One Health: Translational and Reverse Translational Modeling of Inflammatory Bowel Disease using an advanced Boolean Network

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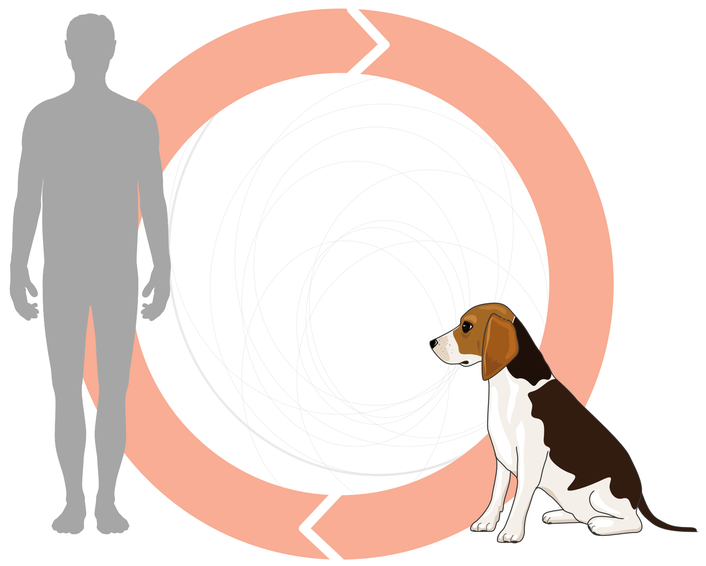
BACKGROUND AND OBJECTIVES

Recent literature [1,2] suggests that the **purinergic receptor P2X7** is a relevant target for treating **inflammatory bowel disease (IBD)**

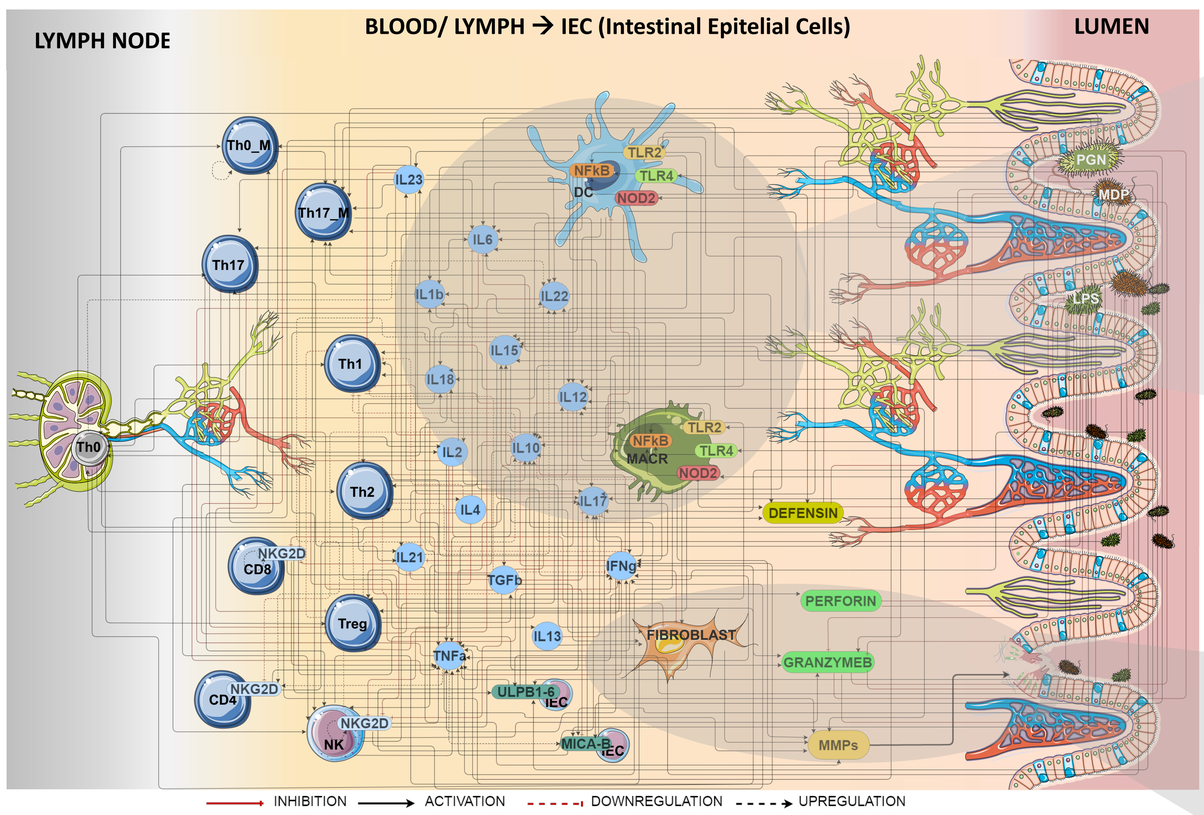
IBD is a **highly prevalent** chronic intestinal disorder in both **humans and dogs**, such as **clinical trials** with naturally occurring cases of **canine IBD** are particularly relevant to study the **efficacy and safety of P2X7 receptor antagonists** (P2X7A)



