Short-term pre-operative dietary restriction in vascular surgery

Kip, P.

Acknowledgements

The work in this thesis would not have been possible without the support of a wide range of people. I will make an (futile) attempt to do them all justice in these next few lines of text.

Dear Jay, it makes me forever sad that you are not among us anymore. Your ideas and drive really started this whole field of "short-term dietary restriction", and your fruitful collaboration with dr. Ozaki certainly laid the foundation for this thesis. The lab movie nights, the 4 o' clock beers in your office, the endless pepperoni pizza jokes, the trips to Rotterdam and Maine, the spontaneous ventures to Penguin pizza or the Mission; all great memories. Thank you for being such a great boss and mentor. It is safe to say that without your creativity, scientific rigor and enthusiasm this thesis would not be the same.

To dr. Ozaki, thank you for your guidance, mentorship and hospitality both in and outside of the lab. Thank you for the opportunity to develop myself as a "clinician-scientist" in your lab and for introducing me to the US and "Southern" way of life, especially during our fishing trip to Florida. Your (seemingly) effortless way of combining your clinical work at the Brigham with leading a pre-clinical and clinical research group (while also maintaining a social life), remains something I hope to achieve one day.

To Paul, I've always appreciated your "*can do*" mentality. Thank you for your continuing support over the years; first as a student of medicine interested in vascular biology, then as a PhD-student, and now as a clinician with a persistent interest in science. I`m grateful for the trust you and Margreet put in me and the gamble you took, by sending me out on a trip to Boston to start this (in retrospect) fruitful collaboration.

To Margreet**,** I've always enjoyed our working relationship, which only got better and more productive during the time I was in Boston. The long days in the Ozaki lab doing the surgeries and coming up with research ideas on the spot (which turned out to be quite fruitful), all good memories. You've been a tremendous support over the years, and always provided me with your honest opinions on things.

To all my former colleagues in the combined Jay and Ozaki labs: Kaspar, Michael, Jon, Sarah, Ming, Thijs, Xiao-Feng, Humberto: Thank you.

To my parents Herman and Stieny, to my brother Hans and my sister Henriette; thank you for your continuous support over the years. It was great to share my experiences in the US during your visits, including the "gefrituurde augurken", whale watching, the trip to cape cod, the bike trip through Cambridge and Boston.

Curriculum vitae

The author of this thesis was born on the ninth of May of 1989 in Emmen, the Netherlands. He grew up in a little border town called “Zwartemeer” in Drenthe. In the city of Emmen he first completed HAVO in 2005 followed by VWO (pre-university) in 2007. Until 2008 he played handball on a (semi)-professional level at E&O. After graduating VWO he studied Life Science and Technology in Groningen, before he was allowed into the Leiden University Medical School in 2009. During his medicine school studies he joined the lab of Professor Paul Quax and Margreet de Vries for extracurricular work on endarterectomy plaques. After graduating in 2017, he started his PhD in the lab of Paul and Margreet, but shortly afterwards moved to Boston to the labs of Prof. Ozaki (department of Vascular and Endovascular Surgery, Brigham and Women’s Hospital/Harvard Medical School) and Prof. Jay Mitchell (Department of Molecular Metabolism, Harvard T. H. Chan School of Public Health). Here he spent the next three years working on pre-operative dietary restriction in vascular surgery preclinical mouse models and patients. In August of 2020, he moved back to the Netherlands and entered a position as surgical resident (not-in-training) in the Alrijne hospital Leiderdorp. In January 2022 he started his training program as a surgical resident in training in Leiden.

List of Publications

Kip P, Sluiter TJ, Trocha KM, MacArthur MR, Tao M, Mitchell SJ, Jung J, Quax PHA, Mitchell JR, Ozaki CK, de Vries MR (2020). Short-term methionine restriction protects from vein graft disease via perivascular adipose tissue dependent AMPK-signaling. *In progress*

Kip P, Sluiter TJ, Moore JK, Hart A, Ruske J, O' Leary J, Jung J, Tao M, MacArthur MR, Heindel P, de Jong A, de Vries MR, Burak FM, Mitchell SJ, Mitchell JR & Ozaki CK (2021). Short-term protein-caloric restriction in elective vascular surgery patients: a randomized controlled clinical trial. *Nutrients,* 2021, 13(11), 4024; https://doi.org/10.3390/nu13114024

MacArthur MR, PhD, Mitchell SJ, Trevino-Villarreal JH, Grondin J, Reynolds J, **Kip P,** Jung J, Trocha KM, Ozaki CK, Mitchell JR**.** Total protein amount, not amino acid composition, differs in plant-based versus omnivorous dietary patterns and determines metabolic health effects in mice. *Cell Metabolism. 2021 July* https://doi.org/10.1016/j.cmet.2021.06.011

