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The natriuretic peptide hormones prevent *Pseudomonas aeruginosa* biofilm formation through a specific bacterial target.

Desriac F¹, Clamens T¹, Rosay T¹, Enault J¹, Roquigny L¹, Bazire A², Dufour A², Racine PJ¹, Cornelis P¹, Bouffartigues E¹, Chevalier S¹, Feuilloley MGJ¹, Lesouhaitier O¹

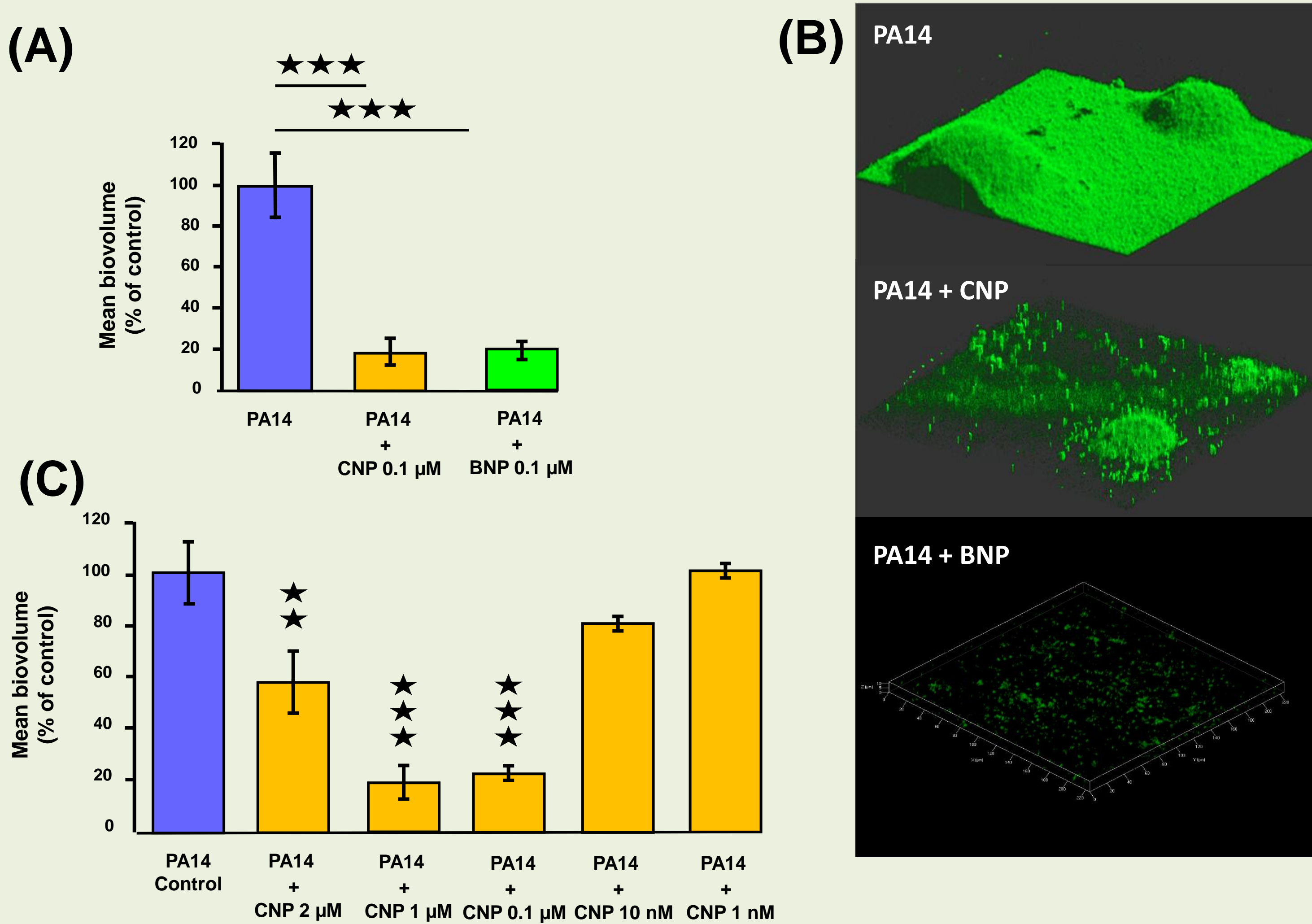
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Introduction

There is now ample evidence that bacterial virulence is modulated by eukaryotic messengers (endocrine or neuro-endocrine modulators) released in its micro-environment. We have previously shown that the C-type Natriuretic Peptide (CNP) a mammalian hormone, enhances global *Pseudomonas* virulence (Blie et al., 2011). Since virulence factor production and biofilm formation are usually inversely regulated, we investigated the effect natriuretic peptide on biofilm formation.

