Centre of Excellence: The Institute of Cardiology at the Università Cattolica del Sacro Cuore, Rome, Italy

Starting From and Coming Back to the Patient, and Not Blindly Accepting the Accepted

Filippo Crea, MD, FESC, FACC, director of The Institute of Cardiology at the Università Cattolica del Sacro Cuore, Rome, Italy, explains to Judy Ozkan, BA, how the design and philosophies of the institute have led to an international reputation for high-profile clinical research.

Many European universities can trace their histories back through the centuries and have seen the development of medicine from a rudimentary science to its current state. Italy’s Università Cattolica del Sacro Cuore represents a relatively recent arrival on the scene. Founded in Milan in 1920 by a group of important religious and cultural figures, the university teaching hospital and medical school came into existence in Rome in the 1960s. The University “Policlinico Agostino Gemelli” took its name in honour of one of the founding fathers, a priest and graduate of medicine, who had dreamed of opening a medical school within the Catholic University. The first doctors graduated in 1967, and 20 years later, the “Policlinico” established the Institute of Cardiology.

What the institute lacks in history, it compensates for in its clinical research track record and unique approach to solving some of the most puzzling issues in cardiology. It has become well known among the scientific community for its contributions to research.

Director Filippo Crea, MD, FESC, FACC, himself only the third person to head up the institute, with a total publication record of more than 400 articles to date and more than 40 in the past year, believes that the institute’s relative newness on the scene has given it an advantage because the institute has avoided having to uproot itself physically, as many other medical schools and hospitals have had to do in order to modernise their premises and facilities.

The Catholic University, a privately funded university, operates as a charity. However, medical roles receive financing from the Italian government, and the state appoints teaching staff. Everyone has access to the services and facilities at the hospital and within the institute, and the national healthcare system pays for the patients. Professor Crea says the charitable status of the university has its advantages in offering an alternative to state funding, and this has helped the institute to grow and establish a good national and international reputation as a place of learning and research.

The late Ugo Manzoli, MD, established the Institute of Cardiology more than 25 years ago; Manzoli’s premature death led to the appointment in 1991 of Attilio Maseri, MD, FACC, FESC, an incisive clinical investigator with a reputation for innovation and for challenging the accepted wisdom of the day. Professor Crea took over in 2002 and likes to acknowledge the great legacy he inherited from Professor Maseri, his mentor, with whom he also worked.

On other pages...

Spotlight: Juhani Knuuti, MD, PhD, FESC
Professor Knuuti is director of the Turku Positron Emission Tomography Centre, Turku, Finland, chair of the European Society of Cardiology Working Group on Nuclear Cardiology and Cardiac Computed Tomography, and inventor of 2 cardiac imaging techniques.

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at Hammersmith Hospital in London, United Kingdom. Many of the research strands initiated by Professor Maseri have remained active since his departure from the institute, and the team continues to reap the benefits of the innovations in research and patient management that stem from his early work.

Seven Associate Professors, 23 Assistant Professors, 26 Trainees, and 12 PhD Students

Luigi Biasucci, MD, FESC, FACC, heads up studies on biomarkers and, with Giovanna Liuzzo, MD, PhD, takes charge of studies on inflammatory mechanisms of acute coronary syndromes. Felicita Andreotti, MD, PhD, FESC, oversees studies on thrombotic mechanisms of acute coronary syndrome. Gaetano Lanza, MD, FESC, and Leonardo Galiuto, MD, PhD, FACC, have responsibility for studies on coronary microvascular dysfunction.

Francesco Burzotta, MD, PhD, and Giampaolo Niccoli, MD, PhD, take charge of studies in the catheterisation laboratory, performing more than 3000 procedures annually, and Antonio Dello Russo, MD, PhD, has responsibility for the electrophysiology laboratory, which performs more than 3000 procedures annually.

Maurizio Pieroni, MD, PhD, and Antonio Maria Leone, MD, PhD, have led more recent studies into cardiomyopathies and stem cells. Much of the ongoing research focuses on mechanisms of coronary instability and on the pathophysiology of coronary microcirculation. Other areas of interest involve the mechanisms of cardiomyopathies and the pathophysiology of stem cells.

