Summary

In this thesis, we describe human cytomegalovirus (HCMV)-encoded viral G protein-coupled receptors (GPCRs), and their implementations in glioblastoma multiforme (GBM). HCMV belongs to the family of herpesviruses and codes for 4 known viral GPCRs: US28, UL33, UL78, and US27, of which US28 is the best characterized. US28 is homologous to human chemokine receptors CX3CL1, CCR2, and CCR2 (Couty & Gershengorn, 2005). US28 is capable of binding a wide range of ligands and signal ligand-dependently, as well as ligand-independently, thereby activating various signaling pathways involved in the regulation of proliferation, migration, angiogenesis, and inflammation (Maussang, Langemeijer, et al., 2009; Maussang, Vischer, Leurs, & Smit, 2009; Slinger et al., 2010) potentially associated with the development of malignancies, encodes the constitutively active chemokine receptor US28. Previously, we have shown that US28 expression induces an oncogenic phenotype both in vitro and in vivo. Microarray analysis revealed differential expression of genes involved in oncogenic signaling in US28-expressing NIH-3T3 cells. In particular, the expression of cyclooxygenase-2 (COX-2). HCMV has been found in GBM patient material in which the virus showed tumor proliferation stimulating properties (Soroceanu et al., 2011). Furthermore, treating GBM patients with Valganciclovir, a virus-inhibiting drug, resulted in a positive outcome of patient prognosis (Söderberg-Nauclér, Rahbar, & Stragliotto, 2013).

GBM is a type of malignant primary brain tumor with a relatively short survival period of around 12 to 15 months (Hanif, Muzaffar, Perveen, Malhi, & Simjee, 2017). The tumors consist of different type of cells, spread in the neighboring healthy tissues, which is the root cause of the challenges in the treatment of GBM. The cells that remain after treatment are usually resistant to therapy and capable of proliferating, which often results in tumor relapse. These cells are also known as cancer stem cells and play an important role in the efficacy of GBM treatment. Furthermore, HCMV is able to infect these cancer stem cells with a higher efficacy compared to differentiated glioma cells (Fiallos et al., 2014) glioblastoma (GBM). For this reason, cancer stem cells are an interesting option for novel treatment methods. The goal of this thesis is to gain insight into HCMV-encoded receptor US28 en its role in the progression of GBM. By gaining knowledge in this, we hope to improve current GBM treatment methods.

Aside from the HCMV-encoded viral GPCRs, other type of herpesviruses...
also exist. These herpesviruses encode for their own specific viral GPCRs, which have been found to be implicated in various types of cancer as well. In chapter II we discuss these viral GPRCs, which include ORF74, a viral GPCR encoded by the Kaposi Sarcoma virus (KSHV), BILF1, encoded by the Epstein-Barr virus (EBV), and US28, UL33, and US27, encoded by HCMV.

To study the role of HCMV and US28 in a clinical relevant model, we started with developing a 3D GBM cell model in chapter III. We show a significant increase in spheroid growth in vitro and tumor growth in vivo upon inducing US28 expression. This was associated with an increase in the secretion of IL-6 and VEGF. In chapter IV we developed US28-targeted nanobodies, which are able to inhibit US28 activity as an inverse agonist. By using our 3D GBM cell model and GBM mouse model, we prove that these US28 nanobodies are able to inhibit US28-mediated growth by 50% in vitro and in vivo. Furthermore, we were able to inhibit IL-6 secretion in these animals via nanobody treatment.

In chapter III and chapter IV we observe an increase of neurosphere formation upon HCMV infection. The formation of neurospheres is characteristic for de-differentiated cells and points to a possible role for US28 in de-differentiating GBM cells. We further elaborate on this in chapter V. Upon US28 expression, we show a shift in the expression of epithelial and mesenchymal genes. The epithelial-mesenchymal transition (EMT) and mesenchymal-epithelial transition (MET) play a role in metastasis of cancer cells. Despite changes in epithelial and mesenchymal genes upon US28 expression, we do not observe a specific shift towards either the epithelial or mesenchymal phenotype. Inducing US28 in U251 GBM cells however, does result in de-differentiation of cells. US28 is able to signal towards major stem cell regulators: Sox2 and OCT4, and stimulate the expression of CD133. These stem cell regulators are in turn regulated by the Hippo pathway, in which YAP is the major transcription factor. This points towards a possible role for US28 in cancer stem cell maintenance, possibly via the Hippo route, and eventually tumor relapse after therapy.

