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Role of astrocyte senescence induced by *Plasmodium* in the pathogenesis of Cerebral Malaria

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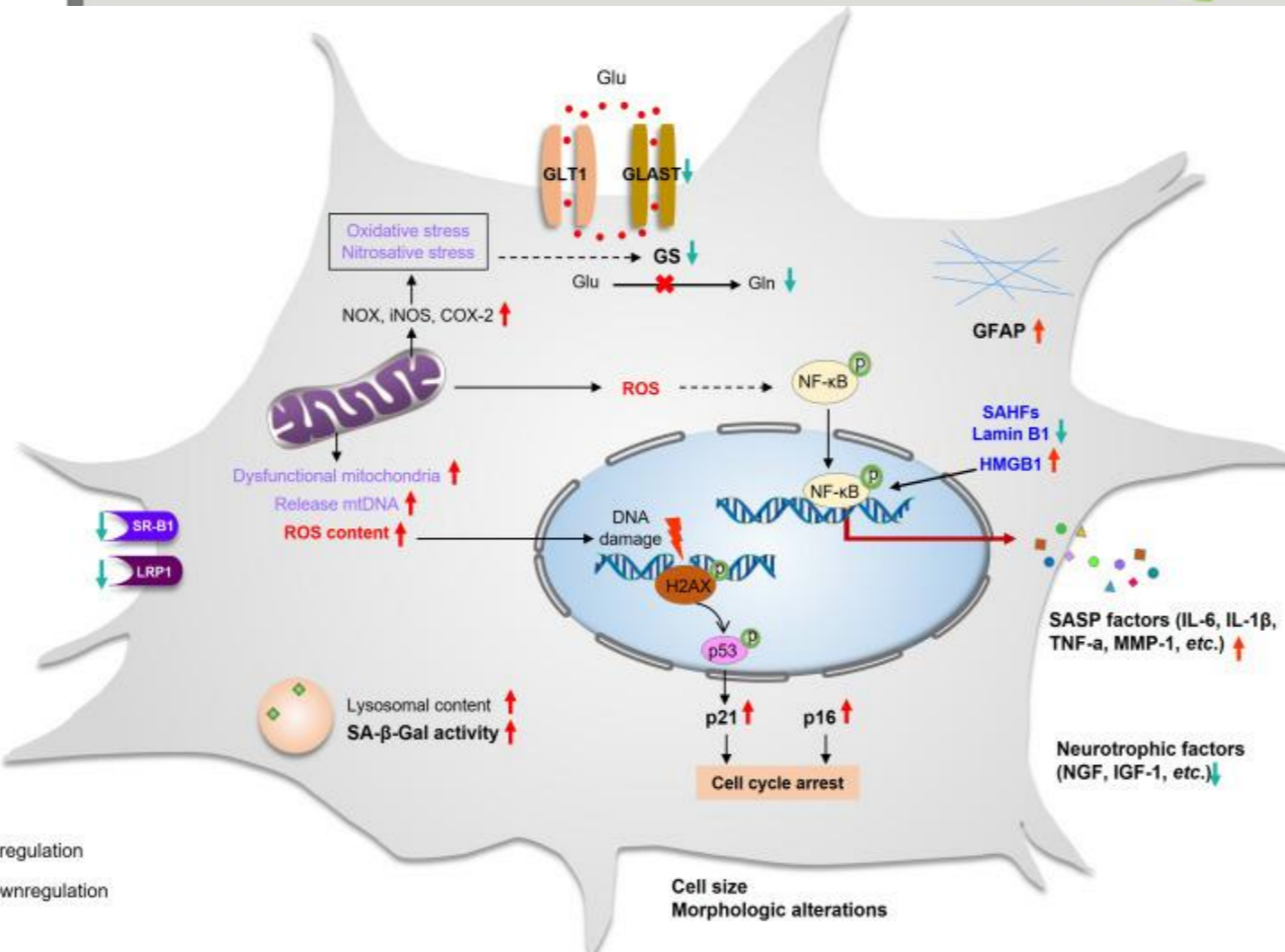
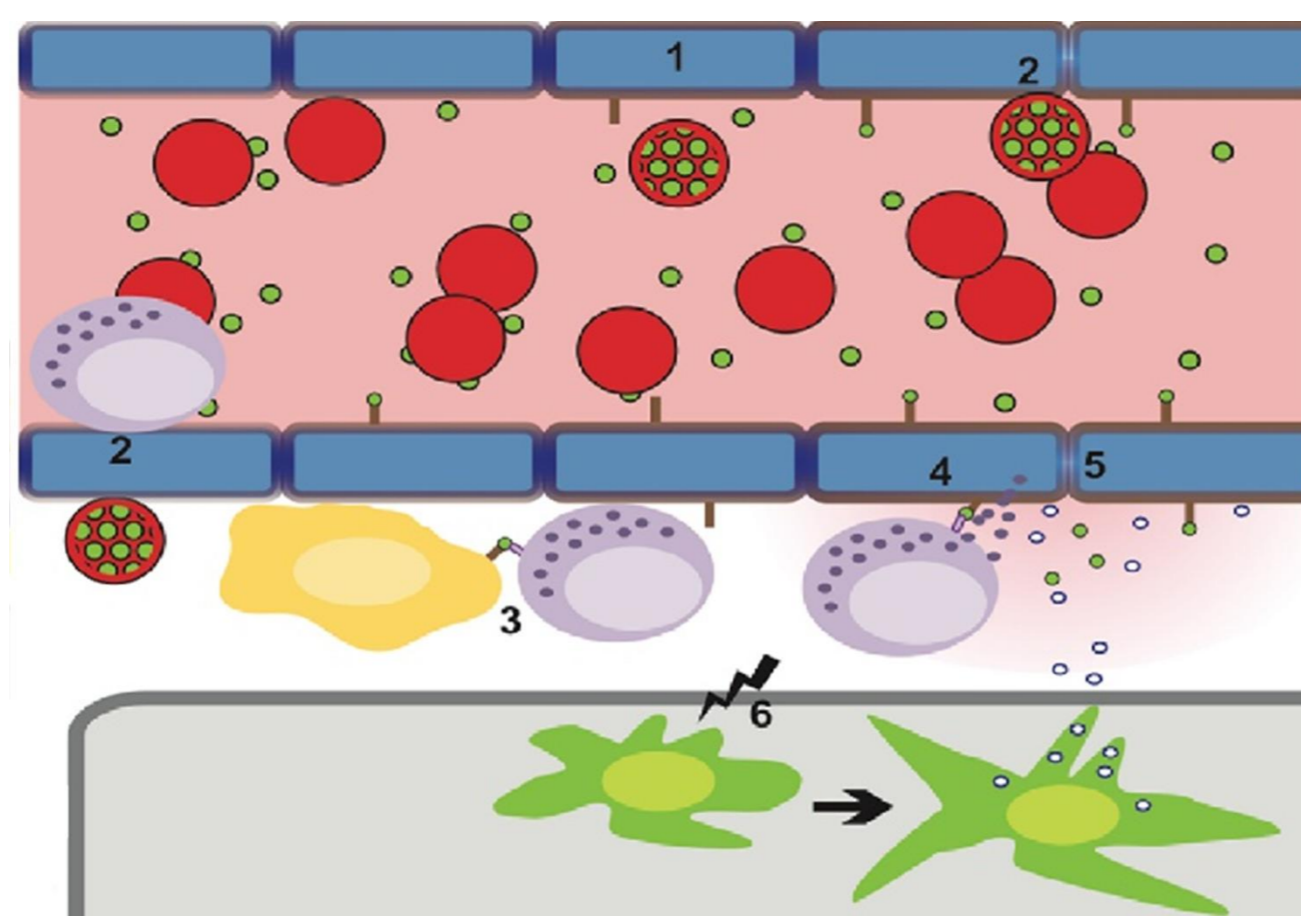
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Introduction

