Can you provide a brief overview of the research you are involved with at the University Medical Center Groningen?

Cardiogenetics can help the treatment of cardiomyopathies (eg. hypertrophic, dilated and arrhythmogenic cardiomyopathy) and primary electrical diseases (eg. Long QT syndrome, Brugada syndrome). It generally does not deal with complex diseases like coronary disease or heart failure, although genetic factors definitely play a role. We have focused our research on dilated and arrhythmogenic cardiomyopathy by performing genetic studies and deep cardiologic phenotyping in families and larger cohorts with these disorders, in order to establish genotype-phenotype relations and interactions.

What first drew you to work in the field of cardiogenetics?

The simple answer is that a retiring colleague asked me to take over the care for a large family with Long QT syndrome about 20 years ago. I have always been drawn to this type of patient care. I love to tease out and understand the mechanisms underlying cardiac diseases, and genetics is essential in this respect. Equally, I like the approach of counselling patients and families, establishing the risk of developing disease and intervening in the early stages. Finally, cardiogenetics is not some esoteric science; rather it encompasses all aspects of clinical cardiology (eg. electrophysiology, imaging, heart failure, pharmacology).

Inherited cardiomyopathies are associated with abnormalities in myocardial structure and function. To what extent are inherited cardiomyopathies heterogeneous?

This is an important issue. Inherited cardiomyopathies are highly heterogeneous, both in terms of genotype and phenotype. Mutations in one gene may cause several types of cardiomyopathy (eg. dilated and arrhythmogenic cardiomyopathy), and the phenotype can also be very diverse even within a single subgroup (eg. hypertrophic cardiomyopathy). This complexity is the reason that understanding these conditions is so challenging and interesting.

Could you outline the principal approaches you have employed to further current understanding of the underlying causes of inherited cardiomyopathies?

We have developed several mouse models of inherited cardiomyopathies by introducing a genetic mutation in these mice that we had previously identified in patients. This enables us to study the disease processes in-depth, including the role of environmental stressors (eg. vigorous exercise) and to test pharmacologic interventions. In addition, we are currently using inducible pluripotent stem cells to recreate the phenotype on a cellular level.

Founder mutations are a frequent cause of inherited cardiomyopathies in the Netherlands. What are founder mutations, and how does their identification present a unique opportunity to investigate additional disease factors?

A founder mutation is a mutation in the DNA originating from a founder of a distinct population, which has passed down to other
generations. In the Netherlands, we have several founder mutations that cause inherited cardiomyopathies. This is due to the fact that the Dutch population is relatively immobile and also due to the high level of cardiogenetic care, which enhances the identification of founder mutations. These mutations provide a unique opportunity to study environmental and genetic disease modifiers.

How has cardiogenetic care improved during the last two decades?

Cardiogenetic care has greatly improved our understanding of several cardiac diseases. This has proved essential for the understanding and acceptance of cardiomyopathies by both patients and families. Also, risk stratification has been enhanced and therapeutic approaches have become increasingly rational.

What are the most challenging obstacles you come across in your clinical work?

A definite obstacle is the fact that genetics is becoming complicated. In the early days of the field, we analysed one gene at the time and stopped testing for mutations after three or four of the most commonly involved genes. This often resulted in missing key mutations in other important genes. Today, we conduct next-generation sequencing allowing simultaneous testing of a batch of 60 genes. As a result, we often end up with a multitude of DNA variants of uncertain significance, which can be confusing, albeit more accurate. Another key roadblock is that the therapeutic capability to react to this research is lagging behind.

Why is tight collaboration important between the different factors involved in inherited cardiomyopathies for the study of its pathophysiology?

By its very nature cardiogenetics entails collaboration between cardiologists and clinical geneticists. However, to cover the full spectrum our team also comprises a molecular biologist and a pathologist. Moreover, experimental cardiology is also involved. This interdisciplinary collaboration is necessary to deal with all aspects of inherited cardiomyopathies, in terms of research, patient care and treatment.

