Neuroscience Letters 740 (2021) 135469

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

Behavioural phenotyping of *thunder* mice with a hypomorphic mutation of heterogeneous nuclear ribonuclear protein L-like (hnRNPLL) and reduced T cell function

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ARTICLE INFO

Keywords:
Heterogeneous nuclear ribonuclear protein L-like (hnRNPLL)
T cells
Depression
Anxiety
Learning and memory
Prepulse inhibition
Locomotor activity

ABSTRACT

Heterogeneous nuclear ribonuclear protein L-like (hnRNPLL) is an RNA binding protein that regulates alternative splicing of mRNA and is abundantly expressed in memory T lymphocytes of the immune system and in the brain. A hypomorphic allele of the gene encoding hnRNPLL (*Hnrpll*^{thunder}) selectively reduces T cell accumulation in lymphoid tissues, but little is known about its effects in the brain. Therefore, we exposed *Hnrpll*^{thunder} mice to a test battery with relevance for a range of psychiatric illnesses. *Thunder* mice showed enhanced immobility in the tail-suspension test for depression-related behaviours, impaired short-term spatial memory in the Y-maze and reduced avoidance learning in the active avoidance test. Thus, in addition to its reported effects on immune function, the hnRNPLL mutation in *thunder* mice selectively affected aspects of behaviour.

1. Introduction

Heterogeneous nuclear ribonuclear protein L-like (hnRNPLL) is a RNA-binding protein that is highly expressed in memory T cells and is implicated in the regulation of alternative splicing of several genes involved in T cell activation [1,2]. Consequently, mice with *N*-ethyl--*N*-nitrosourea (ENU)-induced hypomorphic allele of hnRNPLL, designated *thunder* (T_h cells under the normal range) mice, displayed altered proportions of naïve and memory T subsets and diminished T cell accumulation in peripheral lymphoid tissues but there was no apparent defect in T cell proliferation [3] or NKT cell accumulation [2].

The *Hnrpll* gene is expressed in neurons within the brain [3] including regions such as the frontal cortex, hippocampus, striatum and nucleus accumbens in mice [3,4]. Accumulating evidence suggests that altered immune function, such as T cell deficiency and altered cytokine secretion, can affect neuronal function and be involved in psychiatric conditions such as depression [5] and cognitive decline [6]. The aim of the present study was to examine for the first time the behavioural phenotype of *thunder* mice with a hypomorphic mutation in the *Hnrpll* gene in a battery of behavioural tests with relevance to psychiatric illness. The data show that *thunder* mice display a phenotype of (1) enhanced immobility behaviour in a test with relevance to antidepressant action, and (2) reduced learning and memory. In conclusion, in addition to its role in T-cell function hnRNPLL can impact on behavioural responses *in vivo*.

2. Methods

C57BL/6JSfdAnu-Hnrnpll^{thdr}/AnuApb mice (*thunder* mice) were obtained from a breeding colony at the John Curtin School of Medical Research, Australian National University, Australia (see http://pb.apf.edu.au/phenbank/strain.html?id=78 for detailed strain information). The *thunder* strain was maintained on the C57BL/6 background and all animals used in the present study were obtained by crossing heterozygous breeders, resulting in similar genetic background in wildtype controls and mutants. The mice were held in sex-matched groups of 2–5 in open-top plastic cages with shredded paper as enrichment and received standard mouse chow and tap water *ad libitum.* The animals were 9–12 weeks old at the start of the three-months behavioural testing sequence. There were no overt sex differences in behaviour and, therefore, data for male and female mice are presented here combined. One cohort of mice went through all tests listed, while a second cohort of

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https://doi.org/10.1016/j.neulet.2020.135469
Received 4 July 2020; Received in revised form 23 September 2020; Accepted 27 October 2020
Available online 2 November 2020
0304-3940/

mice was tested only in forced-swim test, Y-maze, and active avoidance learning. Data from a small number of animals were not included because of equipment failure or outlier values. The resulting number of mice per genotype per test and sex ratio is indicated in Table 1. Behavioural testing was done during the light phase of the 12:12 h light: dark cycle. All experiments were done according to guidelines set by the National Health and Medical Research Council of Australia and were approved by the appropriate Animal Experimentation Ethics Committee.

