New avenues in PET imaging of multiple sclerosis
Paula Faria, Daniele de

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2014

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Acknowledgments
After the work of my last 3 years has been described in this thesis, it is time to say thank you to who, directly or indirectly, was part of it.

**Rudi Dierckx**, my first promoter, who allowed me to come to Groningen and learn so much with the NGMB team, thank you for the opportunity.

**Carlos Buchpiguel**, my second promoter, thank you for having recommended me to go to Groningen for the PhD program and for the support during these three years, and especially for receiving me back in the institution where my interest in radiopharmacy started.

**Erik and Sjef**, my co-promoters and daily supervisors, it is so hard to express all my gratitude for you both. I used to say to my colleagues that I was really lucky to have you as my supervisors, each one of you, expert in your field, making my supervision complete.

**Erik**: I learned so much during these 3 years with you! You were always there to discuss experiments and results. I learned how to think as a researcher, at least try, during our discussions, whether in our weekly meetings or in the lab. Your questions and suggestions, although not easy most of the time 😊, made this project progress and give nice results. You gave me the freedom to think and the opportunity to learn different things and techniques, making my time in Groningen unforgettable. I am pleased in knowing that we are still going to work together. All my gratitude to you!

**Sjef**: I liked this project in the first time I read it and it was really nice to work on it. It was nice to discuss problems with you and find alternatives to them. I remember the first day we perfused an animal together, I was so inexperienced, but few months later, when you followed me doing a mouse brain biodistribution, you told, “I am impressed how much you learned”... you made me really proud of myself. You taught me a lot of techniques, including stereotactic surgery and immunohistochemistry analysis. I had a wonderful experience working with different animal models, learning with your expertise. Most importantly, you trusted and helped me during these 3 years... Thank you very much!
Erik and Sjef, I could not forget to thank you also for the help during the thesis preparation. Your fast corrections and precious comments made my earlier defence possible.

**Reading committee:** I would like to thank Prof. dr. Erik Boddeke, Prof. dr. Peter Paul de Deyn and Prof. dr. Jan Booij, for spending time reading this thesis and for their kind comments.

**Fabio Marques:** you introduced me to the research 11 years ago and since then, I wish to work as a researcher. You believed and trusted in my potential and, because of that, recommended me to come to Groningen for a PhD. I will never be able to say thank you enough for the opportunity you gave me. Besides all gratitude I have for you, I consider you as a friend and an inspiration. Obrigada pelo passado, presente e futuro de trabalho juntos.

**Inês:** I met you in my interview in Groningen and I already felt that we could be friends, but I could not expect that we would be SISTERS. You are so sweet, friendly and helpful that I have all pride in the world to call you my sister. We shared moments of complete happiness, but also difficult moments, whether at work or personal life. Many days working until late, where the company of each other made it easier. You taught me many things in the lab, always so helpful and calm (except for few occasions, 😊), that even purification by column seemed to be a nice thing to do (although, making it alone I realized that it is really boring). You received me in your home with open arms and a lot of delicious food, 😊, I felt like I was in my home. You made my time in Groningen much easier and nicer and, because of that it was so hard to say good bye to you. Thanks for everything my sister and my paranymph! I miss you a lot!

**Jurgen:** you were my “right arm” during my PhD. Always ready to help me any time and many times... The work presented in this thesis would not be possible without you. I have to confess that I gave you hard time, more than 70 cannulations in one DEC, where 4 cannulations were during your holidays that you came to the NGMB only to help me! Also the nightmare of tail cannulation of the EAE model, study that was really hard for us... I also had your professional work as “camera man”, making all nice movies and pictures in my experiments! To finalize,
you gave the pleasure in being my paranymph. I have no words to express all my gratitude to you, but please, be sure that it is enormous. Thank you VERY MUCH!

**Bram:** Could I thank you in Portuguese already? Just to be sure, I will write in English, OK? My dear friend you were so important during these 3 years... In the lab you were always there to solve my problems (what was a lot), you were always ready for answering/explain doubts, really helpful all the time! You are so sweet, outgoing, explosive and kind at the same time! We also had a really nice time outside of the lab: barbecue days with Karol, our group trips and many dinners together... Thank you very much for everything and also for being my “personal adviser” after I moved to Sao Paulo! Thanks a lot!

