

# De kracht van het begrijpen

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Prof.Dr. M.E. Rubio Gozalbo

Faculty of Health, Medicine and Life Sciences

# The power of understanding

*μεταβολισμός*

# The power of understanding

Inaugural lecture

Pronounced at the acceptance

Of the Chair *Inborn errors of metabolism with focus on galactosemia*

Maastricht University

January 11, 2019

Prof. Dr. M.E. Rubio Gozalbo

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*Madam Rector Magnificus*

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Acknowledgments

***Madam Rector Magnificus, dear colleagues and students, dear friends and family, highly esteemed listeners,***

Today I am pleased to accept the chair *Inborn metabolic diseases with focus on galactosemia*.

Imagine that you have just become the proud parent of a beautiful child. You dream of a wonderful future for your baby, but after a few days the baby becomes ill and then it becomes increasingly ill. Then you receive the news that your child has a hereditary metabolic disease. Your hopes and dreams are shattered. What do I do now? What is metabolism? What is this disease? What can be done about it? What impact does this have on the life of my child, and on our family?

## **Hereditary metabolic diseases in general and galactosemia in particular**

Let's start by understanding what metabolism is. The word metabolism (from the Greek *μεταβολισμός* "metabolismos") means change or transformation. It is the whole of biochemical processes that take place in our cells from which different chemical compounds originate that we call metabolites.

In the cell, many chemical processes take place at the same time. This can be compared to a small but highly advanced and efficient chemical plant. This requires a tight coordination and regulation of all these processes in the different structures in the cell, where these processes take place. DNA plays a crucial role in this coordination, because it encodes all proteins that are involved in the chemical processes and from which the cell structures are made of. The most important processes which take place in the cell are composition and refinement, transport, energy production and finally the breakdown of the building blocks of the cell. In essence, there are four types of building blocks from which all living organisms are made: amino acids (proteins), nucleotides (DNA), carbohydrates and fats (both energy).

Almost every chemical reaction in the cell needs an enzyme to allow the chemical reaction to take place quickly enough so that we can remain alive. The sequence of steps in which a chemical substance, with the help of enzymes, is converted into other chemical substances, is what we call a metabolic pathway. Hereditary metabolic diseases are caused by abnormalities in these metabolic pathways due to errors in the DNA.

There are a lot of metabolic pathways, all with many steps. You might wonder: why is it so complicated? Many steps mean a lot of intermediates (metabolites), which are also needed for other metabolic pathways. Many steps also mean that the cell does not use more than it is necessary, that there is no waste. An error can occur in each step, which is why we must deal with many different errors that can lead to a variety of hereditary metabolic diseases, hundreds of them, with widely differing forms of expression and severity.

Every year, 800 children are born in The Netherlands with one of these disorders. There are many families with children with hereditary metabolic diseases. For some diseases, there is still no treatment and many children die due to complications. For other diseases, there is a treatment, but this treatment is not able to completely prevent the symptoms of the disease, as a result of which patients, their families and our society suffer the heavy consequences. The care for these diseases is concentrated in University Medical Centers (UMC) because it requires special expertise, knowledge and infrastructure.

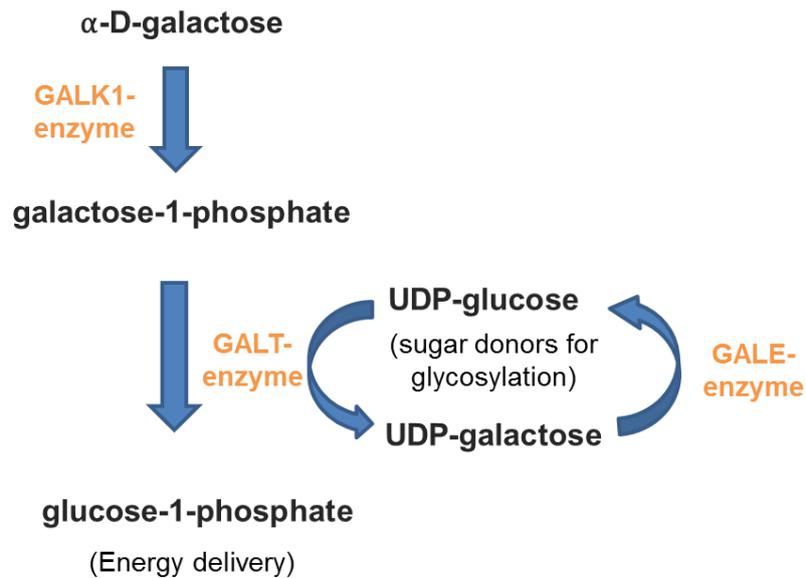
**An inherited metabolic disease has a great impact!!**

