EXHIBIT U

Advances in diagnosis and mechanisms associated with the pathology of sudden unexpected death in infants and children

Professional experience and qualifications

I am Professor Cecelia Caroline Blackwell. I am currently con-joint professor in Immunology and Microbiology, School of Health, University of Newcastle, NSW. I also hold professorial appointments in the meningitis reference laboratory which I helped to found at The National School of Public Health, Athens, Greece and in the Institute of Forensic Medicine, Semmelweis University School of Medicine, Budapest, Hungary. Until I took early retirement from the University of Edinburgh, Scotland in December 2001, I was Reader in Medical Microbiology. My previous appointments were in the United States: Assistant Professor, Department of Microbiology, Medical College of Ohio; Postdoctoral Fellow in Infectious Diseases and Associate in Medicine, Beth Israel Hospital and Harvard University School of Medicine.

My qualifications include the following degrees and fellowships: BS in for Microbiology, Louisiana State University, USA; PhD in Medical Microbiology, Stanford University School of Medicine, USA; DSc in the Faculty of Medicine, University of Edinburgh; membership and fellowship of the Royal College of Pathologists, UK based on my research in susceptibility to infectious diseases. In 2014, I received the Distinguished Researcher Achievement Award from the International Society for Prevention of Infant Deaths for contributions to understanding of the physiology of inflammation and infection in sudden deaths in infancy. In 2015, I was awarded fellowship of the Royal Society of New South Wales (FRSN) for my research in infection and inflammation in sudden death in infancy and susceptibility to infection.

My research has been focussed on genetic, developmental and environmental factors that make individuals more susceptible to infectious diseases and conditions in which infection has been implicated such as sudden unexpected death in infancy. I have nearly 300 publications in refereed journals and refereed abstracts and am invited to present my research at national and international meetings on sudden infant death. I have been invited to contribute chapters on the role of infection and inflammation to major books on sudden infant death. I have edited two special issues of *FEMS Immunology and Medical Microbiology* and one issue for *Frontiers in Immunology* on the role of infection and inflammation in sudden infant deaths.

In 2000, I was asked to review the material relevant to the deaths of Christopher and Harry Clark whose mother, Sally Clark, had been convicted of their murder. It was my observation that the microbiology report was missing from Harry Clark's file that led to its recovery and to the evidence that he had suffered from a disseminated infection with *Staphylococcus aureus*. This and other reassessments of the medical evidence in relation to the infection led to the acquittal of Mrs. Clark at the High Court in London in January 2003.

I have read and agree to be bound by the UCPR.

1. Introduction

Since the conviction of Kathleen Folbigg in 2003 for the murder of her four infants, there have been significant attempts to standardise the definitions of the major categories of infant deaths and attempts to standardise diagnostic protocols for examining these deaths. There have also been significant insights into the mechanisms underlying these infant deaths which need to be considered in relation to the four Folbigg infants. A recent publication from the University of Adelaide Press [Duncan and Byard, 2018] provides a good summary of recent progress.   Advances in the following areas are summarised in the following pages: 1) investigation of the deaths and diagnosis; 2) proposed pathophysiological responses contributing to these deaths; 3) recent advances in identification of genetic markers or biomarkers associated with some of the pathological mechanisms proposed. Comments on how these advances apply to the Folbigg children are provided at the end.

2. Definitions

Sudden unexpected infant deaths have been divided into three major categories: Sudden Infant Death Syndrome (SIDS); Sudden Unexpected Death in Infancy (SUDI); Sudden Unexpected dealt of a child (SUDC).

According to Byard [2018] **SIDS** is the definition used when a sleeping infant who has apparently been in good health is found unexpectedly dead. The diagnosis depends of pathological evaluation, including ancillary testing, the results of which are unable to discern a cause of death [Moon, Horne, Hauk, 2007] .

The definition of **SUDI** includes infants in the age range 7-365 days of age and includes:

1) The death is unexpected and remains unexplained at autopsy;
2) Death during acute illness not recognised as life-threatening;
3) Death associated with acute illness < 24 hours duration or prolonged intensive medical care
4) Death due to a pre-existing occult condition;
5) Death due to accident, trauma or poisoning.

[Blair *et al.*, 2009; 2012]

SUDC is defined as death of a child over 1 year of age, "the sudden and unexpected death of a child older than one year of age which remains unexplained after a thorough investigation complete autopsy with appropriate ancillary testing (Kraus *et al.*, 2005).

