

Dario DiFrancesco

Curriculum vitae

Personal

Born: February 10, 1948 in Milano, Italy

Citizenship: Italian

Work address: Dept. of Biosciences, Lab. of Molecular Physiology and Neurobiology, The Pacelab, University of Milano, via Celoria 26, 20133 Milano, Italy

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Education

Univ. Studi, Milano: Ph.D. (equiv.), 1973 (Physiol./Biophysics)

The Physiological Lab., Cambridge, UK: Postdoc (Cardiac Electrophysiology)

Univ. Lab. Physiology, Oxford, UK: Postdoc (Cardiac Electrophysiology)

Research positions and Academic appointments

9/73- 12/74: Teaching and research fellowship, Institute of General Physiology, Univ. Milano.

1/74- 12/80: Research Assistant, as above

9/76- 3/77: Postdoctoral fellow in Cambridge, The Physiological Laboratory (R.D. Keynes)

4/77- 12/78: Postdoc in Cardiac Electrophysiology in Oxford, The Lab. of Physiology (D. Noble).

1/81- 5/86: Associate Professor, Dept. of General Physiology and Biochemistry, Univ. Milano.

6/86-present: Full Professor, Dept. of General Physiology and Biochemistry, then Dept. of Biomolecular Sciences and Biotechnology, Univ. Milano

10/99-present: external lecturer of Physiology at Vita-Salute Univ., San Raffaele Hospital (HSR), Milano

Primary areas of research interest

-Electrophysiology of cardiac tissue and cells

-Ionic currents and rhythmic activity in heart

-The pacemaker "funny" channel and control of heart rate

-HCN channelopathies in sinus arrhythmias

-Cardiac stem cells

Honors and awards

-Recipient Accademia dei Lincei- Royal Society award 9/1976- 8/1977 (Cambridge- Oxford)

-Recipient Wellcome Trust award Research Grants 9/1977- 7/1979 (Oxford)

-Recipient Wallace O. Fenn Memorial Fund award for XXVIII IUPS Congress 1980 (Budapest)

-Recipient Wallace O. Fenn Memorial Fund award for XXIX IUPS Congress 1983 (Sidney)

-Member of the "Academia Europaea" since 1992

-International Prize of Physiology "Professeur Pierre Rijlant" Academic Foundation, awarded by the Royal Academy of Medicine of Belgium, 1994

-Lectio Magistralis Annual Congress Italian Soc. of Physiology, 1994

-League of European Research Universities mention for L.E.R.U. Research Breakthroughs 2006 as representative of best research in the University of Milano

-Lauréat Grand Prix scientifique pour l'année 2008, Fondation Lefoulon-Delalande- Institut de France, pour les "très remarquables travaux de recherche qui ont conduit à la découverte des canaux ioniques impliqué dans la régulation du rythme cardiaque".

-Lectio Magistralis Faculty of Science Univ. Milan 2008

-Lectio Magistralis and Prize "Control of cardiac rate by "funny" channels in health and disease" Symp. "Translation in Cardiomyopathies: from genes to therapy" Padova 2009

-H.C. Burger Award Lecture "The history of the discovery of funny channels" 23rd Cong. Europ. Soc. Noninvasive Preventive Cardiol. "Cardiovascular Medicine in the Era of Advanced Technology", Brescia 2009

Extra-mural grants (selected)

-CNR International Research Grant (Milano- Oxford) 1982/86, 1987-89, 1990-93

- CNR Research Grant 1989-90
- MDA Basic Research Grant 1985/87
- NIH Research Grant 1987/1989
- CNR Special Project 1991-1992 Italian Coordinator
- European Union Human Capital and Mobility grant 1995 through 1997
- Telethon Grant (1998/2001)
- NATO exchange grant 1998-1999 (Columbia University)
- Servier International 1999-2000; 2002-2003; 2005-2006, 2007-2009
- MIUR FISR CNR Special Projects Functional Genomics 2003-2005
- FIRB Neurobiology 2003-2007
- FIRB Post- genomics 2004-2007
- FIRB New biological therapies for myocardial infarction 2005-2010
- CARIPLO Biological pacemaker 2005-2007
- UE "Normacor" 2006-2009
- MURST Cofin-PRIN from 1997 through to present

