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The epileptogenic trinity

Oxidative stress, brain inflammation and iron in epilepsy

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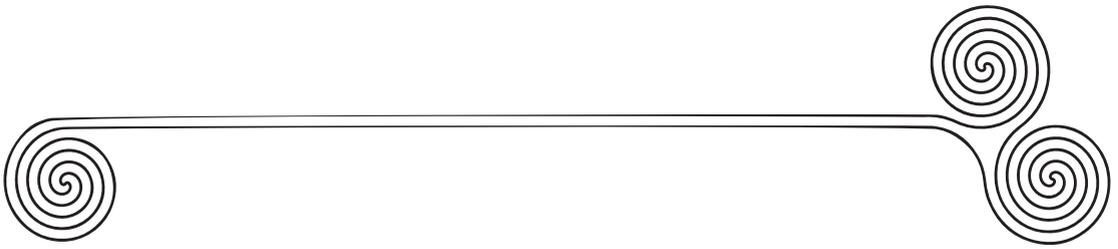
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APPENDIX

Published research articles:

Zimmer TS, Korotkov A, Zwakenberg S, Jansen FE, Zwartkruis FJT, Rensing NR, Wong M, Mühlebner A, van Vliet EA, Aronica E, Mills JD (2021) Upregulation of the pathogenic transcription factor SPI1/PU.1 in tuberous sclerosis complex and FOCAL cortical dysplasia by oxidative stress. *Brain Pathol.* accepted *shared last authorship

Vila Verde D, **Zimmer T**, Cattalini A, Pereira MF, van Vliet EA, Testa G, Gnatkovsky V, Aronica E, de Curtis M (2020) Seizure activity and brain damage in a model of focal non-convulsive status epilepticus. *Neuropathol. Appl. Neurobiol.* Epub ahead of print. doi: 10.1111/nan.12693

Zimmer TS, Broekaart DWM, Gruber V, van Vliet EA, Mühlebner A and Aronica, E. Tuberous sclerosis complex as disease model for investigating mTOR-related gliopathy during epileptogenesis. (2020) *Front. Neurol.* 11:1028. doi: 10.3389/fneur.2020.01028

Zimmer TS, Ciriminna G, Arena A, Anink JJ, Korotkov A, Jansen FE, van Hecke W, Spliet WG, van Rijen PC, Baayen JC, Idema S, Rensing NR, Wong M, Mills JD, van Vliet EA and Aronica E. (2020) Chronic activation of anti-oxidant pathways and iron accumulation in epileptogenic malformations. *Neuropathol. Appl. Neurobiol.* 46(6):546-563. doi: 10.1111/nan.12596

Mühlebner A, van Scheppingen J, de Neef A, Bongaarts A, **Zimmer TS**, Mills JD, Jansen FE, van Spliet WGM, Krsek P, Zamecnik J, Coras J, Blümcke I, Feucht M, Scholl T, Gruber VE, Hainfeller JA, Söylemezoglu F, Kotulska K, Lagae L, Jansen AC, Kwiatkowski DJ, Jozwiak S, Curatolo P, Aronica E. (2020) Myelin Pathology Beyond White Matter in Tuberous Sclerosis Complex (TSC) Cortical Tubers. *J. Neuropathol. Exp. Neurol.* 79(10):1054-1064. doi: 10.1093/jnen/nlaa090

Arena A*, **Zimmer TS***, van Scheppingen J, Korotkov A, Anink JJ, Mühlebner A, Jansen FE, van Hecke W, Spliet WG, van Rijen PC, Vezzani A., Baayen JC, Idema S, Iyer AM, Perluigi M, Mills JD, van Vliet EA and Aronica E. (2019) Oxidative stress and inflammation in a spectrum of epileptogenic cortical malformations: molecular insights into their interdependence. *Brain Pathol.* 29:351–65. doi: 10.1111/bpa.12661. *shared first authorship

Van Scheppingen J, Mills JD, **Zimmer TS**, Broekaart DWM, Iori V, Bongaarts A, Anink JJ, Iyer AM, Korotkov A, Jansen FE, van Hecke W, Spliet WG, van Rijen PC, Baayen JC, Vezzani A, van Vliet EA, Aronica E (2018) miR147b: A novel key regulator of interleukin 1 beta-mediated inflammation in human astrocytes. *Glia* 10.1002/glia.23302