Cerebral malaria (CM) is a fatal neurological syndrome due to *Plasmodium* (*P.*) *falciparum* infection, which kills 405,000 people annually(1). A central event involved in the pathogenesis of CM is the sequestration of infected red blood cells in the brain capillaries and the inflammatory response of activated glial cells (2). However, molecular mechanisms involved in the induction of the pro-inflammatory response of glial cells during CM remains unknown.

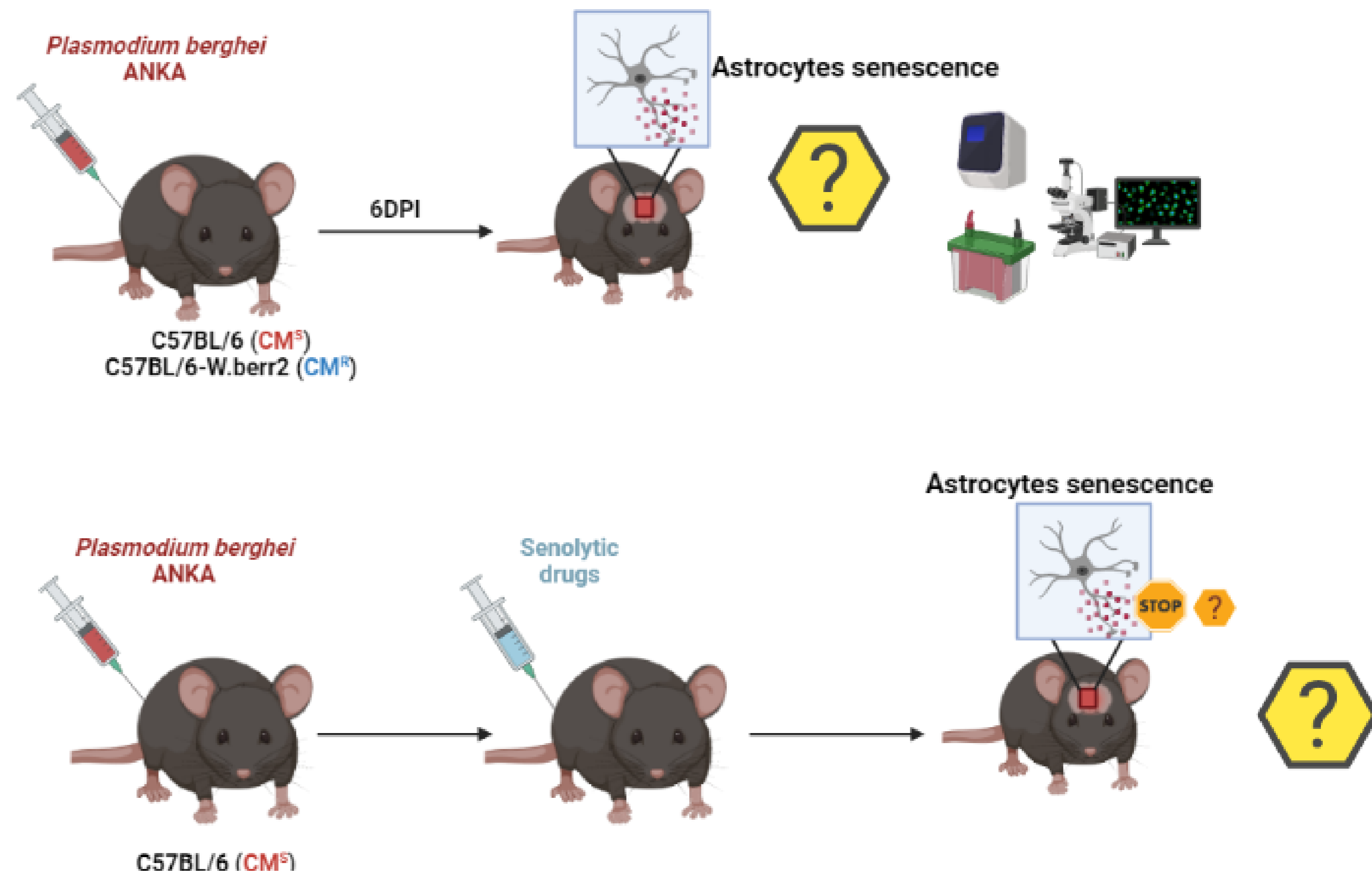
In this study, we have examined if the senescence of glial cells induced by *P. berghei* ANKA infection participates in the neuroinflammatory response associated to CM.

Cellular senescence is a permanent state of cell cycle arrest characterized by morphologic, metabolic and molecular changes (3). The senescence phenotype is often characterized by the activation of a DNA damage response that promotes an increase of senescence-associated-β-galactosidase (SA-β-gal) activity and expression of cell cycle-inhibitory proteins, most frequently p53/p21^{WAF1/Cip1} and/or p16^{INK4a/RB}. In addition to being irreversibly arrested, senescent cells produce a battery of factors including pro-inflammatory cytokines involved in CM characterizing the senescence-associated secretory phenotype (SASP) (4).



(1) Keswani et al, 2020; (2) Shrivastava et al, 2017; (3) Collado et al, 2007 (4) Hernandez-Segura et al, 2018

Materials and methods



Results

1- Increase of SA-β-gal activity and cell cycle inhibitors expression in brain of CM^S mice.

