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Pulsed Dye Laser in psoriasis

A nerve-wrecking event?

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A. NEDERLANDSE SAMENVATTING

Psoriasis is een veelvoorkomende huidaandoening die naar schatting 400.000 mensen in Nederland treft. De aandoening uit zich in rode, schilferige en jeukende plaques. Hoewel de exacte biologische oorzaak nog niet volledig bekend is, staat vast dat psoriasis het gevolg is van een chronische ontsteking van de huid, waarbij een versnelde deling van keratinocyten en een toegenomen groei van bloedvaten optreedt.

De meeste behandelingen zijn gericht op het onderdrukken van deze ontstekingsreactie. Hoewel ze vaak effectief zijn, is hun werking doorgaans beperkt en kunnen ze bijwerkingen veroorzaken. Daarnaast reageren bepaalde lichaamsdelen, zoals de handen, voeten, ellebogen en knieën, vaak minder goed op behandeling. Zonder blijvende therapie keren de plaques meestal binnen enkele weken tot maanden terug.

Een belangrijke recente ontwikkeling zijn de zogenaamde biologicals: eiwit-gebaseerde geneesmiddelen die met behulp van levende cellen worden geproduceerd. Deze behandelingen zijn doeltreffend, maar kostbaar — gemiddeld €16.000 per patiënt per jaar — en leggen daarmee een aanzienlijke druk op het zorgsysteem.

Lasertherapie biedt een interessant alternatief. Deze behandeling kent weinig bijwerkingen, is effectief op moeilijk te behandelen plekken en leidt vaak tot langdurige remissie zonder vervolgetherapie. In het bijzonder heeft behandeling met de pulsed dye laser (PDL) veelbelovende resultaten laten zien, met remissies van drie jaar of langer.

Het belangrijkste knelpunt bij PDL is echter dat het precieze werkingsmechanisme nog onvoldoende wordt begrepen. Hierdoor zijn mogelijk meer behandelsessies nodig dan strikt noodzakelijk, en doordat per keer slechts een beperkt huidoppervlak kan worden behandeld, blijft het bereik van deze therapie beperkt.

Dit project had als doel het aantal benodigde behandelingen te verminderen en de effectiviteit van PDL-therapie te vergroten. De eerste stap daarbij is het beter begrijpen van de biologische processen die in de huid worden geactiveerd door PDL. In dit proefschrift onderzoeken we daarom in elk hoofdstuk een aspect van het onderliggende werkingsmechanisme van lasertherapie, met als uiteindelijk doel het ontwikkelen van effectievere behandeltrajecten voor mensen met psoriasis.

Hoofdstuk 1 onderzocht de mogelijke mechanismen van PDL bij psoriasis op basis van bestaande literatuur en vormde daarmee de basis voor de hypothese dat PDL in essentie een middel is om de zenuwen in de huid te beschadigen. In dit literatuuroverzicht werd verder bewijs geleverd ter ondersteuning van de hypothese dat PDL thermische diffusie van bloedvaten naar perivasculaire zenuwen veroorzaakt. Er zijn een aantal opmerkelijke observaties naar voren gekomen uit de literatuur, waaronder dat er spontane remissie (het wegblijven) van laesies plaatsvindt in gedenerveerde huid zonder enige verdere interventie, en dat een opmerkelijk aantal patiënten vrij zijn van psoriasis op de door PDL behandelde huid 12 maanden na behandeling. We stellen in hoofdstuk 1 een mechanisme voor waarop thermische schade aan zenuwen kan leiden tot een tijdelijke afwezigheid van ontstekingsbevorderende neuropeptiden en hoe herhaalde schade aan zenuwvezels het terugkeren naar een gezonde toestand kan vergemakkelijken.