A Strong National and International Reputation for High-Profile Clinical Research

The guiding philosophy of the institute emphasises not blindly accepting the accepted. Professor Crea points to discoveries such as the role that inflammation plays in acute coronary syndromes as a benefit of this type of thinking. “Previously, all the emphasis had been on lipids and mechanisms of thrombus formation, which are also important, but the important role played by inflammatory cells was totally, entirely neglected.” The studies carried out in the institute and inspired by Professor Maseri established for the first time that inflammation played a critical role in causing coronary instability and affected outcome.1

Going with the conventional flow, therefore, does not represent a governing principle at the institute, according to Professor Crea, “because we believe that biology is extremely complex, and we have to humbly accept this complexity. For instance, in the case of myocardial infarction, it is likely that the causes are instead multiple, and in order to develop really personalised forms of treatment, we have to identify these different causes. We really need to go from syndromes to specific disease mechanisms.”

Another example of the institute’s success in finding answers by exploring less well-trodden paths lies in the area of the pathophysiology of coronary microcirculation. This also represents a long-standing investigation that started more than a decade ago when the focus was on large epicardial vessels. By looking elsewhere to the smaller invisible vessels, researchers at the institute demonstrated, across a number of years, how coronary microvascular dysfunction plays an important role in many cardiac diseases.2

A tradition of studies in the pathology of cardiomyopathies and diseases affecting the myocardium has also paid off. Carrying out more than 100 cardiac biopsies every year, Professor Crea says, is helping to clarify mechanisms of disease in patients with cardiomyopathies.

Newer research into stem cells has demonstrated how, after a myocardial infarction, stem-cell mobilisation limits the damage. The results of this research appeared in a published study that established the importance of individual bone marrow response in determining future patient outcome.3

Professor Crea believes that the institute’s high-profile clinical research has helped establish a strong national and international reputation, which has proved instrumental in attracting talented young doctors and scientists who have made “La Cattolica” their university of choice.

One Hundred and Forty-Five Beds, More Than 5000 Admissions per Year, and an “All-Under-One-Roof” Approach

“Policlinico Gemelli” has more than 2000 beds and more than 200,000 admissions per year, with 145 beds and more than 5000 admissions per year in cardiology. The institute has basic, invasive, and noninvasive laboratories run by doctors and biologists, as well as wards and outpatient facilities. The basic laboratories have all the necessary equipment for cytofluorimetry, confocal microscopy, cell cultures, molecular biology techniques including Southern and Western blotting, and reverse transcription polymerase chain reaction.
A practical advantage at the institute involves the layout, which allows all activities to take place under one roof. Basic research laboratories, invasive and noninvasive diagnostic laboratories, operating rooms, and patient beds all occupy the same floor, with Professor Crea coordinating the clinical and basic laboratory activities. This arrangement fits in with the institute’s belief that to be successful, one must start from the patient and come back to the patient. “We start from a clinical question and use our basic research laboratories in order to give answers under the same roof, and this sort of coordination is extremely important in making steps forward.”

Professor Crea gives an example of benefits of the “all under one roof” approach involving discarded balloons from angioplasty procedures. Rather than disposing of balloons as waste at the end of procedures, the team decided to wash them and found neutrophils, which remained on the surface. They found that neutrophils became activated only in patients with an acute coronary syndrome and with the last anginal episodes within 48 hours of sampling. This study proved that a transient local neutrophil activation plays a key role in the early phases of coronary instability.

Although Professor Crea likes to make sure the institute has the latest tools, he feels satisfied that the research portfolio remains focused on the right areas. “More than expanding our research interests, I would like to go deeper into what we are already doing, particularly in the areas of mechanisms of coronary instability and microvascular dysfunction because the challenge to go from syndromes to specific disease mechanisms is a massive challenge.”

The approach to meeting this massive challenge involves putting aside the conventional teaching of the day. Professor Crea explains, “We believe that, in general, there is a tendency to lump together different types of patients because they have a common phenotype. Myocardial infarction is a good example of this approach, as we tend to believe that its causes are the same in all patients. This means that if we find a treatment that works on the average, then this treatment is to be given to all patients with that particular phenotype.”

This conviction and passion has driven many of the remarkable results the institute has delivered during the past decade, but it does not form the whole story, and it explains only part of the institute’s success. Professor Crea regards a balance between good patient care, teaching, and research as critical for any good institution. The dynamic created by getting these 3 core elements right contributes to the success of an institution and helps it bear fruit.

