Prof Rhys Allan Breakout facilitators: Profs Peter Sly, Paul Robinson, Brian Oliver, Ingrid Laing, A/Prof Rhys Allan
14.20-15.35	Airway injury: from repair to pathology Keynote address and breakout group discussion	Profs Paul Foster & Alan James, Stuart Mazzone, Dr Alen Faiz Breakout facilitators: Profs Paul Foster, Alan James, Phil Bardin, Stuart Mazzone, Dr Alen Faiz
Coffee Break		
15.50-16.40	Pharmacotherapeutics' track record: moving past current treatment paradigms Keynote address and panel Q&A	Profs Gary Anderson and Peter Wark Panel: Profs Gary Anderson, Peter Wark, Carol Armour, Dr Alen Faiz
16.40-17.00	Wrap up, next steps and close	A/Prof John Blakey, Profs Vanessa McDonald and Gary Anderson AA consumer councilor

On behalf of the CURE asthma executive steering committee.



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CURE asthma

Theoretical framework: Executive Summary

This discussion document outlines the background for an ambitious research program seeking to find therapies able to induce true remissions and cures of asthma. It is intended as a point of departure and first framework for consolidating an integrative translational research plan supporting an EOI for the 2024 MRFF Frontier program, or other large-scale funding opportunity, including direct advocacy to government.

The strategic approach we have used is intended to build on past Australian successes: (i) clinical epidemiological and cohort studies that have (ii) identified key risks, stage-of-life transitions and subgroups and (iii) suggested likely underlying disease processes where new science can deconvolute the causative molecular pathogenesis that will lead to (iv) transformative interventions to bring about real change of an order of magnitude, reversing the prevalence trend of the recent decades, furthering real remission outcomes and providing real cures.

We are seeking your intellectual contribution, constructive criticism and material involvement in this program of work which at this stage could cover the following key problems/processes presented here as an initial discussion framework:

Proposed approach

The broad process we envisage is to collectively:

i. Map *dichotomized key epidemiologically and clinical transitions* (e.g. onsets vs apparent remissions, super-responders vs non-responders) where we feel an effective intervention would bring a large benefit
ii. Then we would identify likely *candidate biological processes* (analogous to the highly effective "hallmarks of cancer" strategy) and, perhaps, conceived of as our "(currently) untreatable traits"
iii. We would then consider what complementary scientific knowledge sets (e.g. bioinformatics, mucosal immunology, neurobiology, cell signalling **networks,** developmental biology) we would need to *discover the underlying molecular machinery* (analogous to new endotypes), focusing on therapeutically tractable biology
iv. This would then be articulated as a set of prioritised opportunities structured into 3-5 well-structured research programs, each with defined sub-themes. with careful thought given to translation, implementation, health economics and consumer need.

CURE ASTHMA WORKING FRAMEWORK

Background

The burden of asthma is profound. In Australia, it costs society $28b per year and is responsible for 40,000 hospital admissions and 400 deaths per year. It exerts burden disproportionately on children under 14 and contributes to complications and impacts on quality of life throughout the life course, especially when present in childhood.

Asthma Australia and other health peak organisations over several decades have had to make difficult decisions about how to direct their limited resource. This has resulted in a focus on 'living

well with asthma', 'living well despite asthma', 'breathing better with asthma', and 'living freely with asthma'. This is also understandable given the vast evidence available about how much burden currently experienced by people with asthma is avoidable.

One decisive way to reduce the burden is to CURE people of their disease. Major advances in our scientific understanding of asthma epidemiology, its driving molecular mechanisms and precedents from other comparable chronic inflammatory diseases for the first time make this goal a realistic ambition.

Asthma shows considerable heterogeneity, reflecting distinct and increasingly well understood molecular endotypes. There is strong evidence for an early life origin in the majority of cases, but asthma is rarely detected at birth. Intense research over decades on causes and possible signals for a cure strongly support the early life incident model explained by ***a combination of genetic predisposition and environmental exposures***. Future patients are born with an immunological predisposition that consolidates into persisting symptomatic disease often driven by viral lung infection and environmental exposures. Ironically, our progress in treating prevalent (current) asthma, much of it driven by original Australian research, means that we have stopped looking for ways to cure people of the disease. This situation cannot continue.

> We propose a collaborative, scientific and systemic effort to CURE asthma. CURE ASTHMA means treating a patient who has a validated asthma diagnosis in a way which reverses the mechanisms that cause disease symptoms; permanently, and efficiently producing a lasting disease-free state.

