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Post scriptum.

Post scriptum

This is usually the only chapter of any thesis that people actually read. Traditionally it is used to thank the people who contributed to the thesis because, let's face it, nobody can achieve this on her own. Basically everybody you ever talked to about this subject, everybody who ever encouraged you, everybody that offered a different viewpoint, and even the ones who said you would never make it in time, contributed to the formation of this thesis. The problem is that some people you simply cannot thank enough, and others you can easily give too much credit. So I decided to break with tradition and do things a bit different.

Until a couple of years ago, a list of statements was an important part of a thesis. Unfortunately, that custom has fallen into disuse. Since this chapter is the only part of the thesis a PhD student is free to give her own meaning to, I decided to restore this tradition.

Ask any PhD student and they will tell you that writing a thesis is equal to a lot of problems. Most struggle with techniques, failing experiments, absence of guidance but above all they struggle with time. But it is also about growing and learning new things. I decided to end this thesis with some things I learned. You might even recognize your own contribution ☺.

- 1. Your life has an effect on every life around you, so better make it a positive one.*
- 2. Fear is a bad motivator.*

3. *Strength is not averting your eyes from what you know is wrong.*
4. *You can teach anyone to do research, but being a researcher requires something more.*
5. *Some battles are not worth fighting while others cannot be avoided no matter the cost.*
6. *You choose your own path, so choose one you'll enjoy*
7. *Humans are not meant to be perfect because evolution requires change.*
8. *Some people are just not worth one second of your thoughts, while others can live in your heart forever.*
9. *Everybody smiles in the same language.*
10. *This path was worth travelling because it led me to you.*

Thank you for all the help and for hanging in there with me until the end!

Desirée





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List of publications.

List of publications

1. Kok RM, **Smith DE**, Dainty JR, Van Den Akker JT, Finglas PM, Smulders YM, Jakobs C, de Meer K. 5-Methyltetrahydrofolic acid and folic acid measured in plasma with liquid chromatography tandem mass spectrometry: applications to folate absorption and metabolism. *Anal Biochem*, 2004;326:129-138.
2. Stam F, van Guldener C, ter Wee PM, Kulik W, **Smith DE**, Jakobs C, Stehouwer CD, de Meer K. Homocysteine clearance and methylation flux rates in health and end-stage renal disease: association with S-adenosylhomocysteine. *Am J Physiol Renal Physiol*, 2004;287:F215-F223.
3. de Meer K, Smulders YM, Dainty JR, **Smith DE**, Kok RM, Stehouwer CD, Finglas PM, Jakobs C. [6S]5-methyltetrahydrofolate or folic acid supplementation and absorption and initial elimination of folate in young and middle-aged adults. *Eur J Clin Nutr*, 2005;59:1409-1416.
4. Wamelink MM, **Smith DE**, Jakobs C, Verhoeven NM. Analysis of polyols in urine by liquid chromatography-tandem mass spectrometry: a useful tool for recognition of inborn errors affecting polyol metabolism. *J Inheret Metab Dis*, 2005;28:951-963.
5. de Boo HA, van Zijl PL, **Smith DE**, Kulik W, Lafeber HN, Harding JE. Arginine and mixed amino acids increase protein accretion in the growth-restricted and normal ovine fetus by different mechanisms. *Pediatr Res*, 2005;58:270-277.
6. **Smith DE**, Kok RM, Teerlink T, Jakobs C, Smulders YM. Quantitative determination of erythrocyte folate vitamers distribution by liquid chromatography-tandem mass spectrometry. *Clin Chem Lab Med*, 2006;44:450-459.
7. Smulders YM, **Smith DE**, Kok RM, Teerlink T, Swinkels DW, Stehouwer CD, Jakobs C. Cellular folate vitamers distribution during and after correction of vitamin B12 deficiency: a case for the methylfolate trap. *Br J Haematol*, 2006;132:623-629.
8. Kok RM, **Smith DE**, Barto R, Spijkerman AM, Teerlink T, Gellekink HJ, Jakobs C, Smulders YM. Global DNA methylation measured by liquid chromatography-tandem mass spectrometry: analytical technique, reference values and determinants in healthy subjects. *Clin Chem Lab Med*, 2007;45:903-911.
9. Sipkens JA, Krijnen PA, Meischl C, Cillessen SA, Smulders YM, **Smith DE**, Giroth CP, Spreeuwenberg MD, Musters RJ, Muller A, Jakobs C,