Scientific Societies

- Società Italiana di Fisiologia, 1973-
- Soc. Italiana di Biofisica, 1984-1989
- ABCD, 1987-2000
- The Physiological Society (UK) 1983-
- American Physiological Society (USA), 1985-
- Biophysical Society (USA), 1999-
- Society for Neuroscience (USA), 2011-

Editorial and Committee Experience, Consultancies

- Ad hoc reviewer for all major international journals.
- Editorial Boards:
 - Journal of Cardiovascular Electrophysiology, 1992-2000
 - News In Physiological Sciences (NIPS), 1995-2002
 - Journal of Cardiovascular Pharmacology, 1996-2000
 - British Journal of Pharmacology, 2003-2007
 - Frontiers in Cardiac Electrophysiology, 2011-
- National Group Coordinator of Special Committee Grant Project on "Ionic Channels: functions and control mechanisms" 1991-93
- Commissaire de thèse de troisième cycle: Docteur Guy Champigny, Université de Poitiers, 6/1987
- Commissaire de thèse de troisième cycle: Docteur Patrick Bois, Université de Poitiers 12/1989
- Commissaire de thèse de troisième cycle: Docteur Jerome Petit-Jacques, Université de Poitiers 1/1993
- Consultant, N.I.H. Program Project Grant: Ira S. Cohen, State University of New York, Stony Brook, N.Y., 1988-92
- Grant reviewer NATO research project 1/1989
- Consultant, N.I.H. Program Project Grant: Michael Rosen, Columbia Univ., New York, 1993-98 and further renewals until today
- Grant reviewer NATO research project 1/1994
- Commissaire de thèse de troisième cycle: Docteur Jocelin Bescond, Université de Poitiers 12/1996
- Grant reviewer Human Frontiers 12/1996
- Commissaire de thèse de troisième cycle: Docteur Barbara Renaudon, Université de Poitiers 12/1997
- Grant reviewer NATO research project 9/1997
- Expert européen évaluation Unité INSERM U 446 (Rodolphe Fishmeister) Université de Paris Sud, Châtenay-Malabry, 9/1999
- Grant reviewer Human Frontiers 1/2003
- Grant reviewer for Italian Ministry of University and Research and other national and international granting bodies
- Commissaire de thèse de Doctorat Marie Curie: Docteur Angelo Torrente, Université de Montpellier 07/2011
- Grant reviewer for Fondation de Recherche Médicale 7/2011

-Examiner D. Phil. thesis for Viva of Dr Michael A. Colman, Univ. Manchester 12/2012

Summary of training and research experience

-7/73 - 7/76: Research Assistant, Istituto di Fisiologia Generale, Un. Milano.
-7/76 - 3/79: PostDoc at The Physiological Laboratory, Cambridge, U.K. and then at the Laboratory of Physiology, Oxford, U.K. (Dr Denis Noble)
-3/79 - 12/80: Wellcome Trust Fellowship at Oxford Un. Lab. of Physiology.
Brief periods spent in various Univ. laboratories of Physiology (Homburg/Saar, Paris XI, Tours).
-3/79 - 12/80: Assistant Professor, Istituto di Fisiologia e Biochimica Generali, Un. Milano.
-1/81 - 6/86: Associate Professor.
-6/86 - present: Full Professor, Dipartimento di Fisiologia e Biochimica Generali, then Dipartimento di Scienze Biomolecolari e Biotecnologie, Un. Milano.
-6/86 - 8/86, 6/88 - 8/88, 6/90 - 8/90: Visiting Professor, SUNY at Stony Brook, NY
-Visiting scientist and consultant, Dept. Pharmacology Columbia University, N.Y. periodically since 1990