GBM is relatively difficult to treat and remove, as these cells are able to circumvent the immune system (Razavi et al., 2016). To further study the underlying mechanism of US28, we looked into a possible mechanism for HCMV to modulate the immune response. In chapter V, we found an association between US28 signaling and the Hippo pathway, which is a novel pathway for US28. In chapter VI, we observe nuclear localization of YAP upon US28 expression. Nuclear YAP is the active form of YAP,
during which it can execute its effect as transcription factor. This US28-mediated activation could be inhibited with 50% by using a newly developed US28 nanobody, VUN100b. The ability of US28 to signal via the Hippo pathway resulted in the regulation of PD-L1, a receptor involved in the deactivation of T cells. With this data, we show that US28 is possibly involved in the circumvention of the immune system by tumor cells and eventually also in complicating the removal of GBM tumors.

In this thesis, we show the effect of US28 on GBM tumor growth. We present new mechanisms via which US28 is able to stimulate the growth of GBM tumors i.e. the modulation of the immune system and cancer stem cell maintenance. Furthermore, we offer US28 nanobodies as a potential tool to inhibit US28-mediated activities. Despite these findings, more research is required to propose HCMV and US28 as possible interesting new targets for the treatment of GBM in patients. Despite this, we hope that the research presented in this thesis will aid in improving GBM treatment in the future, with nanobodies as helpful tools.
Nederlandse Samenvatting

In deze thesis wordt het onderzoek naar humaan cytomegalovirus (HCMV)-gecodeerde virale G proteïne-gekoppelde receptoren (GPCRs) omschreven in glioblastoma multiforme (GBM). HCMV behoort tot de familie van herpesvirussen en codeert voor 4 bekende virale GPCRs: US28, UL33, UL78 en US27, waarbij US28 het beste gekarakteriseerd is. US28 is een homoloog van de humane chemokine receptor CX3CL1, CCR1 en CCR2 (Couty & Gershengorn, 2005). Het is in staat aan verschillende liganden te binden en zowel afhankelijk als onafhankelijk van deze liganden te signaleren naar routes die betrokken zijn bij de regulatie van proliferatie, migratie, angiogenese, en inflammatie (Maussang, Langemeijer, et al., 2009; Maussang, Vischer, Leurs, & Smit, 2009; Slinger et al., 2010). HCMV is ook teruggevonden in GBM patiëntmateriaal, waar het proliferatie van tumoren lijkt te stimuleren (Soroceanu et al., 2011). Bovendien heeft het behandelen van GBM patiënten met Valganciclovir, een virus-remmend medicijn, een positief effect op de uiteindelijke prognose van de patiënten (Söderberg-Nauclér, Rahbar, & Stragliotto, 2013).

GBM is een type kwaadaardige primaire hersentumor met een relatief korte overlevingsperiode van ongeveer 12 tot 15 maanden (Hanif, Muzaffar, Perveen, Malhi, & Simjee, 2017). De tumoren bestaan uit verschillende typen cellen, vaak verspreid in de naburige gezonde weefsels, waardoor GBM moeilijk behandelbaar is. De cellen die achterblijven na behandeling zijn veelal resistent tegen therapie en in staat om te prolifereren, waardoor de verwijderde tumoren weer terug groeien. Deze cellen worden herkend als kanker stamcellen en spelen een belangrijke rol in de effectiviteit van GBM behandelingen. Een opmerkelijke observatie gedaan door onderzoekers laat zien dat HCMV in staat is deze kanker stamcellen met hogere efficiëntie te infecteren (Fiallos et al., 2014). Hierdoor zijn kanker stamcellen interessant als optie in nieuwe therapeutische behandelingsmethoden. Het doel van deze thesis is om meer duidelijkheid te krijgen over de HCMV-gecodeerde receptor US28 en wat voor een rol het heeft in de progressie van GBM. Door meer hierover te weten te komen, kunnen we GBM hopelijker beter behandelbaar maken.