## **Understanding errors in hereditary metabolism**

An example of a metabolic pathway is galactose metabolism. Galactose is a sugar present in many nutrients, but especially in animal milk in the form of lactose or milk sugar. Once in the cell, galactose is converted into energy in several steps and in other substances that are necessary for complex molecules. Errors in the DNA during the different steps, cause the group of diseases called galactosemia. The most common is classic galactosemia. In this disease, an error occurs in the piece of DNA that contains the recipe for making the GALT enzyme. But, how was this disease discovered?

The first description was made in 1908 (Von Reuss). A newborn was described with the acute picture of classic galactosemia: nutritional problems, poor growth, vomiting, jaundice, irritability, enlarged liver and cataracts, among other things. In the next decade, it was documented the presence of excess galactose in the urine of an also affected baby (Göppert 1917). In 1935, it was described the case of an infant with high level of galactose in blood and urine (blood: hypergalactosemia and urine: galactosuria) which responded well to a diet with lactose restriction (no breastfeeding/animal milk) (Mason and Turner 1935). Many years later, in 1956, it was discovered that galactose 1-phosphate was increased in the red blood cells of these patients (Schwarz et al.) and GALT was identified as the underlying enzyme that did not work well (Isselbacher et al. 1956). It was not until 1988 that the *GALT* gene was identified (Reichardt and Berg 1988).

But what exactly happens with galactose in our cells? For the understanding of metabolism, we always must go back to biochemistry. It was Federico Leloir who clarified the steps in this route. He was a medical student who wanted to better understand physiology and began studying biochemistry. His work has taught us that the sugar galactose is first converted into galactose-1-phosphate and then in a ping-pong reaction is converted to glucose-1-phosphate and UDP-galactose by means of UDP-glucose. While glucose-1-phosphate is used as a source of energy, UDP-galactose and UDP-glucose are sugar donors for other reactions.



*Figure 1: Galactose metabolic pathway: GALK1-, GALT-, GALE-enzyme representation. GALK1: galactokinase, GALT: galactose 1-phosphate uridylyltransferase, GALE: UDP-galactose 4-epimerase.*

With this knowledge, we can understand why newborns with errors in this metabolic pathway develop high levels of galactose in blood and urine. The enormous amount of galactose present in breast milk or bottle feeding cannot be processed and it is increased body fluids. There is too much of certain substances and a shortage of other ones and this leads to the symptoms of the disease. By adjusting the diet, the neonatal clinical picture clears up and the children do well until they are slightly older. Between 1970 and 1990 it became increasingly clear that diet solves the serious clinical picture of the newborn, but it does not prevent the appearance of complications. Unfortunately, despite their diet, most patients develop complications that especially affect the brain and ovaries, resulting in cognitive, behavioral and neurologic problems, in both men and women (85%), and subfertility in women (80%). In addition, patients are at risk of suffering reduced bone density (26%) (Source: International Galactosemia Patient Registry).

This means that new and better treatments are needed. This requires more understanding about the course and mechanisms of the disease. As our understanding of these diseases increases, we can develop better diagnostic tools and investigate new therapies aimed to improve the future of the patients and their families. We can start treating patients better and treat what was untreatable. However, this is a process that depends strongly on collaboration, open science and available resources.

**We can start treating patients better and treat what was untreatable.**

## Understanding the importance of collaboration

In the past, clinicians and researchers worked mainly from their own perspective. Nowadays, the boundaries between the various disciplines are disappearing. Integrated theories about what the relationship is at different levels between processes and how they influence each other, can only be achieved by joining forces and multidisciplinary and interdisciplinary approaches. Understanding in that sense is a requirement for progress. Collaboration requires an open attitude, trust, transparency, not to envy each other, parking the egos somewhere where they do not stand in the way for collaboration and keeping in mind the common goal. This is what we must continue to realize and transfer to the new generations. Joining forces is not a choice, but a requirement.