Longchamp A*, Macarthur MR*, Trocha KM, Ganahl J, Mann C, **Kip P**, Sharma G, Tao M, Mitchell SJ, Ditrói T, Nagy P, Ozaki CK, Hine C, Mitchell JR. Plasma Hydrogen Sulfide Production Capacity is Positively Associated with Post-Operative Survival in Patients Undergoing Surgical Revascularization. *Frontiers in Cardiovascular Medicine. 2021 October.* https://doi.org/10.3389/fcvm.2021.750926

Jiang X, MacArthur MR, Trevino-Villarreal JH, **Kip P,** Ozaki CK, Mitchell SJ, Mitchell JR. A high-content compound screen identifies H2S production as an autophagy-dependent adaptive response to DNA damage and other stressors. *Cell Chemical Biology 2021 May.* https://doi.org/10.1016/j.chembiol.2021.05.016

Kip P*, Tao M*, Trocha KM, MacArthur MR, Mitchell SJ, Mann C, Sluiter TJ, Jung J, Patterson, Quax PHA, de Vries MR, Mitchell JR & Ozaki CK (2020). Periprocedural hydrogen sulfide therapy improves vascular remodeling and attenuates vein graft disease. *Journal of the American Heart Association.* 2020 Nov 17;9(22): e016391. https://doi.org/10.1161/JAHA.120.016391

Endo Y, Baldino K, Li B, Zhang Y, Sakthivel D, MacArthur M, Panayi AC, **Kip P**, Spencer DJ, Jasuja R, Bagchi D, Bhasin S, Nuutila K, Neppi RL, Wagers AJ, Sinha I. (2020). Loss of ARNT in skeletal muscle limits muscle regeneration in aging. *The FASEB journal.* October 2020 https://doi.org/10.1096/fj.202000761RR

Trocha KM *, **Kip P***, Tao M, MacArthur MR, Treviño-Villarreal JH, Longchamp A, Toussaint W, Lambrecht BN, de Vries, MR, Quax PHA, Mitchell JR, & Ozaki CK. (2020). Short-term preoperative protein restriction attenuates vein graft disease via induction of cystathionine γ-lyase. *Cardiovascular research*, *116*(2), 416–428. https://doi.org/10.1093/cvr/cvz086

Kip P, Trocha KM, Tao M, O'leary JJ, Ruske J, Giulietti JM, Trevino-Villareal JH, MacArthur MR, Bolze A, Burak MF, Patterson S, Ho K, Carmody RN, Guzman RJ, Mitchell JR, & Ozaki CK. (2019). Insights from a Short-Term Protein-Calorie Restriction Exploratory Trial in Elective Carotid Endarterectomy Patients. *Vascular and endovascular surgery*, 53(6), 470–476. https://doi.org/10.1177/1538574419856453

Trocha K*, **Kip P***, MacArthur MR, Mitchell SJ, Longchamp A, Treviño-Villarreal JH, Tao M, Bredella MA, De Amorim Bernstein K, Mitchell JR, & Ozaki CK. (2019). Preoperative Protein or Methionine Restriction Preserves Wound Healing and Reduces Hyperglycemia. *The Journal of surgical research*, 235, 216–222. https://doi.org/10.1016/j.jss.2018.09.071

Wezel A, de Vries MR, Maassen JM, **Kip P**, Peters EA, Karper JC, Kuiper J, Bot I, & Quax PHA. (2016). Deficiency of the TLR4 analogue RP105 aggravates vein graft disease by inducing a pro-inflammatory response. Scientific reports, 6, 24248. https://doi.org/10.1038/srep24248

Grants

American Heart Association Post-Doctoral Research Fellowship. Post-doctoral Fellowship for research proposal titled: *"Vasculoprotective Mechanisms of Endogenous Hydrogen Sulfide in Vein Grafts"*. $104.060 for the period of 01/2019 – 12/2020 at the Brighamd and Women's Hospital and Harvard Medical School. (ranked in percentilel 0.17%, priority score 1.31)

Michael-van Vloten Fonds. *"Kortdurende Preoperatieve Eiwitrestrictie ter Preventie van Veneuze Bypass Falen"*. €8.000; for the period of 2019-2020 at the Brighamd and Women's Hospital and Harvard Medical School

Prins Bernhard Fonds. "*Eiwitrestrictie in Veneuze Graft Ziekte"*. €10.000; van 2018-2020 at the Brighamd and Women's Hospital and Harvard Medical School.