It is important to note there are no commonly applied universal autopsy and investigation protocols. Ancillary testing based on advances in SIDS research might include: molecular testing for infectious agents; screening for bacterial toxins; screening for genetic markers identified in relation to dysregulation of neural, cardiac, respiratory and inflammatory functions; detection of inflammatory mediators that can affect the physiological mechanisms proposed to explain these deaths.

3. Death Review Committee

Death review committees are multidisciplinary consisting of individuals with expertise in a variety of areas, *e.g.*, paediatrics, education, disability, pathology, social work, child protection, public health and justice. The committee considers information gathered about an infant death and the combined information, experience and expertise are thought to provide a better insight into the cause of death.

Garstang, Ellis and Sidebothom [2015] identified four different models for investigating sudden unexpected infant deaths. These authors concluded that the "police-led" model of investigation was the least likely to meet the minimum standards for investigation of sudden and unexpected deaths. New South Wales (NSW) was identified as using this mode of investigation.

The NSW child death review team recommended it was critical the model be improved to reflect best practice standards and a more consistent approach to the definition of sudden and unexpected infant deaths in their jurisdiction. [NSW Child Death Review Team. Child death review report 2015]

4. Diagnostic advances

Automated methods for detection of microorganisms and molecular screening for infectious agents, particularly viruses, should be applied to the protocol for diagnosis of sudden death in infancy. Genetic testing for polymorphisms associated with disruption of physiological responses in cardiac, respiratory, inflammatory and neurological systems might provide additional insight into the underlying conditions of these infants. Screening for cotinine, a metabolite of nicotine, would provide information about exposure to cigarette smoke. Screening for inflammatory mediators would need to be done as soon as possible after death, and there are now automated systems for detection of multiple components of the system [Moscovis *et al.*, 2014].

A number of postmortem biomarkers have been examined for their potential in identification of SUDI; however, none has been found in all samples examined [Haynes, 2018]. This indicates there are likely multiple interactions that can lead to the cascade of events resulting in death . These include: biomarkers associated with serotonin neurotransmission; biomarkers for hypoxia (hypoxanthine); biomarkers related to infection and inflammation, (interleukin (IL)-6, mast cell tryptases); maternal biomarker of SIDS risk, alpha-fetoprotein, higher levels of which are associated with significantly increased risk of SIDS [Smith *et al.*, 2004]

5. Cause of death?

In recent years, there has been a growing consensus that SIDS/SUDI is multifactorial in origin. The Triple Risk Hypothesis proposes that when a vulnerable infant (genetic factors) is at a critical but unstable developmental period in physiological homeostasis control (developmental factors), exposure to an external stress (environmental factors) could trigger

death. The model proposed that infants will succumb only if all three factors are present and genetic vulnerability might be dormant until the critical developmental period is reached and they are exposd to a stress such as a new infectious agent (Figure). Support for this hypothesis comes from numerous physiological studies that indicate the major risk factors for SIDS have significant effects on blood pressure, heart and arousal from sleep [Moon and Hauck, 2018].

Triple risk hypothesis
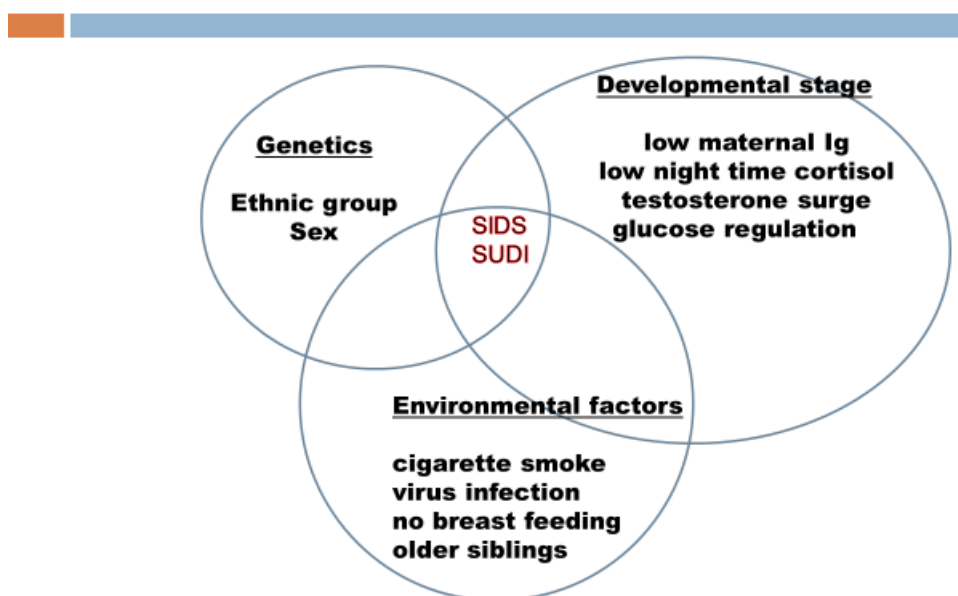
None of the children was assessed for genetic factors affecting cardiac arrythmias or brainstem metabolism abnormalities. The only genetic information was analysis of the samples for variants in one of the genes affecting interleukin (IL)-10,and important cytokine that downregulates inflammatory responses to infection.