- Roos D, Stehouwer CD, Rauwerda JA, van H, V, Niessen HW. Homocysteine affects cardiomyocyte viability: concentration-dependent effects on reversible flip-flop, apoptosis and necrosis. *Apoptosis*, 2007;12:1407-1418.
10. Smulders YM, **Smith DE**, Kok RM, Teerlink T, Gellekink H, Vaes WH, Stehouwer CD, Jakobs C. Red blood cell folate vitamer distribution in healthy subjects is determined by the methylenetetrahydrofolate reductase C677T polymorphism and by the total folate status. *J Nutr Biochem*, 2007;18:693-699.
11. Wamelink MM, **Smith DE**, Jansen EE, Verhoeven NM, Struys EA, Jakobs C. Detection of transaldolase deficiency by quantification of novel seven-carbon chain carbohydrate biomarkers in urine. *J Inherit Metab Dis*, 2007;30:735-742.
12. Oosterveld MJ, de Meer K, **Smith DE**, Kok RM, Langius JA, Gemke RJ. No effect of ornithine alphaketoglutarate on nitrogen excretion or urea synthesis rate in healthy male subjects. *e-SPEN*, 2007;2:75-80.
13. Semmler A, Smulders Y, Struys E, **Smith D**, Moskau S, Blom H, Linnebank M. Methionine metabolism in an animal model of sepsis. *Clin Chem Lab Med*, 2008;46:1398-1402.
14. Prinz-Langenohl R, Bramswig S, Tobolski O, Smulders YM, **Smith DE**, Finglas PM, Pietrzik K. [6S]-5-methyltetrahydrofolate increases plasma folate more effectively than folic acid in women with the homozygous or wild-type 677C-->T polymorphism of methylenetetrahydrofolate reductase. *Br J Pharmacol*, 2009;158:2014-2021.
15. Linnebank M, Popp J, Smulders Y, **Smith D**, Semmler A, Farkas M, Kulic L, Cvetanovska G, Blom H, Stoffel-Wagner B, Kolsch H, Weller M, Jessen F. S-adenosylmethionine is decreased in the cerebrospinal fluid of patients with Alzheimer's disease. *Neurodegener Dis*, 2010;7:373-378.
16. Sipkens JA, Hahn N, van den Brand CS, Meischl C, Cillessen SA, **Smith DE**, Juffermans LJ, Musters RJ, Roos D, Jakobs C, Blom HJ, Smulders YM, Krijnen PA, Stehouwer CD, Rauwerda JA, van H, V, Niessen HW. Homocysteine-Induced Apoptosis in Endothelial Cells Coincides With Nuclear NOX2 and Peri-nuclear NOX4 Activity. *Cell Biochem Biophys*, 2011.
17. Banka S, Blom HJ, Walter J, Aziz M, Urquhart J, Clouthier CM, Rice GI, de Brouwer AP, Hilton E, Vassallo G, Will A, **Smith DE**, Smulders YM, Wevers RA, Steinfeld R, Heales S, Crow YJ, Pelletier JN, Jones S, Newman WG. Identification and characterization of an inborn error of