Bibliometrics

-Over 170 full articles/reviews/chapters in books. h-index: 57; citations: 11740 (Google Scholar 06/2013)

Press

Newspaper articles, press interviews, video interviews and other material can be found on the personal page <http://users.unimi.it/difrancesco/>

Research mentoring records

In the course of more of 3 decades, D. DiFrancesco's lab has hosted a large number of students, postdocs, visitors many of whom have made a career in Physiology and are now established academics/researchers in worldwide locations. Here is a brief, selected list: Damir Janigro, Cleveland Clinic; Antonio Malgaroli, Dept. Physiology, HSR Milano; Richard B. Robinson, Dept. Pharmacology Columbia Univ., New York; Antonio Zaza, Dept Biotechnology & Biosciences, Univ. Milano-Bicocca; Matteo Mangoni, CNRS Montpellier; Gianmaria Maccaferri, Northwestern Univ., Chicago; Sonia Gasparini, School Med. New Orleans; Anna Moroni, Dept. Biology, Univ. Milano; Raimondo D'Ambrosio, Univ. Washington, Seattle

Invited presentations, named lectures etca

1977		-Oxford, Lunch Club Seminar
1978	May	-Bonn (O. Hauswirth)
1979	Feb	-Paris XI (E. Coraboeuf)
1980	Aug Dec	-Budapest, Inv. Lecturer XXVIII IUPS Congress -Amsterdam, Symposium: Cardiac Rate and Rhythm
1981	Apr May	-Abano Terme, Fidia Res. Lab. (A. Gorio) -Lyon (O. Rougier).
1982	Feb March	-Firenze (A. Mugelli) -Ferrara (E. Wanke)
1983	Jan June Sept	-Geneve, Centre Med. Univ. (D. Bertrand, C. Bader) -Abano Terme, Fidia Res. Lab. (M. Prosdocimi) -Sidney, Invited Lecturer XXIX IUPS Congress
1984	March July Sept Sept Sept Sept Sept Sept	-Clermont-Ferrand (Merck-Sharp & Dhome-Chibret) -Tours (D. Garnier) -Oklahoma City, Inv. Lecturer Symp. Int. Society for Heart Research (R. Lazzara) -Atlanta (L. DeFelice) -Baltimore (J. Lederer, T. Lakatta) -Stony Brook (I. Cohen) -New York, Columbia University (M. Rosen)