Mills JD, Iyer AM, van Scheppingen J, Bongaarts A, Anink JJ, Janssen B, **Zimmer TS**, Spliet WG, van Rijen PC, Jansen FE, Feucht M, Hainfeller JA, Krsek P, Zamecnik J,

Kotulska K, Jozwiak S, Jansen A, Lagae L, Curatolo P, Kwiatkowski DJ, Pasterkamp RJ, Senthilkumar K, von Oerthel L, Hoekman MF, Gorter JA, Crino PB, Mühlebner A, Scicluna BP, Aronica E (2017) Coding and small non-coding transcriptional landscape of tuberous sclerosis complex cortical tubers: implications for pathophysiology and treatment. *Sci Rep* 7:8089. doi: 10.1038/s41598-017-06145-8

Submitted articles

Zimmer TS, Broekaart DWM, Luinenburg M, Mijnsbergen C, Anink JJ, Sim NS, Michailidou I, Jansen FE, van Hecke W, van Rijen PC, Lee JH, François L, van Eyll J, Dedeurwaerdere S, van Vliet EA, Mühlebner A, Mills JD, Aronica E (2020) Balloon cells promote immune system activation in focal cortical dysplasia type IIb. *submitted*

Korotkov A, Sim NS, Luinenburg MJ, Anink JJ, van Scheppingen J, **Zimmer T**, Bongaarts A, Broekaart DWM, Mijnsbergen C, Jansen FE, van Hecke W, Spliet WG, van Rijen PC, Feucht M, Hainfellner JA, Krsek P, Zamecnik J, Crino PB, Kotulska K, Lagae L, Jansen AC, Kwiatkowski DJ, Jozwiak S, Curatolo P, Mühlebner A, Lee JH*, Mills JD*, van Vliet EA*, Aronica E* (2020) MicroRNA-34a activation in tuberous sclerosis complex during early brain development may lead to impaired neurogenesis. *submitted*
*shared last authorship

Salamone A, Terrone G, Di Sapia R, Balosso S, Ravizza T, Beltrame L, Craparotta I, Mannarino L, Raimondi Cominesi S, Pauletti A, Marchini S, Porcu L, **Zimmer TS**, Aronica E, During M, Abrahams B, Kondo S, Nishi T, Vezzani A (2021) Cholesterol 24-hydroxylase is a novel pharmacological target for disease modification in epilepsy. *submitted*

1. PhD training	Year	Workload (hours/ECTS)
General courses		
◦ ONWAR Introductory course	2016	0.9 ECTS
Specific courses		
◦ ONWAR Molecular Neurobiology	2017	1.4 ECTS
◦ ONWAR Neuropsychopharmacology	2017	1.4 ECTS
◦ ONWAR Functional neuroanatomy	2017	1.4 ECTS
◦ EUGlia PhD training activities 'How to study epilepsy in experimental mice'	2017	0.5 ECTS
◦ EUGlia PhD training activities 'Advancement in EEG recording- from a clinical perspective'	2017	0.5 ECTS
◦ EUGlia PhD training activities 'Formicablu: Science and media the current scenario'	2018	0.5 ECTS
Seminars, workshops and master classes		
◦ Swammerdam Lectures	2016-2019	0.7 ECTS
◦ ONWAR Annual PhD student retreats	2016-2019	2.7 ECTS
Presentations		
◦ Dutch Neuroscience Meeting, Lunteren, NL	2017	0.5 ECTS
Poster – 'Potential molecular mechanisms involved in the switch to an inflammatory state after oxidative stress'		
◦ SWO Midwinter meeting, Amsterdam, NL	2018	0.5 ECTS
Data blitz & Poster - 'NFκB is a key player in the switch to an inflammatory state after oxidative stress in the neuronal cell line SH-SY5Y'		
◦ EpiXChange meeting, Brussels, Belgium	2018	0.5 ECTS
Poster- 'Activation of the Nrf-2 signaling pathway in epilepsy and its modulation via miRNA-155 in human fetal astrocytes.'		
◦ Dutch Neuroscience Meeting, Lunteren, NL	2018	0.5 ECTS
Poster- ' Activation of the Nrf-2 signaling pathway in epilepsy and its modulation via miRNA-155 in human fetal astrocytes.'		
◦ ONWAR Annual PhD retreat, Woudschoten, NL	2018	0.5 ECTS
Data blitz & Poster - ' MicroRNA-155 modulates antioxidant and inflammatory signaling in astrocytes exposed to oxidative stress'		
◦ SWO Midwinter meeting, Amsterdam, NL	2019	0.5 ECTS
Data blitz & Poster – 'MicroRNA-155 modulates anti-oxidant and inflammatory signaling in human fetal astrocytes'		
◦ Bonn Brain Meeting, Bonn, DE	2019	0.5 ECTS
Poster- 'Dysregulation of the oxidative stress response in epilepsy: implications for microRNA 155'		
◦ European meeting on glial cells in health and disease, Porto, PO	2019	0.5 ECTS
Presentation & Poster 'MicroRNA-155 induces chronic activation of anti-oxidant signaling: implications in epilepsy'		
◦ Dutch Neuroscience Meeting, Lunteren, NL	2019	0.5 ECTS
Poster – 'Dysregulation of the oxidative stress response in epilepsy: implications for microRNA 155'		
◦ ONWAR Annual PhD retreat, Woudschoten, NL	2019	0.5 ECTS
Presentation- 'Chronic activation of antioxidant pathways and iron accumulation in epileptogenic malformations'		
◦ SWO Midwinter meeting, Amsterdam, NL	2020	0.5 ECTS
Data blitz & Poster- 'Oxidative stress and iron metabolism in seizure disorders'		
(Inter)national conferences		
◦ European meeting on glial cells in health and disease, Edinburgh, UK	2017	5 days