2.1. Exploratory locomotor activity

To assess habituation to novelty, mice were individually placed in locomotor boxes (25 × 25 cm, TruScan locomotor, Coulbourn Instruments, USA) and horizontal activity was detected over a one hour session by 32 photocells situated 2 cm above the floor of the arena. Testing was carried out for five consecutive days and the average distance travelled during the first and last 30 min of the sessions was statistically compared.

2.2. Elevated plus maze

The elevated plus maze measures anxiety-like behaviour. At least one week after the last locomotor activity session, this test was carried out as previously described [7]. The apparatus was constructed from opaque grey plastic and consisted of four arms, two of which were enclosed by walls, while the other two were left open. The maze was elevated 30 cm off the floor and testing was carried out in dimmed light. Mice explored the maze for 10 min and their behaviour was recorded on video via a camera above the maze. The number of visits and time spent in the open and closed arms was scored from the videos by an observers blinded to the genotype of the mice.

2.3. Tail suspension test

Two days after the elevated plus-maze test, mice were subjected to the tail suspension test for depression-like behaviours and antidepressant action [8,9]. On two consecutive days, each mouse was suspended for 6 min by adhesive tape that was placed approximately 1.5 cm from the tip of the tail. Animals were tested twice and behaviour was manually scored to assess the amount of time spent immobile or moving [9].

2.4. Prepulse inhibition of the startle response

Prepulse inhibition (PPI) of acoustic startle is an operational measure of sensorimotor gating [10]. Five days after the tail-suspension test, PPI and startle were measured using automated startle chambers (SR-Lab; San Diego Instruments, San Diego, USA). A PPI session started with a three-minute habituation to the enclosure, followed by 104 trials [11] of which the first and last 8 trials consisted of a 40 ms 115 dB pulse-alone startle stimuli. The middle 88 trials consisted of a pseudo-randomised delivery of 16 additional pulse-alone stimuli, 8 trials of no stimuli and 64 prepulse-pulse trials, consisting of a 40 ms startle stimulus preceded by 30 or 100 ms by a non-startling prepulse of 2, 4, 8 or 16 dB above the 65 dB baseline. Startle responses were recorded by the SR-Lab system and expressed as 4 blocks of 8 startle responses (first block at the start of the session, second and third block calculated from the sixteen pulse-alone trials in the main section of the session, fourth block at the end of the session) as a measure of habituation, and %PPI at the respective prepulse intensities (PP2, PP4, PP8 and PP16).

Table 1
Numbers of animals per group for each behavioural test with male/female ratio (m/f) indicated.

Behavioural test/genotype	Wildtype (m/f)	*thunder* mice (m/f)
Locomotor activity	18 (12/6)	9 (4/5)
Elevated Plus Maze	18 (11/7)	9 (4/5)
Tail Suspension Test	20 (14/6)	16 (7/9)
Prepulse Inhibition	15 (9/6)	9 (4/5)
Forced Swim Test	28 (16/12)	19 (8/11)
Y-maze	29 (17/12)	17 (7/10)
Active avoidance	28 (17/11)	19 (8/11)

2.5. Forced swim test

The forced swim test is used to measure depression-like behaviours and antidepressant action [8,12]. One week after PPI, mice were individually placed in a 2-litre glass cylinder filled with approximately 1.5 L of water (15 cm in height) at a temperature of 25 ± 2 °C. On two consecutive days, each animal was forced to remain in the water for 6 min, during which period behaviour was recorded on video. The amount of time spent swimming or immobile was recorded offline by an observer blinded to the genotype of the animals. Data analysis was based on behaviours scored during the last 4 min of each session [8].

2.6. Y-maze

At least three weeks after the forced swim test, short-term spatial memory was assessed using the Y-maze paradigm [13]. The apparatus consisted of three arms (28 cm l x 7.5 cm w x 15 cm h), with visuospatial cues located on the walls inside and outside the maze. The animal explored the maze for 10 min in full room light, with one arm closed. One hour later, the mouse was returned to the maze for 5 min, this time with all arms accessible. Behaviour was recorded on video and the number of times the novel arm was visited compared to the average of the familiar arms, as well as the time spent in the novel vs. familiar arms, was analysed using video tracking system (Ethovision, Noldus, The Netherlands). Animals with intact short-term spatial memory were expected to visit the novel arm more than the familiar arms.

