Modulation of the canonical Wnt signaling pathway in bone and cartilage

Răzvan Lucian Miclea
The studies presented in this thesis were financially supported by an unrestricted educational grant from Ipsen Farmaceutica BV, by a research fellowship from the European Society for Pediatric Endocrinology, by a research grant from The Human Growth Foundation, and by a research grant from the Association for International Cancer Research.

Financial support for the costs associated with the publication of this thesis from the Department of Pediatrics of the Leiden University Medical Centre, the Jurriaanse Foundation, the Dutch Arthritis Association, Ipsen Farmaceutica BV, the Dutch Society for Calcium and Bone Metabolism, Ferring BV (Hoofddorp), Goodlife, Guerbet, Novo Nordisk, Oldelft, Pfizer, Servier, Toshiba and Greiner Bio – One is gratefully acknowledged.

Graphic design: dr. P.D. Feitsma.
Cover: Marleen de Jager.
Printed by: Off Page.

ISBN:

© 2011 R.L. Miclea, Leiderdorp, the Netherlands.
All rights reserved. No part of this publication may be reproduced in any form or by any means without prior permission of the author.
Modulation of the canonical Wnt signaling pathway in bone and cartilage

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. P.F. van der Heijden,
volgens besluit van het College voor Promoties
te verdedigen op
woensdag 30 november 2011
klokke 11.15 uur

door

Răzvan Lucian Miclea

geboren te Oradea, Roemenië
in 1979
PROMOTIECOMMISSIE

Promotor
Prof. dr. J. M. Wit

Co-promotoren
Dr. H. B. J. Karperien (Universiteit van Twente)
Dr. E. C. Robanus-Maandag

Overige leden
Prof. dr. P. ten Dijke
Prof. dr. J. P. T. M. van Leeuwen (Erasmus Universiteit Rotterdam)
Prof. dr. M. Richardson
Celor două mele pupile
Contents

Chapter 1  General introduction  11

Chapter 2  Adenomatous polyposis coli-mediated control of β-catenin is essential for both chondrogenic and osteogenic differentiation of skeletal precursors  39

Chapter 3  Adenomatous polyposis coli-gene dosage controls β-catenin-mediated differentiation of skeletal precursors  63

Chapter 4  Apc bridges Wnt/β-catenin and BMP signaling during osteoblast differentiation of KS483 cells  85

Chapter 5  APC mutations are associated with increased bone mineral density in patients with familial adenomatous polyposis  107

Chapter 6  Inhibition of Gsk3β in cartilage induces osteoarthritic features through activation of the canonical Wnt signaling pathway  127

Chapter 7  Summary, conclusions, directions for future research  157

Samenvatting  167
List of publications  175
Curriculum vitae  179
Dankwoord  183