◦	GliaNed meeting, Risijwijk, NL	2017	1 day
◦	ONWAR Annual PhD retreat, Woudschoten, NL	2017-2019	2 days
◦	Dutch Neuroscience Meeting, Lunteren, NL	2017-2019	2 days
◦	SWO Midwinter meeting, Amsterdam, NL	2017-2020	1 day
◦	Amsterdam Neuroscience Event, Amsterdam, NL	2017, 2018	1 day
◦	EpiXChange meeting, Brussels, BE	2018	1 day
◦	Bonn Brain Meeting, Bonn, DE	2018, 2019	3 days
◦	European meeting on glial cells in health and disease, Porto, PO	2019	5 days
◦	Annual EUGlia PhD meetings	2017-2019	4-5 days
◦	EPICluster (EpiXchange II) meeting, online	2020	1 day
2. Teaching/Supervising			
		Year	Workload (hours/ECTS)
Supervising			
◦	Master student internship – Giulia Ciriminna	2018	6 months / 1.3 ECTS
'Effect of chronic oxidative stress on human fetal astrocytes'			
◦	Bachelor student internship – Sophie Jansen	2018	3 months / 0.7 ECTS
'Ferroptosis in Parkinson's disease and potential treatment options'			
◦	Supervision "Neuropathology Macroscopy" (twice annually for ONWAR PhD and Master students)	2018-2020	2 days / 0.5 ECTS
Other			
◦	Organizer young researcher symposium at the 'European meeting on glial cells in health and disease, Porto, Portugal'	2019	

Curriculum Vitae

Till Stephan Zimmer was born on the 6th of April 1991 in Bonn, Germany. He received his Abitur in 2009 from the 'Gymnasium Leopoldinum' in Detmold, Germany. Thereafter, he served alternative service for a year at the 'Lebenshilfe' institution in Detmold, Germany where he supervised and worked with people living with mental and psychiatric disabilities. Between 2010 to 2013 he studied 'Applied Biology' in Rheinbach, Germany at the 'Hochschule Bonn-Rhein-Sieg' which focused primarily on practical skills in the field of cell biology, microbiology and genetic engineering. Since his final aim was always to study neurosciences, he did his final thesis project investigating the endocannabinoid system in neuron-microglia communication at the 'Institute of Molecular Psychiatry' of the 'Friedrich-Wilhelms Universität Bonn' under the supervision of Prof. Dr. Andreas Zimmer. Building on that, in 2014 he started the master program 'Neuroscience' at the Rheinische-Friedrich-Wilhelms Universität Bonn. In the course of this, he took part in several internships investigating: 1. The lateral line system employing extracellular recording of the fish brain in the Institute of Neurobiology under supervision of Prof. Dr. Horst Bleckmann, 2. Inflammatory responses in CB2 KO mice in the Institute of Molecular Psychiatry under supervision of Prof. Dr. Andreas Zimmer, 3. Electrophysiological characterization using patch-clamp recordings and evaluation of single cell expression of cell-specific markers in astrocytes and NG2 glia in the Institute of cellular Neuroscience under supervision of Prof. Dr. Steinhäuser. His final thesis project built on his bachelor thesis project, investigating the CB2 receptor in inflammatory conditions using a novel CB2 transgenic reporter mouse at the Institute for Molecular Psychiatry under supervision of Prof. Dr. Andreas Zimmer. After receiving his master's degree he worked in 2016 as a bartender in a restaurant while applying for PhD positions. In January 2017, he joined the group of Prof. Dr. Eleonora Aronica at the Academic Medical Center in Amsterdam and started his PhD project focusing on inflammatory processes and oxidative stress in epilepsy, of which the results are presented in this thesis.