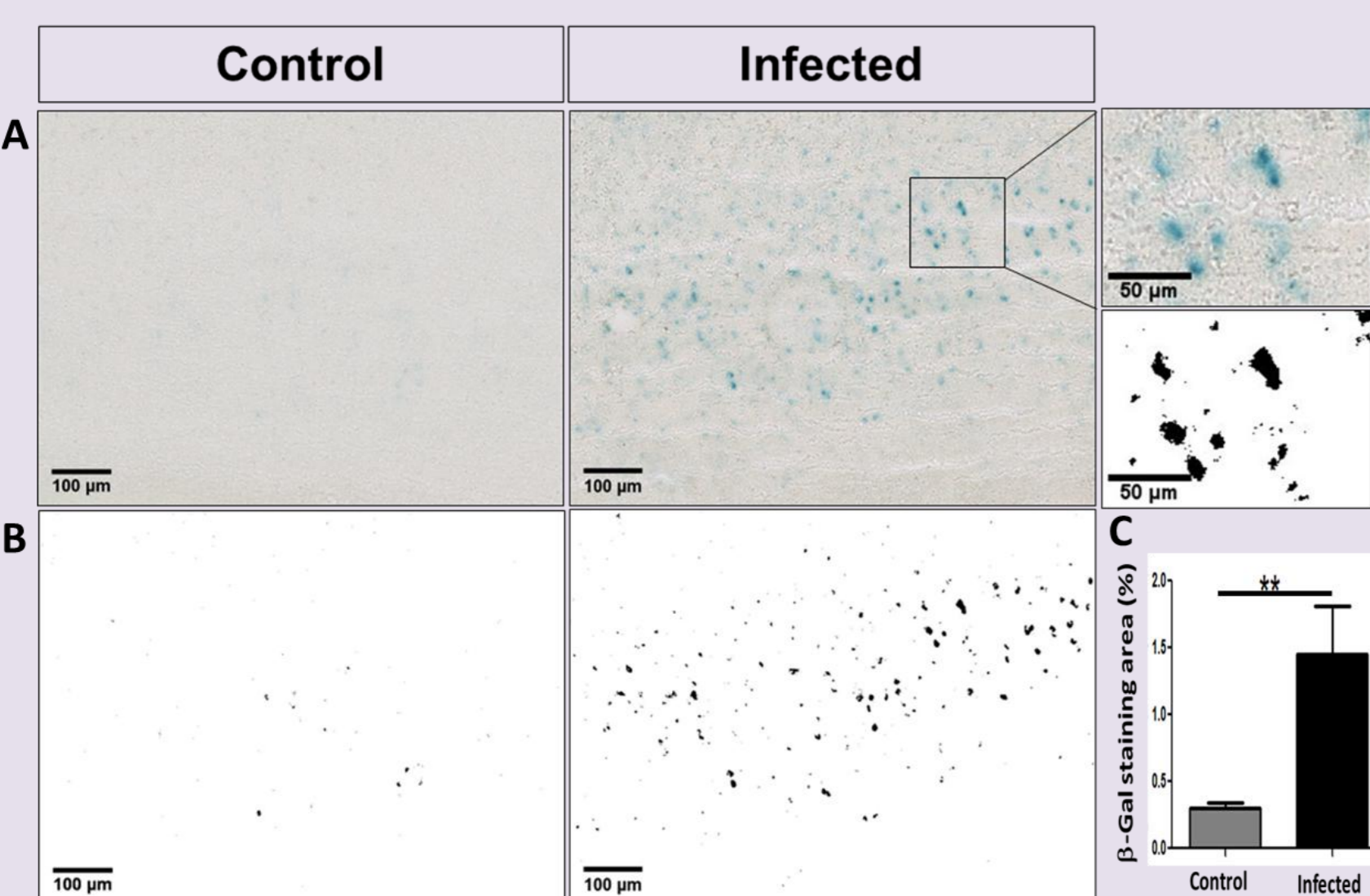


Figure 1: SA-β-Gal was detected in the brain of CM^S infected mice.

(A) Representative image of SA-β-gal staining in the brain of control and infected mice. Scale bars= 100µm. (B) Representative image of the analyzing of SA-β-Gal+ cells in the section (C) Quantification of the % of area blue in control and infected brain by ImageJ software. Data are mean ± SEM from three independent experiments (n = 3). Values were compared to the control group using a Mann-Whitney test. **p < 0.01

2- P. berghei ANKA infection-induced astrocytes senescence in the brain of CM^S mice.