The case

We have a mandate for action

For decades Australia has led the world in bringing asthma evidence into practice and guidelines for international significance. Asthma Australia and friends recently completed a research priority setting exercise, which has been published as the National Asthma Research Agenda (NARA). This agenda was called for in the National Asthma Strategy, 2018, to establish a nationally coordinated, internationally recognised set of research priorities for asthma in Australia.

The National Asthma Research Agenda, developed directly from deep consultation with our consumers-asthma patients and their carers- is our mandate for action. Specific questions within the agenda under priority themes point us towards scientific pursuit of cure and remission. Asthma in Children (*why some children outgrow asthma and how can we harness this, what modifiable interventions can be developed in early childhood to prevent ongoing morbidity)* and Causes, Prevention and Features *(what causes asthma and how can we prevent it?)* are these specific, high priority, end-user derived demands (Majellano, 2022).

The Lancet Commission on Asthma paper called *After Asthma: Redefining Airways Disease,* also calls for such action. It calls for the cessation of the production of further 'me-too' medicines, which they define as palliative treatments, referring to the abundance of ICS and beta-agonist-based inhaler therapies. Based on abundant exposure of available and emerging evidence around the potential for cure and prevention, they say real effort should be directed *towards shifting from control-based treatment to prevention or cure* (Pavord et al, 2018). Moreover, the Lancet Commission on COPD

unequivocally stated the evidence that early life asthma is a major risk factor for devastating loss of lung function in later life. This situation can not continue.

Shifting pharma priorities and emerging health economic modelling

Fundamental disease modification and cures attract a vast economic reward for those bringing innovation to market as witnessed with preventative T2D medication (semaglutide), gene therapy for vision loss (voretigene neparvovec-rzyl) and spinal muscular atrophy (onasemnogene abeparvovec), hepatitis C cures (sofosbuvir), and in respiratory medicine, pulmonary hypertension (Sotatercept) and immune-oncology biologics (pembolizumab), and cystic fibrosis (kaftor class of correctors). The current asthma market is viewed as mature with LABA-ICS therapy being increasingly widely available in off-patent generic formulations. In contrast the biologics sector, mostly comprised of injected monoclonal antibodies, is growing at a compound annual growth rate (CAGR) of around 17% and predicted to be work around $AUS 65Billion by 2034. Severe asthma became a major global focus not only because of the pressing medical need but also because it was the sector where conventional health economic models drawing on the high cost of hospitalisations, could most readily develop a rigourous economic justification for the costs of medicines to payer. With the entire asthma franchise now monetised and more patients increasingly accessing structured care the economic case for developing disruptive remissions and cures has moved rapidly from "too-hard to value" to a business imperative. Increasingly our colleagues in the biopharmaceuticals sector are developing strategies to *induce disease remission*. From an Australian *large competitive grants* application perspective this rapid change in health economics and commercial landscape will allow us to articulate a compelling commercial and translation case for research towards remission - and cure - inducing therapies.

The science and technology is available

In the past 20 years, while focus on finding an asthma cure has faded, we have seen remarkable progress on cure and inducible permanent remission for other diseases, including those in the respiratory and immunological domains. Notable examples are detailed above, many of which are already in the respiratory medicine sector. Further, and closer to home, we're seeing promising results from monoclonal antibody (mAb) treatment in severe asthma which is inducing convincing on-treatment remissions in subsets of patients. In other fields we are seeing the emergence of aggressive treatment of pre-diabetes and pre-cardiovascular disease as primary preventions and in rheumatology the aggressive adoption of early combination therapy to induce true remissions and convincing, if arduous, improvements in MS after myeloablation and transplant in MS. In oncology we no longer accept treatment, but rather CURE as the ambition of therapy and all future research is directed towards developing cures. These discoveries have been made due to the efforts of thought leaders in the space who could visualise and describe what their objective to cure disease looks like and followed the science through to its translation. Importantly, these precedents are also creating new and transformative cost-benefit economic models supporting cure as the most desirable outcome. Accordingly, industry - sensing the possibly of disruptive innovation from competitors' sudden and profoundly eroding established market franchises - is realigning its business models towards remission and cure.

Is therapeutic remission or cure scientifically feasible?