1985	Jan March Sept	-Napoli (T. De Leo) -Torino (E. Meda) -Pisa, Inv. Speaker SIF
1986	Aug Aug Oct	-Banff, Speaker Sat. Symposium IUPS Congress -New York, Columbia Univ -Vienna, Inv. Lecturer Symp. Boehringer Ingelheim
1987	May May June June Oct	-Rotterdam, Lecturer Symp. Pure Bradycardic Agents -Milano, CNR -Padova, (S. Luciani) -Poitiers, Committee Board Thesis Guy Champigny -San Diego, Inv. Lecturer Congress APS
1988	Apr Apr Oct Oct Oct Dic	-Okazaki, Chairman Symp. US-Japan seminar -Tokio, Inv. Lecturer International Symposium Basic Mechanisms of Arrhythmias (H. Irisawa) -Padova, Inv. Lecturer Congress SIB -Spoleto, Inv. Lecturer Congress ABCD -Pasadena, (H. Lester) -London, Inv. Co-chairman, British Heart Foundation
1989	March May Sept Oct Dec	-Pavia, Conference Dottorato Fisiologia (Prof. Rindi) -Ann Arbor, Inv. Speaker Int. Soc. Heart Research -Homburg/Saar, Chairman Symp to honor W. Trautwein -Roma, Inv. Speaker Soc. Ital. Cardiologia -Poitiers, Committee Board thesis Patrick Bois
1990	Feb May May May July Aug Sept Sept Sept Oct	-Frankfurt, Inv. Speaker Symp. A.Thomae -New York, Columbia Univ. -Chicago, Inv. Speaker Symp. Ion channels in heart and the vascular system (H. Fozzard) -Houston (A.M. Brown) -Farmington (A. Pappano) -New London, Inv. Speaker Gordon Conference Ionic Channels (H. Lester) -Firenze, Inv. Lecturer III Congr. Cell Biol. -Perugia, Inv. Speaker Congress SIF -Firenze, Inv. Speaker XVII Int. Congr. Electrocardiology -Islamorada, Florida, Inv. Speaker Hoffman Symp. (M. Rosen)
1991	April May July July Oct Dec	-Il Ciocco, Inv. Speaker NATO Workshop (M. Morad) -Roma, Un. Tor Vergata (S. Morante) -Prague, Inv. Speaker Regional Meeting IUPS (C. Hartzell) -Oxford, Inv. Speaker Symp. Cardiac Background Currents (D. Noble) -Erice, Inv. Lecturer Int. School Bioelectrochemistry -Milano, Inv. Lecturer Scuola Soc. It. Neuroscienze
1992	Feb March April May July Sept Sept Oct Nov Dec	-Pisa, (L. Maffei) -Seattle, WA (B. Hille, W. Crill) -San Diego, CA (K. Chien) -Padova, (S. Schiaffino) -Madrid, Inv. Speaker X Int. Congr. Cell Biology -Ferrara, Inv. Speaker meeting EWGCE -Naples, Inv. Speaker Nat. Congr. Pharmacology -Antwerpen (PP. van Bogaert) -Bologna (C. Rapisarda) -Vienna Inv. Lecturer Symposium Boehringer Ingelheim
1993	Jan Aug Aug Sept Oct	-Poitiers, Committee Board Thesis Jerome Petit-Jacques -Glasgow, Inv. Speaker XXXII IUPS Congress -Keystone, Colorado, Inv. Lecturer Symp. Cardiac Electrophysiology (Medtronic) -Milano, Inv. Speaker ABCD Congress -Poitiers, Inv. Lecturer "E. Coraboeuf Jubilee"
1994	March June	-Firenze, Lettura Magistrale Annuale Soc. Ital. Fisiologia -Montpellier (Sanofi Recherche)

