**Institution:**
University of Cambridge

**Unit of Assessment:**
UoA5

**Title of case study:**
Targeted protection from Sudden Cardiac Death

**1. Summary of the impact** (indicative maximum 100 words)

Sudden cardiac death causes 4.5 million deaths worldwide each year many of which could be prevented by implantable cardioverter defibrillators (ICDs), but these also carry risks. Research in the groups of Huang and Grace has led to diagnostic assays offering three times the predictive accuracy of current approaches in guiding cardiologists concerning indications for ICD implantation. The assay has been clinically trialled; since 2008, through the trial, the lives of three patients identified by the assay as at high risk were saved. Further work led by Grace and colleagues provided an improved, subcutaneous ICD (SICD); Grace also participated in a US-based clinical trial (NCT00399217) providing the evidence required for FDA approval supporting also later inclusion into NICE guidance. Since 2008 the SICD has been implanted in over 2500 patients in 16 countries.

**2. Underpinning research** (indicative maximum 500 words)

Ventricular fibrillation (VF) leading to sudden cardiac death (SCD) is a major public health concern. Conventional ICDs, battery-powered electrical shock generators attached by leads to the heart, are used extensively in its prevention but have high complication rates and are poorly targeted to those who would most benefit. Improved devices and refined risk stratification could thus save many lives.

Christopher Huang, Professor of Cell Physiology, Dept. Physiology, Development and Neuroscience (since 2002; previously Lecturer/Reader there since 1984), and Andrew Grace, (Dept. Biochemistry: 1990-7 BHF Clinical Scientist Fellow, 1997-2002 BHF Senior Research Fellow, since then Honorary Member; in parallel (1996-present): Papworth Hospital, Consultant Cardiologist), have pioneered work on the propagation of the heart beat and thereby developed an assay offering improved risk stratification of SCD. The preclinical programme motivated Grace in his clinical work to execute research leading to a subcutaneous ICD, adding an improved therapeutic intervention.

Several stages of research underpinned the impact:
*1. Electrophysiological measurements on mouse models of human cardiac arrhythmias:*
Mutations of ion channels associated with clinical VF provided the platform for studying arrhythmia mechanisms. Work in Cambridge by Huang, Grace and colleagues (1996-2013) generated and evaluated mice with human disease-associated mutations engineered into ion channel genes. They showed that cardiac sodium channel disruption impaired action potential propagation with conduction block resulting in re-entrant arrhythmias, thereby identifying an important marker of arrhythmic potential (Ref. 1, Section 3). Further research demonstrated that impaired action potential propagation and conduction block constituted a common motif for arrhythmias whatever the underlying genetic defect (Refs 2 and 3, Section 3). It was accordingly anticipated a common motif would be also observable in patients, providing a potential means for identifying high risk patients.

*2. Electrophysiological measurements in patients with noncoronary heart diseases:*
A large-scale study conducted at Papworth by Grace and colleagues from 1998-2002 (with significant contributions from the Institute of Cardiology, Warsaw and others) carried out paced electrogram fractionation analysis (PEFA) on the hearts of 266 patients with a range of non-coronary heart disease, 61 with a history of VF. Comparison with the 205 patients with no VF history (Ref. 4, Section 3) confirmed that defective propagation of the heartbeat, as observed by PEFA in the mouse disease models, is also a common feature of human VF.

*3. Electrophysiological measurements in patients with hypertrophic cardiomyopathy (HCM):*

A focused study validated the assay in patients with HCM, the commonest cause of SCD in young people. This work, conducted largely in Cambridge (again with significant contributions from elsewhere especially Warsaw) by Grace, Huang and colleagues from 1998 to 2005, determined the positive predictive value (PPV) of the PEFA test in relationship to other risk factors for SCD and followed the outcomes of 179 patients with HCM over a mean 4.3 years. Thirteen patients had VF, and the PEFA test identified nine of these patients. The PPV for the identification of SCD in this group was 0.38 (0.17-0.59). Use of two or more conventional markers *e.g.* septal wall thickness and ambulant arrhythmia yielded a PPV of only 0.106 (confidence limits 0.02-0.15). The cardiac propagation assay therefore (Ref. 5, Section 3) identified high-risk patients with greater accuracy than conventional techniques.