Conventional wisdom is that there is no convincing evidence that deep remission or cure for asthma is impossible. But this is not the case. Natural history studies have clearly demonstrated that a substantial fraction of patients achieve spontaneous remission, as is well documented in the analysis

of long-term outcomes over 30 years in the Netherlands. In these 30 year follow-up of asthmatic children cohorts, complete remission of asthma defined as no asthma symptoms, no use of inhaled corticosteroids, normal lung function (FEV1 >90% predicted), and no bronchial hyperresponsiveness (PC10 >16 mg/ml) occurred in 22% of patient and a further 30% were in "clinical remission" defined as no asthma symptoms and no use of inhaled corticosteroids (Vonk et al, 2004). Genome-wide association studies (GWAS) of these cohorts have identified several novel loci associated with establishing a strictly defined remission phenotype, with 3 single nucleotide polymorphisms (SNPs) associated with complete asthma remission, and other SNPs with plausible biology in *FRS2 (Fibroblast Growth Factor Receptor Substrate 2)*, the protein chaperone factor *CCT*, the non-T2 inflammatory genes *IL1RL1, IL18R1* and the critical regulator of T2 immunity *IL13* (Vonk et al, 2018). Epigenetics studies have further identified that differential methylation of CpG regions between remission and persistent asthma identify genetic loci associated with resolution of inflammation and airway responsiveness (Vermeulen et al, 2020). These studies, and precedents from therapeutic immunomodulation trials, builds confidence that it will be possible to de-convolute the underlying molecular pathogenic mechanisms and convert these into effective therapies. The very high quality of Australian long-term cohort studies in asthma further enable deconvoluting pathogenic mechanisms and understanding how remission and cure may be achievable therapeutically.

Remission, Australian science and track record

The very first efforts to transform asthma care were, arguably, Australian with the introduction of management guidelines and first attempts, albeit frustrated, at aggressive early "tight control" treatment regimes, rigorous allergen avoidance and dietary interventions amongst other strategies. Existing insights in this area of research have been generated by outstanding Australian scientists whose work has contributed to the framework understanding of the development of Th2 dominant phenotype in childhood asthma as governed by processes such as epigenetic modifications of epithelium, immune biasing in lymphocyte memory effector populations, peripheral neurobiology, epithelial innate immunity, remodelling lung developmental biology, the discovery of IL-5, catabasis (resolution), genomics and rare disease variants, and advanced translational disease models.

Very recently, our Australian asthma research leaders at the Centre for Research Excellence of Asthma Treatable Traits have begun the work to define asthma remission. This exciting frontier in the definition of disease-modifying treatment goals in asthma is emerging and being potentiated by the traits approach in severe asthma, a framework of precision/personalised care based on analysis of detailed data about people with severe asthma. Such pragmatic scientific expertise provides for strong foundations upon which our CURE ASTHMA ambitions can be setup.
The Australian Asthma Treatable Traits team (Thomas et al, 2023) have drafted useful and implementable summary of asthma remission, based on their further detailed analysis of Australian severe asthma datasets. This summary includes a preliminary definition of remission, the factors that contribute to its achievement, highlighting the treatable traits approach and early intervention specifically, and Australian prevalence estimates.

This summary is provided below, and helps us picture our CURE ambition, by

- Defining cure in asthma, vs remission
- Providing a practical framework to define potential candidate traits, and/or key transition points in disease aetiology, in asthma that may be amenable to cure, and
- Signalling scientific pathogenesis insights that might contribute to cure targets.