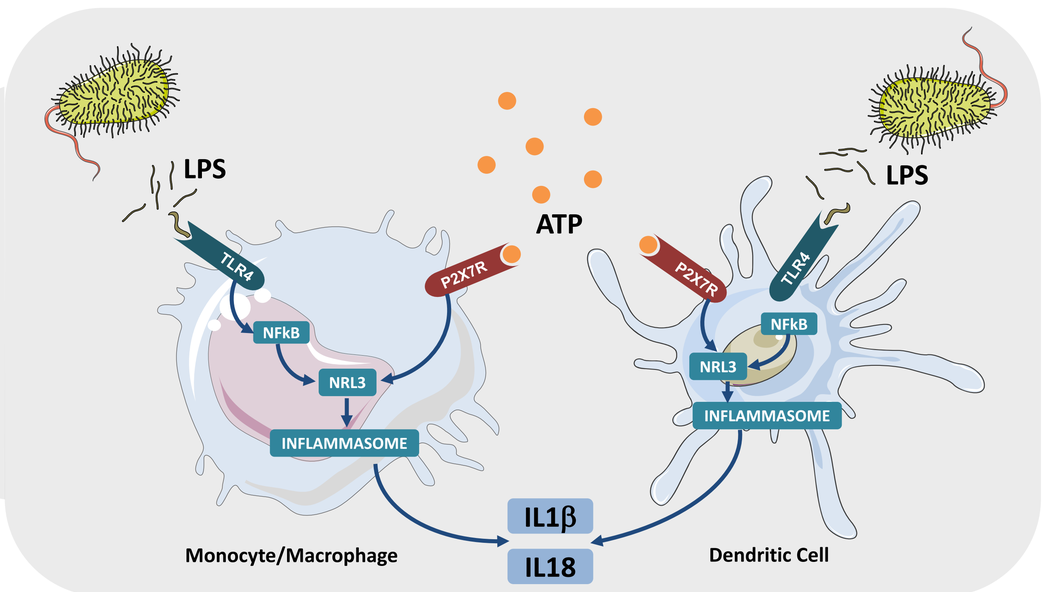
A **model-based approach** was used to **predict** the **effect** of a **candidate non-competitive P2X7A** on biomarkers known to be associated with chronic intestinal inflammation (**IL1b, IL18**) and tissue damage (i.e. Matrix Metalloproteinases, **MMPs**), as well as **to guide dose selection** for an **upcoming clinical trial in IBD dogs**

METHODS

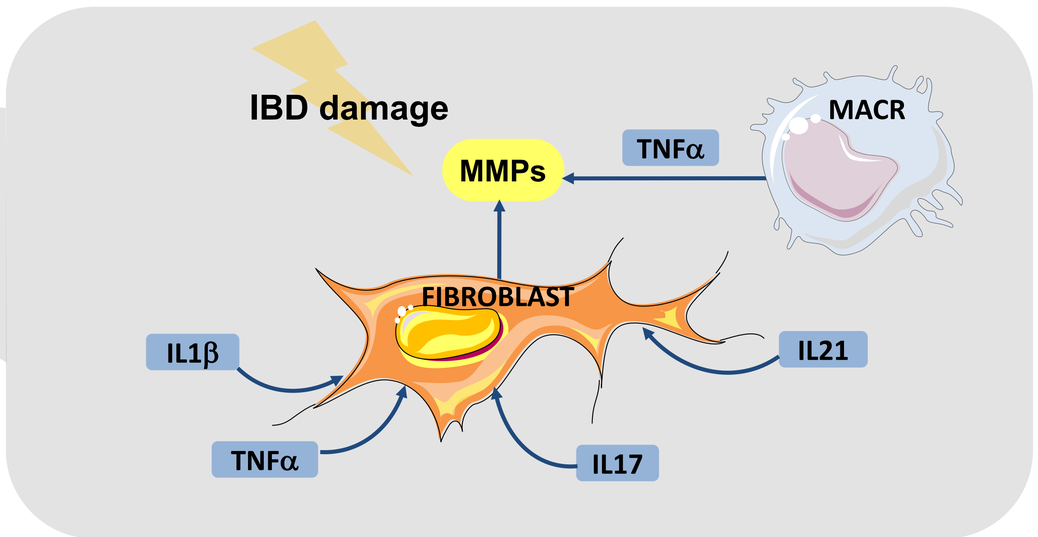
A **Network Systems Pharmacology (SP) model** based on **Boolean equations** of IBD (including 43 nodes and 298 interactions), and implemented in the SP platform **SPIDDOR** [3], was used to simulate the effect of the candidate P2X7A