Acknowledgments

I think everyone that looks back at their PhD will agree that it requires a lot of self-motivation and determination, but also that a web of people surrounding and supporting you is equally important. I consider my time in Amsterdam as the period of steepest personal growth, which I owe to a number of people directly or indirectly involved in the creation of this thesis.

First and foremost my thanks go to you **Eleonora**. You are the mommy/puppet-master of the lab and I think everyone working closely with you cannot help themselves to admire your diligence, multi-tasking and objective-driven nature. I am especially appreciative of the freedom you gave me to explore different routes, finding my own path instead of strictly following the initial project I was hired for. I think that this way of working between us led to very interesting new perspectives on the lab's research lines and successful projects that reinforced my ongoing motivation for science. Apart from that I also appreciate the nature of your guidance and leadership which is not at all based on the sometimes typical academic hierarchy, always giving me the feeling that your door is always open (though physically it is often closed but you know what I mean). In addition to the liberty, I also highly appreciate the responsibilities you trusted me with be it (exciting) forms from the "European Commission" or writing manuscripts. This trust certainly helped me to build confidence in my writing skills and most importantly prepared me for the "other" bureaucratic duties that lie ahead if one wants to continue the path of science. Apart from the professional aspects I also valued that you always tried to enable people in their personal growth (which I am convinced is not easy at times) allowing everyone to reach out to you also on personal matters. All in all I think we are a good team that allowed me to reach all the goals I set for myself.

The next person on the line is obviously you **Erwin**. If I would have to guess, I probably listened to more words coming from your mouth than from anybody else. We often make jokes about that but this trait of yours undoubtedly created hilarious moments, be it in Homburg, during ecstatic borrels or just in the office. While science can be quite a serious endeavor you always managed to make it appear less serious to me, which by now I consider essential to keep one's motivation/sanity in the long run. Although, we often joke about your "On the one hand....(30 minutes later)....but on the other hand... (another 30 minutes)"-approach, I must say that I really valued your vague answers to questions, stimulating own thinking rather than giving a single answer likely not reflecting the most probable truth (however, sometimes it would have been nice to just answer "Good! And yours?" when I asked you about your weekend....just saying). Initially, a direct companion in the lab, your career path forced you to move out of the neuropathology to SILS in the middle of my project. Though, this was of course very sad in terms of chatty-chatty about science (and/or your neighbors' lawn at times), it also allowed me to become progressively independent and confident in my skills. As Eleonora, you always trusted in my decision making, leaving me the freedom to explore and shape the projects I worked on to my liking, while still providing valuable input. Apart from that you are of course invaluable to all manuscripts. Although your meticulous way of correcting our documents always evoked sighs and eye rolling once one would open the still rainbow-colored, corrected version of the "manuscript_final_final.doc" I have to say for myself (especially looking back) that this exercise was an integral part of my education in terms of accuracy and efficiency in scientific writing. Moreover, it taught me that an increase is rarely an increase and rather just higher/

more/elevated etc. (at this point I would like to thank the MS Word developers for the “Replace all”-function). I also have to say that our last adventure at Science Park that brought us back together, really highlighted the growth of our relationship from initially supervisory to (at least to me) more collegial. Similar to Eleonora, I never had the feeling of conflict, purely empowerment. Thank you.