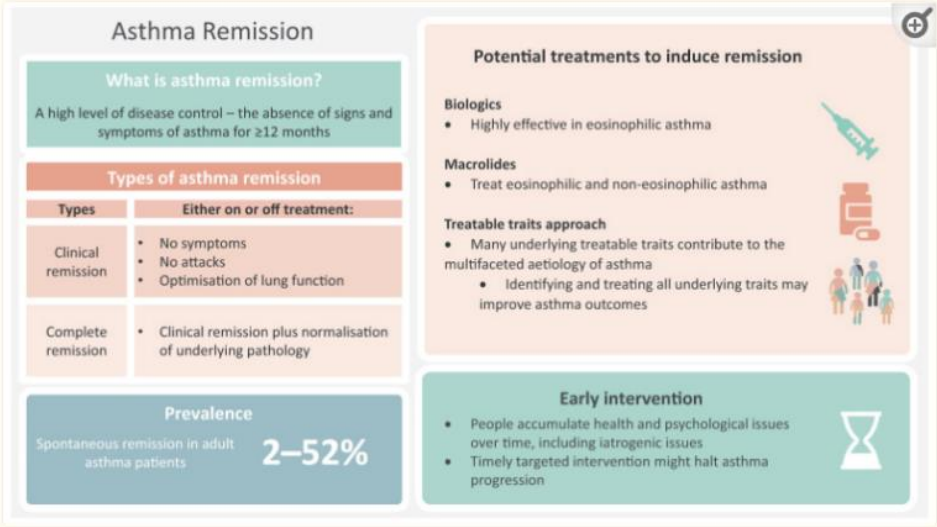


FIGURE 1

A visual summary of remission. Content has been reproduced with permission from the Centre of Excellence in Treatable Traits, originally developed as part of the Centre of Excellence in Treatable Traits (https://treatabletraits.org.au).

CURE ASTHMA

The recent Lancet commission on asthma "*After asthma*" summarised key knowledge about the natural history of asthma and key clues around the underlying likely disease processes. These are reproduced on the next page.

We also now know from extensive molecular profiling that asthma, like other chronic inflammatory diseases, is a heterogenous condition of the airways that can emerge and be diagnosed at any stage of the life course. Although this may have contributed to the perception that CURE may be elusive in asthma, we believe that our ability to define and describe distinct patterns of onset will provide us the platform to describe and pursue distinct curative treatment targets. Indeed, innovation from Australian researchers over decades has quite literally helped to rigorously frame the possibility of remissions and cure, and provided fundamental insights into tractable underlying disease mechanisms.

These distinct patterns suggest that we should be able to develop a number of curative strategies so that the majority of all people with asthma will progressively benefit. Australian researchers have literally contributed *hundreds* of field-shaping landmark studies to the world scientific literature, shaping our understanding of disease and providing the foundation stones of international guidelines.

Panel 6: Important findings of birth cohort studies

- Transgenerational factors (eg, grandparents smoking) increase the risk of airway disease.[138]
- Antenatal factors such as exposure to tobacco smoke[145] and pollution[144] affect airway disease in the fetus by affecting gestational age and birthweight, through direct effects on lung structure, and through effects on the fetal immune system, which lead to abnormal responses to allergens and viruses.[145]
- Location of birth (home *vs* hospital[206]) and mode (vaginal *vs* caesarean section[64]) of delivery might affect the risk of future airway disease.
- In the immediate postnatal period, further decline in lung function occurs in individuals who develop persistent wheezing illnesses, particularly in neonates with airway hyper-responsiveness.[67]
- Antenatal and postnatal environmental microbial exposures (farm animals, dogs, siblings, day care) modulate the risk of childhood asthma by affecting atopy, responses to viral infections, and skewing immune responses.[71,203,208]
- Postnatally, passive smoking,[63] pollution,[144] moisture damage,[209] obesity,[210] pesticide exposure,[211] and multiple early atopic sensitisation[73,74] increase asthma risk.
- Five childhood risk factors (maternal or paternal asthma, maternal smoking, childhood asthma and respiratory infections) account for at least half the risk of developing chronic obstructive pulmonary disease (COPD) in later life.[137]
- Lung function tracks over many decades: in most circumstances no catch-up lung growth is observed.[140]
- Airway disease in children aged younger than 5 years might recur after quiescence in adulthood or manifest for the first time in adulthood.[58]
- Adolescent girls with premature menarche might have an increased risk of developing asthma.[212]
- Multiple trajectories to COPD have been identified. A longitudinal analysis[140] showed that of the individuals with a forced expiratory volume in 1 s of 80% or higher in early adult life, 158 (7%) of 2207 had a rapid decline in lung function and developed COPD. Another group had a forced expiratory volume in 1 s of less than 80% in early adult life, and 174 (26%) of 657 developed COPD with normal rates of decline in lung function on spirometry. Both trajectories contributed equally to the burden of COPD, although the trajectories differed in the rate of decline in lung function in later life.[140] Subsequently, follow-up of the CAMP study bridged the gap between adult and childhood studies.[213] Four asthma spirometry trajectories were identified, comprising combinations of normal or reduced plateaux of lung growth, and normal or early decline in spirometry, independent of treatment prescribed (nedocromil, budesonide, or placebo).
- In the many large studies[214–217] of spirometry in adult life, no single environmental factor, including smoking, consistently predicted an accelerated decline.