	July Sept Sept	-Trento (R. Antolini) -Milano, DiBit (Neurobiology Course Open Univ.) -Palermo, Invited Speaker Congress SIBPA
1995	April June Sept Oct Oct Dec	-Versailles, Inv. Speaker Workshop on Bradycardic Agents and Cardiac Arrhythmias (Servier) -Trieste, SISSA (E. Cherubini) -Leuven, Symposium to honor E. Carmeliet -Bruxelles, Lecture for <i>Prof. Pierre Rijnlant Prize</i> at Royal Academy of Medicine -London, King's Coll, Symposium on Cyclic-nucleotide gated channels -New York, Columbia Un. (R. Robinson)
1996	June Nov	-Banff, Inv. Speaker Symp. in honour of Denis Noble -Banff, Inv. Speaker Conference AV node
1997	Jan June July	-Nice-Sophia Antipolis (M. Lazdunski) -Erice, Symposium Synaptic Communication (E. Cherubini) -St. Petersburg, Inv. speaker Symposium Cell Oscillators (A. Noma)
1998	Oct	-Jülich (B. Kaupp)
1999	March April Sept Sept Sept Sept	-Miami, 2 nd Workshop Cardiac rate inhibitors. (Servier) -Rome, Ph.D. school seminar (A. Trentalance) -Orsay, Inv. speaker E. Coraboeuf Symposium (R. Fishmeister) -Oxford, Session Chairman XXIII meeting EWGCCE (Denis Noble) -Hyerres, Inv. speaker Colloque Canaux Ioniques (S. Richard) -Rome, Inv. speaker Hodgkin Symposium
2000	Jan Oct	-Milano Dept. Pharmacology (A. Panerai) -Parma, Inv. speaker SIBPA Congress
2001	Feb July Sept. Nov	-New York, Columbia Un. (R. Robinson) -Paris, Inv. speaker 3 rd Workshop Cardiac rate inhibitors. (Servier) -Ancona, Inv. speaker Congresso SIF -Goettingen (D.W. Richter, E. Neher)
2002	July Sept Sept Sept	-Courbevois Paris seminar (Servier) -Berlin, Inv. speaker Eur. Soc. Cardiol. Congress 2002 -Leeds, Inv. speaker Physiol. Soc. meeting - Montpellier, Inv. chair EWGCCE 2002 meeting
2003	March March May June Aug Sept Dec Dec	-Courbevois Paris seminar (Servier) -Les Arcs, Inv. speaker European Winter Conference on Brain Research -Milano, Organizer Symposium to honor A. Ferroni -Strasbourg, Inv. speaker Heart Failure Congress ISHR 2003 -Vienna, Inv. speaker Eur. Soc. Cardiol. Congress 2003 -Erice, Inv. speaker 2nd L. & H. Fairberg Workshop Cardiac Engineering -Milano, Ph.D. School in Physics seminar (PF Bortignon) -Milano, Accademia dei Lincei (F. Clementi)
2004	Jan Aug Sept Nov Dec	-Milano, Newron seminar -Sidney, Inv. speaker XVIII World Congress Intern. Soc. Heart Research -Montpellier, Inv. speaker Cardiac Cell. Electrophysiol: From funny currents to the current Physiome, Celebration for Denis Noble retirement -Napoli, Inv. speaker VI Convegno Nazionale INBB -Roma, Inv. speaker 65 ^o Congresso Naz. Soc. Italiana Cardiologia
2005	Feb Apr June Sept Dec	-Milano, Newron Pharmaceutical (R.G. Fariello) -Roma, Istituto Dermopatico Immacolata (M. Capogrossi) -New York, Dept. Pharmacol. Columbia Univ. (R.B. Robinson) (no seminar) -Milano, CC Monzino (M. Pesce) -Neully sur Seine, Procoralan Meeting (Servier)
2006	Apr Apr June	-S. Francisco, Inv. speaker Exp. Biology meeting FASEB (S. Siegelbaum) -Athens, Inv. speaker Cardiology Update 2006 Evangelismos General Hospital -Milano, H San Raffaele (A. Malgaroli)
2007	Feb June Sept Sept	-Darmstadt (G. Thiel) -Bologna, Inv. speaker XIX World Congress Intern. Soc. Heart Research -Manchester, Inv. speaker Cardiac Electrophysiol. meeting (M. Boyett) -Antalya, Inv. speaker 5 th Fairberg workshop (S. Sideman)