6. Cardiac dysfunction

It has been suggested approximately 10% of SIDS cases ae due to cardiac channelopathies [Tfelt-Hansen *et al*., 2011]. In a subset of SIDS,a pathogenic variant in one of several genes tha disrupt ion channel function has been identified [Sarquella-Brugada *et al*., 2016]. These include long QT syndrome, Brugada syndrome (a genetic disorder in which the electrical activity within the heart is abnormal) and catecholaminergic polymorphic ventricular tachycardia (CPVT) which is an inherited disorder that predisposes those affected to potentially life-threatening abnormal heart rhythms or arrythmias..

Four genes examined in relation to SIDS include *SCN5A, KCNQ1, KCNH2, RYR2.* No biomarkers have been identified for these variants [Brownstein *et a*l., 2018].

7. Brainstem abnormalities

Seratonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter in the central and peripheral nervous system. It plays an important role in brainstem, cardio-respiratory and thermo-regulatory activities and is involved in regulation of breathing, blood circulation, heart rate, body temperature and the sleep-wake cycle.

Variants of the SLC6A4 gene have been reported for infants in studies of SIDS in both Japan [Narita *et al.,* 2001] and the United States [Weese-Mayer *et al*., 2003]. Other studies have not replicated these observations [reviewed by Brownstein *et al*., 2018].

Biomarkers assessed in relation to this hypothesis include levels of 5-HT in the brain stem and serum. In SIDS, there were significantly decreased levels of 5-HT in the brain stem [Paterson *et al*., 2006] and decreases in 5-HT receptor expression [Ozawa and Okado, 2002]. Serum levels of 5-HT were found to be higher in SIDS infants [Haynes *et al*., 2017].

8. Dysregulation of inflammatory mediators

The inflammatory response to infectious agents or their soluble products have profound effects on physiological responses proposed to trigger SIDS/SUDI. A number of risk factors identified in epidemiological studies can affect these responses – cigarette smoke, virus infection, hormonal levels associated with peak incidence of SUDS [Blackwell *et al*., 2015]. Both genetic variations in inflammatory genes and biomarkers have been identified in studies of SIDS/SUDI [Opdal, 2018]

Genetic variations coding for enhanced production of pro-inflammatory cytokines and decreased production of anti-inflammatory cytokines have been identified [Ferarnte *et al*., 2008; 2010; Highet *et al*., 2010; Moscovis et al., 2004a,b; 2006; 2015a,b]. Recent genetic analysis of a large number of SIDS infants identified evidence for two independent mannose binding lectin 2 (MBL2) variants. This is a component of the inflammatory system that plays a crucial role in early prevention and termination of infection [Fard *et al*., 2016]. They concluded that the evidence was "consistent with the hypothesis that infection may play a role in SIDS pathogenesis".

Both environmental and hormonal factors can affect inflammatory responses. Experimental studies indicate the important anti-inflammatory IL-10 is reduced by components of cigarette smoke and variants associated with low levels of IL-10 responses was most significantly

affected [Moscovis *et al.*, 2004a]. Cortisol and testosterone can also affect inflammatory responses in these model systems [Blackwell *et al.*, 2015].