We therefore propose an ambitious research program, harnessing our local strengths, and building out from the best understanding and most tractable major groups.

POTENTIAL FOR PROFOUND IMPACT

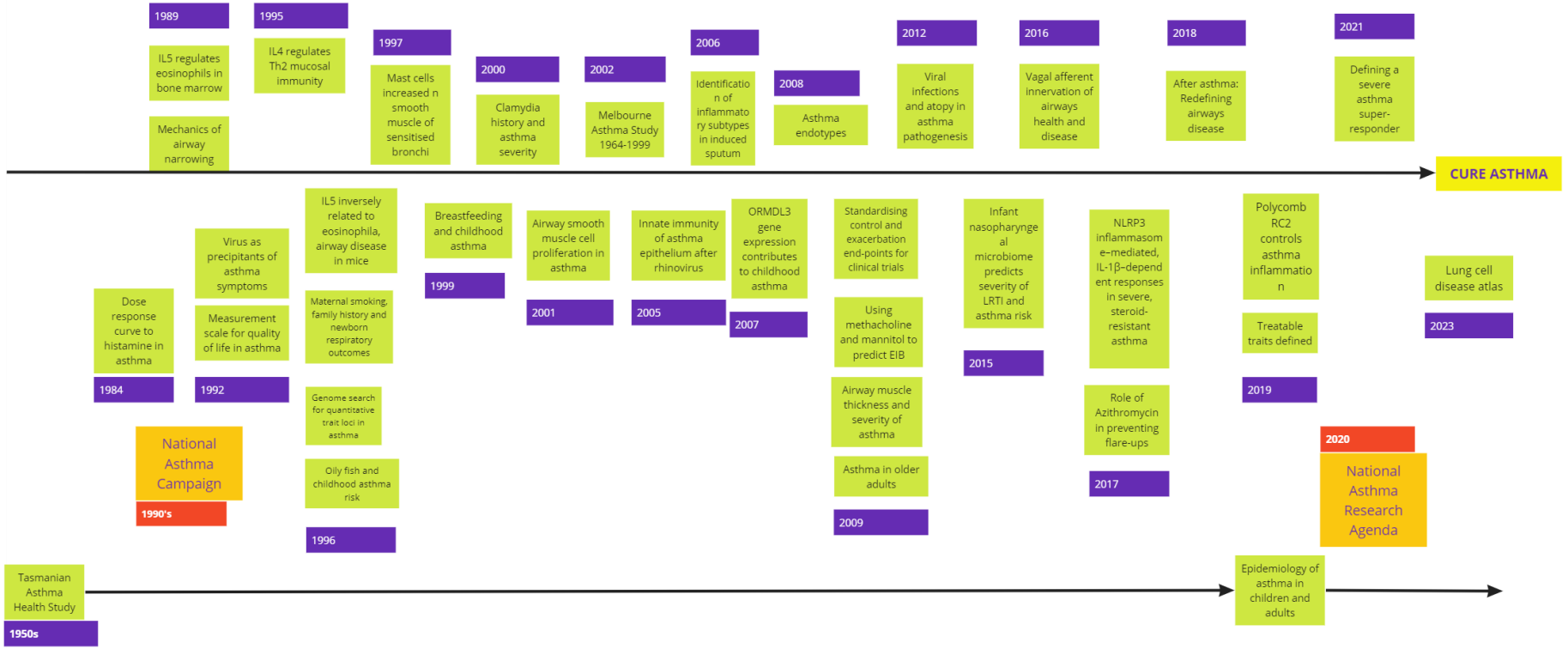
Asthma has been a National Health Priority for decades, yet profound progress to arrest its prevalence and insidious burden has been limited at best. The potential for impact of CURE ASTHMA is immense. At the CURE asthma symposium we will dive deep into the theoretical framework, specifically focusing on:

- Defining CURE and remission
- Focusing in on the life course trajectories and transitions
- Unpacking the early life injury and sequelae, and susceptibility to the sequelae
- Identifying gaps in our understanding of why injury doesn't repair to healthy state in asthma
- Exploding the current treatment paradigms in asthma.

And build the research clinical<>translational science partnerships we need to CURE asthma.

Appendix A: Landmark Australian contributions to asthma research

Please note that this is by no way comprehensive *or even adequate*, but merely a sampling of a few studies that reflect the hundreds of studies that have been made by Australians that have driven our understanding of the fundamental nature of asthma and led to major advances in therapy and care. Suggest more- map your own contributions here!!