To avoid any ranking of supervisors I also want to thank my “other” co-supervisor **James** (phonetic pronunciation: xa.mes). You came later to the party as supervisor, but provided valuable input long before your official function. To me you represent the torch of positivity, uplifting the spirit of everybody around you with your calm, analytical but overall positive attitude. Moreover, always having an open ear and valuable input, even when analyzing datasets from 6 projects at a time. Most importantly, if the supervision of Eleonora and Erwin was sometimes equivalent to a hurricane, your way of mentoring reminded me of the refreshing breeze between those storms. What I appreciated the most was sharing and discussing data with you. Oftentimes I was already excited about something I wanted to share with you, but your electrified eyes and fired up nature making you scratch marks into the carpet because of the meteoric dash using your wheeled office-chair towards my screen excited me even more. This was especially apparent and beneficial in light of my own, more pragmatic (I dare say German) nature as well as Erwin’s on-the-one-hand-on-the-other-hand approach. In addition to excitement, I also highly valued your scientific input, often coming from a different angle of big data rather than the single protein/RNA focus. This perspective certainly helped me to appreciate the omics side of things, triggered me to also explore this aspect (mostly with your help due to a lack of R skills) and, ultimately, also improved the quality of our publications. In addition, although not as extensive as Erwin, I also greatly benefited from your feedback to manuscripts and really enjoyed the process of writing the SPI1 paper together. Besides our professional relationship, I also always loved our conversations (most often with Anatoly) philosophizing about things, talking about overly specific knowledge from the NBA or unnecessarily exploring facts about Australia. I am glad we shared an office bouncing back and forth between quiet focus and relieving chats. If I would have to tell any person who I think is the incarnation of a good guy it would be you. Thanks mate.

Imagining the journey of a PhD as the metaphor of sailing on a ship through stormy weather, it is self-evident that it needs not only captains but also fellow sailors. **Anatoly**, over the years you promoted yourself from comrade to friend. Your scientific spirit and enthusiasm not only led to our many exciting lunch conversations, but also kindled me to know more about the world. Moreover, if there was a role model for a hard-working PhD that printed data (figure of speech of course....) and filled freezers with samples, trying to uncover mechanisms instead of merely describing them, it was you. In this you clearly were an example to me. And although many people did not agree with the way you did things (often based on prejudice towards a so called “Russian mentality”) I always respected you for the alternative to the norm. Apart from your scientific vigor, I think we grew especially closer towards the end of our projects. Both being ESRs, sharing rooms (and even beds like in Scotland leading to you slapping me on the face in your sleep...) on several occasions and many of the Marie-Curie-specific activities contributed to this shared experience. I think in our insatiable interest in the (scientific) world I would consider us brothers in spirit and I have to admit that I met few people in my life with whom I could spend as much time talking as with you (willingly that is...sorry Erwin). In doing so, you made me look at things from another perspective

(and this indeed probably comes down to our different countries of upbringing), often outside of the typical “Western” view. And although you saw yourself as someone not too fond of people, I had the feeling that you certainly cherished the ones you liked. Пусть твоё будущее будет светлым, мой друг.

If people consider the professor the parent of a group, then **Caro** is probably the sister in the neuropathology. On the outside a quiet, polite and always fancily dressed person, I discovered that you are quite the opposite. Although I am not sure how deep the abyss goes, your black humor certainly is strong. Besides, I think we (me) always had a lot of fun when you still sat with the back to the office door and fell victim to my many attempts to scare you. Thanks for always having an open ear, adding a less science-glorifying voice to conversations and always keeping me updated on all the gossip. And although you might have had your doubts, you were a big help to my work in bringing order to the chaos called databases, similar to Jasper saving a lot of time and effort that could be spend on other things. Also thanks for being a reliable source of laughter to my stupid jokes (I think there was some pity laughter in between). Cheers Caro.

Jasper! (JJJJJJJ) Such good times we had communicating purely in sounds (puzzling our co-workers), lavish gestures, face-in-a-holing, “essential” Youtube clips and new “Techno Bunker” finds. Thanks for always being the comedic relief on all of those days that could have been more boring or disappointing at times. Thank you also for the cutting and mounting of tissue (must have been kilo’s), that, if I would have done it myself, probably would have been unpublishable. You were always helpful and always made time for my many questions. Surprisingly, you also knew most answers if it came to finding something (even if it was located in bouwdeel W19). On average I would say that you required ca. 3 minutes to find things I was looking for over the course of weeks by just opening a random drawer of a cupboard I would have never seen before. Classic JayJay. Since I assume that fatherhood can be tiring, I hope I could also help you stay awake by always brewing the strongest coffee I could. Thanks for everything man.