Results for detection of cytokines in autopsy material varies. Many of the inflammatory mediators are short lived and time between death and autopsy can vary greatly. The pro-inflammatory IL-6 was significantly higher in the cerebrospinal fluid of SIDS infants in Norway compared to those who did of violent deaths [Vege *et al.*, 1998; 1999], but a later study in a German population found no difference [Vennemann *et al.*, 2012]. New methods can measure multiple cytokines in small samples and would be useful ancillary tests in investigation of sudden infant deaths [Moscovis *et al.*, 2014].

While it might be difficult to detect the inflammatory mediators or the new methodology might be too expensive for routine use in the autopsy protocol, the evidence for microbial involvement in some of these deaths is now extensive. Several reviews of microbiological findings in relation to autopsy indicate that if specimens are taken under appropriate aseptic conditions, the results are of significant value in assessing the cause of death [Morris *et al.*, 2006]. The longer the interval between death and obtaining a sample for microbiological analysis, the lower the chances of isolation of bacteria [Telford *et al.*, 1989;]Weber *et al.*, 2010]. In a report by Weber *et al.*, [2010], among over 500 autopsies, the percentage of positive cultures decreased from 83% for samples obtained within 24 hours of death to 67.5% when the post mortem interval equated to more than five days. Significantly fewer polymicrobial (mixed) cultures were obtained if the samples were collected after a longer interval 61% decreasing to 46% (P= 0.0003). This evidence does not support the hypothesis of post mortem translocation from mucosal surfaces leading to microbial overgrowth. *Escherichia coli* was found in significantly more samples for children with unexplained diagnosis than those who died of non-infective causes (P = 0.003) [Weber *et al.*, 2008].

Coliform organisms were found in normally sterile sites of three of the Folbigg children, Patrick, Sarah and Laura. For Caleb, no samples were taken for microbiological analysis. The paper by Weber *et al.* [2008] concluded the high rate of group 2 pathogens, particularly *E. coli* and *Staphylococcus aureus* in otherwise unexplained cases of SUDI suggests the bacteria could be associated with this condition.

9. **How could these advances have provided a more complete assessment of the deaths of the four Folbigg children?**

10. **Caleb**

The only abnormal finding for Caleb appears to be in the histology of the lungs, "congested and in places show incomplete aeration, in other sections their alveoli contain extravasated red blood cells and a small amount of eosinophilic exudate. These are proteins that pick up the eosin stain and a common finding in post mortem lungs and often seen in samples from children diagnosed with SUDI (Prof. J. A. Morris, personal communication).

The source of Caleb's eosinophilic exudate was not investigated. No microbiology examination was carried out on samples from the child. This is important as a variety of

infectious agents identified in SIDS/SUDI can elicit inflammatory responses. These include a variety of viruses, bacteria, *Chlamydia trachomatis* [Lundemose *et al.,* 1990], and *Pneumocystis carinii* [Vargas et al., 1999] *Pneumocystis jerovici* (Prof. P.N. Goldwater, personal communication).

There was also no assessment of lung immunoglobulins which were also found to be raised in SIDS/SUDI [Forsyth *et al.*, 1989].

Advances in molecular detection of pathogens associated with SUDI might be used to screen for potential pathogens that elicited the inflammatory exudate, but this would depend on optimal storage conditions of the samples.

11. Patrick

Patrick had an ALTE, was resuscitated and was diagnosed with a seizure disorder and respiratory tract infection. This was followed less than a month later by fever, upper respiratory tract infection, rash and conjunctivitis and adenovirus was identified in an eye swab. Following a fever and second ALTE, the autopsy performed on the day of death found mixed blood cultures which were attributed to contamination. It should be noted that the dismissal of microbiological findings as contamination has been criticised (Morris, Harrison, Partridge, 2006). As the post mortem examination was conducted two hours after the death, it is difficult to dismiss the finding of three potential pathogens in his blood sample as contamination following breakdown of mucosal barriers. There was evidence of infection prior to death – vomiting, fever and sweating [case record of the Regional Medical Genetics Laboratory, A. Colley, ref. no. 1564]. (Attachment)

Based on research carried out after 2003, screening for genetic markers associated with dysregulation of the neural system might provide new insights.

Recent evidence for associations between SIDS and Sudden Unexplained Death in Epilepsy (SUDEP) has been reported. "SUDEP is sudden, unexpected, non-traumatic death of individuals with or without evidence of seizure, in whom postmortem examination does not reveal a structural or toxilogical cause for death (Brownstein *et al.*, 2018). The hypothesis proposed is that death due to seizures initiates pathogenic signalling between the brain and heart resulting in lethal cardiac arrythmias [Jehi and Najm, 2008; Ravindran *et al.*, 2016].