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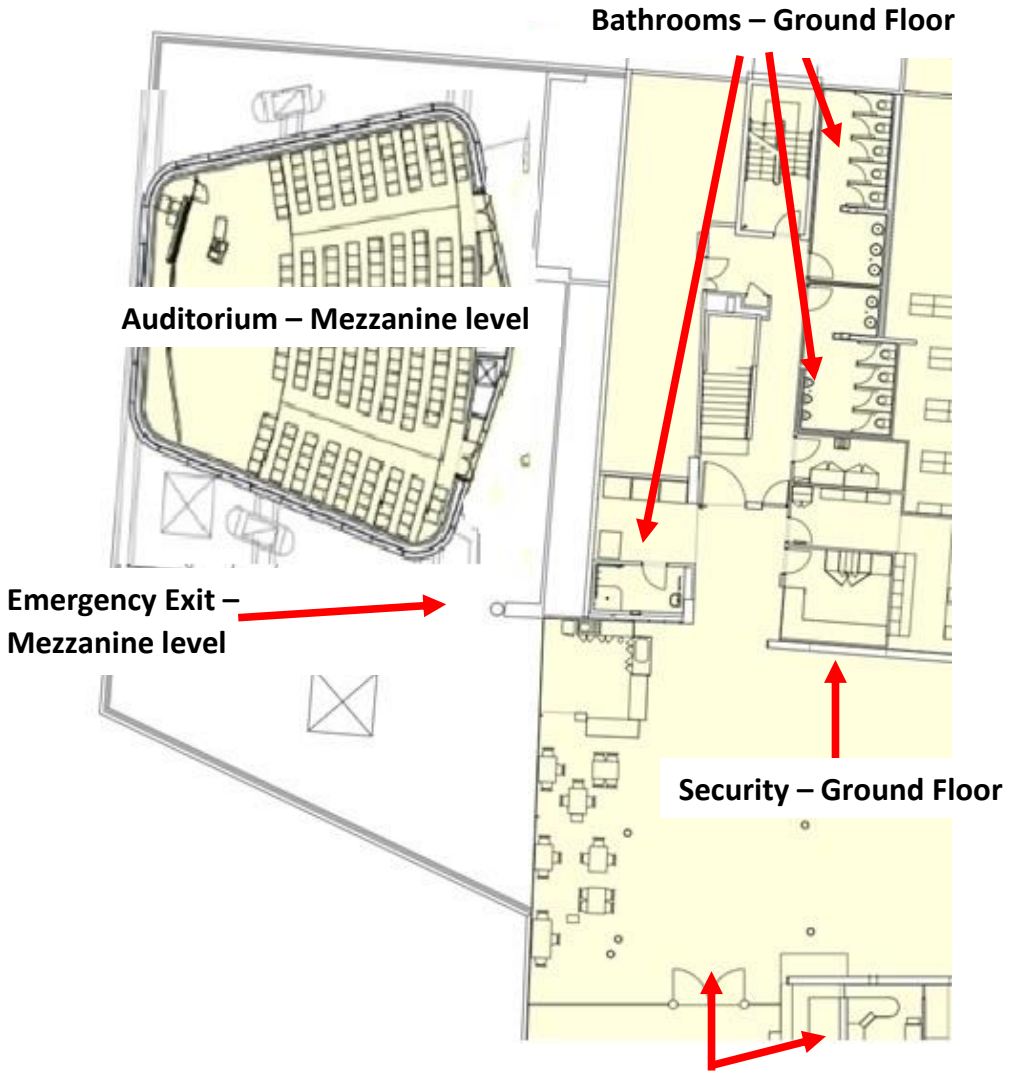

