EXHIBIT BT

ISTITUTO AUXOLOGICO ITALIANO
Istituto di ricovero e cura a carattere scientifico

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Centro per lo Studio e la Cura delle Aritmie Cardiache di Origine Genetica
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Milan, June 20 2019

Professor Carola G. Vinuesa LMS (MBBS), PhD, FFSc (RCPA), FAA
Elizabeth Blackburn NHMRC Principal Research Fellow
Co-Director, Centre for Personalised Immunology (NHMRC CRE)
John Curtin School of Medical Research
The Australian National University

Re: Folbigg case

Dear Carola:

The following are my comments on the material received from you.

1) Many genetic diseases can kill in the first 6 months of life (when then people talk of SIDS) or later on. Same disease killing different people at different ages;
2) The CALM2 p.G114R is indeed novel. Pathogenicity, though, seems likely. However, while it is reported as residing in the EF-hand III domain, this is not correct. The variant is located in the interdomain linker between EF-hands III and IV of the Ca^{2+} binding terminal lobe. In the gnomAD data base there is not a single variant around that position. As among > 140,000 genomes/exomes in gnomAD there are only 8 missense variants in CALM2, its presence in 2 cases of the Folbigg family is statistically significant.
   In our Registry of Calmodulinopathies (Crotti et al. Eur Heart J 2019 doi: 10.1093/eurheartj/ehz311. [Epub ahead of print] PMID:31170290) there is a variant in CALM3 affecting the same aminoacid (p.G114W) in a family with IVF-SUD. The proband had a cardiac arrest at age 5 while playing. A brother carrying the same variant died suddenly at age 4. The variant was inherited by the mother who is a mosaic (asymptomatic).
   In the Folbigg family, the 2 female children and the mother carry the CALM2 variant.
3) The mother apparently had a couple of syncope and we don't have as yet a full cardiological assessment. She could very well be a case of mosaicism. This could account for a milder phenotype in the mother and a more serious one in the children. It is essential to obtain different sources of DNA from the mother to test for possible mosaicism.
4) The report I have seen links the CALM variant only to a LQTS phenotype, thus ignoring the possibility that the phenotype could be CPVT. Two data argue in favor of CPVT in these cases: 1)

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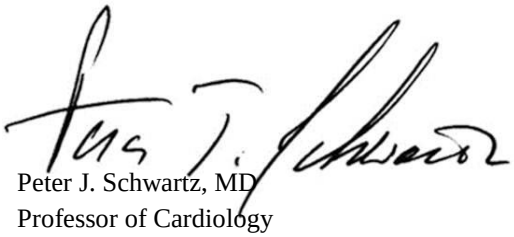
inter EF-hand mutations have so far been only found in CALM-CPVT cases; 2) and more important, the variants are de novo in 93% of CALM-LQTS and only in 78% of CALM-CPVT which is thus inherited in 22% of cases.

5) It should be crystal clear of course that without an exercise stress test, a diagnosis of CPVT is still fully on the table. Skepticism may remain about the "normal" cardiological work-up of the mother, given that there are patients with LQTS and at risk of SCD with normal QT intervals.
6) The identification of the CALM2 variant justifies fully re-opening the case because it raises significant doubts to a significant extent (in addition to the other pathogenic non-cardiac variant in the third infant with encephalopathy). Whether a functional assay may follow or not (it probably should) is another issue.

My conclusion is that the accusation of infanticide might have been premature and not correct.
With my best regards,



Peter J. Schwartz, MD
Professor of Cardiology
Director, Center for Cardiac Arrhythmias of Genetic Origin
Istituto Auxologico Italiano IRCCS

Peter J. Schwartz

Curriculum vitae

2019

Personal and Positions

Peter J. Schwartz was born in Huntingdon (UK) on January 29, 1943. He is married with Luisella since 1966 and he is the father of Barbara, Nicola, and Zoltan, and the grandfather of Francesca, Samuele, Delphina and Laszlo.

Dr. Schwartz graduated in Medicine in 1967 at the University of Milan (Italy), and in 1973 he became specialist in Cardiology. Currently, he is the Director of the Center for Cardiac Arrhythmias of Genetic Origin and of the Cardiovascular Genetics Laboratory at the Istituto Auxologico Italiano, IRCCS, Milan, Italy; Extraordinary Professor in Internal Medicine at the University of Stellenbosch, and Honorary Professor in the Department of Medicine and member of the Board of the Hatter Institute for Cardiovascular Research in Africa of the University of Capetown, South Africa.