In **Hoofdstuk 2** testten we de hypothese dat PDL zenuwen beschadigde via hitte diffusie. Met behulp van celculturen vergeleken we de thermische gevoeligheid van endotheelcellen van bloedvaten, keratinocyten, gladde spiercellen en zenuwvezels. Celculturen van deze verschillende celtypen werden blootgesteld tussen 2 tot 20 seconden aan thermische stress (45 - 70 °C) waarna het ATP-gehalte werd gebruikt om de viabiliteit van de cellen te meten. Onze resultaten tonen significante verschillen in overleving tussen celtypen ($p < 0.0001$). Vooral binnen het bereik van 50-60 °C was de overleving van neuronale cellen en keratinocyten significant minder dan die van endotheelcellen en gladde spiercellen. Bij het modelleren van de thermische schade vonden we geen statistisch significant verschil in de letale dosis (LT50) van thermische energie tussen neuronale cellen en keratinocyten. Wel zagen we in een ander thermisch schademodel, het *cumulative equivalent minutes at 43 °C* (CEM43) model, dat er tussen alle celtypes een significant verschil te zien was van benodigde tijdsduur voor lethale schade. De resultaten impliceren dat er een celtype-afhankelijke gevoeligheid is voor thermische schade, hetgeen suggereert dat neuronale cellen en keratinocyten in het bijzonder, gevoeliger zijn voor warmte veroorzaakt door de laserbehandeling.

Voortbouwend op de bevindingen van het celkweekonderzoek, werd in **hoofdstuk 3** onderzocht of dezelfde verschillen in celtype afhankelijkheid voor thermische schade ook meetbaar waren middels een functionele test van een bloedvat dat alle drie celtypen (endotheelcellen, gladde spiercellen en perivasculaire zenuwen) bevat. Het doel van deze studie was om de functionaliteit van geïsoleerde bloedvaten na

een blootstelling van 30 seconden aan gematigde hyperthermie (45-60°C) te beoordelen door de functie van endotheelcellen, gladde spiercellen en vasculaire zenuwen te evalueren. Onze studie is de eerste die thermische stress combineert met elektrische veldstimulatie op een breed temperatuurbereik (37-70°C) in een draadmyograafopstelling met geïsoleerde bloedvaatjes. Onze bevindingen tonen een substantiële afname in functionele respons voor alle drie de celtypen na blootstelling aan 55-60°C, zonder cel-specifieke verschillen voor thermische schade. Voor alle celtypen trad een afname van 50% van de vaatfunctie op tussen 55.9°C en 56.9°C. De *ex vivo* experimenten van dit hoofdstuk lieten zien dat zenuwen geen groter functieverlies vertoonden na hyperthermie in vergelijking met endotheelcellen, hetgeen verschilt met de bevindingen van hoofdstuk 2, waar gekweekte zenuwcellen gevoeliger waren voor thermische stress dan endotheelcellen.

In **Hoofdstuk 4** hebben we huidbiopten van onbehandelde psoriatische huid van 23 patiënten geanalyseerd om de morfologie van perivasculaire zenuwen en de variabiliteit tussen patiënten te onderzoeken. Dankzij het gebruik van dikkere coupes (80 µm) en geavanceerde 3D-beelden konden we zenuwen nauwkeurig in kaart brengen tot een diepte van 1,6 millimeter, wat een uitgebreide afbakening van hun distributie mogelijk maakte.

We ontdekten dat zenuwen slechts 0,1% van het huidvolume uitmaken maar complexe netwerken vormen rond haarvaatjes in de papillaire dermis, terwijl ze in de epidermis verder van bloedvaten liggen. De grootste variabiliteit tussen patiënten werd waargenomen in de epidermale en papillaire zenuwvezels, met significante correlaties tussen epidermale dichtheid en erytheem, epidermale dikte, en leeftijd. Er werden echter geen correlaties gevonden tussen zenuwdichtheid en klinische ernst, jeukcores, BMI of biopsielocatie, wat suggereert dat zenuwactiviteit een belangrijkere rol speelt in psoriasis symptomen dan dichtheid. Zenuwvezels werden ook vaak aangetroffen nabij clusters immuun cellen, wat hun betrokkenheid bij ontstekingen ondersteunt. Deze gedetailleerde 3D-dataset biedt een belangrijke basis voor het modelleren van de thermische effecten van op licht gebaseerde behandelingen, zoals gepulseerde kleurstoflasertherapie, en dient als referentie voor het beoordelen van histologische veranderingen die worden veroorzaakt door verschillende psoriasisbehandelingen.

In **hoofdstuk 5** onderzochten we het effect van PDL op de huid van psoriasispatiënten. Voor deze studie analyseerden we 120 huidcoupes van 20 patiënten, zowel vóór als na twee PDL-behandelingen.