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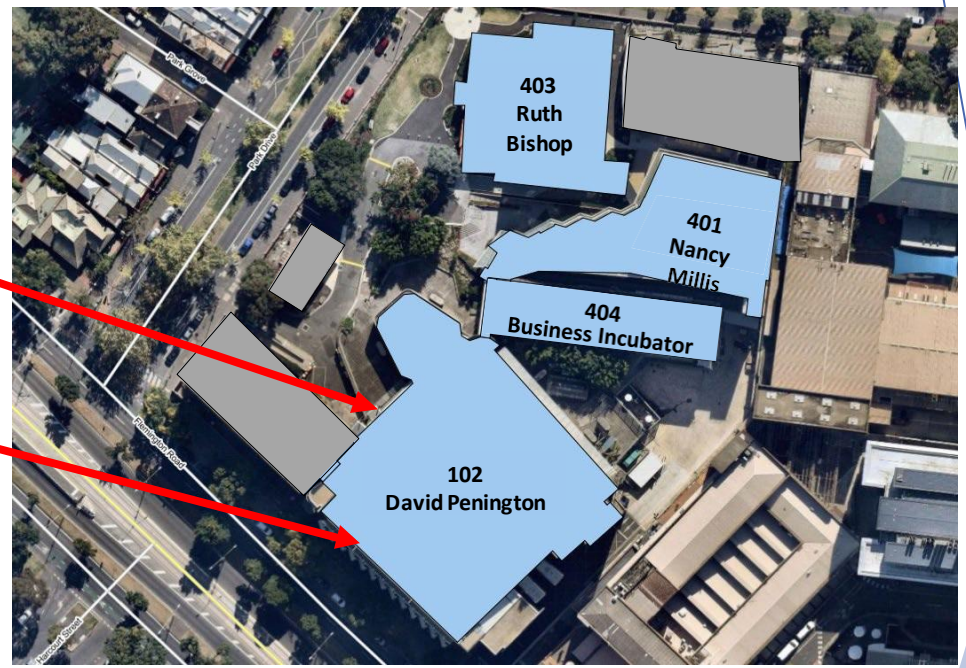

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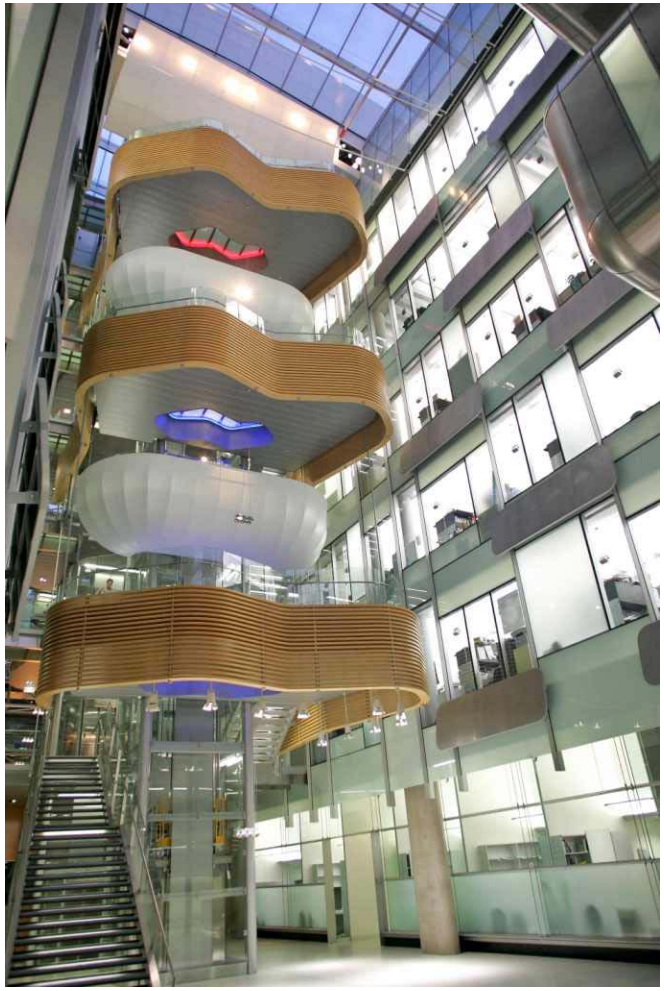