**Chantal:** you are so kind! I really liked to work with you! You were always there to teach and help in the lab. Besides the wonderful colleague in the lab, you are my friend, it is really nice to spend time and talk to you about anything!!! I miss you!

**Andrea:** Oi Bello!!! I was thinking if I should write this message in English or in Portuguese....as you can see, I decided to write in English, because then, everybody could read it and know how special you were/are for me! In the beginning, you were an Italian, who likes Brazil and know how to speak Portuguese, but then we start to know each other, especially when you moved to our office, and then you became my nice and dear friend!! We worked a lot together and it was always nice... Even how to cannulate animals you learned only to help me! Anytime I needed, you were there ready to help. Besides to be this kind and stylish friend, you are a really good bike fixer and a wonderful cooker! I have all reasons to thank you very much for all time we spent together in the last 3 years and say that we will probably see each other really often, since you want to live in Brazil! To finish, I express all my gratitude and ask you one more favor: please, keep your hair short!!! 😊

**Alex:** we met in the airport going to Groningen for our interview, but then you started at NGMB 1 year after me... It does not look like we shared the same office for only 1 year, we became friends really fast and easily (although I know I am not easy person, ☺). You were always there when I needed, always ready to help me.
Of course, I could not forget to thank you for the nice time together outside of the work: dinners, barbecues and trips!!! You were/are my Brazilian friend in Groningen and I am sure we will still be friends in Brazil. Thanks!

**Mehrsima**: my dear! We did not work in the lab together, but the moments we shared in our office were precious... You are so intelligent and work so hard... it was really nice to come back to the office, after many hours of work, and find you still there... and still have a nice conversation before going home! I also have to say that you were my match for the temperature in our office, 😊... you help me to leave that office warm and pleasant.

**Lian**: I have to confess that you were a really nice surprise for me. I did not expect to have a master student so dedicated and helpful as you were. You helped me a lot in the long days of stereotactic surgeries and PET scanning. I am sorry for the late lunches!!!

**Philip**: your questions during Monday morning meeting presentations and during routinely work in the lab were really helpful. Thank you also for the experience in the GMP lab.

**Antoon**: thanks for sharing your knowledge about kinetic modeling and for discussing results with me. You accepted to give a really nice presentation for the PhD students and gave me extra explanations before leaving Groningen. It was really nice of you, thanks!

**Aren**: Thank you for being so kind and helpful any time I needed your help.

**Hilde**: you helped me a lot in the lab and with ordering material, thank you! I will remember the many early mornings we were together in the PET lab, only us before 7:30 am, preparing Rooty and Resy for synthesis!!!

**Gert**: thanks for allowing me to be in the planning (and have beam) so often during these 3 years.
Acknowledgments

**Michel Koole:** thanks for helping me with image reconstruction problems and also for reviewing part of my thesis. I also would like to thank you for the help in Sao Paulo with the “new” problems I was/am dealing with.

**Miriam van der Meulen-Frank:** welfare officer of CDP. Thank you very much for your help, showing the best and respectful way to work with animals. Our meetings were always helpful.

**CDP:** thanks to everybody from the animal facility for helping with animal matters. Special thanks to the microsurgery team and animal caretakers from the isotope unit.

**TNO (José, Frans, Herma and Marijn):** It was a pleasure to collaborate with you in the EAE study, and learn with your experience!!!

**Ietje:** you showed me how to cut “perfect” brain sections (without bubbles!!!) and make a nice staining. Thank you very much for your time and for sharing your expertise with me.

**Annegrit:** thanks for your help during my PhD and especially during my extension.

**Sarita:** your help was really important to solve administrative issues and in the PhD defence process. Thank you!

**Trix:** thanks for helping me with ordering material and paper work in the neuroscience department.

**Valentina and Giuseppe:** it was so nice to have you both as friends. Vale, your intelligence and way to work were an inspiration, besides the delicious Tiramisu you make of course, and I also have to say thank you for trusting me with part of your work when you left Groningen. Giuseppe: I have to say that the first thing that comes to my mind when I hear your name is your jokes in my office. We already knew who was responsible when something thing was not working or in the wrong place in my office 😊. However, I had the opportunity to work together
with you, and I can say, you are so good worker as you are a good joker (That is a compliment)!

Mariangela: It was really nice to meet you and share the same office, although not for long time. You are really sweet and really easy to work with. I admire you, especially to be able to live with those 2 crazy guys!