From 1995 to 2013 he was Professor and Chairman of Cardiology and Director of the School for the Board in Cardiology in the Department of Molecular Medicine at the University of Pavia, and Chief of the Laboratories for Research in Cardiology at Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy.

From January 1999 to December 2000 he was the President of the Italian Society of Cardiology, and the Chairman of the Committee for European Affairs and Health Care Resources of the European Society of Cardiology. Starting June 2011 and until June 2013 he was a member of the EHRA International Affairs Committee.

From 1988 to 1992 he was the Chairman of the Working Group on Arrhythmias of the European Society of Cardiology. During this period (and also afterwards) he promoted many high profile scientific projects, particularly the constitution of three Task Forces: the first concerning CAST (Cardiac Arrhythmias Suppression Trial); the second on a new approach to the classification of antiarrhythmic drugs ("The Sicilian Gambit"); and the third on the problem of the early termination of clinical trials. Each Task Force produced a document that was published simultaneously in Circulation and in the European Heart Journal. These articles had a considerable impact in the field of arrhythmias study and management.

Research Overview

Dr. Schwartz's main area of research has always been that of sudden cardiac death, from different angles including pathophysiology, risk stratification, therapeutic approaches, and genetic mechanisms. As a result of a >45 years long efforts, Dr. Schwartz has provided unequivocal experimental, clinical, and molecular links between the autonomic nervous system, the long QT syndrome (LQTS), Sudden Infant Death Syndrome (SIDS) and sudden cardiac death. His discoveries have had a major impact in terms of early diagnosis and clinical care with broad implications in cardiology. The two main areas of his research are the autonomic nervous system and the long QT syndrome, a genetic disorder which is a leading cause of sudden cardiac death in the young.

Autonomic Nervous System

In his autonomic work Dr. Schwartz has contributed to the study of cardiac reflexes, developed the concept of "sympathetic imbalance" and extensively investigated the pathophysiology and therapeutic efficacy of left cardiac sympathetic denervation (LCSD). The translational impact of his

work lies in: 1) the demonstration that LCSD is extremely effective in preventing life-threatening arrhythmias in genetic disorders associated with sudden death. LCSD has now become standard therapy for high risk patients; 2) post myocardial infarction patients at high risk for sudden death can be identified by depressed baroreflex sensitivity, a marker of reduced vagal activity; 3) direct right vagal stimulation can improve the condition of some patients with heart failure. The main studies/findings in these 3 areas is summarized below.

As LCSD is concerned, the need to find an additional therapy for his patients affected by the long QT syndrome and not fully protected by beta-blocker therapy led him to a series of studies on the different roles of right and left cardiac sympathetic nerves. The realization of the particularly high arrhythmogenic effect of left-sided nerves and the many experimental studies on the effects of unilateral cardiac sympathectomy were key to the clinical development of LCSD as an important therapeutic tool for the management of patients at high risk of sudden death. After having championed almost alone for 20 years the clinical value of LCSD, this procedure is now used worldwide and has entered the Clinical Guidelines. It is now fully accepted that LCSD reduces the risk of ventricular fibrillation, and thereby of sudden death, in several different cardiac diseases.

In the early 80s, with his associates he introduced the assessment of baroreflex sensitivity for the identification of patients at risk for sudden death after a myocardial infarction. After a series of experimental studies, as this has always been his research approach, he moved to clinical translation. This has evolved in a large prospective clinical trial (ATRAMI - Autonomic Tone and Reflexes After Myocardial Infarction); ATRAMI enrolled 1,284 patients in Europe, the Unites States, and Japan. Its results were published in “The Lancet” and demonstrated that depressed baroreflex sensitivity (a marker of impaired vagal reflexes) was associated with a markedly higher risk of sudden and non-sudden death.