Onze resultaten tonen aan dat, in tegenstelling tot onze oorspronkelijke hypothese, het onduidelijk is of zenuwvezels verdwijnen bij patiënten die klinisch goed reageren op de behandeling. Hoewel er geen verschil werd vastgesteld in de dichtheid van zenuwvezels, sluit dit mogelijke functionele veranderingen van zenuwen na PDL-behandeling niet uit; deze fysiologische veranderingen zijn niet waarneembaar met confocale microscopie. Wel was duidelijk dat de epidermale dikte significant afnam bij patiënten met een gunstige klinische respons. Een onverwachte bevinding was de aanwezigheid van sterk gevasculariseerde clusters van cellen net onder de dermo-epidermale overgang. Immuncelkleuring bevestigde dat deze clusters voornamelijk uit CD3⁺ T-cellen bestonden, waarvan de aanwezigheid (zowel in de epidermis als dermis) na PDL-behandeling significant afnam.

Verder werden subtiele veranderingen waargenomen in 3D-fluorescentiebeelden van de huid, zoals een lichte afname in de dichtheid van bloedvaatjes in de bovenste huidlaag en een toename van zenuwvezels in de opperhuid, hoewel deze veranderingen statistisch niet significant waren. Er werd bovendien geen correlatie gevonden tussen deze histologische veranderingen en de ernst van psoriasis zoals beoordeeld door dermatologen. Deze resultaten zijn gebaseerd op analyses na twee behandelingen, terwijl een volledig traject meestal zes tot acht sessies omvat. Vanwege tijdslijmieten kunnen latere effecten van de behandeling in deze studie zijn gemist.

De resultaten van **hoofdstuk 5** leidden tot een nieuwe hypothese: PDL veroorzaakt warmteverspreiding in de bloedvaten rondom clusters van immuun cellen, wat samen met mogelijke thermische schade aan zenuwvezels kan bijdragen aan het herstel van de huid naar een niet-inflammatoire toestand. Deze hypothese wordt verder onderzocht in **hoofdstuk 6**, de algemene discussie van dit proefschrift.

B. ENGLISH SUMMARY

Psoriasis is a dermatological condition that affects approximately 400,000 individuals in the Netherlands. The lesions are characterized by itchy red plaques with scaling and may appear anywhere on the body, though they are more frequently observed on the elbows and knees. The precise underlying pathophysiology of psoriasis remains unclear. However, it is evident that there is a problem within the skin which manifests as inflammation, accompanied by excessive angiogenesis and accelerated keratinocyte division. The majority of treatments for psoriasis are designed to target the underlying inflammation. The current existing treatments are efficacious, but to a limited extent, and some have an unfavorable safety profile. In particular, treatment resistance is observed in areas such as the hands, feet, elbows, and knees. In the absence of continuous treatment, most plaques will recur within a period of weeks to months. The cost of newer treatments for psoriasis, known as biologicals (protein-based drugs produced using living cells), is an average of €16,000 per year per patient, which places a significant financial burden on healthcare systems. Laser therapy is an exception to the above considerations. Laser treatment has few side effects, high efficacy for difficult-to-treat areas, and a long duration of treatment-free remission. Especially Pulsed Dye Laser (PDL) treatment, has shown good clinical efficacy with remission times of three or more years. The primary obstacle impeding the efficacy of PDL treatment in psoriasis is the incomplete understanding of its underlying mechanism, necessitating the implementation of multiple treatments. The limited capacity for treatment of the affected skin area in a given timeframe is a further limitation. The overall goal of this project was to reduce the number of treatments required, thereby enhancing the competitiveness of this therapy in comparison to systemic treatments. This thesis aims to contribute to a more comprehensive understanding of the biological mechanisms underlying laser therapy, with the ultimate objective of developing more effective treatment regimens.

Chapter 1 explored the potential mechanisms of PDL in psoriasis and the hypothesis that PDL is, in essence, a means of damaging the skin nerves. This literature review provided further evidence to support the hypothesis that PDL causes thermal diffusion from blood vessels to perivascular nerves. A number of noteworthy observations also emerged, including the efficacy of PDL in psoriasis treatment, the spontaneous remission (absence) of lesions in denervated skin without intervention, and a notable proportion of patients achieving over 12 months of remission following

PDL treatment. We propose a pathway by which thermal damage to nerves may result in a temporary absence of inflammatory-inducing neuropeptides, and how repeated damage to nerve fibers may facilitate the reversal of the skin's inflammatory state towards a healthy state.