The effect

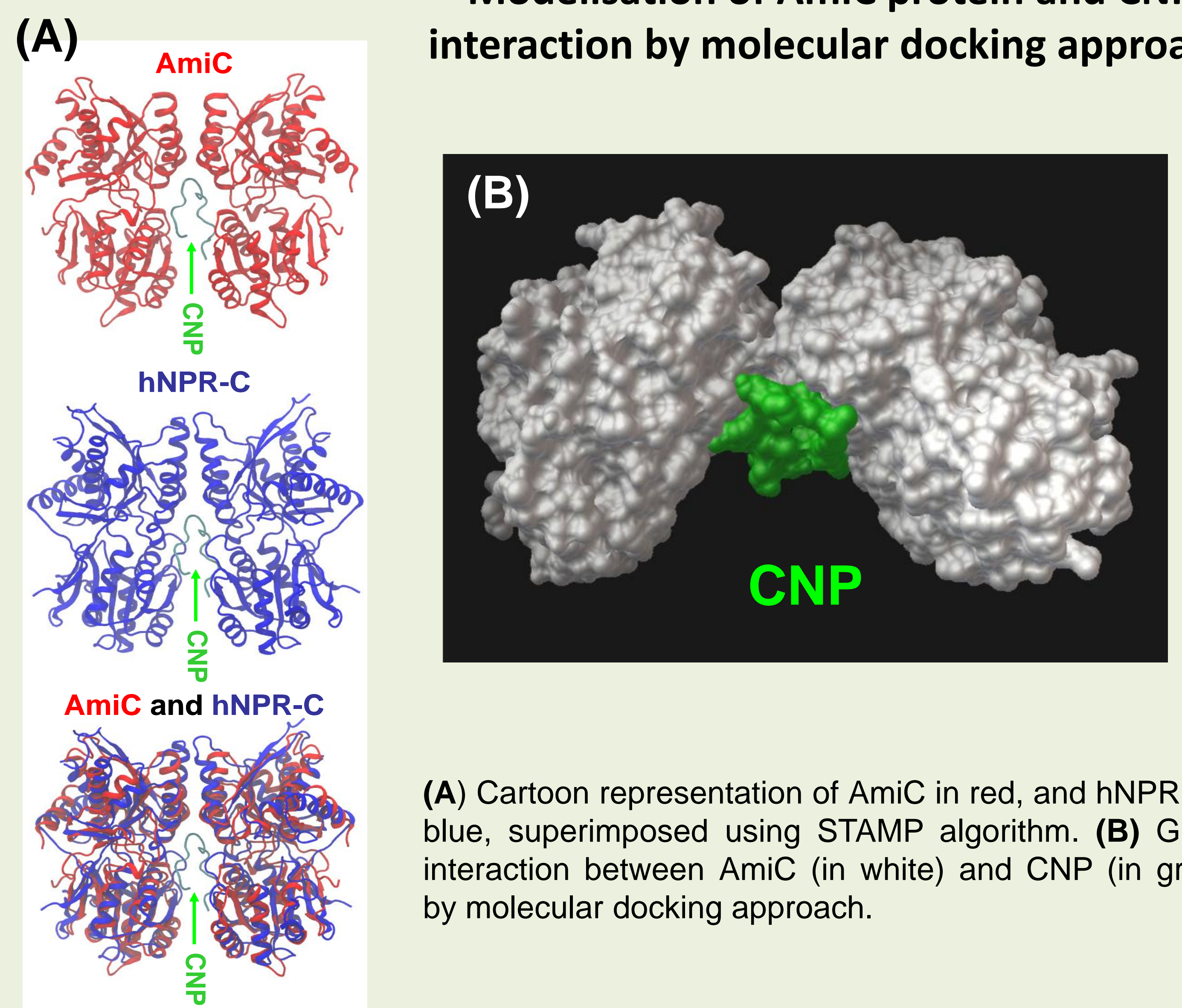
Effect of CNP and BNP on *P. aeruginosa* biofilm formation



(A) COMSTAT analyses of *P. aeruginosa* PA14 biofilm formation in control or exposed to CNP or BNP. (Mann and withney test **** p < 0.001; *** p = 0.009). (B) 3D-shadow representations of the biofilm structures developed under dynamic condition by *P. aeruginosa* PA14 control or exposed to CNP or BNP (0.1 μM). (C) Dose effect of CNP on *P. aeruginosa* biofilm formation.