2.7. Active avoidance learning

Active avoidance learning and memory was assessed one week after the Y-maze, using the GEMINI system (San Diego Instruments, USA). The two-way automated shuttle-box apparatus consisted of a test chamber (23 × 50 × 23 cm), divided into two equal-sized compartments with a motorised guillotine door, and contained a stainless steel grid floor. Photocells recorded the location of the animal. During five days of training, each day the mice were subjected to seven trials. The inter-trial interval was randomly set by the system between 10 and 50 s. Each trial consisted of a 7 s conditioned stimulus (a light cue) paired with a mild 2 mA foot-shook (unconditioned stimulus) delivered during the last 3 s of the conditioned stimulus. In order to avoid this foot-shock the animal was required to move to the opposite compartment within the initial 4 s of the conditioned stimulus, at which point both the light and shock were disabled. Learning was represented by an increase in the number of shocks avoided over the 5-day period. Inter-trial crosses were defined as movement from one compartment to the other during the time between trials.

2.8. Statistical analysis

All data are expressed as mean ± standard error of the mean (SEM). Group differences were analysed by analysis of variance (ANOVA, SPSS) with genotype and sex as between-group factors and day (active avoidance), prepulse intensity (PPI), block (startle habituation) and time (exploratory locomotor activity) as within-group factors. Sex differences were not observed and therefore data are presented here as male and female combined. Differences between groups were considered statistically significant if $P < 0.05$.

3. Results

Immobility in the tail suspension test and forced swim test has been used as an indicator of depression-like behaviour and antidepressant drug action [8]. Immobility in the tail suspension test tended to be higher on the second day of testing compared to the first day but this did not reach statistical significance (main effect of Day: $F(1,30) = 4.0$, $P = 0.055$). Analyzing the average score of the two days of testing (Fig. 1A) revealed a highly significant main effect of genotype ($F(1,34) = 8.2$, $P < 0.01$), reflecting greater immobility in *thunder* mice than in wildtype controls. Mobility score was significantly lower in *thunder* mice than in wildtype controls ($F(1,34) = 8.9$, $P < 0.01$). Similar to the tail-suspension test, immobility in the forced swim test tended to be higher on the second day of testing but this difference did not reach statistical significance (main effect of Day: $F(1,43) = 3.9$, $P = 0.054$). Analyzing the average score of the two days of testing did not reveal a significant effect of genotype for either immobility or swimming (Fig. 1B).

An increase in open-arm activity on the elevated plus maze has been used as an indicator of reduced anxiety-like behaviour [14]. In this study, all mice predominantly visited the closed arms and there were no significant differences between the genotypes in the %number of open arm visits or the total number of arm visits (Fig. 1C).

In the Y-maze test, the number of visits to the novel arm in the second trial is used as an indicator of intact short-term spatial memory [13]. Mice visited the novel arm significantly more than the other arms (main effect of Arm (novel vs. average of familiar): $F(1,42) = 34.8$, $P < 0.001$) and this was seen in both wildtype mice ($F(1,27) = 37.0$, $P < 0.001$) and *thunder* mice ($F(1,15) = 7.5$, $P < 0.02$). However, the percentage number of visits to the novel arm was significantly lower in *thunder* mice than in wildtype mice (main effect of genotype: $F(1,42) = 6.7$, $P < 0.02$) suggesting a relative deficit in short-term spatial memory (Fig. 1D). The same trend was observed for time spent in the novel arm although the differences did not reach significance between wildtype and *thunder* mice (Fig. 1D). The total number of arms visited did not differ between the genotypes (27.3 ± 2.0 in wildtype vs. 30.6 ± 1.5 in *thunder* mice).