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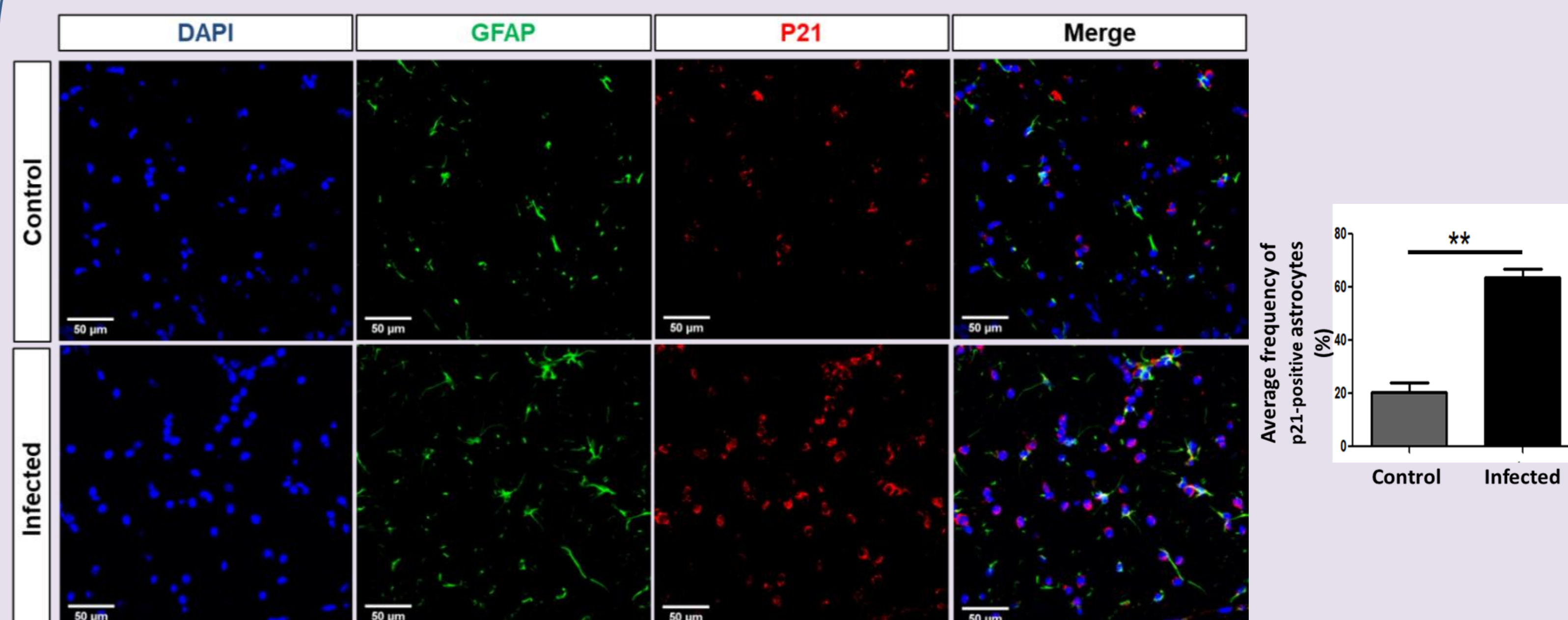


Figure 3A: Pba Infection induces the senescence process in the astrocytes of mice developing CM. Representative image of brain section of CM^S mice compared to non infected controls. Double immunofluorescence staining by glial fibrillary-associated protein (GFAP) (Green) and p21 (Red) counterstained with DAPI (blue) nuclear stain on brain section of control and infected mice. All images are representative of at least three replicates. Scale bar is 50µm.

Figure 2: Pba Infection modulated the expression of cell cycle inhibitory genes in the brain of infected CM^S mice. RT-qPCR profiles of cell cycle inhibitory genes expressed in whole brain extracts from CM^S and CM^R mice. Expressions of p53, p21^{WAF1}, GADD45y, p38MAPK, p16^{INK4a} and pRB were normalized to the control uninfected group. Data are mean fold-change ± SEM. Values (n= 6-10 per group) were compared to the control group or between selected groups using a Mann-Whitney test. *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001.