Finally, his experimental autonomic studies revealed that stimulation of the right cervical vagus could protect from ventricular fibrillation during acute myocardial ischemia occurring time after a myocardial infarction (Circ Res 1991). This led to other studies which culminated in the first attempt to reduce mortality and improve symptoms in patients with severe and advanced heart failure. Dr. Schwartz and his colleagues performed a first pilot study and a small clinical trial which provided very encouraging results (Eur Heart J 2011). This was followed by the large clinical trial INOVATE-HF, whose results were inconclusive probably because of the insufficient intensity of stimulation of the vagus nerve. The concept of vagally-mediated protection is still being explored in other ongoing clinical trials.

The long QT syndrome

For almost 50 years Dr. Schwartz has relentlessly investigated in detail the congenital long QT syndrome for which he is now recognized worldwide as the leading expert. He has defined the multiple clinical characteristics of the disease, developed the two leading pathogenetic hypotheses known as "sympathetic imbalance" and as "intracardiac abnormality" (which eventually proved to be the correct one, as the disease is due to mutations in genes expressed in the heart), provided essential information on the long term successful effects of antiadrenergic therapy, has contributed to the understanding of the relation between genotype and phenotype, and has opened the fields of

gene-specific therapy and of the identification of “modifier genes”. He has also provided the first data-based prevalence of the disease, which occurs in 1/2000 live births, through a huge prospective ECG study which enrolled almost 45,000 infants and in which the findings were validated by genetic testing (Circulation 2009). The current approach to therapy of LQTS is largely the consequence of his work.

He took care of his first patient in 1971 and already in 1972-73 he began to collect information on the few existing cases, especially on the outcomes of therapy; by the late 70s his informal registry already included over 500 patients. In 1979, with his partner Arthur Moss, he established the International Registry for LQTS, funded by NIH, which for >30 years played a fundamental role not only in defining the natural history of the disease and the response to therapy but made possible the genetic discoveries by providing the molecular biologists with huge numbers of large pedigrees with well-defined affected and unaffected individuals (Circ Res 2005).

He has contributed to the identification of the linkage on chromosomes 3 (the sodium channel gene *SCN5A* causing LQT3) and 7 (the potassium channel *HERG* causing LQT2) and has co-authored the identification of the genes encoding I_{Ks} and I_{CaL} causing respectively LQT1 and LQT8; in 2013 he and his colleagues have identified Calmodulin as a new gene causing one of the most deadly forms of LQTS in infants. In December 1995 he provided the first demonstration of differential responses to a variety of interventions according to the specific genotypes and he introduced the first gene-specific therapy: the sodium channel blocker mexiletine for patients with mutations on the cardiac sodium channel gene SCN5A. This therapy is now recommended by the Guidelines, is routinely used for LQT3 patients and represents one of the first examples of Precision Medicine. He has now extended the concept to LTQ2 patients, and provided the initial evidence that mexiletine shortens the QT interval also in the majority of these patients (Circ Arrhythm Electrophysiol 2019). He has performed the pioneering studies in the relationship between genotype and phenotype, which represents a “bridge” between molecular biology and clinical cardiology. As an example, he has provided uniquely large data on the relation between specific genetic subgroups and the factors (“triggers”) involved in the of initiation of the life-threatening arrhythmias of this disorder. Relevant examples are the specific risks associated to swimming and to sudden noises for LQT1 and LQT2 patients, respectively. These findings have contributed to the development of gene-specific therapy and are now allowing behavioral gene-specific management of the patients beyond pharmacologic therapy.

He has pioneered the studies on "modifier genes" and since 2005 he has identified numerous of these genetic variants which increase or decrease the risk associated with disease-causing mutations. These new findings are beginning to allow a much more refined risk stratification (Eur Heart J 2018). Very recently, using cardiomyocytes derived from patient-specific induced pluripotent stem cells, he found that proarrhythmic mutations causing trafficking defects of the hERG channel can be rescued by a drug, currently in use for cystic fibrosis, which specifically restores the normal ion channel expression (Eur Heart J 2018). Recently he tested this drug repurposing strategy in his patients whose cells have responded to the drug. This mutation-specific therapy is the most advanced example of Precision Medicine for cardiac diseases (Eur Heart J 2019).

Dr. Schwartz sees every day 2-3 LQTS families and his patients, many followed for over 20-30 years, fully understand that they now benefit by what he has been learnt in previous patients; accordingly, they are always willing to participate to his studies and to contribute to the progress of science.