Based on the conviction of the importance of collaboration, in 2009 I started exploring the possibilities of establishing an international galactosemia network. In 2009 and 2011, I organized the first and second international galactosemia workshop at the Medical Center of Maastricht University, with subsidies from the Dutch Organization for Scientific Research (NWO), and in 2012 the galactosemia network (GalNet) was established.

In the meantime, professionals from 20 different countries are participating. GalNet was founded with support of the Dutch and European Galactosemia Patient Associations. Networks of professionals are crucial but require the networks of patients. The existence of the Dutch Galactosemia Association, under the leadership of Jeroen van Bruggen and Karen 't Hoofd, and the European Galactosemia Association with Jeroen and Maaïke van Kempen as president and vice president, is very important for the treatment, monitoring and research of galactosemia.

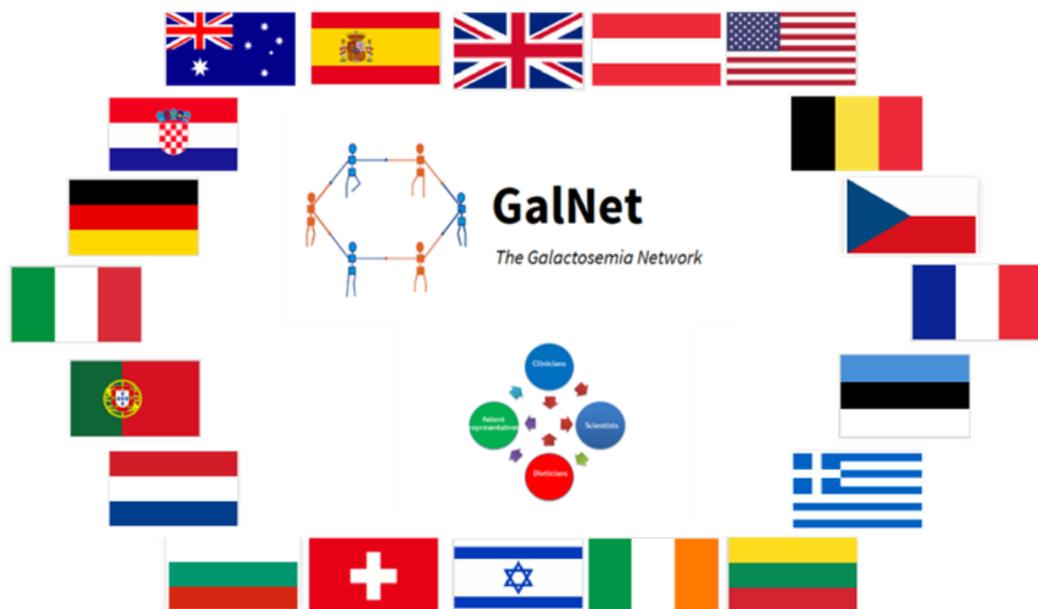


Figure 2: Galactosemia Network (GalNet).

GalNet focuses on the promotion of education, research, diagnosis, treatment and aftercare of patients with galactosemia through close cooperation between clinicians, researchers and nutritionists, and patient organizations. Since the formation, we have achieved together several important goals and we are fully engaged on the road to achieve optimum care and treatment. What is the power of such a network? What can we do together? Let me give a few examples.

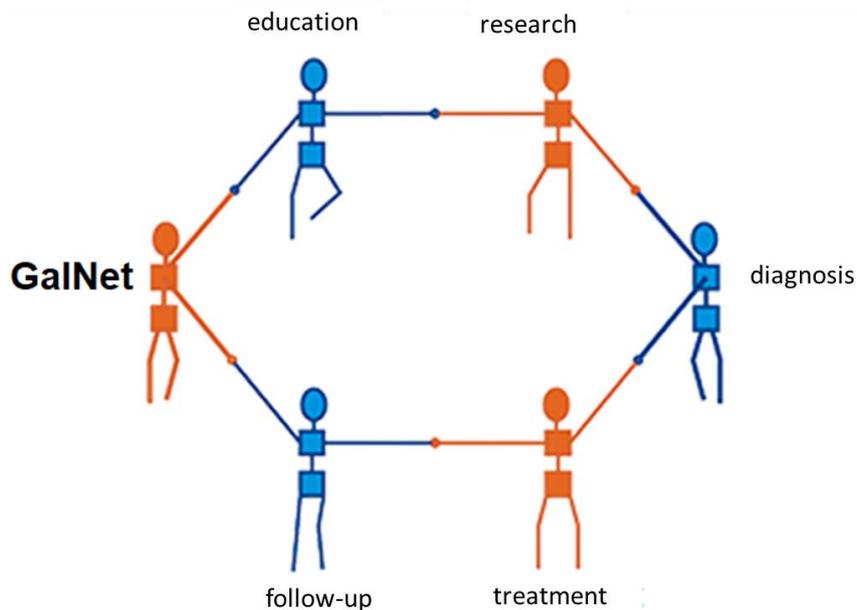


Figure 3: GalNet focuses on education, research, diagnosis, treatment and follow-up.