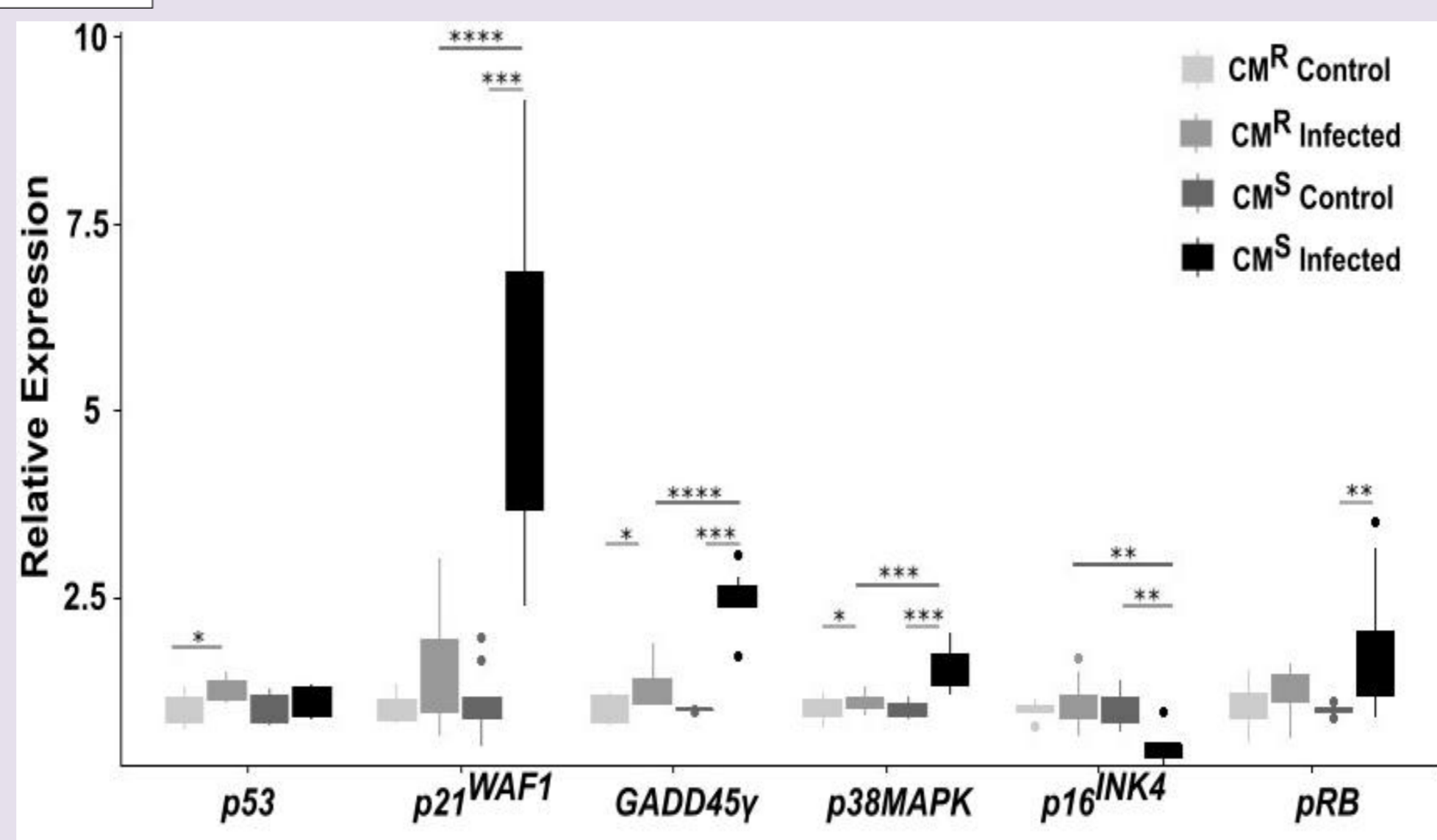