Sudden Infant Death Syndrome

In 1976, when all the hypotheses to explain what is called the Sudden Infant Death Syndrome (SIDS) were implying almost exclusively a respiratory abnormality, Dr. Schwartz proved that he was an original and lateral thinker, not bound to the prevailing views. Indeed, he hypothesized that part of the SIDS victims could die because of a life-threatening arrhythmia based on mechanisms similar to those present in the long QT syndrome. In this way he advanced what became known as the "cardiac hypothesis" for SIDS. To test the hypothetical correlation between prolonged QT interval and SIDS he designed and initiated a prospective study based on ECG standard recordings in 3-4 old newborns. Given the low incidence of SIDS (0.5 to 1 per 1000 live births), neonatal electrocardiograms were collected in a very large population (34,000 infants were studied between October '76 and December '94), and these infants were followed for one year to assess the occurrence of SIDS and deaths from other causes. The results of this study, published in 1998 in the "New England Journal of Medicine", demonstrated unequivocally that a QT interval prolongation in the first week of life constitutes a major risk factor for SIDS.
Subsequently, Dr. Schwartz and his research group provided the first demonstration of the molecular link between LQTS and SIDS. These data, published in July 2000 in the New England Journal of Medicine and in October 2001 in The Lancet, represented "proof of concept" for the relation between LQTS and SIDS, confirmed the conclusions of their prospective study, and supported the concept of widespread neonatal ECG screening indicating that the infants with prolonged QT interval at high risk for sudden infant death can be diagnosed early on and that their impending death can probably be prevented. Furthermore, in 2007 his genetic studies in over 200 SIDS victims provided the evidence that LQTS causes SIDS in close to 10% of cases.

Clinical Trials

Dr. Schwartz has been and is actively involved in the design and conduct of clinical trials. He served as a member of the Steering Committee of some of the major clinical trials in post myocardial infarction patients: EMIAT (European Myocardial Infarct Amiodarone Trial); SWORD (Survival With ORal D-sotalol); SADHART (Sertraline AntiDepressant Heart Attack Randomized Trial), ALIVE (AzimiLide post-Infarct surVival Evaluation study), and PRINCESS (PRevention of re-INfarction by early treatment of CErivaStatin Study); and in other major RecordAF (REgistry on Cardiac rhythm disORDers assessing the control of Atrial Fibrillation), CardioFit Multicenter Trial Investigators, INOVATE-HF (INcrease Of VAgal TonE in CHF).

Honors, Funding, and Scientific Productivity

- In 1993 Dr. Schwartz was invited to give the “Grüntzig lecture” during the annual meeting of the European Society of Cardiology. This lecture is traditionally given to one of the members of the Society who has made special contributions to Cardiology.
- In 1994 the American Heart Association invited him to give the "Paul Dudley White International Lecture" during its 67th Scientific Sessions in Dallas, TX. This is regarded as the greatest sign of recognition given from the American Heart Association to non-American investigators. Since 1950 only three Italian investigators have been invited to give this lecture.
- In 1995 he became the 4th Fourth Gordon K. Moe Visiting Professor at the Masonic Medical Research Laboratory, Utica, NY in recognition of his “outstanding contributions to science and medicine in the fields of clinical and basic cardiology”.
- On May 1999 he gave the keynote talk at the opening plenary session of the 20th Annual Scientific Sessions of NASPE. Both these lectures were on the long QT syndrome, and they can be considered as an international recognition to Dr. Schwartz’s research activity in this field.
- On April 10, 2001 he received the “Michel Mirowski Award” for his work on sudden cardiac death, and on May 5 during NASPE’s 22nd Annual Scientific Session in Boston he received the ”Distinguished Scientist Award 2001” for his “contribution to the advancement of scientific knowledge in the field of cardiac electrophysiology”.
- In 2004 during the 31st International Congress on Electrocardiology in Kyoto, Japan, he gave the keynote “P. Rijlant Lecture”.
- On September 3, 2005 he received the “Arrigo Recordati” Prize 2005 for lifetime achievement in scientific research in the field of sudden cardiac death as he “very well focused on a single idea for a long period, developing his research from a primitive start to full maturity and highly complicated cases from which we learnt a lot”.
- In 2007 in Marseille (France) he received the Outstanding Achievement Award the European Cardiac Arrhythmia Society. This award “is given to colleagues who have contributed enormously to the development of our field”. On the same date and place he gave the “Philippe Coumel Lecture” in recognition of his contribution to the field of cardiac arrhythmias and pioneering work in clinical electrocardiology.
- On November 1st, 2007 he was invited to give the 15th Annual Leonard Horowitz Memorial Lectureship at the Heart Center in Philadelphia, PA, USA.
- In 2008 Dr. Schwartz was invited to give the “Renè Laennec” Lecture on Clinical Cardiology during the annual meeting of the European Society of Cardiology.
- On March 26, 2009 he was invited to give the inaugural Robert L. Krakoff international lecture in cardiovascular medicine, instituted by Professors Peter Libby and Marc Pfeffer, at Brigham and Women’s Hospital Cardiovascular Grand Rounds in Boston. Libby and Pfeffer commented in writing this lecture with the following words: “*You beautifully illustrated through your personal examples how carefully conducted basic and clinical studies can improve our mechanistic understanding of the pathogenesis of arrhythmias predisposing to sudden death. In the best definition of translational research you have also shown how this new insights provided the underpinnings for you to develop the hypothesis and design clinical directed*