SNC1A mediates the voltage-dependent sodium ion permeability of excitable membranes. Mutations can result in generalized epilepsy with febrile seizures plus (GEFS+) and Dravet syndrome(a rare and catastrophic form of epilepsy that begins in infancy). In one published family history, one child had Dravet syndrome and the other had sudden death after a history of febrile seizures. Both children had inherited a pathogenic variant of SCN1A from their unaffected father [Halvorsen *et al.*, 2016].

SCN1B codes for changes in a sodium channel beta-1 subunit. It is associated with GEFS+, Brugada syndrome and defects in cardiac conduction [Tan *et al.*, 2010]. A case report found a SCN1B variant (R214Q) in assessment of three individuals, including one female SIDS [Hu *et al.*, 2012].

DEPDE5 is associated with familial epilepsy and pathogenic variants in SUDEP [Nascimento *et al*., 2015]. Other variants identified in SUDEP include KCNA1 [Klassen *et al*., 2014], and SCN8A [Poduri, 2015].

Both Prof. Cordner and Prof. Duflou agree Patrick's death was brought on by the consequences of hypoxic-ischaemic encephalopathy resulting from an acute life threatening event (ALTE). Studies reported in 2004 found mucosal immune dysregulation in response to a respiratory infection might trigger an ALTE. Both increased salivary IgA and exposure to cigarette smoke were predictors of an ALTE [Gleeson *et al*., 2004].

12. Sarah

Time of death was estimated at about 1:30 am on 30 August 1993. The rectal temperature of the body at 11 am when it arrived at the mortuary was 25°C. The body would have been refrigerated, minimising bacterial growth until the samples were obtained during the autopsy. The autopsy was carried out at 8 am on 31 August 1993. In the lungs, Sarah had **profuse** numbers of coliforms, alpha haemolytic streptococci and scanty numbers of *S. aureus*. The lungs are normally considered to be sterile sites. In model systems of SIDS (animal or human tissue cultures), mixed infections or virus plus bacteria induced stronger inflammatory responses than those elicited by individual microbes [Sayers *et al*., 1995; Blood Siegfried, 2015; Moscovis *et al*., 2015].

The report recorded **profuse** numbers of coliforms. Coliforms are not normal flora of the respiratory tract. One report indicated a finding of coliforms in an infant conferred an increased risk for SIDS of 29 [Gilbert *et al*., 1992]. The comment about profuse numbers of coliforms is important. For most bacterial infections, the numbers of microbes is important; exposure to low numbers of bacteria might result in clearance and development of immunity to a second exposure. Exposure to larger numbers are more likely to result in infection or damage [Nash *et al*., 2000].

Other findings consistent with SUDI/SIDS include petechial haemorrhage in lungs, pericardium and thymus. There were some signs of inflammation in the lungs including polymorphonuclear (PMN) cells which are found in early stages of infection. There was some aspiration of gastric contents which might be an artefact or possibly vomiting associated with infection or toxin production.

Both Prof. Cordner and Prof Duflou agree that Sarah's death can be classified as Sudden Infant Death Syndrome, Category 2

13. **Laura**

The autopsy on Laura was performed within 12 hours of death. According to the autopsy reports, in the heart there was moderately dense lymphocyte infiltration with degenerate muscles cells. The spleen showed a marked increase in lymphocytes in the red pulp. There was an increase in lymphocytes in the lungs. Laura had **profuse** numbers of coliforms in the

lungs and in the spleen, **profuse** numbers of alpha haemolytic streptococci and moderate numbers of *S. aureus.* The finding of increased numbers of lymphocytes in the lungs and spleen indicate that the child had mounted an inflammatory response and that the bacteriological findings are not *post mortem* contamination as these must occur before death. (See comments above for Sarah in relation to the findings of profuse numbers of bacteria and presence of coliforms in relation to their potential role in pathogenesis).

The reports of reviews of the evidence by Prof. Cordner and Prof. Duflou conclude that the most likely cause of death was myocarditis. Prof. Duflou notes that as in the case of Laura where the inflammation was also predominantly lymphocytic in type, research has found this form of myocarditis tends to have a worse prognosis than other forms [Cooper, 2009].

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