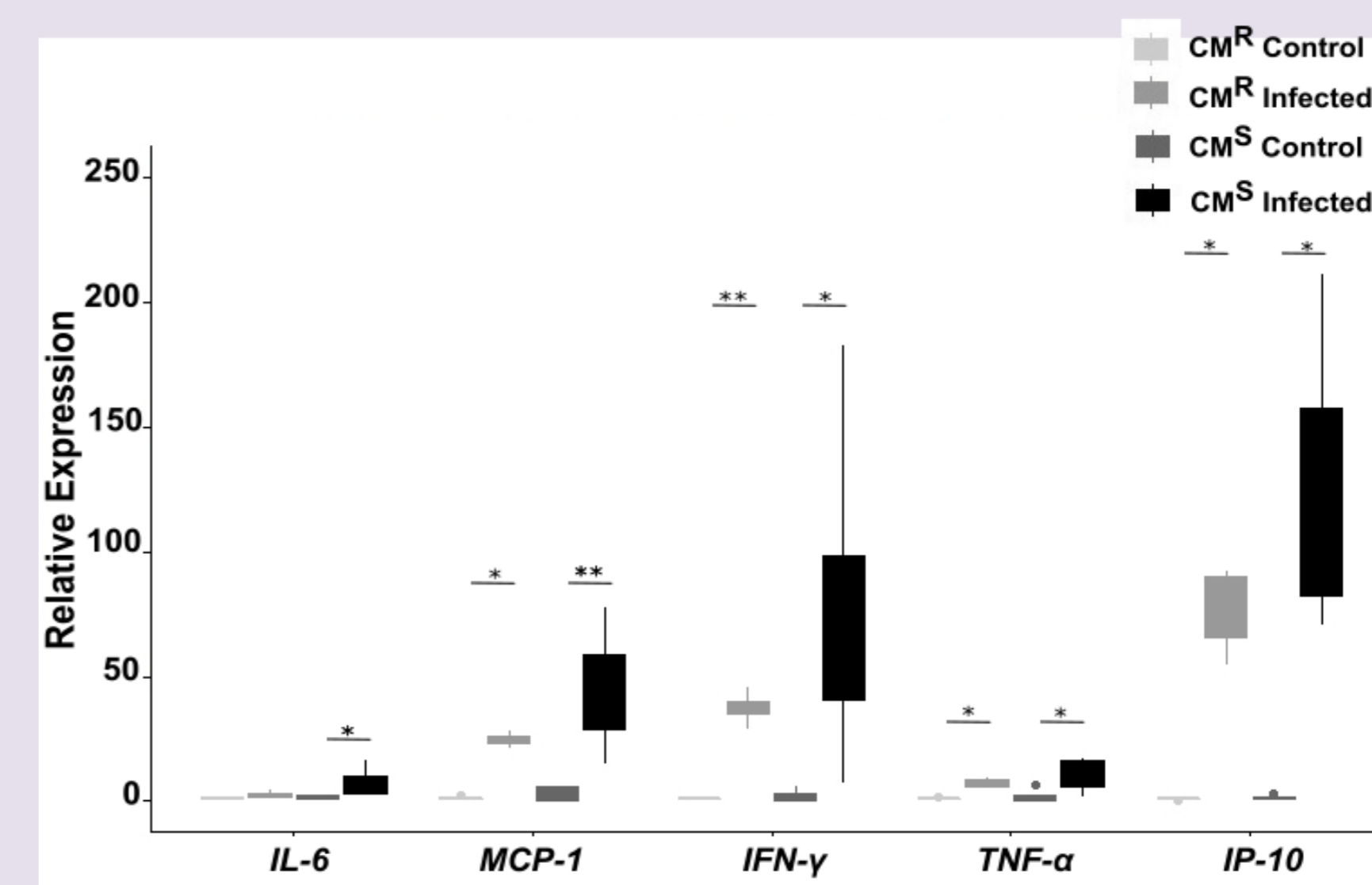