In the active avoidance test, increasing numbers of correct avoidance responses in a two-way shuttle box is used as an indicator of intact Pavlovian and instrumental learning where the animal avoids an aversive event (shock) by taking action (move to the other chamber) [15]. Over the five consecutive days of testing (Fig. 1E), the mice progressively increased their number of correct avoidances (main effect of Day: $F(4,172) = 15.6$, $P < 0.001$) reflecting intact learning. As shown by a lack of a Genotype x Day interaction, both groups showed this measure of learning, however *thunder* mice produced consistently lower avoidance scores (main effect of Genotype: $F(1,43) = 7.5$, $P < 0.01$). On the

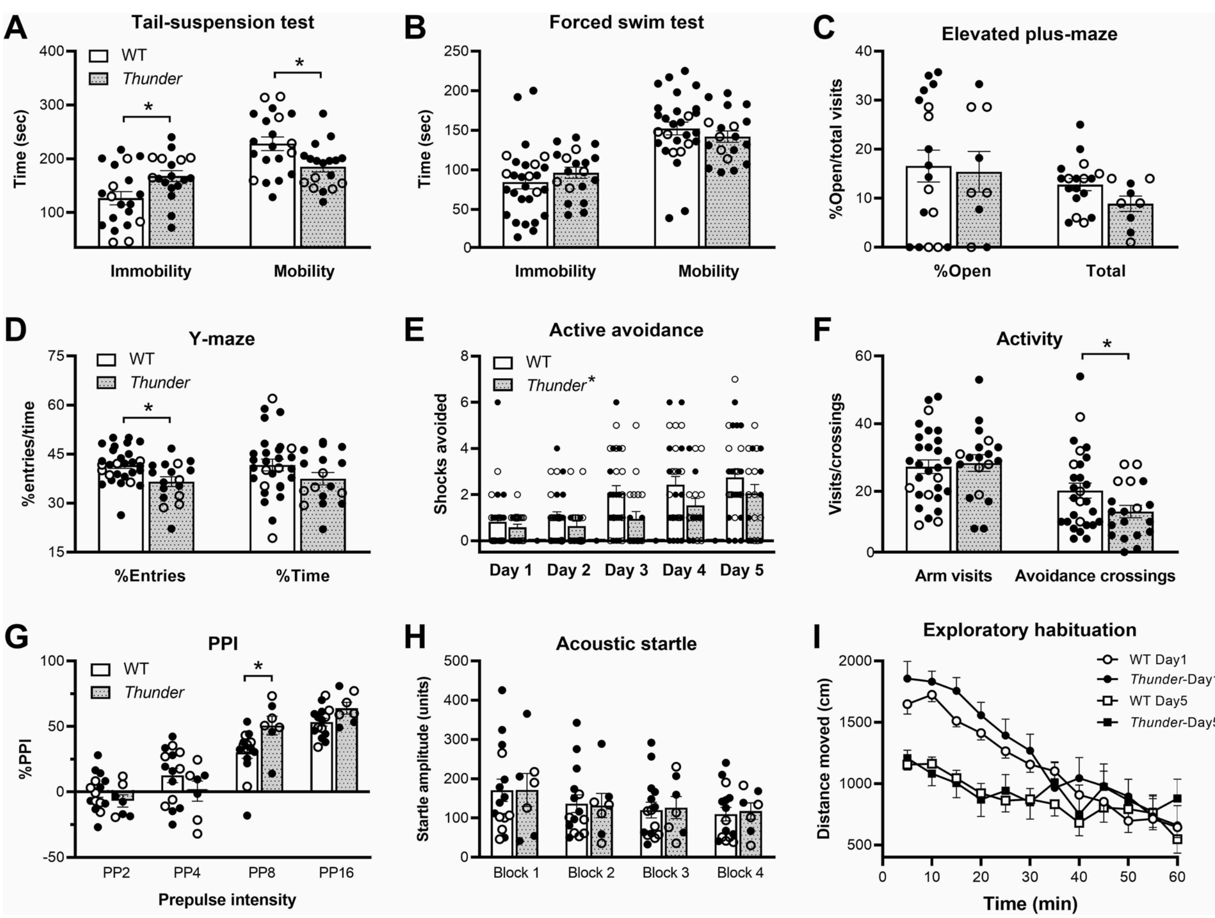

Fig. 1. Behavioural characterisation of *Thunder* mice (grey bars) compared to wildtype (WT, white bars) controls. Closed circles are male data; open circles are female data. *Thunder* mice displayed significantly higher immobility and lower mobility times in the tail suspension test (A). There were no effects of genotype in the forced-swim test (B) or elevated plus-maze (C). *Thunder* mice showed significantly lower %number of entries into the novel arm of the Y-maze (D). The amount of time spent in the novel arm was also lower but this did not reach statistical significance (D). Active avoidance learning on 5 consecutive days (E) and the number of inter-trial crossings (F) were significantly lower in *thunder* mice than in wildtype controls. Analysis of prepulse inhibition (PPI) of acoustic startle expressed for individual prepulse intensities of 2, 4, 8 and 16 dB over background (G) revealed that PPI was significantly higher in *thunder* mice than in wildtype controls at PP8. There were no genotype differences in startle amplitudes or its habituation (H). Spontaneous novelty-induced locomotor hyperactivity in locomotor photocells, expressed as distance moved, was lower on the fifth day of testing compared to the first day, but there were no genotype differences (I). * $P < 0.05$ for difference with wildtype controls.

first day of testing, the mice also showed high exploratory activity, reflected by a high number of inter-trial crossings (Fig. 1F). This activity was significantly lower in *thunder* mice than in wildtype controls (main effect of Genotype: $F(1,43) = 4.1$, $P < 0.05$). The high first-day level of inter-trial crossings rapidly subsided over the course of the five days of testing and was no longer significantly different between the genotypes (not shown).

Prepulse inhibition (PPI) is an operational measure of sensorimotor gating, which reflects intact sensory information processing and filtering [10]. There was no main statistical effect of the ISI or sex of the animals on PPI. Therefore, male and female data at the 30 msec and 100 msec ISI were combined (Fig. 1G). As expected, increasing prepulse intensities produced increasing levels of PPI resulting in a main effect of prepulse intensity ($F(3,54) = 77.9$, $P < 0.001$). However, there was also an interaction of prepulse intensity and genotype ($F(3,54) = 4.8$, $P < 