Every stumbling, squeaking toddler-PhD needs someone holding their hand in the beginning. Thanks **Jackelien** for teaching me at the beginning of my project. Thanks for giving me the correct OCDish cues by audibly clearing your throat or scratching your feet on the floor when I would spill a drop of medium or uncontrollably poke my pipet in the general direction of the qPCR plate. And although we often made fun of that, in doing so you contributed greatly to the neat experimentation I aim for today. Dankjewel baas.

Similarly, **Andrea** helped me in the beginning. While we only shared a short period of time together, you sparked the topic I would work on and I would start to like (and talk about) so much: oxidative stress. Thanks for helping me in the beginning with all the small stuff and also teaching me in patience or how you would say: “We have to study.” Grazie mille.

Although I am almost gone, do not worry **Lucia** I will always be there (at least via email) to answer your trademark request: “Till I have a question for you.” (or alternatively: “Till! Can I ask you something?”). Of course you can. Unfortunately, you only were here part-time but I think we always had a good time and I hope your many projects succeed. I hereby pass the torch of the much better office room to you and hope you will take good care of it. Also a small shout out to **Anand** who I only met briefly, but introduced me to ELISA (nice girl....the method not Anand).

Marco and **Diogo** thanks for the hospitality in Milan. I really enjoyed my time there and learned a lot about *in vivo* experiments and the guineas. It was also nice to have you here Diogo and I hope you liked it as well. Moreover, you also functioned as my independent supervisor in the EU Glia consortium and now are also part of my PhD committee Marco. Unfortunately, we could not spend more time together, because the few times we did, I really enjoyed our conversations. I also think that our collaborative publication is a great example of European collaboration and spirit. Obrigado and grazie.

Anika, also we had a lot of fun. Although we did not share much in terms of projects, you certainly were an integral part of the core of people making my PhD experience. And if I needed help you still were there. Thank you.

Hester (Hes-T) though we did not spend much time together, the few times we hung out was always chill. From my perspective (German) I am deeply impressed by your omnipositive attitude and hope you will find the diet Anatoly always craved for. Success.

Now there is also a group of newcomers, I dare say baby-PhDs. We did not spend as much time (also due to a certain COVID virus) but I wish you all the success and hopefully an experience as nice as mine **Alessia, Annemieke and Mark**.

At this point I would also like to acknowledge **Bram** (Bramster) and **Durk** (Durkster) that certainly are an equally important part of the neuro-family. Thanks for the occasional conversations and help if needed. Also thanks for broadening my perspective on music Bramster (I would summarize your music taste as: absolutely random).

To all my colleagues upstairs thanks as well, be it for borrels, tips & tricks, reagents (especially to the kidneys) and general fun times. **Hildo** (Hildman) thanks for always being the chatty person upstairs. While everyone was in their own world (including me) you always were the social glue keeping things together, coming up to people, being talkative and always genuinely nice. Also helpful and from what I can tell (lymphocytes, cancer, something something, chemokines, MYD88) also knowledgeable. And before your fatherhood you certainly were the main engine behind hilarious borrel stories (voluntary as well as involuntary). Another important factor for the smooth operations upstairs certainly was the soothing bass of **Guus** (Guusta). Although many people might have misunderstood your seemingly grim glance through the window to the myco-positive side, I always saw right through your facade and know by now that your hard shell contains a rainbow shooting, puppy loving, squishy-squeaky heart (call me if you tear up reading this). Also thanks to **Timon and Jeroen** that were a staple core of pathology people reminding me of the Sith in Star Wars trying to destroy the empire (empire = miRNA research). Although you utterly failed in the end, it was still amusing to see you struggling. You were the best nemesis imaginable...a harmless one. If you read this thesis you might also notice that I had little to do with miRNAs....I appreciated your dry humor (I guess mostly Guus and Jeroen; Timon is more Teddy), but also how you always wanted to top each other's dry jokes like a puppy trying to catch its own tail (which was entertaining in itself). To not undermine your credibility as P.I., also thanks for the occasional flash of brilliance between the bullshit Jeroen. At this point special props to another side of this cynical group, to two of the nicest people: **Linda and Djera**. You are the necessary contrast to these dudes. Also thanks to my buddy **Jerry** (dʒærry dʒænsen) for sharing the passion for old-school hip-hop, as well as teaching me how to combust yellow pipet tips for his favorite girlfriend ELISA.