The potential target

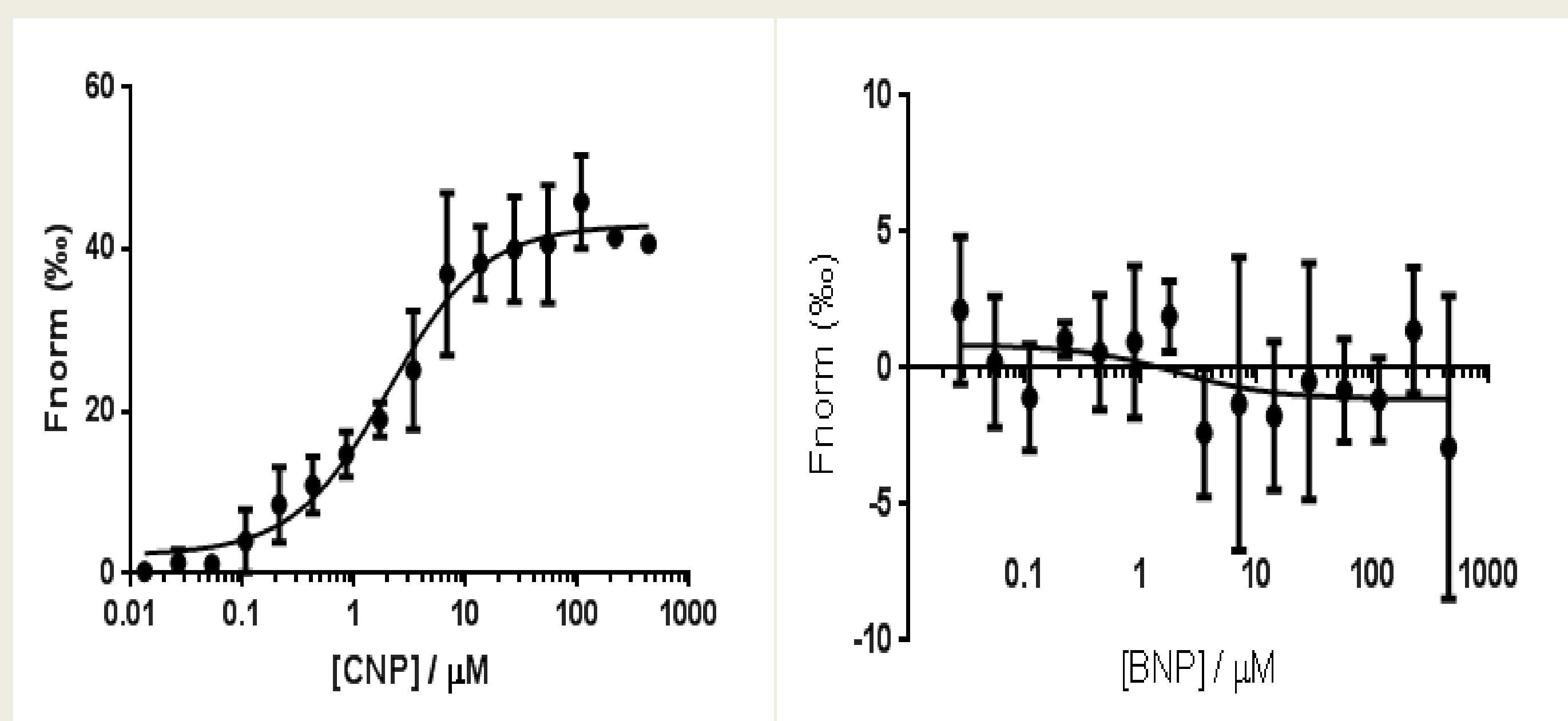
Modelisation of AmiC protein and CNP interaction by molecular docking approach



(A) Cartoon representation of AmiC in red, and hNPR-C in blue, superimposed using STAMP algorithm. (B) Global interaction between AmiC (in white) and CNP (in green) by molecular docking approach.

The affinity for the target

CNP, BNP affinities for AmiC *in vitro*.

