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Dysregulation of autoreactive B cell responses in autoimmune diseases: from initial triggering to persistent activation

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PhD Portfolio

PhD trajectory overview

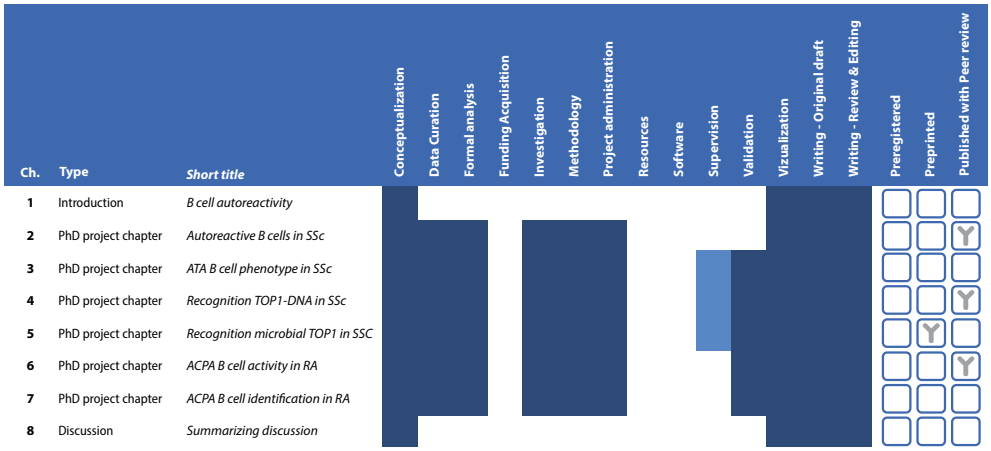
Sam started his PhD trajectory in the research group of Prof. Dr. Uli Scherer and Prof. Dr. Rene Toes in September 2020 with the aim to unravel mechanisms underlying the dysregulation of autoreactive B cells in autoimmune diseases. His first project focused on the relation between the activity of autoreactive B cells and clinical disease activity in rheumatoid arthritis (RA). With initial help of Nienke Blomberg and Sanne Kampstra, a previously established experimental technique of the lab was applied to phenotypically characterize autoreactive B cells in RA patients treated with different anti-inflammatory drugs. Interestingly, Sam found that autoreactive B cells in RA are highly active irrespective of clinical disease activity and treatment. The findings of this project are presented in chapter 6 and were shared with the scientific community by publication of a manuscript in a peer-reviewed journal and by presentations during scientific meetings. In addition, during this project, the inefficient identification of a subset of autoreactive B cells prompted the idea to optimize the method used to identify autoreactive B cells in RA. The optimized approach enabled to track the dynamics of autoreactive B cells in RA in more detail. This method is presented in chapter 7 and is currently broadly applied by other colleagues in the lab.

In parallel with his work on autoreactive B cells in RA, Sam started working on a project focusing on the autoreactive B cell response against topoisomerase 1 (TOP1) in systemic sclerosis (SSc). This project was triggered by interesting findings generated by Corrie Wortel and initially consisted of the acquisition of tools to investigate the TOP1-reactive B cell response, which included the generation of TOP1 (in collaboration with Robbert Kim, protein facility LUMC), patient-derived monoclonal antibodies and TOP1-reactive B cell lines. A serendipitous finding on the generated TOP1-reactive monoclonal antibodies led to a study in which the molecular characterization of anti-TOP1 autoantibodies identified DNA binding by TOP1 as important determinant of the immunostimulatory properties of TOP1 and of the potential of TOP1 to stimulate autoreactive B cells. This detailed characterization was possible through collaborations with Danique van Rijswijck (lab of Albert Heck, University Utrecht) and Martina Erbì (lab of Bart Everts, LUMC). In addition, Sam supervised student Marjolein Wetzels who also contributed to this project. Findings of this project, presented in Chapter 4, were shared with the scientific community by publication of a manuscript in a peer-reviewed journal and by presentations during scientific meetings.

