Modulation of the Extracellular Matrix in Advanced Atherosclerosis

Nooijer, Ramon de

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Mapping the Pathobiology of Plaque Rupture

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PROEFSCHRIFT

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van de Rector Magnificus Dr. D.D. Breimer,
hoogleraar in de faculteit der Wiskunde
en Natuurwetenschappen en die der Geneeskunde,
volgens besluit van het College voor promoties
te verdedigen op maandag 12 december 2005
te klokke 14.15 uur

door

Ramon de Nooijer
geboren te Rotterdam
In 1976

Promotiecommissie

Promotores:	Prof. Dr. E.A.L. Biessen
	Prof. Dr. J.W. Jukema
	Prof. Dr. Th.J.C. van Berkel
Referent:	Dr. C.L. Jackson
Overige leden:	Prof. Dr. M. Danhof
	Prof. Dr. G. Pasterkamp
	Prof. Dr. C. Vrints
	Prof. Dr. E.E. van der Wall

The studies presented in this thesis were supported by a grant of the Netherlands Heart Foundation (NHF-M93.001) and were performed at the Division of Biopharmaceutics, Leiden/Amsterdam Center for Drug Research, Leiden University, Leiden, the Netherlands. Financial support by the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged.

The printing of this thesis was also financially supported by:

- LACDR
- Leids Universitair Fonds
- J.E. Juriaanse Stichting
- Dr. Ir. Van der Laar Stichting
- Pfizer

One often hears that successive theories grow ever closer to, or approximate more and more closely to, the truth. Apparently generalisations like that refer not to the puzzle-solutions and the concrete predictions derived from a theory but rather to its ontology, to the match, that is, between the entities with which the theory populates nature and what is "really there."

Thomas S. Kuhn, The Structure of Scientific Revolutions (1962)

Ter nagedachtenis aan Jacobus Koors

Aan mijn familie

Cover: Sigurd W. den Haan

Printing: PrintPartners Ipskamp, Enschede, The Netherlands

ISBN-10: 90-9020068-1
ISBN-13: 9789090200682

De Nooijer, Ramon
Modulation of the Extracellular Matrix in Advanced Atherosclerosis
Mapping the Pathobiology of Plaque Rupture
Proefschrift Leiden.
Met literatuur opgave – Met samenvatting in het Nederlands

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Preface

Eleven years ago the Netherlands Heart Foundation (NHF) took up the initiative to start its ambitious Molecular Cardiology Program (MCP). Considering the importance of the application of molecular technologies in cardiovascular research, the NHF initiated this program to give an incentive to basic science in the field of heart failure and atherosclerosis. The principal objective was to compete with international research on a level of excellence, and to introduce molecular biology techniques in a clinical context, thus bridging the exciting gap between clinical and basic science.

In 1994, the first two research programs regarding atherosclerosis were launched in Leiden, under supervision of prof. dr. Th.J.C. van Berkel, and in Amsterdam, directed by prof. dr. H. Pannekoek. Atherosclerosis research in Leiden was effectively run at the division of Biopharmaceutics by dr. E.A.L. Biessen, at TNO-PG by dr. P. Quax and at the division of Antropogenetics by Dr. J.A.P. van Dijk. Initially, the main focus was to develop gene therapeutic techniques for atherosclerosis and restenosis to complement current pharmacotherapy based on for instance the very successful cholesterol lowering statins. While TNO-PG continued its research in the development of strategies to prevent and treat restenosis, the division of Biopharmaceutics gradually, particularly after 1997, shifted its focus from liver directed drug targeting to therapeutic target finding in the process of plaque rupture, the most common cause for obstructive thrombosis and acute ischemic events. Within this theme not only the molecular processes involved in plaque rupture are being studied, but also imaging techniques for vulnerable atherosclerotic plaques are being developed.

The generous NHS funding initiated a vast expansion of atherosclerosis research within the division of Biopharmaceutics which covers many aspects of this disease, both pathophysiologically as therapeutically, from the perspective of basic science. This thesis reports the progress that has been made in mapping the pathophysiology of plaque rupture with respect to extracellular matrix modulation. Several other PhD students and Postdocs, financed by other grants, are currently studying other aspects of the vulnerable plaque, such as apoptosis and inflammation, and are developing new molecular research techniques.

Recently, the jump to the clinic has been made and several clinical studies regarding end stage atherosclerosis are presently being conducted in cooperation with the Leiden University Medical Centre (dr. Jukema), the University Medical Centre Utrecht (dr. Pasterkamp, dr. Prakken), Oosterschelde Hospital in Goes (dr. Liem) and the Haaglanden Medical Centre in The Hague (dr. Veldhuizen, dr. De Groot). The objective of these new projects is not only the elucidation of the molecular processes that may eventually lead to acute ischemic events and restenosis, but also the identification of diagnostic and prognostic markers in patients with myocardial infarction and the discovery of therapeutic targets for acute ischemic events. Observations in humans will be further elaborated in animal models of atherosclerosis, thus contributing to our understanding of vulnerable plaque pathobiology, to therapeutic target finding and to individual cardiovascular risk stratification.

In order to translate these findings from basic science towards applicable medicine, it must be noted that ongoing cooperation between basic scientists and physicians in conjunction with technological development is of utmost importance. This thesis is one of many in the Molecular Cardiology Program to make a contribution to a better mutual understanding of both basic and clinical research perspectives and a tighter translational cooperation. However, building bridges is not done overnight and it will take the effort of many to establish a solidly founded integrative platform for atherosclerosis research in the Netherlands.

Ramon de Nooijer

Leiden, 31 August 2005