	Oct	-Lugano, Inv. speaker Cardiocentro Ticino Cong Cardiac Frequency (T.Moccetti)
2008	Jan	-Vellore, India, Inv. speaker 6 th Winter Symp. Cardiov. Sciences
	Feb	-Geneve, Hôpitaux Universitaires de Genève -Servier (B. Wagner)
	May	-Athens, Inv. speaker XXVIII Europ. Section Meeting ISHR
	June	-Paris, Coupole Institut de France award of Grand Prix Scientifique Fondation Lefoulon-Delalande
	June	-Milano, Keynote Lecture Giornate del Gruppo Biologico
	June	-Sassari seminar Dip. Scienze Biomediche (L. Deiana)
	July	-New London, NH Inv. speaker Gordon Res. Conference Colby-Sawyer Cardiac Regulatory Mechanisms (D. Eisner, J. Lederer)
	Oct	-Imola XV Cong. Soc. Ital. Ric. Cardiovasc. (G. Losano)
	Oct	-Milano Inv. speaker Circolo della Stampa, Premio Galeno 2008 (R. Paoletti)
	Oct	-Roma Inv. speaker Giornate Ricerca Servier (B. Millet)
	Oct	-Venice Inv. speaker Multiple Risk Factors in CVD Venezia Lido (R. Paoletti)
	Nov	-St Louis, MO CBAC Seminar (Y. Rudy)
	Nov	-New Orleans Inv. speaker CES Annual Meeting
	Dec	-Milano, Lectio Magistralis Faculty of Science Univ. Milan
2009	Feb	-Paris Croissy, seminar Servier (L. Alliot)
	Feb	-Il Ciocco, chair session GRC Cardiac Arrhythmia Mechanisms (N. Trayanova)
	March	-Milano, Lecture Istituto Lombardo Accademia Scienze e Lettere
	April	-Padova, Lectio Magistralis and Prize Symp. "Translation in Cardiomyopathies: from genes to therapy" (G. Thiene)
	May	-Boston Inv. speaker Heart Rhythm 2009 Cong. (D. Packer)
	May	-Brescia, H.C. Burger Award Lecture "The history of the discovery of funny channels" 23rd Cong. Europ. Soc. Noninvasive Preventive Cardiol. "Cardiovascular Medicine in the Era of Advanced Technology" (C. Rusconi)
	May	-Paris Suresnes, seminar/talks Servier (J.-P. Vilaine)
	June	-Berlin, Inv. speaker Europace 2009 Cong. (J. Brugada)
	June	-Lousanne, Inv. lecturer Colloques Formation Continue, CHUV (Andres Jaussi, Servier Barbara Fritsche)
	June	-Kyoto, Inv. speaker 36 ^o IUPS Cong. "Pacemaker mechanisms" (D. Eisner, D. Noble); organizer & speaker Luncheon Seminar (Servier) "Targeting funny channels for clinical applications"
	Aug	-Ovodda, Sardinia, Lecturer meeting "Studio comparativo della longevità di quattro comuni della Sardegna (Ovodda, Tiana, Erula e Perfugas) primi risultati demografici e genetici" (L. Deiana)
2010	Apr	-Levico Terme, Inv. speaker Congress SICOA -Le aritmie nel III millennio
	June	-Nice, Inv. speaker Cardioslim 2010, 10th World Congr. Cardiac Arrhythmias
2011	Feb	-Milano Ist Besta (S. Franceschetti)
	Oct	-Venice, Inv. speaker 2011 Venice Arrhythmias Congress (Raviele, Natale)
	Nov	-Porto, Inv. speaker Reunião Anual Núcleo de Técnicos de Cardiologia da SPC (Medtronic)
	Nov	-Roma, Inv. speaker Advances in Cardiac Electrophysiology (Calò)
	Dec	-Roma, Inv. speaker Soc Ital Cardiol
2012	May	-Milano, Lecture Istituto Lombardo Accademia Scienze e Lettere
	May	-Boston, Inv. speaker Heart Rhythm 33rd Annual Sci Sessions
	June	-Paris Suresnes, Servier seminar (J.-P. Vilaine)
	Sept	-Manchester, Inv. speaker Phys. Soc. Cardiac & Resp. Themed Meeting Cardiac Arrhythmias (H. Zhang)
2013	March	-Pavia, Inv. Lecturer PhD School Collegio Borromeo (V. Ricci)
	May	-Montpellier, Inv. Lecturer Colloque du Patch-Club

Synopsis of work

The heart of an adult person beats normally some 100,000 times a day, with a fairly regular rhythm. The heart rate is finely regulated at any time during our life according to need: for example it slows at night and accelerates at wake-up, and changes rapidly during physical exercise or in response to varying metabolic and emotional conditions. A major physiological controller of heart rate is the autonomic nervous system, which causes acceleration by sympathetic stimulation and slowing by vagal stimulation through the release of the neurotransmitters noradrenaline and acetylcholine, respectively. How is the cardiac spontaneous activity generated, and how is rate controlled so rapidly and efficiently? These are central questions which have always attracted the interest of physiologists and cardiologists.