The next step in the PhD trajectory of Sam was to explore a potential role of microbes in stimulating the autoreactive B cell response targeting TOP1 in SSc. Based on TOP1 from a fungus, which was obtained by a collaboration with Theo van Laar (lab of Nynke Dekker, TU Delft), Sam demonstrated cross-recognition of TOP1-reactive antibodies towards TOP1 of microbial origin. With help of clinical researchers Sophie Liem and Jeska de Vries-Bouwstra, presence of these cross-reactive antibodies could be linked to clinical features of SSc. The findings of this project, also presented in Chapter 5, were used in a patent application and are publicly shared on a preprint server. In this project, Sam (co-) supervised exchange student Runa Ozaki and PhD candidate Tessa Liesker, who continues to work on this project.

Alongside the characterization of the reactivity of autoantibodies in SSc, Sam also investigated the B cell response against TOP1 in SSc on the cellular level. He established a staining method capable of identifying TOP1-reactive B cells which was applied to determine the phenotypic and functional characteristics of these cells. Interestingly, these TOP1-reactive B cells display a highly activated and proliferative phenotype in SSc. In addition, together with Renee van de Wetering and Wieke van Oostveen, strong clonality of this autoreactive B cell response was observed. During this project, Sam supervised student Jens van der Meer. Findings of this research project, which resulted in Chapter 3, were presented during an information meeting for SSc patients and various scientific meetings.

Credit Table



Overview of completed courses/training and other scientific activities

Scientific courses, workshops and other training activities

Month/Year	*Title*	*Hours*
09/2020	Flow cytometry beginner course	5
11/2021	Cytoflex SRT cell sorter training	5
01/2022	Leiden Institute for Immunology - PhD Course Infection and Immunity	40
04/2022	Spectral flow cytometry course	5
03/2022	Dutch Society for Immunology - Lunteren Symposium	16
05/2022	Dutch Society for Immunology - Annual Meeting	16
11/2022	Target2B Consortium - Closing Symposium	12
12/2022	Dutch Society for Immunology - Annual Meeting	16
06/2023	Keystone Symposium: B Cell Biology in the Context of Infection Diseases, Autoimmunity and B Cell Cancers	32
11/2023	Dutch Society for Immunology - Joint Belgian-Dutch Immunology Meeting 2023	16
01/2024	LUMC - Boerhaave Symposium	3
02/2024	Experienced competency test flow cytometry - Cytoflex SRT + spectral flow cytometry	4
07/2024	EMBO Workshop: Lymphatic Tissues and Germinal Centres in Immune reactions	28
12/2024	Dutch Society for Immunology - Annual Meeting	16
12/2024	ImmuneHealthSeed - Consortium meeting	4
11/2024	LUMC Research Conference	3

Mandatory activities

Month/Year	*Title*	*Hours*
02/2020	PhD introductory Meeting	10
01/2021	Basic methods and reasoning in Biostatistics	42
09/2022	eBROK	42

Transferable skill courses, workshops and other training activities

Month/Year	*Title*	*Hours*
12/2021	Data visualization workshop	1
12/2021	CV building workshop	1
03/2022	Van Aula naar Binnenhof - workshop	6
09/2022 - 05/2023	Supervision of Master student Biomedical Sciences for Junior Research Project 2	80
05/2023 - 07/2023	Supervision of Master student Biomedical Sciences for Scientific Review	12
06/2023	Career Roundtable Discussion at Keystone Symposium	2
01/2024 - 01/2025	Supervision of Master student Biomedical Sciences for Junior Research Project 1	74
01/2024 - 03/2024	Supervision of research intership of exchange student from Japan	40
04/2024	Workshop - Career opportunities after the PhD	2
04/2024 - 08/2025	Co-supervision of PhD student	80
07/2024	Meet-the-speaker lunch at EMBO Workshop	2
09/2024 - 10/2024	Academic Writing for PhDs - workshop	56
10/2024	Workshop thesis printing	1
11/2024	Job Search skills	12
01/2025	Data analysis using R	42

Other scientific activities related to this thesis

Month/Year	*Title*	*Linked to ch.*
06/2023	Poster presentation - Keystone Symposium: B Cell Biology in the Context of Infections Diseases, Autoimmunity and B Cell Cancers	6
11/2023	Oral presentation - Joint Belgian-Dutch Immunology meeting	4
07/2024	Poster presentation - EMBO Workshop: Lymphatic Tissues and Germinal Centres in Immune Reactions	6
08/2024	Oral presentation - Jubileumdag zorgpad sclerodermie	3
10/2024	Oral presentation - ImmuneHealthSeed consortium meeting	6
10/2024	Oral presentation - CTD-ILD Rheumatology Preceptorship program	3
12/2024	Poster presentation - Dutch Society for Immunology Annual Meeting	3
01/2025	Oral presentation - B cell meeting (LUMC)	3, 4
10/2025	Patent application - Patient stratification in systemic sclerosis	5