Stichting de Drie Lichten. "*De Effecten van Sulfaat Aminozuur Restrictie en Waterstofsulfide op Post-interventionele Inflammatie in Veneuze Grafts"*. €12.000; van 2017-2019 at the Brighamd and Women's Hospital and Harvard Medical School **LUF-fonds.** "*Kortdurende Eiwit Restrictie ter Verbetering van de Uitkomsten na Veneuze Bypass Chirurgie"*. €1000

Awards

Finalist fo the 2019 Stepping Strong Innovator Award. Finalist with proposal and elevator pitch titled: *"Hydrogen Sulfide Gels to Accelerate Traumatic Wound Healing."* For the Brigham and Women's Hospital Gillian Reny Stepping Strong Center for Trauma Innovation.

BWH Department of Surgery John A. Mannick Research Day Award 2019. Best abstract *"Endogenous and Exogenous Hydrogen Sulfide Upregulation as Novel Strategies to Improve Vein Graft Durability.* $400 award and oral presentation.

Vascular Research Initiatives Conference Trainee Award 2019. Best abstract titled *"Peri-procedural Local Hydrogen Sulfide Therapy Impairs Vascular Remodeling and Improves Vein Graft Patency."* Award and oral presentation

8th Annual Harvard-Longwood Surgical Research Day Award 2019. Best abstract titled: "*Peri-procedural Local Hydrogen Sulfide Therapy Impairs Vascular Remodeling and Improves Vein Graft Patency."* Award and oral presentation

BWH Peripheral Artery Disease Symposium 2018. Top 3 ranked abstract titeld: *"Hydrogen Sulfide Improves Vein Graft Patency and Limits Intimal Hyperplasia".* $600 award and oral presentation

North American Vascular Biology Organization Travel Award 2018. $250 award and poster-presentation

ATVB/PVD Travel Award 2018. $1000 award and (poster) presentation

Society of Vascular Surgery Resident Research Award for Best Manuscript 2017-2018. *"Pre-Operative Protein-Restriction Attenuates Vein Graft Disease Via Induction of Cystathionine gamma-lyase"* Trocha K*, **Kip P*** et al. $5000

(Oral) Presentations

Kip P. Moore J. Hart A. Ruske J, O'Leary J, Sluijter TJ, Jung J, Tao M, MacArthur MR, Mitchell SJ, Mitchell JR & Ozaki C Keith. *Short-term Pre-operative Protein Caloric Restriction in Elective Vascular Surgery Patients: A Randomized Clinical Trial*. 2nd Protein-calorie restriction workshop: Short-term Dietary Interventions to Improve Surgical Outcomes and Beyond (Oktober 2020); online conference. *Oral*

Kip P, Tao M, Trocha KM, MacArthur MR, Mitchell SJ, Mann C, Sluiter TJ, Jung J, Patterson S, Quax PHA, de Vries MR, Mitchell JR & Ozaki CK. *Endogenous and Exogenous Hydrogen Sulfide Upregulation as Novel Strategies to Improve Vein Graft Durability*. John A. Mannick Surgical Research Day 2019. (2 oktober, 2019); Brigham and Women's Hospital, Boston, MA. *Oral*

Kip P, Tao M, Trocha KM, MacArthur MR, Mitchell SJ, Jung J, Quax PHA, de Vries MR, Mitchell J.R., Ozaki CK. Short-term methionine restriction protects from vein graft disease via perivascular adipose dependent mechanisms. Vascular Research Initiatives Conference (May 13, 2019); Atherosclerosis, Thrombosis, and Vascular Biology (14-16 mei, 2019), Boston, MA. *Poster*

Kip P, Trocha KM, Tao M, O'leary JJ, Giulietti JM, Trevino-Villareal JH, MacArthur MR, Bolze A, Burak MF, Patterson S, Ho KJ, Carmody RN, Guzman RJ, Mitchell J, Ozaki CK. Insights from a short-term protein-calorie restriction exploratory trial in elective carotid endarterectomy patients. Vascular Research Initiatives Conference (13 Mei, 2019); Atherosclerosis, Thrombosis, and Vascular Biology (May 14-16, 2019), Boston, MA. *Poster*

Kip P, Tao M, Trocha KM, MacArthur MR, Mitchell SJ, Patterson S, Jung J, Quax PHA, de Vries MR, Mitchell JR, Ozaki CK. *Periprocedural hydrogen sulfide therapy impairs vascular remodeling and improves vein graft patency*. Vascular Research Initiatives Conference (May 13, 2019); Atherosclerosis, Thrombosis, and Vascular Biology (14-16 Mei, 2019), Boston, MA. *Oral*

Kip P. Tao M, Trocha KM, MacArthur MR, Mitchell SJ, Mann C, Sluiter TJ, Jung J, Patterson S, Quax PHA, de Vries MR, Mitchell JR & Ozaki CK. *Dietary Restriction in Vascular Surgery*. 1st Protein-Calorie Restriction Workshop: Short-term Dietary Interventions to Improve Surgical Outcomes and Beyond; (April 2019), Leiden. *Oral*

Kip P, Tao M, Trocha KM, MacArthur MR, Mitchell SJ, Patterson S, Jung J, Quax PHA, de Vries MR, Mitchell JR, Ozaki CK. *Novel Therapeutic Approaches to Improve Vascular Conduit Durability*. Department of Vascular and Endovascular Surgery. Brigham and Women's Hospital. *Oral*: *Visiting Professor Dr. Fairman, University of Pennsylvania*. April 2019. Boston, MA.