Nathalie: we shared a lot of time in the lab and it was a pleasure to see you working so hard (so many reactions at the same time). Thanks for the company during the long days and sometimes weekends!

Janine, Ate and Gaurav, thanks for all your help and fruitful discussions during the last 3 years.

For all other colleagues (David, Khayum, Leila, Vladimir, Siddesh, Shiva, Anniek, Nisha, Xiaoyum, Willem Jan, Ewelina, Heli, Ilia and Marcin): Thank you for the nice time shared in last 3 years (I am sorry if I forgot someone).

Rolf, Michel, Joost, Marianne and Petra: It was a pleasure to work with you all in the lab. Thank you for your help and for making the lab a place so nice to work.

NGMB and Neuroscience departments: thanks for everybody! It was really nice to be part of these two departments for the last 3 years.

Fabio Duran: muito obrigada pela ajuda na formatação das imagens para os meus artigos. Sua precisão e paciência fizeram as figuras muito mais bonitas!!!

Koos and Simone: it was a pleasure to stay for 2.5 years in your house. You made my stay much easier; after many hours of work, I always felt like I was arriving at home. Thank you!

Minha família (pais – Nivaldo e Neusa; irmãos – Marcio e Daiane e sobrinha - Beatriz): não foi fácil ficar tão longe por tanto tempo, mas o apoio de vocês foi essencial para o sucesso deste trabalho. Muito obrigada pelo apoio e compreensão.
Minha família 2 (Tio João, Tia Cida, Lenycia, Júnior e Letícia): obrigada pela acolhida e apoio em São Paulo em todos os momentos que eu precisei.
List of abbreviations
List of abbreviations

1TCM  One tissue compartment model
2TCM  Two tissue compartment model
2TCMR Reversible two tissue compartment model
AIC   Akaike information criterion
AUC   Area under the curve
BBB   Blood-brain barrier
Bq    Becquerel
\[^{[11}C\] Carbon-11
\[^{[11}C\]CIC \[^{[11}C\]Case imaging compound
\[^{[11}C\]MeDAS \[^{[11}C\]Methyl diaminostilbene
\[^{[11}C\]PIB Pittsburg compound B
CNS   Central nervous system
DA rat Dark Agouti rat
DEX   Dexamethasone
EAE   Experimental autoimmune encephalomyelitis
\[^{[18}F\] Fluor-18
\[^{[18}F\]FB-IL2 N-(4-[18F]fluorobenzoyl)interleukin-2
\[^{[18}F\]FDG \[^{[18}F\]Fluorodesoxiglucose
\[^{[18}F\]SFB N-succinimidyl 4-[18F]fluorobenzoate
FCS   Fetal calf serum
HPLC  High performance liquid chromatography
IFA   Incomplete Freund’s Adjuvant
Iba1  Ionized calcium binding adapter molecule 1
i.p.  intraperitoneal
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_i$</td>
<td>Metabolic rate</td>
</tr>
<tr>
<td>LFB</td>
<td>Luxol fast blue</td>
</tr>
<tr>
<td>LOR</td>
<td>Line of response</td>
</tr>
<tr>
<td>LPC</td>
<td>Lysolecithin, lysophosphatidylcholine</td>
</tr>
<tr>
<td>MBP</td>
<td>Myelin basic protein</td>
</tr>
<tr>
<td>MOG</td>
<td>Myelin oligodendrocyte glycoprotein</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MS</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>NGS</td>
<td>Normal goat serum</td>
</tr>
<tr>
<td>OPC</td>
<td>Oligodendrocyte precursor cell</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PPMS</td>
<td>Primary progressive multiple sclerosis</td>
</tr>
<tr>
<td>PRMS</td>
<td>Primary relapsing multiple sclerosis</td>
</tr>
<tr>
<td>RRMS</td>
<td>Relapsing-remitting multiple sclerosis</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of interest</td>
</tr>
<tr>
<td>SPMS</td>
<td>Secondary progressive multiple sclerosis</td>
</tr>
<tr>
<td>SUV</td>
<td>Standardized uptake value</td>
</tr>
<tr>
<td>TAC</td>
<td>Time activity curve</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin-layer chromatography</td>
</tr>
<tr>
<td>TSPO</td>
<td>Translocator protein 18kDa</td>
</tr>
<tr>
<td>$V_T$</td>
<td>Volume of distribution</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>