Curriculum vitae

Sam Neppelenbroek was born on the 30th of May in 1997 in Drijber, The Netherlands. In 2015, he completed his pre-university education (VWO) at RSG Wolfsbos in Hoogeveen. Subsequently, he started his Bachelor's study Biology at the University of Groningen. His Bachelor's thesis focused on the effector mechanisms of antibodies directed against influenza virus under the supervision of Prof. Dr. Anke Huckriede (University Medical Center Groningen). He completed his Bachelor's degree in Biology (*cum laude*) and the Honours Bachelor's Programme in 2018. He then proceeded with the Master's study Molecular Medicine and Innovative Treatment at the University of Groningen during which he completed research internships on the interaction between B cells and epithelial cells in Sjögren's syndrome (lab of Prof. Dr. Frans Kroese and Dr. Sarah Pringle, University Medical Center Groningen) and on the role of T-bet in B cells residing in inflamed tissue (lab of Prof. Dr. Andreas Hutloff, Deutsche Rheuma-Forschungszentrum, Berlin, Germany). In 2020, he obtained his Master of Science degree (*cum laude*). Based on his profound interest in the biology of B cells, he started his PhD trajectory at the Rheumatology department of the Leiden University Medical Center under supervision of Prof. Dr. Hans Ulrich Scherer and Prof. Dr. René Toes. During his PhD, he studied the dysregulation of autoreactive B cell responses in the autoimmune diseases rheumatoid arthritis and systemic sclerosis. Following his PhD, he continued his scientific career as a postdoctoral researcher studying B cells in the context of chronic viral infections by joining the lab of Prof. Dr. Daniel Pinschewer in 2026 at the University of Basel, Switzerland.

Publications

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[#]Authors contributed equally.

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Mijn promoteren wil ik bedanken voor de leerzame en fijne omgeving waarin ik mijn promotietraject heb mogen doen. Uli, ik bewonder je pragmatische aanpak en vermogen om basale bevindingen over autoreactieve B cellen in klinisch perspectief te plaatsen. Onze effectieve dynamiek die gedreven werd door nieuwsgierigheid heeft ten grondslag gelegen aan de interessante bevindingen die we tijdens mijn PhD hebben gedaan. René, jouw kritische wetenschappelijke blik is een inspiratie. Onze scherpe discussies, vaak samen met Uli en verrijkt met een vleugje humor, zijn erg waardevol geweest en hebben meermaals op cruciale momenten tijdens mijn promotietraject tot nieuwe inzichten geleid.

Tijdens mijn promotietraject heb ik het geluk gehad omringd te zijn geweest door een fantastisch groepje mede-PhD studenten. Door op dezelfde golflengte te liggen vormden we een hecht team waarin we over onze wetenschappelijke uitdaging konden sparren, tot oplossingen kwamen, efficiënt konden samenwerken, elkaar ondersteunden en mooie en gezellige momenten konden delen. Sanne, jij was mijn veilige haven in het LUMC. Vanaf het begin dat wij samen als Jip en Janneke bij de reuma begonnen deelden we veel met elkaar. Er ontstond een speciale band waarvan ik hoop dat we die nog lang zullen doorzetten. Wieke, samenwerken met jou is fantastisch. Jouw energie en gekkigheid brachten een fijne stemming in het lab. Het was en is geweldig om "reuring" met jou te veroorzaken. Miles, onze wetenschappelijke discussies waren vaak met vele afdwalingen en duurden soms eindeloos, met name als we nog in de late uurtjes het lab omtoverden tot het serieuze "mannenlab". Renee, de mama van het gezelschap, jouw efficiëntie, kritische manier van denken en mentaliteit zijn een inspiratie. Sorry dat ik je tientallen keren om dezelfde protocollen moest vragen en dat ik je elke keer om hulp vroeg om mijn moeilijke verstandhouding met computers en codes op te lossen. Sophie-Anne, Anouk en Roxane, met jullie positieve energie en lieve karakters maakten jullie dit groepje absoluut compleet.

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