In 2017, guidelines for diagnosis, treatment and follow-up of patients with the most common form of galactosemia were published under the inspiring guidance of my colleague Dr. Annet Bosch of Amsterdam UMC. The next step is that these guidelines are known and used among the involved professionals and patients. Only publishing is not enough. We are now working on a strategy for dissemination and implementation led by a colleague from Denver and the vice president of the European Galactosemia Association Maaïke van Kempen.

In 2019 the natural course of classic galactosemia based on data from 509 patients from 32 centers in 15 different countries from the international patient registry that is coordinated by me is going to be published. For a rare disease, these are big numbers. The *conditio sine qua non* for the development of new treatments is to know the natural course of a disease based on a large number of data.

In addition, we are fully engaged in the development of new therapies for galactosemia using the newest insights and technologies in our field. With this knowledge and resources, and together with other leading metabolic centers, we can move forward to obtain better treatments. Important recent contributions from our MUMC+ galactosemic research team have been 1- the development of a zebra fish animal model for this disease and 2- the identification of the neuronal networks related to the cognitive problems of these patients.

How might a new treatment look like? Let me give a few examples of promising approaches we are currently working on. The first one is the correction of the DNA error using mRNA therapy. This is a form of gene therapy, in which instead of directly repairing the error, the correct recipe is offered to the cell so that it can produce the specific enzyme. mRNA, or messenger RNA, is RNA that has been transcribed nucleotide by nucleotide from a gene. Based on the nucleotide sequence in this mRNA, a protein of amino acids is composed. An error in the *GALT* gene means that the mRNA contains a different nucleotide sequence. This results in a GALT enzyme with a wrong amino acid composition and, therefore, it does not function properly. By administering the correct mRNA, we bridge the defect. The second one is the improvement of the stability and the efficacy of the GALT enzyme by adding small pharmacological molecules. Due to errors in the *GALT* gene an enzyme is made that is much less stable, and the addition of pharmacological molecules can be helpful. The effect of both strategies in our zebra fish model will provide essential information. The existence of GalNet and Patient Registry, together with the European Patient Association constitute a great platform to later translate the preclinical results into the clinical phase.

Another promising approach is noninvasive brain stimulation (NIBS) in which alternating current is administered via electrodes to neural networks in order to modulate them with a favorable effect. The latter is the result of a wonderful collaboration with Prof. Dr. Bernadette Jansma and Dr. Teresa Schuhmann from the Maastricht Brain Imaging Center (M-Bic).

According to MUMC+ Innovation Circle, with this we are acquiring new knowledge and putting it into practice, create value and promote the health of patients with hereditary metabolic diseases.

The foregoing would not have been possible without joining forces. These partnerships are not always easy, people, interpersonal relationships and divergent interest can continue to stand in the way of work. The medication for this is to keep the common goal in mind and hope that everyone takes the medication consistently.

As a metabolic center we see a very wide spectrum of metabolic diseases. There is more good news for this whole group. Recently, it was established *United for Metabolic Diseases* (UMD), a great initiative of our colleagues from Amsterdam UMC (Dr. Clara van Karnebeek and Prof. Dr. Hans Waterham). This is a unique collaboration between doctors and researchers from six different UMCS, including MUMC+, and the patient association "Association for Children and Adults with Metabolic Diseases", to accelerate and improve diagnostics and treatment. Financing is possible through the Stichting Meta Kids and the Dutch lottery VriendenLoterij. This initiative is also supported by Number 5 Foundation, which was founded by Princess Laurentien and her husband, to provide innovative social projects a platform to realize shared ambitions.