In **Chapter 2** we continued our work based on the hypothesis that PDL damaged nerves. Using cell cultures we tested if there was a difference in thermal sensitivity between endothelial cells from blood vessels, keratinocytes, smooth muscle cells, and nerve fibers. Cell cultures of the different cell types were exposed to 2-20 seconds of thermal stress (37–70 °C) after which the ATP content was used to measure cell viability. Our results showed significant differences in cell survival between cell types ($p < 0.0001$). Especially within the range of 50–60 °C, survival of neuronal cells and keratinocytes was significantly less than that of endothelial and smooth muscle cells. No statistically significant difference was found in the lethal dose (LT50) of thermal energy between neuronal cells and keratinocytes. However, CEM43 calculations showed significant differences between all four cell types. The results showed that there is a cell-type-dependent sensitivity to thermal damage, with neuronal cells and keratinocytes being particularly susceptible to the diffusing heat from laser treatment.

Building on the findings of the cell culture study, in **Chapter 3** we continued research by utilizing a blood vessel containing all three cell types (endothelial cells, smooth muscle cells, and perivascular nerves) rather than separate cell cultures. The aim of our study was to assess the functionality of isolated blood vessels after a 3-second exposure to moderate hyperthermia (45 to 60°C) by evaluating the function of endothelial cells, smooth muscle cells, and vascular nerves. Our findings demonstrated a substantial decrease in functional response for all three cell types following exposure to 55°C-60°C, with no cell-specific differences for thermal damage. For all cell types, a 50% reduction of vessel function occurred between 55.9°C and 56.9°C. Previous studies have reported on the chemical response to blood vessels, but our study is the first to combine thermal stress with electrical field stimulation on a wide range of temperatures (37–70 °C) in a wire myograph setup with isolated arteries. The *ex vivo* experiments conducted in this chapter demonstrated that there was no significant difference in functional loss between nerves and endothelial cells following hyperthermia. This finding contrasts with the results of Chapter 2, where cultured nerve cells exhibited greater sensitivity to thermal stress compared to endothelial cells.

In **Chapter 4**, we analyzed skin biopsies of untreated psoriatic skin from 23 patients in order to investigate the morphology of perivascular nerves and variability between patients. The use of thicker sections (80 μm) and advanced 3D imaging technology allowed us to accurately map nerves to a depth of 1.6 millimeters, which facilitated a comprehensive delineation of their distribution.

Our findings revealed that nerves constitute a mere 0.1% of skin volume yet form intricate networks around capillaries in the papillary dermis, while in the epidermis, they are farther from blood vessels. The epidermal and papillary nerve fibers exhibited the most significant variability between patients, with substantial correlations observed between epidermal density and erythema, epidermal thickness, and age. However, no such correlations were found between nerve density and clinical severity, itch scores, BMI or biopsy location, suggesting that nerve activity plays a more significant role in psoriasis symptoms than density. Nerve fibers were also frequently found near clusters of immune cells, supporting their involvement in inflammation. This detailed 3D dataset provides a valuable support for the modelling of the thermal effects of light-based treatments, such as pulsed dye laser therapy, and serve as a reference for assessing histological changes induced by various psoriasis treatments.

In **Chapter 5**, the impact of pulsed dye laser (PDL) therapy on the skin of patients with psoriasis was investigated. In this study, a total of 120 skin sections from 20 patients were analyzed, with data collected both before and after two PDL treatments. The results indicate that, contrary to the original hypothesis, there was no apparent reduction in total nerve fiber density following PDL treatment for psoriasis. Furthermore, no notable discrepancy was identified in nerve fiber density between patients who exhibited more favorable treatment outcomes and those who demonstrated less favorable responses to PDL treatment. The absence of a significant reduction in nerve fiber density does not rule out potential functional changes, as physiological alterations are not perceptible with confocal microscopy. However, it was evident that there was a notable reduction in epidermal thickness among some patients following PDL treatment, which seemed to relate to clinical improvement. More subtle changes in the skin following PDL, as observed in 3D fluorescence images, included a slight reduction in the density of blood vessels in the upper dermal layer and an increase in nerve fibers in the epidermis. However, these changes were not statistically significant when the entire study population was analyzed. Furthermore, no correlation was identified between these histological

alterations and the severity of psoriasis as assessed by dermatologists. These results are based on analyses after two treatments, while a full course usually involves six to eight sessions. Due to time constraints, subsequent treatment effects may have been missed in this study.