Figure 3B: Relative mRNA expression of (A) cell cycle arrest markers (p53, p21^{WAF1} and GADD45y) in astrocytes sorted from brains of CM^S and CM^R control and infected mice. Data are mean fold-change ± SEM. Values (n= 3-5 per group) were compared to the control group or between selected groups using a Mann-Whitney test. *p < 0.05; **p < 0.01.



3- Treatment with senolytic drugs prevents the development of CM in PbA infected CM^S mice

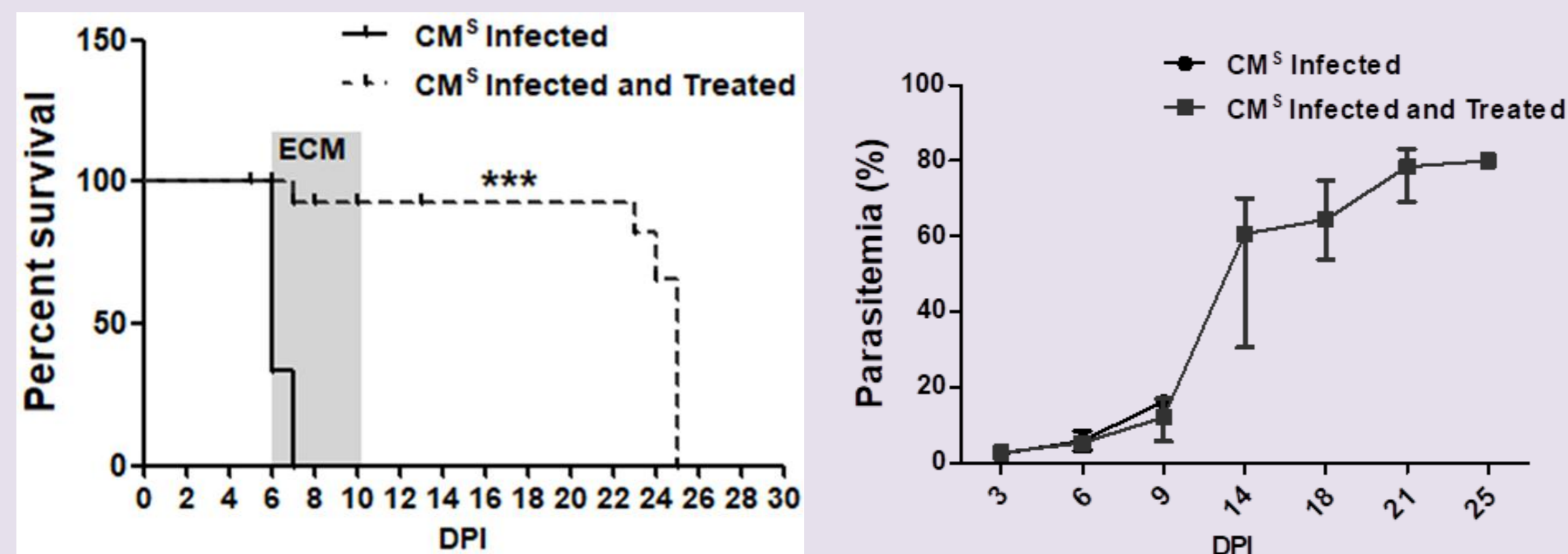
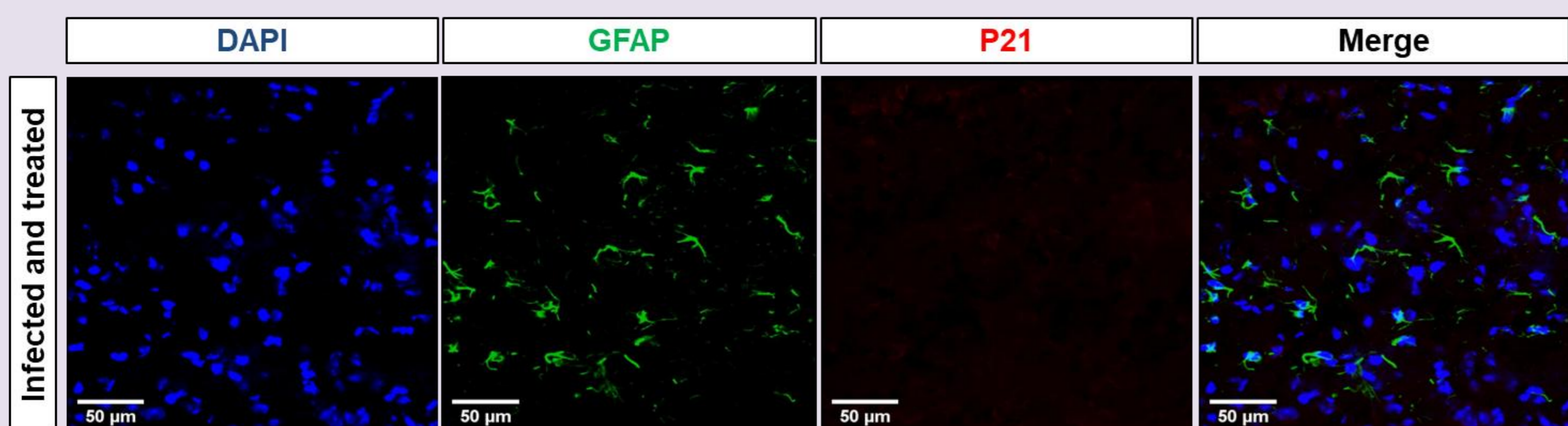


Figure 4: Senolytic drugs prevented CM with no effect on parasitemia (A) Survival and (B) parasitemia rate of mice infected with PbA or with PbA and treated with D + Q (PbA + D&Q).



(C) Representative immunofluorescence images showing p21 protein level (red) with GFAP (Green) and DAPI (blue) on section brain of infected and treated CM^S mice. Scale bar is 50µm.

Conclusion