0.01$). Inspection of the data suggested that this was caused by PPI being slightly lower in *thunder* mice compared to wildtype controls at PP2 and PP4 but higher at PP8 and PP16 (Fig. 1G). Analysis at individual prepulse intensities revealed significantly higher PPI in *thunder* mice compared to wildtype controls at PP8 ($F(1,18) = 5.2$, $P < 0.05$), but not other prepulse intensities (Fig. 1G). Startle amplitude significantly habituated over the course of the PPI session ($F(3,54) = 7.3$, $P < 0.001$) but there were no genotype difference in either startle habituation or average startle (Fig. 1H).

Spontaneous exploratory locomotor activity can be used as a measure of ambulatory activity, anxiety-like behaviour and habituation to a novel environment [16]. On the first day of locomotor activity testing, all mice displayed initial high distance moved which habituated over the course of the 60-minute session (Fig. 1I). On day 5 of locomotor testing, locomotor distance moved was much lower, particularly in the first 30 min (Day effect: $F(1,23) = 27.2$; Time effect: $F(11,253) = 39.0$; Day x Time interaction: $F(11,253) = 15.8$, all $P < 0.001$). However, there were no significant differences between wildtype and *thunder* mice in locomotor activity levels or habituation (Fig. 1I).

4. Discussion

We have previously shown that hnRNPLL functions in exon silencing during mRNA alternative splicing in T cells and that it and a number of its target genes were abundantly expressed within brain and neural tissues [3,4]. We therefore considered that hnRNPLL may play a role in behaviour. In this study we found that *thunder* mice, which express a hypomorphic allele of hnRNPLL, displayed enhanced immobility in the tail-suspension test reduced learning and memory with no changes in several other behavioural domains. Thus the hnRNPLL mutation in *thunder* mice affects aspects of behaviour in addition to its reported effects on immune function [1–3].

Several studies have suggested a role of T cells in mood disorders such as major depression [5] with these cells proposed to play a protective role against maladaptive behavioural responses associated with excess HPA axis activation. *Thunder* mice have reduced numbers of naïve CD4+ and CD8 + T cells in the peripheral circulation and in secondary lymphoid tissues, and they displayed enhanced immobility in the tail-suspension test. Surprisingly this behavioural change was not observed in the forced swim test which is widely used to assess antidepressant activity [8]. Disparate outcomes have been noted between the tail suspension test and forced swim test by others [8]. For instance, ketamine reduces immobility in the forced swim test but not the tail suspension test [17]. The underlying mechanisms between the differential outcomes of the two tests remains unclear. There were no genotype differences in the present study in the elevated plus-maze test nor in spontaneous locomotor activity, suggesting the selective increase in immobility in the tail suspension test was not caused by altered anxiety-like behaviour or deficits in locomotor coordination.