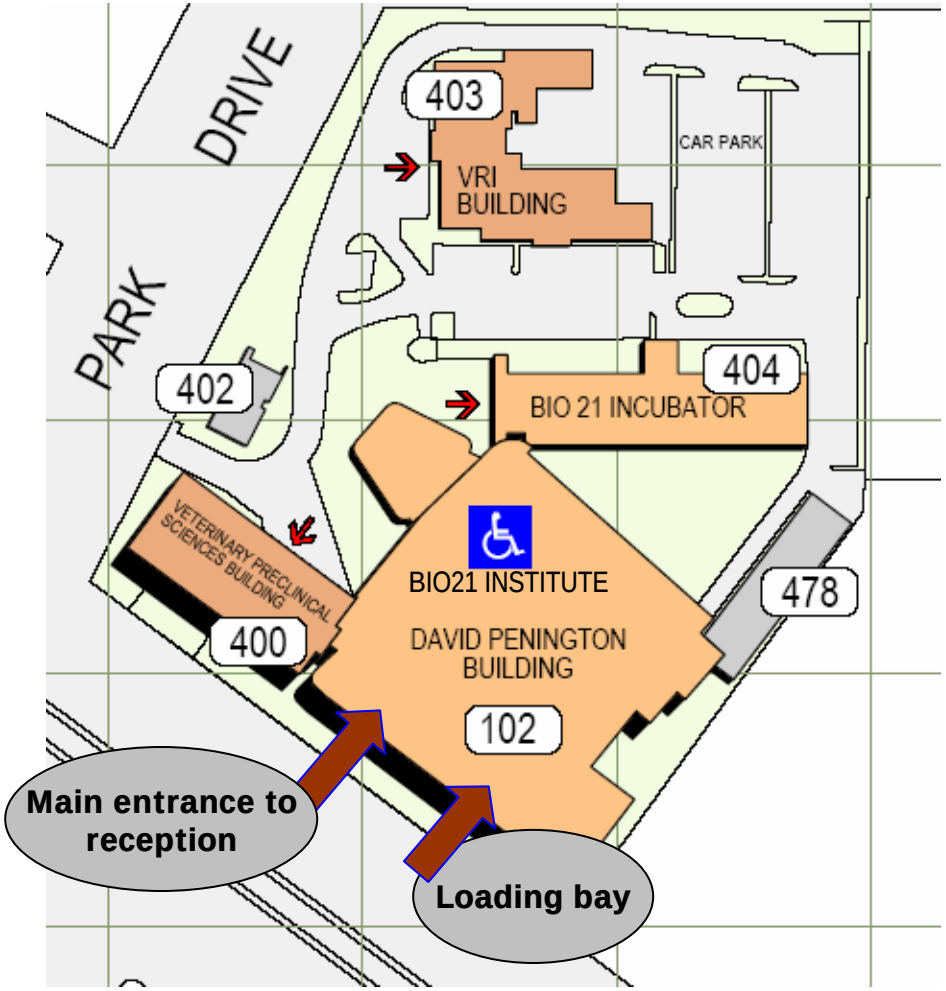

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of _____ *(insert address)*

For parents/legal guardians of children (if applicable)

1. **declare** that I am the parent/legal guardian of the following child or children

Child 1 Name	*Child 2 Name*	*Child 3 Name*

2. **agree** to Asthma Australia
   a) making images or recordings, whether sound, digital or otherwise, of me and the Children (Images and Recordings);
   b) using, publishing or reproducing the Images and Recordings in any form (in whole or part) and by any medium, including but not limited to newspapers, magazines, brochures, television advertisements, promotional videos, websites, CD-ROM or other multi-media, for public relations, promotions, commercial and advertising purposes (Promotional Materials); and
   c) retaining or storing the Images and Recordings (including those incorporated into Promotional Materials), in hard copy or digitally, including but not limited to, deposit of the Images and Recordings into an Asthma Australia Image Library;

3. **agree** that the rights granted to Asthma Australia under clause 2 of this Photo Consent Form are perpetual and that I will not receive any payment, royalty or other consideration (whether monetary or otherwise) from Asthma Australia in connection with the making, use or storage of the Images and Recordings;

4. **agree** to Asthma Australia collecting, storing, handling, accessing, managing, transferring, using and disclosing personal information about me and the Children, including but not limited to our name, details and image, in connection with the Images and Recordings or the Promotional Materials;

5. **acknowledge and agree** that any Promotional Materials which refer to me and the Children, expressly or by implication, are, at the date of publication, made in good faith and are not intended to defame or offend me or the Children or bring me or the Children into disrepute and, to the best of Asthma Australia's knowledge, are true and correct;

6. **agree** that Asthma Australia is the owner of the copyright in the Images and Recordings and the physical Images and Recordings; and

7. **acknowledge** that a representative of Asthma Australia has explained the contents of this Photo Consent Form to me and I am signing this Photo Consent Form of my own free will, on the full understanding and comprehension of the terms of this Photo Consent Form.

Signed by:	**Witnessed by:**
	Address
Print name	Print name
Signature Date	Signature Date