Just over a hundred years ago, Keith and Flack first observed that the heartbeat originates from a special region within the right atrium, the sinoatrial node (SAN). Only about seventy years later, however, did the cellular basis for the initiation of the heartbeat become apparent thanks to microelectrode recordings of electrical activity. Indeed, cells from the SAN region, termed “pacemaker” cells, generate action potentials with a special shape, characterized by the presence of a phase called “pacemaker” or “slow diastolic” depolarization. After termination of an action potential, rather than stabilizing to a certain “resting” level as in working atrial or ventricular myocytes, the membrane potential of a pacemaker cell slowly depolarizes until reaching threshold for another action potential, thus giving rise to spontaneous activity.

The discovery of the cellular mechanism underlying diastolic depolarization and driving pacemaker activity and control of heart rate has been the major achievement of the early research of the author.

In the late '70s, working in Denis Noble's laboratory in Orford with Hilary Brown and Susan Noble, the author described for the first time the cardiac so called “pacemaker” current, a large inward current which slowly activated on hyperpolarization within the range of diastolic voltages. The current had very atypical biophysical properties, since no other known current at the time had similar features, and was dubbed “funny” (I_f) for this reason. These features were, however, perfectly suited for generating the diastolic depolarization phase of the action potential of pacemaker cells, hence spontaneous activity. So, I_f could be a real “pacemaker” current! A second finding made during the same study was even more striking: I_f was increased by adrenaline, and could therefore be the current responsible for the acceleration of rate during sympathetic stimulation.

These were breakthrough findings which identified what appeared to be the long sought cellular mechanism able to induce spontaneous activity in pacemaker cells. According to this mechanism, pacemaking was generated by activation of the funny current at the end of an action potential, which initiated diastolic depolarization; also, the funny current controlled the rate of diastolic depolarization, hence the heart rate, and was responsible for frequency acceleration during adrenergic stimulation.

These first basic findings were published in 1979 in a Nature paper, and were followed by several studies in the following years. Many more data were collected by the author and by other laboratories on the properties of the funny current which further confirmed its role in the generation of cardiac pacemaking and in the control of rate. Some of the most relevant findings are outlined below.

In 1981, a major advance in the understanding of pacemaking was the reinterpretation of the pacemaker mechanism in another type of myocyte capable of spontaneous activity, the Purkinje fibres of conduction tissue. The pacemaker mechanism thought at the time to operate in these cells was the decay of a potassium current, the so called I_{K2} current, occurring during diastole. This theory was well established and universally accepted by the scientific community. In two

companion papers in the Journal of Physiology, the author showed that I_{K2} , previously interpreted as a K^+ current, was instead a disguised funny current, and that the two pacemaker mechanisms in SAN cells and Purkinje myocytes were therefore not different but just the same, mediated in both cases by activation of the inward funny current during diastole. This result allowed for the first time an integrated view of pacemaking in the heart. A theoretical model incorporating these and other experimental data was developed in collaboration with Denis Noble. This model allowed the reconstruction of spontaneous action potentials and represented the paradigm from which subsequent cellular models of the heart were developed.

The first single-channel recording of I_f was reported by the author in 1986 in a Nature paper. This was a particularly demanding achievement because of the very small single-channel conductance (about 1 pS), today still among the smallest single-channel recordings ever published. This difficulty is reflected by the fact that only 20 years later have similar recordings been made by another laboratory, which fully confirm the 1986 results.

Another important result obtained in the mid '80s concerns the vagal modulation of heart rate. Until the late '80s, the generally accepted interpretation of the action of the vagus nerve on rate was that parasympathetic-induced slowing is due to activation of an acetylcholine-dependent K^+ current in pacemaker cells. However, the existence of a pacemaker mechanism based on funny channels raised the question whether this latter mechanism could also participate in the vagal control of rate. In a series of papers in 1987-1989 from the author's lab, it was found that acetylcholine had a strong inhibitory action on the funny current, according to a mechanism opposite to that exerted by noradrenaline. These findings challenged the established view of a K^+ permeability increase as the cellular process underlying vagal control of rate. Indeed, the author and collaborators showed in a 1989 paper published in Science that the funny current inhibition, and not the K^+ -conductance activation, was responsible for the slowing of pacemaker rhythm at low acetylcholine concentrations.