Was really nice having you around in the kweek and also seeing steak (?) and tick (?) immunos probably for the first and last time in my life. **Alessandra** grazie for your advice and the occasional reagents at times. As Anatoly mentioned in his thesis you guys really always had everything. Thanks **Nike**! Like Jasper for the neuro's, you are the mind behind the many things working without a second thought. Thanks for always having an open ear, solving problems, an always positive attitude and giving me the chance to practice my Dutch. Also a big thanks for the support to **Annemieke, Willem, Loes and Leonie**. Cheers also to my fellow co-workers **Martin, Marthe, Maria, Ryan, Zemin, Nathalie, Ingeborg, Tijmen, Sander, Naomi, Yvonne, Hans, Gerrit, Richard, Rogier, Per, Mahnouch and all the rest of our team**.

Auch vielen Dank an dich **Angelika** für die Hilfe und Zusammenarbeit bezüglich papers und reviews und deine letztlichen Bemühungen in Utrecht. Alles Gute für die Zukunft. Mein Dank geht auch an **Victoria** für die Zusammenarbeit bezüglich des Review-Artikels Gliopathie in TSC. Ich wünsche dir alles Gute. My thanks also go out to **Gabriele** for helping me with the data that culminated in a nice manuscript hopefully published soon. All the best for your future man. Grazie mille. Also grazie to **Prof. Vezzani**, I really enjoyed the collaboration with you. Shout out also to **Clifton**, it was always nice to meet you randomly. Grazie **Marianna** for the nice and enlightening conversations we had. In addition, I also have to thank you and your parents for letting me stay in your apartment in Milan, it was a pleasure. Of course I also have to acknowledge **René, Rijn and Frank** for dry humor and for helping to improve my Dutch or your German (mostly René). Cheers guys. Thank you also **Jan and Taco** for tips and tricks at Science Park and also **Helmut** for allowing me to conduct my experiments and also being part of my PhD committee.

Finally, thanks to the European Commission and the EU Glia consortium for funding my project. It was a blast. Special thanks go to my colleagues from my secondments: **Diogo** (again), **Lukas, Laura and Davide**. Moreover I would like to thank **Marco, Prof. Steinhäuser** and **Prof. Kirchoff** for allowing me to join their groups in the course of my secondments.

Lastly, I would like to acknowledge and declare my gratitude to and respect for the laboratory animals we used in conducting scientific discovery in this thesis.

Despite the importance of a nice working environment, there are people outside of the office/lab that have to be acknowledged. Because the connection with them is often much more fundamental and far-reaching than any single period in one's life.

When I first arrived in the Netherlands I did not anticipate I would meet a friend for life. However, with you **Luciano** (Luci) I felt an instant connection. Despite the living conditions, shady people and our busy lifestyle, the time on the campus in Diemen was amazing, rejuvenating and the set-up for a great friendship. I still remember like yesterday how we met in the gym the first time and you admired my pull-up/burpy workout from afar. And besides all the trash-talk we give each other, the different levels of "flashiness" in our lifestyle or our different craving for ready-made AH pancakes,

we share our love for nature, science, sports and for healthy competition. I value your openness, pro-active nature, honesty and kindness. We picked each other up in hard times during our period in Diemen and (at least from my side) trust each other completely. Thanks for all the adventures vecchio, be it on Sardegna or in Amsterdam. Maybe my (German) way of appreciation is not clear to you at times, but I really valued and still value you being at my side on this journey. To honor this connection I chose you as my paranymph, both to celebrate our friendship but also cherish your contribution. Thanks vecchio. Also thanks to you **Chiara** for joining the club, for sharing nice moments and for making Luci an overall better person.

Was soll ich dir sagen **Jan**. Nach meiner Familie die Person die ich schon am längsten kenne, mittlerweile beinahe die Hälfte unserer Lebenszeit. Zwischenzeitlich waren wir immer mal wieder getrennt, sei es als ich für mein Studium nach Bonn zog, oder du nach Amsterdam. Komischerweise haben wir immer wieder zueinander gefunden und das auch oft trotz zwischenzeitlicher Pausen. Die Zeit die wir uns kennen, die Dinge die wir schon miteinander erlebt haben und das Vertrauen was wir zueinander haben entspricht dem Klischee einer langen Freundschaft. Auch wenn unsere professionellen Lebenswege weit auseinandergehen, sehe ich dich immer als wichtige Konstante meines Lebens und somit auch des Abschnitts in Amsterdam den wir zwischenzeitlich teilten. Darum an dieser Stelle natürlich ohne Frage auch ein Danke an dich, Bruder. Egal wo ich demnächst sein werde, du bist dabei.