Last year, it was also established an important partnership for our hospital: The Academic Alliance between MUMC+ and Radboudumc. The clinical genetics departments with the laboratory of metabolic diseases and colleagues from the transmural metabolic laboratory in Nijmegen are working closely to create a virtual center for diagnostic. This is a considerable

improvement in efficiency and use of expensive infrastructure. For the clinical part, pediatric metabolic diseases, we are working to intensify our collaboration. For research we have started with the use of our shared interest in nucleotide sugars and are working with Prof. Dr. Dirk Lefeber to clarify how deviations relate to disease symptoms.

Let me also give you an example of how we work in the clinic. A boy is admitted with complaints after practicing sport intensively. He has cola-colored urine and enormous pain in his muscles. These complaints are consistent with muscle breakdown. Because the kidney is threatened, the necessary measures are taken to prevent the threat of kidney damage and parallel to this a diagnostic work-up is used in which a hereditary metabolic disease is considered. We know this presentation, among other things, from defects in the oxidation of long chain fatty acids. These are the fats present in our foods that we metabolize to release energy.

A few diagnostic tests are run and from the results we can conclude that there is indeed a specific defect in the metabolism of long chain fatty acids. We can do this diagnostic at metabolite level quickly, in several hours. Confirmation at enzymatic and genetic level takes longer, but it is not necessary for the acute situation. This result means that in addition to the protection of the kidney, enough energy in the form of sugar via infusion is to be given to stop the disease process. This diagnostic gives clarity and opens the doors to an adequate treatment. In order to run smoothly, this process requires that all participants have the right knowledge, that there is the necessary infrastructure (think, for example, of the metabolic laboratory), an excellent communication between all participants, including patient and family, and a flawless logistics.

## **Understanding that reallocation of resources is necessary**

The great diversity, complexity and rarity of hereditary metabolic diseases requires more focused attention and financial support of the costly infrastructure and scientific research. This is necessary to improve the prospects for patients and their families over the coming years. In our center, the number of clinicians involved in hereditary metabolic diseases is very low. The number of diagnosed patients with these diseases is increasing and also the number of patients who survive the disease and become a chronic patient. In addition, due to the expansion of neonatal screening in 2007 in several metabolic diseases it has been a steady increase in the number of diagnosed patients. The upcoming extra expansion will only strengthen this. This is a huge field of tension. Why should we spend so much money with neonatal screening to find patients, and invest so little in the long-term care of these people? Due to neonatal screening and that treatment is improving, we are constantly faced with new questions. With the new partnerships we will reduce our vulnerability. However, in order to continue these partnerships, it is also necessary to distribute the existing resources in such a way that we can also treat optimally patients with this group of diseases.

Patients with rare hereditary metabolic diseases have the same right to optimal care as patients with more common diseases. Many of the great advances that have been made in medicine can be traced back to the understanding of hereditary metabolism. Nowadays, *societal impact* is used as one of the indicators to finance research.

In our socio-economic driven model, this makes it relatively easy for many common diseases to win the competition. But if we go back to the beginning of my lecture, and you are the parent of the baby with a hereditary metabolic disease, you also want that the treatment is optimal. For you it is not relevant that it is a rare disease, but that it is your child with the right to optimal care.

The diseases individually are rare but as a group are common. In recent years, these diseases are fortunately more often on national and international agendas but there is still much more to be achieved. Many of the principles that have been investigated and applied in my field, are highly relevant for more common clinical pictures.

## **Understanding the need for education**

If you are the parent of the sick baby with whom I started my lecture, you expect that the doctor will recognize the symptoms as possibly fitting in a hereditary metabolic disease and that appropriate action is taken promptly. However, this presupposes that, ideally, the physician has already been in contact with this group of diseases in the medical curriculum during his studies of medicine. Unfortunately, this is not always the case. These diseases are very unknown, usually people don't think about them or when they think about them it is already too late. Here is for universities, as responsible for medical curricula, the task to pay more attention to biochemistry and hereditary metabolic diseases. Taking note of the importance of this is essential for this group of diseases that are not sufficiently known and, therefore, are inadequately recognized. Many of us working as a university lecturers should take the responsibility to ask for attention and come up with proposals in order to implement this education. At Maastricht University an optional block on hereditary metabolic diseases has been added to the curriculum of medicine for students in the 2<sup>nd</sup> year, which is a good start.

It is important to give the new generation of medical professionals the knowledge about hereditary metabolic diseases. However, it is also equally important that experienced doctors, from general practitioners to academic medical specialists, can recognize this group of diseases.