In the early '90s, in a publication in Nature the author demonstrated for the first time the action of the intracellular second-messenger cAMP on funny channels. This molecule acted by direct binding to the channel protein, and not by a phosphorylation process. Activation by cAMP represented the mechanism responsible for I_f increase by sympathetic stimulation, and for I_f inhibition by parasympathetic stimulation. An important consequence of these findings is that they led to an integrated view of the entire process by which the autonomic nervous system modulates heart rate by means of the funny current. In brief, sympathetic stimulation leads to increased intracellular levels of cAMP, a consequent increase of the funny current, and therefore to an increased slope of diastolic depolarisation and rate acceleration; conversely, parasympathetic stimulation leads to exactly the opposite set of events and therefore to rate slowing.

These fundamental early discoveries, integrated by other data such as the cloning of the molecular correlates of native funny channels (the HCN channels, for Hyperpolarization-activated, Cyclic Nucleotide-gated), have eventually led to the development of major clinically-relevant applications.

1. Application to the genetics of cardiac rhythm disorders. The author's lab has shown that a form of asymptomatic sinus bradycardia, found in a large Italian family, is associated with a point mutation of HCN4, the HCN isoform most expressed in the SAN. The mutation reduces I_f during diastole, and therefore slows spontaneous frequency and generates bradycardia. This result is important in that it may represent a specific case of a broader mechanism for rhythm disturbances based on constitutive alterations of funny channels. Other rhythm disturbances caused by HCN4 mutations have indeed been reported by other laboratories, and more are likely to be found with further investigation.

2. Application to the field of "biological pacemakers". These are autorhythmic cellular substrates able to induce or control pacemaker activity, which may eventually replace the electronic pacemakers used today. These new biological devices are based upon the induction of pacemaker

function in silent cardiac tissue by the transfer of funny (or HCN) channels. This can be achieved by means of viral transfection or by transfer of cells engineered to overexpress HCN channels, or expressing funny channels constitutively. The author's laboratory has recently shown the isolation from mouse Embryonic Stem cells of a non-teratogenic population of cardiac precursors able to mature and form a fully functional pacemaker-like tissue (Scavone et al., 2013).

3. Application to pharmacological control of heart rate. This is the most important application of the concept of funny channel-based pacemaking, since it has led to the development of a therapeutic tool now commercially available for the cure of specific cardiac diseases.

The beneficial effect of heart rate slowing in cardiac diseases such as angina, ischaemic heart disease, heart failure is well known; also known is the association between high resting heart rate and cardiovascular or all-cause mortality. Presently used therapies with beta-antagonists and calcium blockers ameliorate mortality risk in part because of their heart rate-slowing effects. However, these drugs affect other cardiovascular and non-cardiovascular parameters and may also have adverse side-effects (for example a reduced inotropim).

Since funny channels have a basic role in heart rate modulation, they clearly represent an important target for the development of drugs aimed to specifically control heart rate, without complicating side effects. Several drugs acting on funny channels have indeed been developed by drug companies in the last two decades, with the aim of reducing heart rate specifically. Among them ivabradine, developed by Servier, is the only drug having passed all clinical tests. The author's laboratory has clarified some molecular aspects of the mechanism of action of ivabradine on funny-channels and consequent heart rate-reducing effect. These results provide a detailed explanation for the "use-dependence" of ivabradine, a clinically very useful property according to which high rates are affected more vigorously than slow rates.

Ivabradine is available with the commercial name of Procoralan, and is presently prescribed against chronic *angina pectoris* and heart failure. Several large trials have confirmed the clinical efficiency of ivabradine in reducing morbidity/mortality of coronary heart disease and systolic heart failure patients (for example BEAUTIFUL and SHIFIT).

In summary, the discovery of the funny current and its role in the generation of spontaneous activity and control of heart rate was an important achievement in the understanding of the basic physiology of the heart, and has also resulted more recently in the development of important clinical applications.