*4. Improved (subcutaneous) ICD:*

The unique position of Grace, embedded in the Dept of Biochemistry, but also working as a clinician, made possible the efficient development of the diagnostic tool, described in the previous sections. The anticipated provision of an improved diagnostic procedure gave a strong incentive to develop an improved therapeutic device for the same condition. Complications with the current transvenous systems are severe and include *inappropriate* large voltage shocks, the need for the extraction of leads from the heart and blood vessels and infection, all of which have associated mortality. An entirely subcutaneous ICD system, requiring neither direct contact with the heart muscle nor a transvenous lead, was therefore subsequently brought into the clinic through work carried out by Grace (the main single contributor to all the early work) and colleagues in Cambridge and elsewhere (US, New Zealand, UK, Russia, Italy, Germany, Netherlands) between 2002 and 2012. Two short-term clinical trials first identified a suitable device configuration and energy requirements. Both a pilot study and a full trial then evaluated long-term use (Ref. 6, Section 3). The device does not interfere with normal heart function, thus allowing streamlined and more accurate assessment of the diagnostic electrophysiological biomarkers identified in the experimental studies (Refs 1-5, Section 3). The development of both the means of assessment and the therapeutic intervention by the same group (that were responding to the same core need) has accelerated progress to clinical application.

**3. References to the research** (indicative maximum of six references)

1. Papadatos GA, Wallerstein PM, Head CE, Ratcliff R, Brady PA, Benndorf K, Saumarez RC, Trezise AE, Huang CL, Vandenberg JI, Colledge WH, Grace AA (2002): Slowed conduction and ventricular tachycardia following targeted disruption of the cardiac sodium channel, *Scn5a*. *Proceedings of the National Academy of Sciences, USA.* 99:6210-5 doi: 10.1073/pnas.082121299
2. Zhang Y, Wu J, Jeevaratnam K, King JH, Guzadhur L, Ren X, Grace AA, Lei M, Huang C L-H, Fraser JA. (2013) Conduction Slowing Contributes to Spontaneous Ventricular Arrhythmias in Intrinsically Active Murine RyR2-P2328S Hearts. J Cardiovasc Electrophysiol. 24:210-8 doi: 10.1111/jce.12015
3. Matthews GD, Guzadhur L, Grace AA, Huang CL. (2012): Nonlinearity between action potential alternans and restitution which both predict ventricular arrhythmic properties in *Scn5a+/-* and wild-type murine hearts. *J Appl Physiol.* **112**:1847-63 doi: 10.1152/japplphysiol.00039.2012
4. Saumarez RC, Chojnowska L, Derksen R, Pytkowski M, Sterlinski M, Huang C L-H, Sadoul N, Hauer RWN, Ruzyłło W, Grace AA (2003): Sudden death in non-coronary disease is associated with delayed paced ventricular activation. *Circulation.* 107: 2595-2600 doi: 10.1161/01.CIR.0000068342.96569.A1
5. Saumarez RC, Pytkowski M, Sterlinski M, Bourke JP, Clague JR, Cobbe SM, Connelly DT, Griffith MJ, McKeown PP, McLeod K, Morgan JM, Sadoul N, Chojnowska L, Huang CL, Grace AA. (2008): Paced ventricular electrogram fractionation predicts sudden death in hypertrophic cardiomyopathy, *European Heart Journal.* 29:1653-1661 doi:10.1093/eurheartj/ehn111
6. Bardy GH, Smith WM, Hood MA, Crozier IG, Melton IC, Jordaens L, Theuns D, Park RE, Wright DJ, Connelly DT, Fynn SP, Murgatroyd FD, Sperzel J, Neuzner J, Spitzer SG, Ardashev AV, Oduro A, Boersma L, Maas AH, Van Gelder IC, Wilde AA, van Dessel PF, Knops RE, Barr CS, Lupo P, Cappato R, Grace AA. (2010): The Subcutaneous only Implantable Cardioverter Defibrillator. *New England Journal of Medicine*. 363:36-44 doi: 10.1056/NEJMoa0909545