## **Women at the top**

As a female professor I want to stand still for a moment upon the matter of women at the top. A few years ago, I followed at the MUMC+ a trajectory for female talent. It is important that organizations support this kind of initiatives. Female talent is there, not always clearly visible, but it is findable. As a doctor, researcher, teacher and now, as a professor, I try to be a role model for many female talented colleagues, PhDs and students. At MUMC+ and UM I have many women who are role models for me, and who have inspired me and continue to inspire me in my career. Waste is sin, so let us strive not to waste female talent, we will all benefit from it. If we want to achieve this, women themselves will also need to change their way of thinking.

## Acknowledgments

I am very grateful to the Executive Board for the trust they have placed in my person with the establishment of this chair. The field of hereditary metabolic diseases is making great progress, more patients are diagnosed, more treatments are available, more patients survive and become adults. There is an increasing social awareness at the various levels that these patients deserve the same standards of care as patients with more general disorders. The proposed activities related to this chair are aimed at contributing to this objective for the MUMC+.

I feel enormously privileged that I can practice this work, my passion, and contribute to this process, but above all, that I am surrounded by fantastic colleagues, friends, family and my great pillar, my family.

In particular, I would very much like to thank the chair of the Department of Pediatrics Prof. Dr. Luc Zimmermann. I would also like to thank the chair of the Department of Clinical Genetics, Prof. Dr. Han Brunner and the director of GROW research institute, Prof. Dr. Manon van Engeland.

Many thanks also to my dear colleagues from pediatrics and clinical genetics. There is a huge fresh wind in both departments, we are doing very well, and it is a privilege to be part of this.

I would like to thank Prof. Dr. Connie Stumpel as well, for our regular brainstorming sessions with a lot of wise advice. Also, thanks to Prof. Dr. Jan Smeitink of Radboudumc, where I was trained in metabolic diseases and promoted under his inspiring leadership.

There are many national and international colleagues who are very dear to me, several of them are present here today. Many thanks that you are here, it makes this day even more special. I want to thank personally two of them because of our special friendship: Dr. Stephanie Grunewald, from Great Ormond Street Hospital in London, and Prof. Dr. Gerard Berry from Boston Children's Hospital, Harvard Medical School.

I would also like to thank Marike Groenendijk. She is chairman of Stofwisselkracht, a foundation that raises funds for metabolic diseases. Thanks to this funds a lot of research has been financed in recent years in the Netherlands.

In addition, I would like to personally thank the members of our metabolic team, Dr. Jorgen Bierau, Dr. Daphne Habets, Dr. Irene Keularts, Dr. Laura Steinbusch, Liesbeth van de Ploeg and Dr. Martijn Brouwers. You are great, and it is tremendously pleasing to undertake the metabolic challenges with you. I also want to thank Dr. Joost Nicolai, an indispensable force to solve very challenging neurometabolic puzzles.

Very special for me are the core members of my research team: Dr. Ana Coelho, my right hand for years, Dr. Jo Vanoevelen, our zebra fish expert, our current enthusiastic and talented PhDs Minela Haskovic and Britt Derks and, again, Dr. Jorgen Bierau, we do both clinic and research together, and that's fun. We have worked very intensively and hard, but

the results are there. We are in a roller coaster of new developments, opportunities, and challenges that promise exciting times. Many of you are not only colleagues but we are also very good friends.

Also, many thanks to Dyonne Schols, our excellent secretary and always the sunshine in the house. You're great in a word!

And then, my dear family, my dear parents are no longer there, but they would be extremely proud. It was a shock for them that I left for the Netherlands as a young girl because I had met a special boy from Amsterdam. They have taught me two qualities, modesty and hard work.

My dear sister, Xelo, present here, *mil gracias*. My Dutch family, I could not have been luckier. Specially mama, I want to thank you. From you I have learned to always see the positive side.

Finally, my children, Robert and Arthur, Robert's girlfriend, Amber, and my dear husband, Henk. Robert and Arthur, you are two great boys. You bring happiness in my life and I am very proud to be your mum. Amber, you are a very nice girl and I am very happy with your coming into our family. Henk, my rock, the special boy from Amsterdam for whom I moved to the Netherlands. You are the one who is prouder of me, thank you!

**"I have said."** - Prof. Dr. M. Estela Rubio Gozalbo