Furthermore, how is such tight collaboration between Dutch cardiologists facilitated?

Cardiology in general, and cardiogenetics in particular, are tightly organised in the Netherlands. For instance, we have: Interuniversity Cardiology Institute Netherlands (www.icin.nl) with the Inherited Heart Diseases Working Group, Gencor (www.gencor.nl), a national cardiogenetics database; and Durrer Center (www.durrercenter.nl), a national biobanking facility.

The Netherlands has a revered history of scientists who have made a significant contribution to improving cardiology. What has been your greatest achievement?

I am one the founding cardiologists of cardiogenetics and the first professor of cardiogenetics. I am proud to see that cardiogenetics is now firmly established in the clinical arena and also that cardiogenetics in the Netherlands is a ‘role model’ worldwide.
HEART DISEASE CONTINUES to be a leading cause of death in the developed world. However, identifying the genetic factors that predispose individuals to heart disease could hold an important key for preventing the condition. Research in the field of cardiogenetics is dedicated to identifying, screening and treating cardiomyopathies – a heterogeneous group of heart muscle disorders – that may arise from gene mutations. It has evolved along with genetic analysis tools, allowing for a far more nuanced yet broad approach to tackling heart disease. A significant proportion of cardiomyopathies are ‘inherited’, developing from mutations in genes that are essential to the proper function of heart muscle.

The variety of inherited cardiomyopathies is diverse; however, there are three main forms. Hypertrophic cardiomyopathy (HCM) is the thickening of the left ventricle, often caused by mutation in any one of the genes related to the contractile apparatus of the heart muscle. Mutations in the same genes and a host of other genes, however, can also lead to dilated cardiomyopathy (DCM), which is a weakening and dilation of the left ventricle, resulting in contractile dysfunction. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a different subtype that causes weakening of the heart through mutations in the genes responsible for linking the muscle cells together. The result of such weakening is an irregular heartbeat. All of these cardiomyopathies weaken heart muscle and greatly increase the chances of sudden cardiac death in those affected.

Working to advance cardiogenetics is Professor Maarten van den Berg of the University Medical Center Groningen, Netherlands, who has pursued innovative research and patient care in the field for over 20 years. van den Berg and his colleagues take an interdisciplinary approach to their work, examining the interplay between genetics and cardiomyopathies at several different levels. Indeed, the Netherlands has a very well connected network involved in research that allows cardiogeneticists to share a wide range of resources (See: ‘Heart to heart’). This essence of collaboration is instrumental to the advancement of research in the field.

GENETIC CLUES
The team’s initial work involves identifying genes that may be involved in the onset of cardiomyopathy. Taking advantage of the latest techniques, van den Berg and his colleagues are able to screen for new gene candidates in patients with cardiomyopathies. These candidates can then be sequenced and compared with the normal gene sequence. This has allowed the researchers to identify novel genes not previously associated with cardiomyopathies.

A recent discovery for the team has been the implication of a mutated copy of the phospholamban gene in 10-15 per cent of Dutch patients with ARVC or DCM. Phospholamban is a membrane protein of heart muscle cells that regulates the calcium pumps essential to muscle function. van den Berg has identified a deletion mutation in the gene that appears to alter the normal functioning of phospholamban. Given that this same mutation is found in all the cases involving the gene, it is seen to be a ‘founder’ mutation. It is important to identify such founder mutations as they can be instrumental in the early identification of cardiomyopathies and therefore in risk assessment for the patient.

DEGREES OF DISEASE
The presence of a founder mutation does not reveal the severity of the cardiomyopathy. In order to learn more about how and when symptoms will manifest in the patient, van den Berg must establish the phenotype of these mutations. This involves taking into account a wide range of factors capable of changing the severity of the disease. Gene expression varies between individuals and therefore it is important to determine the role of environmental factors in the phenotype, for instance, hypertension, excessive physical exertion, pregnancy and use of toxic substances.