**Funding:**
***Wellcome Trust:***
AA Grace, C Huang, Integrative Physiology of Cardiac Arrhythmias, 2005-2008, £573,072
C Huang, AA Grace (& M. Lei, Manchester) Electrophysiological and molecular characterization of cardiac conduction system in murine models of Scn5a sodium channel, 2007-2010, £372,044
***Medical Research Council:***
AA Grace, C Huang, WH Colledge, RW Farndale, JC Metcalfe, Co-operative Group Grant on translational cardiovascular biology: atherosclerosis, thrombosis and arrhythmias, 2002-2006, £473,352
***British Heart Foundation:***
AA Grace, C Huang, Molecular physiology of cardiac sodium channel mice, 2002-2004, £128,609
AA Grace, Senior Research Fellowship, 1997-2002, £438,973

**4. Details of the impact** (indicative maximum 750 words)

**Impacts on health and welfare**:
*New clinical interventions, with improved outcome for patients:*
***1. Improved diagnostic technology, predicting risk of VF with increased accuracy (clinically applied conduction assay):*** Clinical trials lead by Grace and Richard Saumarez (Honorary Member, Depts. Engineering and Medicine: 1998-2008) from 1998 to 2002 demonstrated that their observations in mice translated to human hearts (see Sections 2.1, 2.2). This allowed development of a **new diagnostic technology** which has been **trialled with patients**, yielding a **definite outcome**: In a trial of 179 patients, 156 patients tested negative and 23 tested positive; the latter, being identified as at high-risk, were fitted with an ICD. 9 of these 23 patients (39%) developed an event (6 in the period of observation leading in 2008 to the publication of Ref. 5, Section 3, a further 3 since then), compared to 3% (4 out of 156) of the patients that tested negative. Thus, during the eligible impact period three lives were saved in this relatively small clinical trial of 179 patients because they had been fitted with an ICD due to identified high risk, with the positive predictive value of the new assay (0.38) being at least three-fold that of conventional assessments (0.106) (Ref. 5, Section 3). In addition, the quality of life of 152 patients who were identified as not being at risk improved as they were strongly reassured that they need not live in fear of SCD and were also spared the unnecessary implantation of an ICD.
***2. Improved therapeutic intervention combating VF with fewer side effects (subcutaneous ICD)*:** A diagnostic assay is only of value if an effective therapeutic intervention exists for the diagnosed condition. The development of the propagation assay with improved risk stratification by Grace and Huang provided a strong incentive for the clinical work of Grace and colleagues to develop a safer, improved ICD device. The development of this, the subcutaneous ICD (SICD), progressed effectively through all stages of clinical development also fulfilling stringent international regulatory assessment and has been implanted in more than 2500 patients in 16 countries world-wide (Refs 1,3 & 4, Section 5).

**Impacts on commerce:**
***Conduction assay:***
A provisional patent application has been filed by Grace in the United States ('Systems for assessing risk of sudden cardiac death, and related methods of use'; Application Number 61/860,854). The assay is being commercialised through a spin-out company, Electus Medical Inc (EIN assigned: 46-3330185) founded by Grace, Huang, Van De Sluis and Wigdahl (the latter two are respectively US- and UK-based entrepreneurs). The company is in the advanced fund-raising stage.
The assay provides a powerful basis for a systems approach to human disease (Grace AA, Roden DM. (2012): Systems Biology and Cardiac Arrhythmias. Lancet 380:1498-508) and Illumina Inc. have entered into an agreement to conduct whole genome analysis comparing patients with high and low risk characteristics, with the objective to extend personalised approaches to the identification of those at risk of SCD to the largest possible population (Ref. 2, Letter of support from Illumina, Section 5).
***SICD:***
The SICD technology has been commercialised by Cameron Health Inc, which in 2012 were

acquired (having hit key milestones) by Boston Scientific for $1.35 billion (ca £870 million). They have to date sold 2500 SICDs into 16 countries generating revenues of approximately $50M (ca £32M) (Ref. 1, Section 5).