To our surprise the skin sections revealed something else: clusters of cells right below the dermo-epidermal junction that were highly vascularized. Immune cell staining confirmed that these clusters consisted mainly of CD3⁺ T-cells. This led us to a new hypothesis that PDL may cause heat diffusion in the blood vessels around immune cell clusters, which together with the thermal damage to nerve fibers, may aid in the restoration of the skin to a non-inflammatory state. This hypothesis is further explored in **Chapter 6**, the general discussion of this thesis.

C.CURRICULUM VITAE

Meagan Doppegieter was born on June 4, 1996, in Terneuzen. At the age of nine, she auditioned for the pre-professional program at the Royal Ballet Academy in Antwerp. From ages 9 to 12, she was enrolled in this program, training and performing at a professional level in classical ballet. Due to a long-term Achilles injury, she was unable to gain admission to the Royal Ballet Academy (KBA). Instead, she pursued a conventional educational path and obtained her VWO diploma in 2014 at SSG de Rede in Zeeland, with a focus on science, nature, and technology. She first thought about pursuing a career in psychology when she got into a conversation with a student of biomedical sciences at an open day in Leiden and discovered her love for all the things left to discover in medical science.

She relocated to Amsterdam and completed her Bachelor's in 2017. In her final year, Meagan started her first internship at Prof. Dr. Ans van Pelt's lab at the AMC. She worked on preserving spermatogonial stem cells for young boys diagnosed with cancer. In 2017, she was accepted into the 'Internal Medicine' track in the research master's program in Biomedical Sciences at the University of Amsterdam. During her first master's research project, Meagan worked on preserving and determining the fertility of horse oocytes at Utrecht University. With Dr. Marta Villiani's guidance, she developed a way to quantify chromosomal damage in horse oocytes, which can be used as a quality control measure for horse fertility clinics. For her second master's internship, Meagan moved for nine months to St. Gallen, Switzerland, where she worked with Prof. Dr. Inge Herrmann and Dr. Tino Martin on developing antimicrobial nanoparticles to combat antibiotic resistance of MRSA, which resulted in a co-authorship for the published work. Her interest in working on practical applications for medicine and healthcare, and developing and optimizing novel methods, led her to start her PhD project in 2019 on unraveling the mechanism behind Pulsed Dye Laser therapy in the treatment of psoriasis at the Amsterdam University Medical Center in collaboration with ZBC Multicare. She was supervised by Prof. Dr. Ton van Leeuwen, Dr. Erik Bakker, Prof. Dr. Maurice Aalders, and Dr. mr. Nick van der Beek.

The project entailed a variety of experiments ranged from *in vitro*, to *ex vivo*, to *in vivo* studies, with administrative roles such as writing a DEC and an METC, building and strengthening an interdisciplinary team with regular meetings to discuss the progress and next goals. The work of this project led to a published a review article

and 4 original (pre)published manuscripts, and a second authorship on a collaborative effort. Apart from the project goals, and with the support of her supervisors, she studied for seven months to obtain a NOCBO-certified coaching degree with over 150 hours of practical experience. In her third year, she joined the board of ASAP (Association of Amsterdam UMC PhDs) on the external affairs team, which led her to discover the fun behind policy making and strategy within the research institutes and the hospital. During her time at ASAP, she took part in board meetings of the Amsterdam Research Board (ARB) and the doctoral school. She also helped organize career events, gave workshops on having a positive mindset when setting goals, and organized and moderated the 2023 Symposium on mental health of PhD students (recognition and reward movement) for PIs and senior researchers in a management role at the Amsterdam UMC. In her last year, she participated in the BioBusiness Summer School to gain more knowledge about entrepreneurship in the life sciences and health sector. She finished her PhD in December 2024 and defended it in May 2025. After her PhD she continued to innovate laser treatments for skin conditions at ZBC Multicare.

D.LIST OF PUBLICATIONS

Doppegieter M, van der Beek N, Bakker ENTP, Neumann HAM, van Bavel E. Effects of pulsed dye laser treatment in psoriasis: A nerve-wrecking process? *Exp Dermatol.* 2023;32(7):1165-73.