- metabolism caused by dihydrofolate reductase deficiency. *Am J Hum Genet*, 2011;88:216-225.
18. Cario H, **Smith DE**, Blom H, Blau N, Bode H, Holzmann K, Pannicke U, Hopfner KP, Rump EM, Ayric Z, Kohne E, Debatin KM, Smulders Y, Schwarz K. Dihydrofolate reductase deficiency due to a homozygous DHFR mutation causes megaloblastic anemia and cerebral folate deficiency leading to severe neurologic disease. *Am J Hum Genet*, 2011;88:226-231.
 19. Bjursell MK, Blom HJ, Cayuela JA, Engvall ML, Lesko N, Balasubramaniam S, Brandberg G, Halldin M, Falkenberg M, Jakobs C, **Smith D**, Struys E, von DU, Gustafsson CM, Lundeberg J, Wedell A. Adenosine kinase deficiency disrupts the methionine cycle and causes hypermethioninemia, encephalopathy, and abnormal liver function. *Am J Hum Genet*, 2011;89:507-515.
 20. Sipkens JA, Krijnen PA, Hahn NE, Wassink M, Meischl C, **Smith DE**, Musters RJ, Stehouwer CD, Rauwerda JA, van H, V, Niessen HW. Homocysteine-induced cardiomyocyte apoptosis and plasma membrane flip-flop are independent of S-adenosylhomocysteine: a crucial role for nuclear p47(phox). *Mol Cell Biochem*, 2011;358:229-239.
 21. Davids M, Swieringa E, Palm F, **Smith DE**, Smulders YM, Scheffer PG, Blom HJ, Teerlink T. Simultaneous determination of asymmetric and symmetric dimethylarginine, l-monomethylarginine, l-arginine, and l-homoarginine in biological samples using stable isotope dilution liquid chromatography tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci*, 2012;900:38-47.
 22. Semmler A, Frisch C, **Smith D**, Blom H, Linnebank M. The ratio of S-adenosylmethionine and S-adenosyl-homocysteine is increased in the brains of newborn rats in a model of valproic acid teratogenicity. *Toxicology*, 2012;293:132-133.
 23. **Smith DE**, Smulders YM, Blom HJ, Popp J, Jessen F, Semmler A, Farkas M, Linnebank M. Determinants of the essential one-carbon metabolism metabolites, homocysteine, S-adenosylmethionine, S-adenosylhomocysteine and folate, in cerebrospinal fluid. *Clin Chem Lab Med*, 2012;50:1641-1647.
 24. **Smith DE**, Mendes MI, Kluijtmans LA, Janssen MC, Smulders YM, Blom HJ. A liquid chromatography mass spectrometry method for the measurement of cystathionine beta-synthase activity in cell extracts. *J Chromatogr B Analyt Technol Biomed Life Sci*, 2012;911:186-191.
 25. Imbard A, Smulders YM, Barto R, **Smith DE**, Kok RM, Jakobs C, Blom HJ. Plasma choline and betaine correlate with serum folate, plasma S-

- adenosyl-methionine and S-adenosyl-homocysteine in healthy volunteers. *Clin Chem Lab Med*, 2013;51:683-692.
26. Farkas M, Keskitalo S, **Smith DE**, Bain N, Semmler A, Ineichen B, Smulders Y, Blom H, Kulic L, Linnebank M. Hyperhomocysteinemia in Alzheimer's disease: the hen and the egg? *J Alzheimers Dis*, 2013;33:1097-1104.
27. Gent YY, Weijers K, Molthoff CF, Windhorst AD, Huisman MC, **Smith DE**, Kularatne SA, Jansen G, Low PS, Lammertsma AA, van der Laken CJ. Evaluation of the novel folate receptor ligand [18F]fluoro-PEG-folate for macrophage targeting in a rat model of arthritis. *Arthritis Res Ther*, 2013;15:R37.
28. Semmler A, Prost JC, Smulders Y, **Smith D**, Blom H, Bigler L, Linnebank M. Methylation metabolism in sepsis and systemic inflammatory response syndrome. *Scand J Clin Lab Invest*, 2013;73:368-72.
29. **Smith DE**, Hornstra JM, Kok RM, Blom HJ, Smulders YM. Folic acid supplementation does not reduce intracellular homocysteine, and may disturb intracellular one-carbon metabolism. *Clin Chem Lab Med* 2013;51:1643-50.
30. Mendes MI, Colaço G, **Smith DE**, Ramos RJ, Pop A, van Dooren SJ, Tavares de Almeida I, Kluijtmans LA, Janssen MC, Rivera I, Salomons GS, Leandro P, Blom HJ. Reduced response of cystathionine beta-synthase to S-adenosylmethionine: identification and functional analysis of cystathionine beta-synthase gene mutations in homocystinuria patients. *J Inherit Metab Dis* 2013 [in Press].