**Impacts on practitioners and services:**

***Influence on professional standards and guidelines***

The SICD has received approval by the FDA in September 2012 (Ref. 3, Section 5), and a positive guidance from NICE in April 2013 (Ref. 4, Section 5).

Grace serves as a Member of the MHRA Cardiovascular, Diabetes, Renal, Respiratory and Allergy Expert Advisory Group of the Commission on Human Medicines (2006-present; Ref. 5, Section 5) and the Cardiovascular Specialist Advisory Group of the European Medicines Agency (EMA; 2010-present; Ref. 6, Section 5). This contribution is informed by the body of work described in Section 2.

***Influence on training and subsequent work of practitioners***

Implantation of the SICD has a rapid learning curve but training has facilitated this process. Grace completed the first permanent implants in the Netherlands (02.2009, Amsterdam), the United Kingdom (02.2009, Birmingham) and Germany (06.2010, Münster) with subsequent cases then completed by local physicians under his immediate supervision. Since 2009 numerous UK-based doctors (e.g. Lambiase (London), Barr (Birmingham), Till (London) etc.) attended SICD implants at Papworth to facilitate skill transfer. An animated video of an implantation based on movies made at Papworth in which Grace demonstrated the technique is one of the main tools for training used worldwide (Ref. 7, Section 5).

**Impacts on society, culture and creativity:**

The benefits to heart patients arising from the research described in Section 2 has been brought to the attention of the public through press coverage, including BBC News, the Daily Telegraph, the Daily Mail (Refs 8-10, Section 5), as well as internationally renowned medical press such as the Lancet. It has been featured on YouTube (143 views between 23/5/13 and 31/7/13; Ref. 11, Section 5), in an *Expert ConsultBook* (Ref. 12, Section 5), and by medical webpages. Through the newspaper articles alone, 1.5 million people have been informed of the research (based on their traffic figures).

**5. Sources to corroborate the impact** (indicative maximum of 10 references)

1. Letter from Vice President at Boston Scientific
2. Letter from Chief Scientific Officer at Illumina
3. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm321755.htm
4. http://guidance.nice.org.uk/IPG454
5. Membership of Dr Grace in MHRA Cardiovascular, Diabetes, Renal, Respiratory and Allergy Expert Advisory Group of the Commission on Human Medicines: http://www.mhra.gov.uk/Committees/Medicinesadvisorybodies/CommissiononHumanMedicines/ExpertAdvisoryGroups/CardiovascularDiabetesRenalRespiratoryandAllergy/
6. Membership of Dr Grace in Cardiovascular Specialist Advisory Group of the European Medicines Agency: http://www.ema.europa.eu/docs/en_GB/document_library/contacts/gracea_DI.pdf
7. http://www.bostonscientific.com/cardiac-rhythm-resources/cameron-health/sicd-implant.html
8. BBC News: http://news.bbc.co.uk/1/hi/health/4601316.stm
9. Daily Telegraph: http://www.telegraph.co.uk/health/9193021/A-life-saver-for-a-weak-heart-sufferers.html
10. Daily Mail: http://www.dailymail.co.uk/health/article-1281120/Cardiac-death-New-zapper-keeps-ticker-working-order.html
11. *YouTube:* Video intro into the device http://www.youtube.com/watch?v=ZOynfG80m40
12. *Entry in the Expert ConsultBook:* http://www.expertconsultbook.com/expertconsult/ob/book.do?method=display&type=bookPage&decorator=none&eid=4-u1.0-B978-1-4377-1616-0..00019-9&isbn=978-1-4377-1616-0