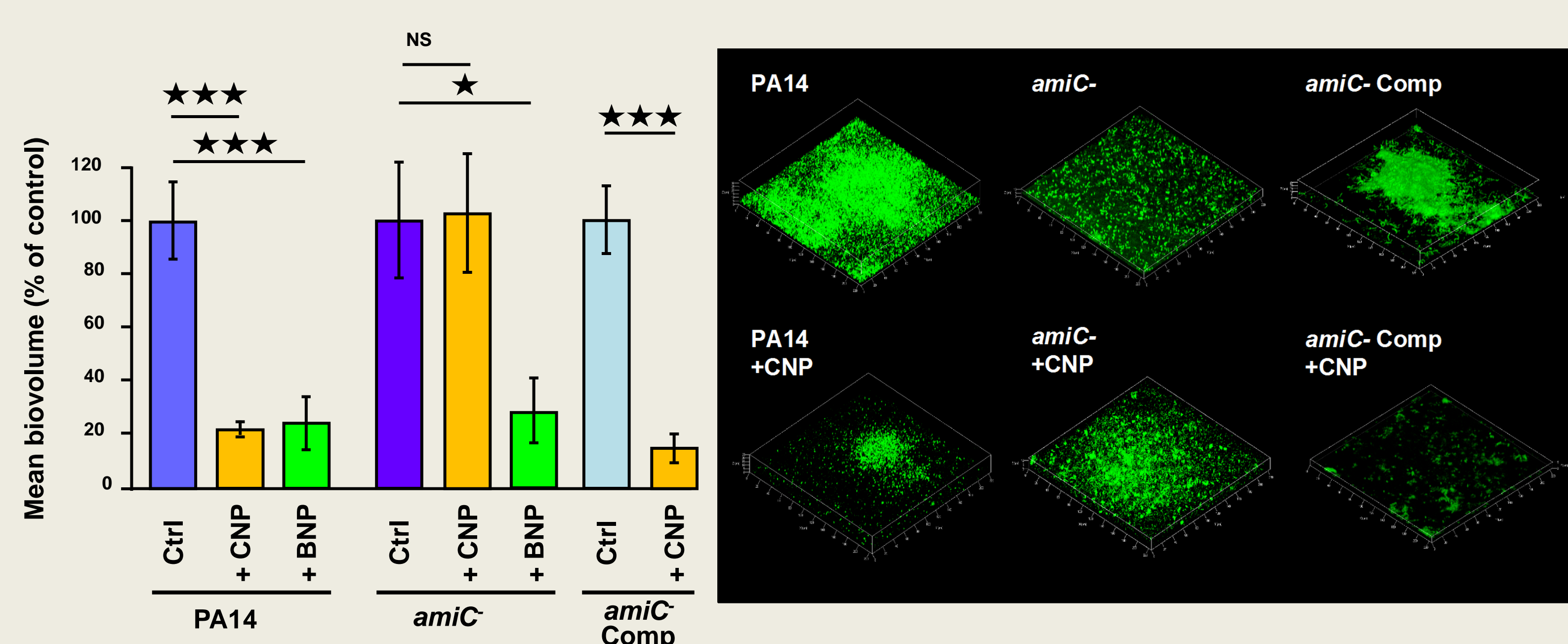


Ligands	Kd
CNP	2.0 ± 0.3 μM
BNP	No interaction

(A) Recombinant AmiC was fluorescently labeled and incubated with varying concentrations of natriuretic peptides. These mixtures were then analysed using by microscale thermophoresis. (B) The fitted values for *KD* are shown for CNP, BNP.

Target validation

Involvement of AmiC protein on *P. aeruginosa* biofilm formation



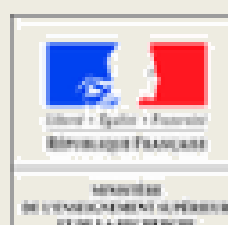
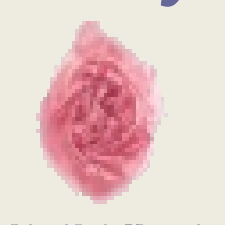
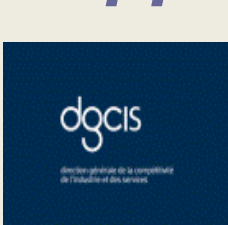
(A) COMSTAT analyses of *P. aeruginosa* PA14 biofilm formation in control or exposed to CNP or BNP. (Mann and withney test ** p = 0,0022). (B) 3D-shadow representations of the biofilm structures developed by *P. aeruginosa* PA14 WT (PA14) and mutant strain (*amiC*-) exposed or not to CNP.

Conclusion

Previous studies shown that CNP enhances *P. aeruginosa* virulence. We observed that natriuretic peptides (BNP and CNP) decreases the ability of PA14 to form biofilm, confirming that the biofilm formation is inversely regulated to the virulence factor production.

The comparison of the 3D structure of the eukaryotic receptor for CNP (NPR-C) with the AmiC protein showed a high homology between these two proteins, and molecular docking approach suggested that AmiC could interact with CNP. Microscale thermophoresis experiment indicates that AmiC and CNP interact with a *Kd* in the low micromolar range whereas BNP and AmiC do not. Biofilm formation of *amiC*- strains support the hypothesis that AmiC could act as a bacterial sensor for CNP that mediates the action of the peptide on biofilm formation. The mechanism of action of BNP on *P. aeruginosa* is different and is under investigation. Experiments are under study with the atrial natriuretic peptide

Supported by :



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