Doppegieter M, van Leeuwen TG, Aalders MCG, de Vos J, van Bavel ET, Bakker ENTP. The impact of temperature on vascular function in connection with vascular laser treatment. *Lasers Med Sci.* 2024;39(1):122.

Doppegieter M, van Leeuwen TG, van Weert A, Aalders MCG, Bakker ENTP. Subminute thermal damage to cell types present in the skin. *Int J Hyperthermia.* 2024;41(1):2354435.

Wilk LS, **Doppegieter M**, van der Beek N, van Leeuwen TG, Aalders MCG. Modeling pulsed dye laser treatment of psoriatic plaques by combining numerical methods and image-derived lesion morphologies. *Lasers Surg Med.* 2024;56(5):508-22.

Doppegieter M, van der Beek N, Aalders MCG, Neumann MHA, Bakker ENTP, van Leeuwen TG. 3D Characterization Of Nerve Fiber Morphology In Psoriatic Skin And It's Relation To Clinical Evaluation'
Submitted

Doppegieter M, van der Beek N, de Vos J, Aalders MCG, Neumann MHA, Bakker ENTP, van Leeuwen TG. The Effect of Pulsed Dye Laser Treatment on Neurovascular and Immunological Changes in Patients with Psoriasis.
In preparation

E. PORTFOLIO

PhD Period: November 2019 – November 2024

Promotoren: Prof. Dr. Ton van Leeuwen, Prof. Dr. Maurice Aalders

Co-promotoren: Dr. Erik N.T.P. Bakker, Dr. Mr. Nick van der Beek

PHD TRAINING (Total of 43.7 ECTS)

Courses	Year	ECTS
Data Analysis in MATLAB	2020	1.4
Scientific Writing in English	2020	1.5
AMC world of Science	2020	0.7
Practical Biostatistics	2020	1.4
e-BROK	2020	1.0
Entrepreneurship in Health and Life Science	2021	1.5
NOBCO Coach Practitioner	2022	5.7
Project management	2023	0.6
Be Your Best, Be Yourself	2023	0.8
Clinical Observational Epidemiology	2023	0.6
BioBusiness Summer School	2024	1.5
Meetings, seminars, and workshops		

Cardiovascular Engineering weekly Meeting (CVENG)	2019 – 2024	4.0
Workshop: The winning presentation	2020	0.1
Photonics weekly Meeting	2021 – 2024	3.0
PhD career Event	2021	0.2
PhD skills lab: Present like a boss	2021	0.1
Data visualization: GIF workshop in science	2022	0.2
Power of Storytelling	2022	0.7

Annual Meeting of Amsterdam Public Health	2022	0.5
Data visualization by Maarten Boers	2022	0.2
Annual meeting of Institute for Positive Health (iPH)	2023	0.5
Personal Leadership	2023	0.1
ACS PhD retreat	2023	1.0
Connect for Health – APH Spring meeting	2023	0.5
Science communication with Improv – ACS afternoon	2023	0.2
BCF career event	2024	0.5
Workshop Imposter syndrome	2024	0.1

Tutoring, mentoring, and supervising

Lecture at Master Cardiovascular research	2022	0.5
Supervision Master Student, Biomedical Sciences, Research Project	2023	1.0
Supervision Bachelor Student, Medicine, literature review	2024	0.5

Conferences, presentations, and talks

European Association for Dermatology and Venereology (EADV), Online <i>Attended</i>	2020	1.2
European Association for Dermatology and Venereology (EADV), Berlin <i>e-Poster</i>	2022	1.3
Netherlands Vascular Biology Meeting (DEBS), Biezenmortel <i>Attended</i>	2022	1.3
ACS annual meeting, Amsterdam <i>Poster presentation</i>	2023	0.5
ANS annual meeting, Amsterdam <i>Poster presentation</i>	2023	0.5
ACS PhD retreat, Soesterberg <i>Poster presentation</i>	2023	0.5

European Society for Microcirculation, Denmark	2023	1.3
<i>Poster presentation</i>		
ACS symposium on microcirculation	2024	0.5
<i>Oral presentation</i>		

Other contributions

Interview for Psoriasis Magazine NL	2023	0.5
Instruction Tutorials for laboratory methods	2022	0.5
Board member of Association for Amsterdam UMC PhDs (ASAP) – External affairs	2023-2024	3.0
Organization of PhD symposium ‘Recognition and Rewards in AUMC’	2023	1.0
Workshop on Visualizing your success and positive mindset, <i>PhD career event 2021</i>	2021	0.5