A good PHORECAST
Cardiogeneticists at the University of Groningen, Netherlands, are developing a way to prevent certain cardiomyopathies through the PHORECAST project, resulting in world-leading research.
HEART TO HEART

Collaboration has been the key to the success of cardiogenetics in the Netherlands. There are multiple facilities through which patient information, samples and data can be shared and accessed by all. This level of collaboration has enabled the country to become a world leader in cardiogenetics, as van den Berg explains: “Cardiogenetics in the Netherlands is very advanced, both scientifically and in terms of patient care, which in turn is a result of this strong national collaboration”.

The Netherlands has several well-established centres that facilitate collaboration between cardiologists across the country. One such establishment is the Durrer Center, a national biobanking facility run by the Netherlands Heart Institute that stores high-quality patient and cell samples. Principal investigators, such as van den Berg, are able to store useful biological data in the cryogenic facilities. These samples are available to other users of the Center, allowing for straightforward data sharing between experts nationwide. The Center provides additional resources to researchers, which include logistical help for the collection and distribution of samples, as well as research support, including bioinformatics and molecular biology services.

At the University of Groningen, van den Berg and several colleagues have been instrumental in the creation of the arrhythmogenic right ventricular cardiomyopathy (ARVC) genetic variants database. The concept behind the software is to enable all cardiogenetics research groups to share genetic and clinical data pertaining to ARVC. This provides a valuable research and educational resource and clearly shows the spirit of collaboration in the field.

Similar in scale to the Durrer Center is G-CURE, a company linked to the Department of Cardiology at the University Medical Center Groningen, specialising in the aiding of cardiovascular clinical trials for researchers in the country. It offers development plans, preclinical data generation and different clinical trial phases. Having facilities and services readily available means that Dutch cardiologists and cardiogeneticists are able to transform their research into real patient benefit.

POSITIVES FOR PATIENTS

Another factor being investigated by van den Berg is the location of patients and families containing founder mutations. Through a nationwide investigation of DCM and ARVC patients in the Netherlands, it was found that most of those with a mutation were from the eastern portion of the Friesland region. Very few mutations were found in the southern regions of the country. This stark contrast has led van den Berg to hypothesise that similar mutations found in the German, American and Canadian populations are most likely due to immigration from this region over the last 300 years.

It is important to investigate the full range of factors surrounding cardiomyopathies, in order to provide better treatment. Indeed, this is prime motivation for the research, as van den Berg states: “Our team is heavily involved in patient care and treatment, including family screening and identification of pre-symptomatic mutation-carriers. In fact, the University Medical Center is primarily meant for patient care and treatment”. The fruits of this approach can be seen in the notable successes of the work. For example, van den Berg and his colleagues have demonstrated that peripartum cardiomyopathy can be an initial stage in developing DCM that has been inherited.

FORECASTING THE FUTURE

In order to further explore his recent work in genetics, van den Berg continues his collaborations and investigations into the phenotypic variation of patients. In this regard, van den Berg is leading the Intervention PHoospholamban RELated Cardiomyopathy STody (i-PHORECAST), which aims to identify and prevent both DCM and ARVC through the administration of eplerenone, a known anti-fibrotic agent. van den Berg and his colleagues have hypothesised that eplerenone will reduce the disease progression by largely nullifying the effect of the phospholamban founder mutation. He elaborates: “This is a proof-of-principle study. I hope to show that treatment of presymptomatic carriers will retard underlying disease progression and postpone overt disease. This would be really very innovative in establishing a preventive approach in patients carrying a genetic risk of developing a serious disease”.

It is clear from studies such as i-PHORECAST that cardiogenetics holds both scientific and tangible patient benefits. Indeed, an important patient benefit has been the impact of this research on the ability of cardiologists to accurately assess the risk to a particular patient. By investigating inherited cardiomyopathies utilising this approach, van den Berg and his colleagues across the Netherlands are providing hope to the many families affected by serious heart conditions.