rigorous investigations that have led to a better understanding and treatment of cardiovascular diseases".

- In September 2011, during the 26th Scientific Session of the Japanese Heart Rhythm Society in Fukuoka, he gave the Eiichi Kimura Memorial Lecture.
- In December 2012, during the 73rd National Congress of the Italian Society of Cardiology, he received the "Leonardo da Vinci" prize for "*his original and significant contribution to the study of cardiac arrhythmias on genetic basis and for having contributed to the development of the knowledges on the relationship between autonomic nervous system and life-threatening arrhythmias and between autonomic reflexes and post-MI sudden death*".
- On September 15, 2012 in Kanazawa during the 60th Annual Scientific Session of the Japanese College of Cardiology he was invited to give the "Sakamoto Lecture".
- In July 2015 he was invited to give two keynote lectures during in the Joint Meeting of the 30th Annual Meeting of the Japanese Heart Rhythm Society and the 32nd Annual Scientific Meeting of the Japanese Society of Electrocardiology held in Kyoto.
- On December 6, 2018 he gave the "The Michael Davies Memorial Lecture" during "The A-Z of Sudden Cardiac Death in the Young" meeting which took place in London, UK.
- On May 7, 2019 he was invited to give the *Stanford CVI's Frontiers in Cardiovascular Science / 2nd Annual Gootter Foundation Lecture at the University* of Stanford, CA, USA.
- On June 5, 1019 in Paris he shared with Pedro Brugada the "*Fondation Lefoulon-Delalande-Institut de France Prix scientifique dans le domaine cardio-vasculaire*".

Currently, Dr. Schwartz is Fellow of the: American Heart Association and the Council on Clinical Cardiology; American College of Cardiology; Heart Rhythm Society; European Society of Cardiology; European Heart Rhythm Association, Associazione Italiana di Aritmologia e Cardiostimolazione, and International Honorary Member of the Japanese College of Cardiology.

From 1974 to 2017 Dr. Schwartz received funding for his research activity from the National Institutes of Health (NIH); he is the only European investigator with uninterrupted funding for over 40 years. In 2017 he received a 5-year grant entitled "European Sudden Cardiac Arrest network: towards Prevention, Education and New Effective Treatment - ESCAPE-NET" by the European Community through the Horizon 2020 program (PI: Dr. H. Tan). In 2018, as the European co-PI (the American co-PI is Dr. J. Wu), he was funded by the Fondation Leducq for a 5-year project entitled "Towards Precision Medicine with Human iPSCs for Cardiac Channelopathies"; this prestigious 6 million dollars grant is shared with 5 other members of the Consortium.

Dr. Schwartz serves the leading cardiology journals as a member of the Editorial Board and/or as a reviewer. Since September 2016 he is one of the Deputy Editors of the International Journal of Cardiology; from July 2017 he is the International Associate Editor for Basic Sciences for the European Heart Journal.

He is the author of 1528 publications: 12 books, 164 chapters, 582 original articles, and 770 abstracts. His Impact Factor in the period 1969-2017 is 3329, and his current *h*-index is 123 (source: Scopus – May 31, 2019).

(updated June 14th, 2019)