**Funding Will Prove Crucial to the Institute’s Plans for Future Investment in Molecular Imaging**

Even though the institute is new and dynamic, Professor Crea faces on a daily basis the old problem of funding and budgeting for work, which grows ever more complex and expensive to carry out. The private status of the university means that although it provides space for basic laboratories, the director must find funding for filling the space with often very expensive equipment and facilities. Professor Crea accepts this as part and parcel of his job, and he considers himself no different from other directors of European institutes in feeling the pressure over budgets.

Funding will prove crucial to the institute’s plans for future investment in molecular imaging. He says, “This is an expensive area of research which has really developed in the past few years, and it’s important because although images are not the whole truth, we need to interpret them in order to put together the parcel.”

The approach of the institute does not involve going against conventional wisdom for the sake of it, but it stems from the need to deliver results and solutions to pressing clinical problems under the constraints of limited funds, time, and resources. “Throughout the world, there are examples of excellent basic research, which is too far away, however, from clinical needs. Of course, basic research has to be free, but we are living in a world where resources are less and less, which means that clinical research should be more focused on patient care.”
Passing on Knowledge and Learning

One of the most appealing aspects of working at the institute involves teaching and the chance it gives to pass on knowledge to future generations. Professor Crea says that the backflow of ideas and suggestions from students can benefit everyone. Photograph courtesy of Professor Crea.

Professor Crea with students. An appealing aspect of working at the institute involves teaching and the chance it gives to pass on knowledge to future generations. Professor Crea says that the backflow of ideas and suggestions from students can benefit everyone. Photograph courtesy of Professor Crea.

References


Judy Ozkan is a freelance medical journalist.
PET, and, later, magnetic resonance imaging and x-ray computed tomography (CT) in a unit that gained a strong reputation in advanced cardiovascular imaging. He says, “The field was quite immature at that time—especially cardiovascular PET imaging—and I could establish my own research programme, and research funding was very stable.”

Following on from his initial interest in cardiac disorders, Knuuti found himself focusing on spatial structures and developing his technical skills. He comments, “I became fascinated by echocardiography (especially colour Doppler imaging, which was really new in the mid-1980s) because I could see the pumping heart and the valves, etc, noninvasively. This led me to other imaging modalities, first to visualise myocardial perfusion, then to cardiac metabolism, and then to noninvasive visualisation of coronary arteries, and finally to hybrid imaging: putting more than one imaging modality together and ultimately being able to see both anatomy and function at the same time.”

**Director of the Finnish National Research Centre for Molecular Imaging**

In 1995, Knuuti became senior lecturer (associate professor) and, in 1996, director of the Turku PET Centre, the Finnish national research centre for molecular imaging, an up-to-date multimodality imaging facility with PET, CT, echocardiography, and magnetic resonance imaging, which employs more than 100 staff and researchers. It has this year gained the status of Centre of Excellence from the Academy of Finland, guaranteeing research funding amounting to $9 million during the next 6 years.

As PET Centre director, Professor Knuuti’s role consists of administration, scientific leadership, and clinical work, which mainly relates to cardiac CT and PET hybrid imaging. He also serves as a consultant at Turku Heart Centre and has a role at Turku University Hospital teaching medical students, residents, and specialists in cardiovascular imaging.

Professor Knuuti has won a number of special investigator awards for his work, and he concedes that he feels happiest during sabbatical periods when he can concentrate on data analysis and writing articles without administrative work. Most of the funding for his work comes through the research centre, via host organisations and industry to support scientific research, enabling his team to perform expensive imaging and procedures, or from foundations including the Academy of Finland.

Several people have helped shape Professor Knuuti’s career, including the head of imaging when he began his residency, Jaakko Hartiala, MD, PhD, and Uno Wegelius, MD, the director of the Turku PET Centre when Professor Knuuti started his research programme, who “gave unique freedom and amazing resources to young but enthusiastic investigators,” he says.

In research, Professor Knuuti has worked closely with endocrinologist Pirjo Nuutila, MD, PhD, in a collaboration that bridged cardiology and endocrinology and led to more than 100 joint publications, many of them related to the heart and diabetes mellitus.