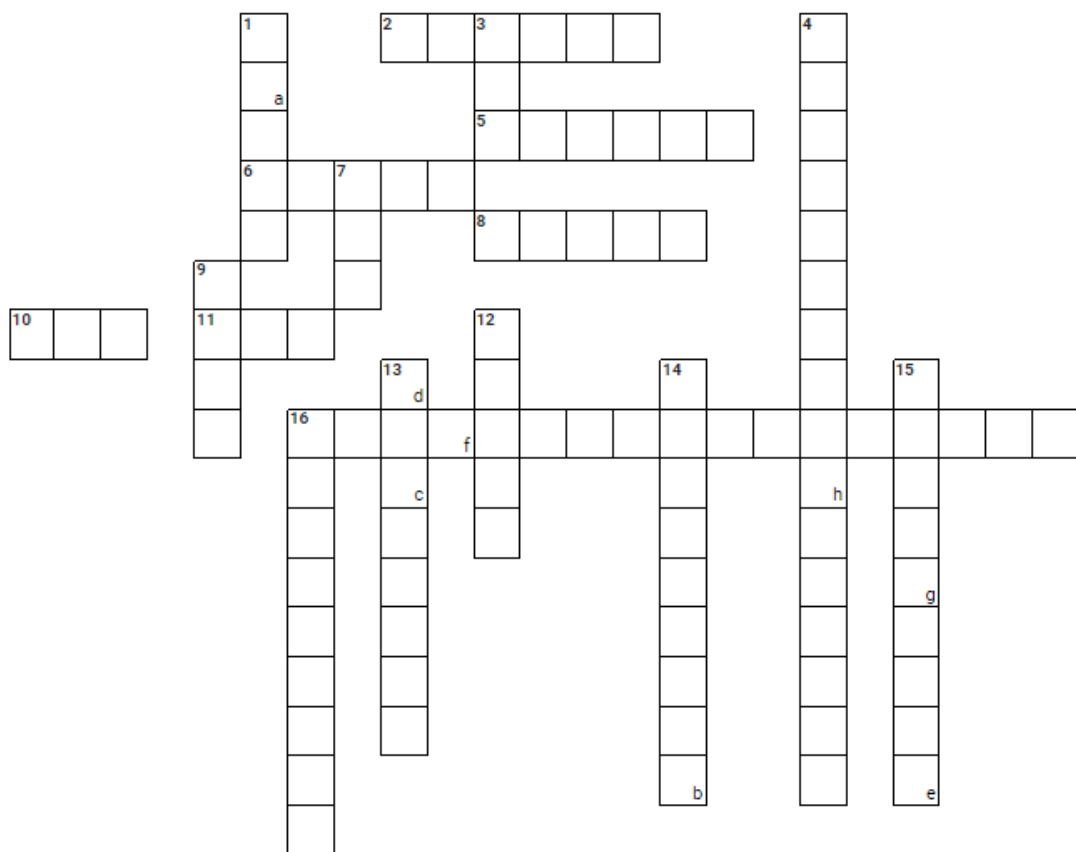
Thesis puzzle

Horizontaal

- 2** Software meagan used a lot for images
5 Search machine for scientific literature
6 antibody used for staining nerves
8 brand of the confocal microscope
10 wavelength of PDL
11 abbreviation for dermo epidermal junction
16 thin fiber around blood vessels

Verticaal

- 1** abbreviation for biomedical engineering & physics
3 molecule that indicates cell viability
4 technical term for thermal destruction by light
7 laser that heats blood vessels
9 Antibody used for staining blood vessels
12 name of common endothelial cell line
13 software to make graphs and do statistics
14 Name the dermatology center we collaborated with
15 clinical term for absence of psoriasis
16 skin condition with red patches, itch, and scaling