Naast de HCMV gecodeerde virale GPCRs, bestaan er ook andere typen herpesvirussen, welke coderen voor een specifieke virale GPCR. Deze
virale GPCRs zijn betrokken gevonden bij verschillende processen van tumorgroei en ontwikkeling. In hoofdstuk 2 beginnen we met het uitgebreid behandelen van deze virale GPCRs, inclusief ORF74, een virale GPCR gedoceerd door het Kaposi Sarcoma virus (KSHV), BILF1, gecodeerd door het Epstein-Barr virus, en US28, UL33, en US27, gecodeerd door HCMV.

Om de rol van HCMV en US28 in een klinisch relevant model te kunnen bestuderen, beginnen we in hoofdstuk 3 met het ontwikkelen en opzetten van 3D GBM cel modellen en GBM muis modellen. We laten zien dat het induceren van US28 in cellen leidt tot een significante toename in sferoïde grootte en een snellere progressie in tumorgroei in muizen. Dit gaat verder gepaard met een toename in secretie van IL-6 en VEGF. In hoofdstuk 4 hebben we US28 specifieke nanobodies ontwikkeld, welke de activiteit van US28 kunnen inhiberen als inverse agonisten. Door gebruik te maken van ons 3D GBM cel model en GBM muis model, laten we zien dat we in zowel in vitro als in vivo in staat zijn de US28-gemedieerde groei met 50% te remmen. Daarnaast zijn we in staat de IL-6 secretie in deze dieren ook te inhiberen met de nanobodies.

Zowel in hoofdstuk 3 als in hoofdstuk 4 laten we zien dat infectie van U251 GBM cellen met HCMV de vorming van neurosferoïdes stimuleert. Dit is een karakteristiek van geda-differentieerde cellen en wijst naar een mogelijke rol van US28 in de-differentiatie van GBM cellen. In hoofdstuk 5 gaan we hier verder op in. We zien dat de inductie van US28 effect heeft op de expressie van epitheel en mesenchymale genen. De epitheel-mesenchymale-transitie (EMT) en mesenchymale-epitheel-transitie (MET) spelen een rol in onder anderen de metastasering van kankercellen. Er wordt echter geen specifieke epitheel of mesenchymaal fenotype geïnduceerd als gevolg van US28 expressie. De inductie van US28 in U251 GBM cellen leidt echter wel tot de-differentiatie van cellen. US28 is in staat te signaleren naar de belangrijkste stamcel regulatoren, Sox2 en OCT4, en CD133 expressie te stimuleren. Deze stamcel regulatoren worden op hun beurt gereguleerd door de Hippo route, waarin YAP een belangrijke transcriptiefactor is. Dit duidt op een rol van US28 in het onderhouden van kanker stamcellen, mogelijk via de Hippo route, waarmee het uiteindelijk invloed kan hebben op terugkerende tumoren na therapie.

GBM is relatief moeilijk te behandelen en verwijderen, omdat deze tumorcellen in staat zijn het immuunsysteem te omzeilen (Razavi et al., 2016). Bovendien zijn de tumorcellen welke niet compleet zijn verwijderd ook hier tot toe in staat. Om het onderliggend mechanisme van US28 verder te onderzoeken, gingen we op zoek...

In deze thesis laten we het effect van US28 op de groei van GBM zien. We stellen tevens nieuwe mechanismen voor waarmee US28 kan bijdragen aan de groei van GBM tumoren, namelijk via modulatie van het immuunsysteem en het onderhouden van kanker stamcellen. Verder bieden we US28 nanobodies aan als mogelijk middel om US28-gemedieerde activiteiten te remmen. Meer onderzoek is vereist om HCMV en daarmee US28 een potentiële target te maken ter behandeling in GBM patiënten. Desondanks, hopen we met dit soort onderzoek GBM beter behandelbaar te maken in de toekomst en wellicht bieden we met nanobodies de juiste tools.
Final Words

Finally! You have reached the final words or as most of us like to call it the “dankwoord”. If you have read my whole thesis, kudos to you! Of course, you would not be holding this book today if it weren’t for a lot of people in my life. So I would like to take some time to show my gratitude to a few people whom helped me during my PhD. First of all, I would like to express my sincere gratitude to my promoter/supervisor Martine. Thank you for your guidance, support, patience, motivation, and wisdom during these last 4 years (and a few months). I would never been able to start or finish this project and get my degree if you haven’t given me the opportunity to run this project. Many thanks to you too Marco, for your input and feedback on my projects.