Professor Knuuti also discusses cardiovascular imaging issues with colleagues and friends in the field including Jeroen Bax, MD, PhD, FESC, from Leiden, the Netherlands—whom he describes as “without question, the most productive scientist in cardiovascular imaging”—and Frank Bengel, MD, at Johns Hopkins Medical Institutions, Baltimore, Md, whom he regards as “outstanding in molecular imaging.” He adds, “These kinds of friends can give valuable scientific and professional feedback but also give honest opinions, and they can help a lot in fitting together demanding work and family life.”

Born in Kemi, Finland, in Lapland—a mere 60 miles from the polar circle—on April 8, 1960, Professor Knuuti now lives in the Turku region of southwest Finland. He is married, with 2 daughters aged 24 and 22, and 2 sons aged 11 and 5. Away from medicine, his main interest involves music; he enjoys playing keyboards and saxophone.

**Significant Breakthroughs at an Early Stage of His Research Career**

Professor Knuuti recalls 2 studies as particularly satisfying in that they enabled him to invent new techniques for cardiac imaging. He explains, “These were simple but novel solutions for the preparation of patients for imaging of myocardial viability. The first one was inventing the use of ’glucose–insulin clamping’ in preparation of patients, especially diabetic patients for FDG [fluorodeoxyglucose] PET imaging for myocardial viability. That was also my first publication.1 The second one was a simplified and more practical version of the patient preparation, with glucose insulin-clamping achieving excellent image quality by just giving 1 pill to the patient beforehand.2 I remember these studies as enjoyable because I was a very young and...
inexperienced researcher at that time and could still figure out such new innovations, which are nowadays established as standard procedures.”

“Good Science Does Not Need Large Populations but a Good Question”

Professor Knuuti regards as his most important work a study that aimed to understand the substrate metabolism in myocardial hibernation. “There were theories about what happens to glucose and FFA [free fatty acid] metabolism in the hibernating myocardium, and these were based on animal experiments,” he says. “However, myocardial hibernation in the human heart could be very different from that of experimental animal models. We managed to perform a very demanding study in patients with hibernating myocardium and could show that the hypothesis of rigid substrate switch towards glucose in hibernating myocardium was not true in the human heart. The unique issue in this study was that it enrolled only 7 patients, but it was published in Circulation. This shows that good science does not need large populations but a good question.”

Professor Knuuti also feels proud of the studies and publications he has conducted in subjects who have various risk factors for coronary artery disease. “I could demonstrate that healthy subjects with risk factors have subclinical abnormalities in coronary function, and we were able to demonstrate this by using noninvasive imaging,” he explains. And, in studies in patients with heart failure, he has managed to elucidate the metabolic changes in a failing heart and to assess the potential of metabolic modulation in the treatment of heart failure.

Professor Knuuti serves as chair of the European Society of Cardiology, Working Group on Nuclear Cardiology and Cardiac CT, and as coordinator of imaging on the European Society of Cardiology Congress Programme Committee. He played a key role in the recent International Conference of Nuclear Cardiology on the scientific committee and cochaired the programme committee in 2004 and 2005. In 2004, he served as congress president of the European Society of Nuclear Medicine Congress Helsinki 2004, and next year he will cochair the Ninth ICNC (International Conference of Noninvasive Cardiovascular Imaging—Nuclear Cardiology and Cardiac CT). He also sits on a number of editorial boards including that of the newly launched Circulation: Cardiovascular Imaging.

In the future, Professor Knuuti would like to extend his research into larger clinical populations. He says, “I am planning to start large-scale multimodality imaging studies in patients with suspected coronary heart disease. These studies aim to solve the role of noninvasive imaging in the diagnosis of CAD [coronary artery disease] and also to demonstrate whether imaging-guided therapy can influence the prognosis of the patients.” He believes that the technical developments in noninvasive imaging will further speed up, but he adds, “It is likely that technical development is faster than what doctors can really use because we have to show the value of new techniques before wider use.”

The future in cardiology and cardiac surgery, says Professor Knuuti, will see a move toward prevention of cardiovascular disease and more personalised medicine with expensive therapies. “In both areas,” he adds, “cardiovascular imaging may play a crucial role: in the early detection of disease and in selecting candidates for new therapies.”

For people wanting to follow careers in cardiology, Professor Knuuti advises, “Follow your heart, be persistent, and enjoy. Make your decisions based on interest, not because of money.”

References


Mark Nicholls is a freelance medical journalist.
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