The other behavioural domain where *thunder* mice showed deficits was learning and memory. Thus, in the Y-maze and in active avoidance learning, *thunder* mice displayed reduced visits to the novel arm and lower acquisition of shock avoidance, respectively, consistent with the view that *thunder* mice display reduced memory function. As with the tail suspension test result, the lack of genotype difference in the elevated plus maze and in spontaneous exploratory locomotor activity suggests that the apparent changes in cognition could not be explained by non-specific changes in anxiety or motor coordination.

We also observed subtle differences between *thunder* and wildtype controls in PPI. The relationship between increasing prepulse intensities and the inhibition of startle was altered in *thunder* mice, with these animals showing significantly higher PPI at the prepulse intensity of 8 dB over baseline. It is unclear what this subtle change in PPI reflects functionally but it is important to note that a range of neurological and psychiatric illnesses is associated with significant reductions of PPI. These deficits are thought to reflect impaired sensorimotor gating which in turn reflects a reduced ability of the brain to filter out irrelevant or distracting environmental stimuli, resulting in less efficient cognitive processing [10]. Numerous genetically-modified mouse models of a variety of illnesses exhibit reduced PPI [10], including models with altered immune function [18,19]. Clearly *thunder* mice did not show disrupted PPI.

The molecular mechanism involved in the behavioural changes in thunder mice remains to be established. HnRNPLL is expressed at medium to high levels in the brain [3,4] but its role in neuronal function is unknown. Recently, hnRNP-L was detected in the mouse striatum and may be involved in regulation of dopamine D2 receptor function [4], which in turn could be involved in behaviour in mice. However it is unknown if hnRNPLL plays a similar role. A role of hnRNPLL in behaviour may be via its well-described function as a regulator of mRNA alternative splicing and consequent effects on T cell development and activation [1,2]. Alternative splicing of neuronal specific genes plays a crucial role in neuronal differentiation, plasticity and memory [20,21] and hnRNPLL exon silencing targets a large number of neural genes [3]. Because alternative splicing within neural tissues occurs similarly in T cell populations in *thunder* mice, this could reflect a shared molecular control for memory in these quite disparate tissues. Although immunological and neural memory reflect distinct biological pathways they both require cells to undergo temporally regulated patterns of differentiation in response to environmental cues or stimuli.

In summary, we provide the first behavioural characterisation of mice with altered expression of hnRNPLL highlighting distinct alterations in specific behavioural domains. Thus, we begin to appreciate that the effect of hnRNPLL extends beyond its role in the immune system where we have previously shown that it can control mRNA splicing of a wide range of target genes that support peripheral T cell homeostasis. Future studies may focus on underlying vulnerability of *thunder* mice to further alterations in behaviour by environmental factors and could highlight genetic links between the regulation of immune function and behaviours relevant to human psychiatric conditions.

Funding

M. van den Buuse was a Senior Research Fellow of the National Health and Medical Research Council of Australia (NHMRC). These studies were furthermore supported by the Percy Baxter Charitable Trust, Australia, and Operational Infrastructure Funding from the State Government of Victoria, Australia. These funding sources did not play a role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Ethics approval

All experiments were performed according to guidelines set by the National Health and Medical Research Council of Australia and were approved by the appropriate Animal Experimentation Committee.

CRediT authorship contribution statement

Maarten van den Buuse: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing - review & editing. **Paul Halley:** Formal analysis, Methodology, Project administration, Validation, Writing - original draft. **Gerard F. Hoyne:** Conceptualization, Funding acquisition, Resources, Validation, Writing - review & editing.

Declaration of Competing Interest

None.

Acknowledgements

The authors are grateful to Ms Sally Martin for expert technical assistance. M. van den Buuse was a Senior Research Fellow of the National Health and Medical Research Council of Australia (NHMRC). These studies were furthermore supported by the Percy Baxter Charitable Trust, Australia, and Operational Infrastructure Funding from the State Government of Victoria, Australia.

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