Beside my supervisors, I would like to thank the Vici team as well. All of this would not be possible without your support! Thank you Jeffrey, for your help/advice, and the fun (yes, you read it correctly) times we had while writing our review. Thank you Timo, for being part of the let's-science-at-7/8am-team and providing me with a never ending stock of nanobodies (and you too, Nick). Don’t stop believing! Thank you Raimond, for your effort and input in all of my projects and raising the phoenix in the basement of the RNC. Thank you Maarten (my favorite colleague) for always being positive. Of course many thanks to the rest of the Vici team for the interesting discussions and all the support during our (very long) meetings.

There are also some people I would like to address my appreciation to outside of the Vici team. So, thank you Hendrik, for your incredible taste in music (really). Also, you never got the chance to answer my question if we are human or dancers… Thank you Payman for providing me with girl talk now and then with all of these guys surrounding us (especially the last month without you was difficult). Thanks to Sabrina and Dan for helping me get rid of all my frustrations. Thanks to my internship students, Pei Pei, Renske, Betty, and Alessandro for helping me out. Many thanks to the rest of the receptor biochemistry and signaling department for keeping my spirits up and the interesting subjects during lunch! Even though I do not like to admit it, I did enjoy most of our lunches…most (Heeey Daniel!).

A lot of work in this thesis was performed at the Karolinska Institutet in Stockholm. For this reason, I would like to take some time to thank the lab of Cécilia too. Thank you Cécilia, for the hospitality, your involvement in my projects, and helping
me fall in love with Stockholm. Many thanks to you Maral, for your time, input, and help during all of my projects. I enjoyed all of our Skype sessions. Also special thanks to Belghis, for teaching me how to do immunohistochemistry. Of course I would like to thank the rest of the Department of Medicine for making me feel welcome on each and every one of my trips. Tack så mycket!

Having thanked everyone whom was involved in my research, there are also a few people outside of the VU and KI I would like to thank as well. These people provided me with a social life and a place to blow off some steam after my long days at the lab.

So, thanks to my wu(taart)shu team for the fun Thursday evenings! I would also like to take some time to thank my family: my sisters 姐姐 and Shao Ping, for dealing with my grumpy face and many of my bad moods. Also, many thanks to 妈妈 and 阿姨妈妈 for the encouraging words and support! 我爱你们! Another person who I consider family and would like to thank is Stephanie. Steef, thank you for all the lovely dinners, talks, and support not only during the course of my PhD, but also during our Bachelors and Masters. It really helped having someone who went through the same struggles as I was.

There are (probably) still people I have not mentioned here who were involved with my work in some way or another. To those people I would like to say, thank you too! Before using this excellent piece of printed knowledge as coaster, doorstop, toilet paper, fly swatter, notepad, origami paper, firewood, source for paper airplanes, or for elevating your monitor, there are some take-home messages/lessons/pieces of wisdom that I have learned and collected during these years and I would like to share them with you:

“The secret of life, though, is to fall seven times and to get up eight times.”

- Paolo Coelho, The Alchemist

“Don’t stop believing.”

- Steve Perry, Journey
“The only true wisdom is knowing you know nothing.”

- Socrates

“Being a PhD student is like becoming all of the Seven Dwarfs. In the beginning, you are Dopey and Bashful. In the middle, you are usually sick (Sneezy), tired (Sleepy), and irritable (Grumpy). But at the end, they call you Doc, and then you are Happy.”

- Unknown

“If you knew what you were doing, it would not be called research.”

- Albert Einstein

“The only way to find out how to do a PhD is to do one. Therefore all advice is useless.”

- Unknown

“Hope for the best, expect the worst. Science is a play, we are unrehearsed.”

- (adapted from) Mel Brooks

“Yesterday is history. Tomorrow is a mystery, but today is a gift. That is why it is called the present.”

- Master Oogway, Kung Fu Panda
“Uuuuuuuuuuuur Ahhhhhhhrrrrrrrrrr Uhhhhhhhhrrrrrrrrrrr Ahhhhhrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr rr
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