Oplossing

a	b	c	d	e	f	g	h
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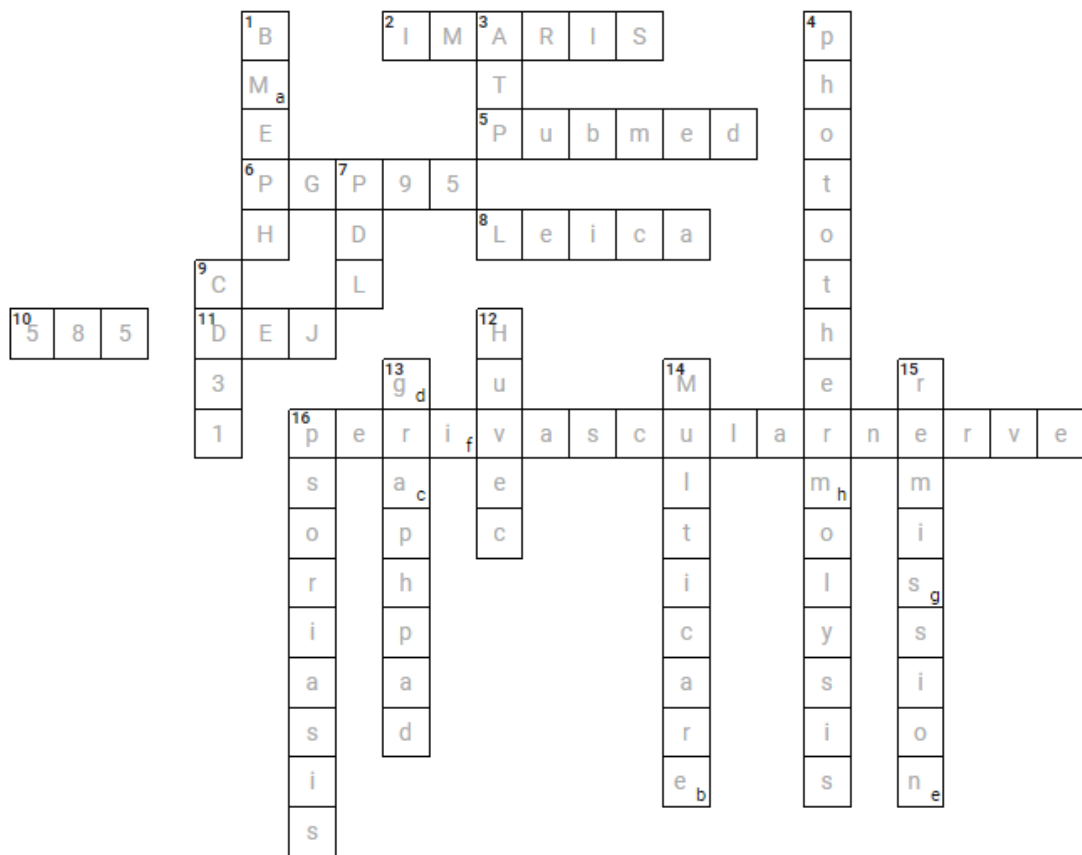
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Oplissing

a M b e c a d g c a e n f i g s h m

G. DANKWOORD

I am beyond grateful to all the wonderful people who provided me with guidance and support throughout this project. A PhD is a huge project, and I couldn't have done it on my own. Therefore, I want to thank a lot of people. **Ton**, you were such a great supervisor! You were always relaxed and you have the best intentions with your PhD students. You helped me grow in many ways, both in my academic skills and in my personal life. You were always full of kind words, but you also made sure I didn't get too comfortable and kept me on track with my progress. You noticed quickly when things weren't going as planned and helped me figure out what I needed to focus on first. I am happy that you gave me space and support in the pursuit of a coaching degree and explore entrepreneurship in life science by attending the Biobusiness course!

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Max, we've been on many adventures together! We met during our first week at university for the bachelor of biomedical sciences. We decided to pursue the same master's degree, even though we took different tracks. We started our PhD one month apart, and we even had job interviews on the same days! We went on 'the best holiday' together, driving the camper van all the way up to the north of France just to find out we were alone at the camping because they would defuse bombs from WWII the next morning. It was one of my favorite times with you! I am grateful for your friendship over the years, and I really hope we'll stay in touch and be there for each other for a long time to come. **Lianne**, I just love thinking about you and those hilarious clumsy moves you had! They provided year-long entertainment, like rolling out of the bus as it stopped abruptly or turning your salad upside down by accident. You're such a joy to be around! I am happy you're finding your way back to the Netherlands because you're such a blessing to all of our lives. I wish you all the best in finding a satisfying job and a career that will make you the happiest.

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