Kip P, Tao M, Trocha KM, MacArthur MR, Mitchell SJ, Patterson S, Jung J, Quax PHA, de Vries MR, Mitchell JR, Ozaki CK. *Peri-procedural Local Hydrogen Sulfide Therapy Impairs Vascular Remodeling and Improves Vein Graft Patency*. 8th Annual Harvard-Longwood Surgical Research Day. (Boston, Massachusetts). Maart 2019. *Oral*

Ruske J, O'Leary JJ, Trocha KM, Giulietti J, Tao M, Mitchell JR, Carmody R, Ho K, Furkan B, Patterson S, Bolze A, Guzman R, Ozaki CK, **Kip P**. *Short-term Pre-Operative Dietary Protein and Calorie Restriction to Improve Vascular Surgery Outcomes*. Discover Brigham at Brigham & Women's Hospital. (Boston, Massachusetts). Oktober 2018. *Poster*

Kip P, Tao M, Trocha KM, MacArthur MR, Mitchell SJ, Quax PHA, de Vries MR, Mitchell JR, Ozaki CK. *Short-Term Methionine Restriction Limits the Arterial Intimal Hyperplastic Response*. American College of Surgeons Clinical Conference. (Boston, Massachusetts). Oktober 2018. *Oral*

Kip P, Tao M, Trocha KM, MacArthur MR, Mitchell SJ, Patterson S, Quax PHA, de Vries MR, Mitchell JR, Ozaki CK. *Hydrogen Sulfide Improves Vein Graft Patency and Limits Intimal Hyperplasia*. Peripheral Artery Disease Research Symposium. Brigham and Women's Hospital. (Boston, Massachusetts). September 2018. *Oral*

Kip P, Tao M, Trocha KM, MacArthur MR, Mitchell SJ, Patterson S, Quax PHA, de Vries MR, Mitchell JR, Ozaki CK. *Hydrogen Sulfide Improves Vein Graft Patency and Limits Intimal Hyperplasia*. North-American Association of Vascular Biology. (Newport, Rhode Island). Oktober 2018. *Poster*

Trocha KM*, **Kip P*,** Tao M, MacArthur MR, Treviño-Villarreal JH, Longchamp A, Toussaint W, Lambrecht B, de Vries MR, Quax PHA, Mitchell JR, Ozaki CK. *Short Term Preoperative Protein Restriction Attenuates Vein Graft Disease via Induction of Cystathionine Gamma-Lyase*. Vascular Annual Meeting, Society for Vascular Surgery. (Boston, Massachusetts). Juni 2018. *Oral*

Kip P*, Trocha KM*, Tao M, MacArthur MR, Treviño-Villarreal JH, Longchamp A, Toussaint W, Lambrecht B, de Vries MR, Quax PHA, Mitchell JR, Ozaki CK. Novel (Dietary) Strategies to Enhance Vascular Surgery Operations. Research Presentations for Visiting Professor Dr. Andres Schanzer, Brigham & Women's Hospital. (Boston, Massachusetts). 15 mei 2018. *Oral*

Kip P*, Trocha KM*, Tao M, MacArthur MR, Treviño-Villarreal JH, Longchamp A, Toussaint W, Lambrecht B, de Vries MR, Quax PHA, Mitchell JR, Ozaki CK. *Short-term Protein Restriction Attenuates Vein Graft Disease Via Induction of Endothelial Cystathionine gamma-lyase.* ATVB; from genes to medicine, (San Francisco, California) Mei 2018. *Poster*

Kip P*, Trocha KM*, Tao M, MacArthur MR, Treviño-Villarreal JH, Longchamp A, Toussaint W, Lambrecht B, de Vries MR, Quax PHA, Mitchell JR, Ozaki CK. *Short-Term Protein Restriction Attenuates Vein Graft Disease and Upregulates Endogenous Hydrogen Sulfide.* 2018 Harvard Surgery Research Day. (Boston, Massachusetts). April 2018. *Poster*

Kip P. *The role of toll like receptors and its endogenous ligands in angiogenesis in atherosclerotic lesions*. LUMC Afdeling Heelkunde Jaarlijkse Onderzoeksdag. (Leiden, the Netherlands). Maart 2016. *Oral*