



Universiteit
Leiden
The Netherlands

From stem cells to functional lymphocytes: cell differentiation and gene therapy implementation for RAG-SCID

García Pérez, L.

Citation

García Pérez, L. (2021, October 6). *From stem cells to functional lymphocytes: cell differentiation and gene therapy implementation for RAG-SCID*. Retrieved from <https://hdl.handle.net/1887/3214836>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/3214836>

Note: To cite this publication please use the final published version (if applicable).

ACKNOWLEDGEMENTS

I would like to express my gratitude and appreciation to all the people who in some ways have helped me to complete this work and without whom I would not have made it through my PhD degree.

First of all, I would like to thank my promotor and co-promotor of this thesis, Frank Staal and Karin Pike-Overzet, for accepting me as a PhD student after my master thesis in the group and trust me to work in this complex but rewarding project. Thank you both for your continuous support, guidance and knowledge during these last 5 years and a half. Many thanks for giving me freedom during my experiments and the projects, and for giving me many opportunities to share our work in meetings and conferences worldwide allowing me to grow and meet.

This adventure, that started during my master internship, would not have been possible without all the members (past and present) of the Staal group. I learned a lot as a student which help me to start my PhD smoothly. Thank you Lieke and Marcel from the department for your support and expertise on in vivo work during this trajectory. Special thanks to Marja and Sandra for your exceptional daily assistance, support and advice in the lab and office (rather offices). Besides, thank you Jolanda, Amiet, Anita, Kirsten, Stefanie and Imen for the shared time together. I would like to thank my fantastic PhD colleagues Parisa, Veronica, Xiaolin and Martijn for the mutual support in this journey, the long hours shared in the lab, dinners, drinks, and adventures. Thanks, Martijn for sharing your bioinformatic knowledge and team up with me. I will keep some sweets nearby, so you can visit me from time to time as you did in the office. Finally, a key part of this journey was shared with enthusiastic students (Melina, Saskia, Federica) joining the group with fresh energy and sharing good moments re-discovering The Netherlands. Especial thanks to you Elisa Maietta. I totally enjoyed teaching and supervising you during your internship. Thank you for appearing and joining as a student and a friend with your infinite energy.

Thanks to the former and present members of the (IHB) department of Immunology, especially to Jacques van Dongen group, for the valuable discussions, advice, shared knowledge and pleasant activities/borrels. Especial thanks to Edwin for your flow cytometry expertise essential for this work and the other members of the flow cytometry facility for their support and time along all FACS analysis and sortings. I also would like to thank the animal facility of the LUMC for their assistance during animal experiments. Thanks also to the Pediatris department of the LUMC for sharing precious samples with me and Arjan, Marco and Dagmar for the valuable collaborations. Thanks to all the partners involved in SCIDNET and RECOMB, I enormously enjoyed our pleasant meetings in the different locations and great collaborations.

I would also like to thank the people with whom I had the opportunity to share good times outside work. Thanks to the Gang of Leiden for the lovely time learning Dutch (at least trying), dinners, travels, and movie nights (especially during Covid times). Gracias Susana por tu alegría y energía infinita en cada clase de zumba, siempre un buen momento de aire fresco y de recargar pilas sobretodo en las temporadas más difíciles y cansadas. Gracias también a Marta y Gemma por mantener nuestro ritual de viajar juntas una vez al

año, una excusa buenísima para reencontrarnos, vivir nuevas aventuras juntas y volver a Holanda con fuerzas renovadas.

Mil gracias a mis chicas de Cappont que, por estar ahí siempre presentes, apoyando y compartiendo momentos juntas. Que ganas de un nuevo reencuentro de los nuestros donde se para el tiempo después de tantos meses, de conocer a los nuevos miembros de esta familia y con muchas ganas de ver como sigue creciendo.

No puc oblidar-me de vosaltres, Noe, Sara i Meri, el meu pilar andorrà. Gràcies per estar sempre allà i no oblidar-vos de mi en la distància. Gràcies per poder comptar amb vosaltres sempre, encara que no puguem compartir tants moments com m'agradaria.

Quero agradecer-te a ti também Hugo o teu apoio e generosidade. Tu ensinaste-me a trabalhar desde casa. Sem o teu apoio, escrever esta tese não teria sido o mesmo. Obrigada por confiares em mim e por conseguires sempre tirar a melhor versão de mim mesma. Obrigada por partilhares esta fase da vida comigo.

Por último, me gustaría agradecer el apoyo incondicional de mi familia. Gracias a mis padres, Armando y M^a Jesus, y a mi hermano, Sergio, por aceptar que al elegir esta carrera seria difícil volver a casa y darme alas para seguir y volar. Gracias por confiar en mi y por vuestra ayuda siempre que la he necesitado y abrimme las puertas para llegar hasta aquí.

CURRICULUM VITAE

Laura García Pérez was born on June 7th, 1990, in Andorra La Vella, Andorra. After graduating from Lycée Comte de Foix in 2008 (Andorra), she moved to Spain where she followed her bachelor's degree in biotechnology at the University of Lleida. For the last 6 months, she entered the Erasmus Programme and was able to pursue her studies at Hedmark University, Norway. After obtaining her diploma in 2012, she moved to the Netherlands and started in 2013 her master program in Biomedical Sciences, research specialization, at Leiden University Medical Center (LUMC). During this period, she performed two research internships within the LUMC: one at the Nephrology Department on type-2 diabetes and a second one in the Stem Cells and Lymphocyte Development group at the Department of Immunology. Her master thesis focused on understanding the role and functional definition of T cell-specific transcription factors regulating T lymphocyte lineage commitment. She graduated with her master's degree in 2015.