Auch wenn wir uns leider nicht mehr so oft sehen **Basti** (Buzzy), ist doch jedes Mal mehr als nice. Ich finde es Hammer, dass wir es am Ende geschafft haben zusammen ein kleines Projekt zu starten. Die kurze Zeit die ich in Bonn war und die Bonn Brain meetings waren auch mega. Ich finds zwar schade, dass du eventuell nicht mehr dem Weg der Wissenschaft folgst, aber wünsche dir trotzdem success (hoffentlich was worüber du reden darfst). Danke dir diggah.

Ein kleiner shout out an dieser Stelle auch an meine guten Freunde **Marco** (Embe) und **Oli** (Lollipopter), die ohne ihr Zutun und trotz ihrer Verpflichtungen als Familienväter doch noch weiterhin ein wichtiger Teil meines Werdegangs bis zu diesem Punkt sind. Unsere Zeit in Neunkirchen und während des Studiums ist zwar mittlerweile schon recht lange her, nichtsdestotrotz seid ihr trotzdem immer ein Anker nach Deutschland gewesen. Was ich an euch schätze muss ich glaub ich an dieser Stelle nicht ausführen (bei Marco ist es der heiße Hass und bei Oli die üppigen Waden). Danke kids.

Een grote dank en een geweldige knuffel gaat natuurlijk ook naar mijn uitgebreide familie **Broekaart**. Je hielp ons samenwonen en steunde altijd ons leven. We waren altijd welkom in Zeeland en dankzij jullie spreek ik ook een beetje Nederlands. Je zorgde altijd voor de belangrijke time-out vanuit Amsterdam tussendoor. Tot nog meer jaren. Bedankt schoonfamilie (**Lily, Pierre en Merten**).

Liebe **Mama**, ohne Frage ist der Dank an die Eltern in gewisser Weise obsolet, da man ohne sie niemals das Licht der Welt erblickt hätte. Ich denke trotzdem, dass das angebracht ist, da ich in gewisser Weise die Knetfigur deiner Erziehung war und dementsprechend alle Qualitäten die mir geholfen haben an dem Punkt anzugelangen an dem ich jetzt bin, meiner Erziehung verdanke. Danke für die absolute Unterstützung an die stärkste Frau die ich kenne, meine Mamer (Platz 2 ist Mecki). Im selben Atemzug auch danke an die immerwährende Unterstützung aus der Ferne an meine aunties

Sarah und Petra.

Danke **Vatter**, dass du dich beim Elternsprechtag für mich bei Herrn Leßmann eingesetzt hast. Ich bin mir sicher, dass das ein ausschlaggebender Faktor war, dass ich jetzt promoviere. Zweifellos habe ich auch von deiner uneingeschränkten Unterstützung und deinem allgegenwärtigen Zuspruch profitiert, sei es im Studium oder eben jetzt. Unsere Gespräche haben mir immer geholfen klarer zu sehen, das große Ganze im Auge zu behalten. Ich denke dieses Buch ist ein Zeichen dafür, dass deine Unterstützung gut funktioniert hat. Danke für alles Vatter.

Hey du, liebes Schwesterlein! Ich möcht' dir schenken diesen Reim. Und dir offen, ehrlich sagen, es ist schön, jemanden wie dich zu haben. Ich hoffe mit diesem schrottigen Reim konnte ich ein Lächeln auf dein Gesicht zaubern **Mecki**. Danke an dich, **Anton und Maria** für den support. Schön zu sehen wie wir gemeinsam erwachsen werden sister.

How does a pot keep its food warm without a lid on it? If a pot boils too violently and things threaten to splash everywhere, the lid keeps everything contained. However, if the pot boils for too long without its lid, its contents vaporize, burn or disappear. If the pot forgets the birthday of a friend, the lid is there to remind him with its intricately organized calendar (compared to the pot's napkin with unreadable writing). A pot without a lid is only half its worth. My lid is **Didi**. It fits perfectly. Dankjewel voor alles bab.