Soon after, January 2016, she started her PhD at the same department in the Stem Cells and Lymphocyte Development research under the supervision of Prof.F.J.T. Staal and Dr. K.Pike-Overzet. Her main focus is to develop hematopoietic stem cells-based gene therapy for severe combined immunodeficiencies due to Recombinase-Activating Gene deficiency and optimizing related protocols under the European Union's Horizon 2020 research and innovation programme SCIDNET.

LIST OF PUBLICATIONS

1. Staal, F.; Famili, F.; Garcia Perez, L.; Pike-Overzet, K., Aberrant Wnt Signaling in Leukemia. **2016**, 8 (9), 78.
2. Famili, F.; Perez, L. G.; Naber, B. A.; Noordermeer, J. N.; Fradkin, L. G.; Staal, F. J., The non-canonical Wnt receptor Ryk regulates hematopoietic stem cell repopulation in part by controlling proliferation and apoptosis. *Cell Death & Disease* **2016**, 7 (11), e2479-e2479.
3. Roefs, M. M.; Carlotti, F.; Jones, K.; Wills, H.; Hamilton, A.; Verschoor, M.; Williams Durkin, J. M.; Garcia-Perez, L.; Brereton, M. F.; McCulloch, L.; Engelse, M. A.; Johnson, P. R. V.; Hansen, B. C.; Docherty, K.; De Koning, E. J. P.; Clark, A., Increased vimentin in human α - and β -cells in type 2 diabetes. *Journal of Endocrinology* **2017**, 233 (3), 217-227.
4. Rahman, S.; Magnussen, M.; León, T. E.; Farah, N.; Li, Z.; Abraham, B. J.; Alapi, K. Z.; Mitchell, R. J.; Naughton, T.; Fielding, A. K.; Pizzey, A.; Bustraan, S.; Allen, C.; Popa, T.; Pike-Overzet, K.; Garcia-Perez, L.; Gale, R. E.; Linch, D. C.; Staal, F. J. T.; Young, R. A.; Look, A. T.; Mansour, M. R., Activation of the LMO2 oncogene through a somatically acquired neomorphic promoter in T-cell acute lymphoblastic leukemia. **2017**, blood-2016-09-74.
5. Mansour, M. R.; He, S.; Li, Z.; Lobbardi, R.; Abraham, B. J.; Hug, C.; Rahman, S.; Leon, T. E.; Kuang, Y.-Y.; Zimmerman, M. W.; Blonquist, T.; Gjini, E.; Gutierrez, A.; Tang, Q.; Garcia-Perez, L.; Pike-Overzet, K.; Anders, L.; Berezovskaya, A.; Zhou, Y.; Zon, L. I.; Neuberg, D.; Fielding, A. K.; Staal, F. J. T.; Langenau, D. M.; Sanda, T.; Young, R. A.; Look, A. T., JDP2: An oncogenic bZIP transcription factor in T cell acute lymphoblastic leukemia. *The Journal of Experimental Medicine* **2018**, jem.20170484.
6. Cordes, M.; Pike-Overzet, K.; Van Eggermond, M.; Vloemans, S.; Baert, M. R.; Garcia-Perez, L.; Staal, F. J. T.; Reinders, M. J. T.; Van Den Akker, E. B., ImSpectR: R package to quantify immune repertoire diversity in spectratype and repertoire sequencing data. *Bioinformatics* **2019**.
7. Garcia-Perez, L.; van Eggermond, M.; van Roon, L.; Vloemans, S. A.; Cordes, M.; Schambach, A.; Rothe, M.; Berghuis, D.; Lagresle-Peyrou, C.; Cavazzana, M.; Zhang, F.; Thrasher, A. J.; Salvatori, D.; Meij, P.; Villa, A.; Van Dongen, J. J. M.; Zwaginga, J.-J.; van der Burg, M.; Gaspar, H. B.; Lankester, A.; Staal, F. J. T.; Pike-Overzet, K., Successful Preclinical Development of Gene Therapy for Recombinase-Activating Gene-1-Deficient SCID. *Molecular Therapy - Methods & Clinical Development* **2020**, 17, 666-682.
8. Garcia-Perez, L.; Ordas, A.; Canté-Barrett, K.; Meij, P.; Pike-Overzet, K.; Lankester, A.; Staal, F. J. T., Preclinical Development of Autologous Hematopoietic Stem Cell-Based Gene Therapy for Immune Deficiencies: A Journey from Mouse Cage to Bed Side. *Pharmaceutics* **2020**, 12 (6), 549.
9. Garcia-Perez, L.; Famili, F.; Cordes, M.; Brugman, M.; Van Eggermond, M.; Wu, H.; Chouaref, J.; Granado, D. S. L.; Tiemessen, M. M.; Pike-Overzet, K.; Daxinger, L.;

Staal, F. J. T., Functional definition of a transcription factor hierarchy regulating T cell lineage commitment. *Science Advances* **2020**, 6 (31), eaaw7313.

10. Garcia-Perez, L.; Van Eggermond, M. C. J. A.; Maietta, E.; Van Der Hoorn, M.-L. P.; Pike-Overzet, K.; Staal, F. J. T., A Novel Branched DNA-Based Flowcytometric Method for Single-Cell Characterization of Gene Therapy Products and Expression of Therapeutic Genes. *Frontiers in Immunology* **2021**, 11.

11. Garcia-Perez, L.; Van Roon, L.; Schilham, M. W.; Lankester, A. C.; Pike-Overzet, K.; Staal, F. J. T., Combining Mobilizing Agents with Busulfan to Reduce Chemotherapy-Based Conditioning for Hematopoietic Stem Cell Transplantation. *Cells* **2021**, 10 (5), 1077.