Graphical representation of the Boolean Network for IBD. Input nodes are the microbial antigens Lipopolysaccharide (LPS), Muramyl dipeptide (MDP) and Peptidoglycan (PGN). The output node is MMPs., responsible of tissue damage → ***see IV-13 poster***



Effect of P2X7 Receptor activation on the inflammasome



Matrix Metalloproteinases (MMPs) expression

Simulations were performed **assuming chronic response to 3 different microbial antigens** (Lipopolysaccharide, Muramyl dipeptide and Peptidoglycan), and a **direct effect of P2X7 antagonism on the inflammasome**

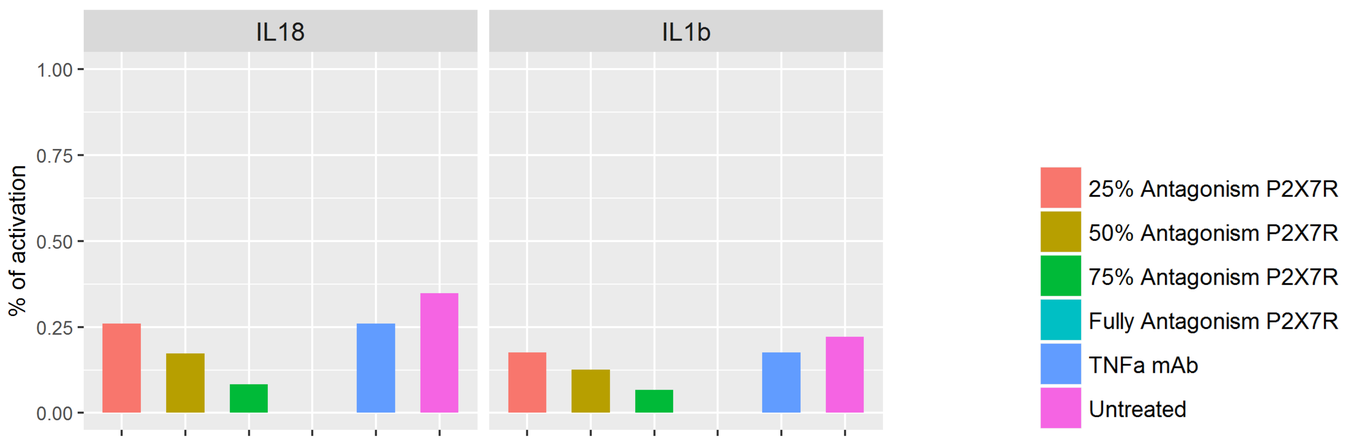
Results were expressed as **relative percent change of IL1β, IL18 and MMPs** from control for an increasing fraction of P2X7 being antagonized (from 25% to 100%, with 25% increments)

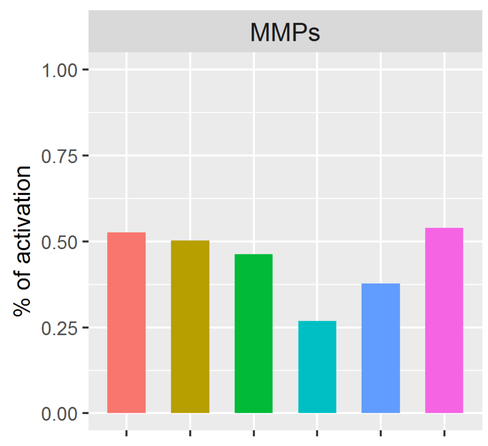
Matrix Metalloproteinases (MMPs) expression is correlated with canine IBD Activity Index **(CIBDAI) Score**

RESULTS

Simulations showed a reduction by half of IL1β and IL18 systemic levels when antagonizing 50% of P2X7, but only moderate effect on MMPs

The effect of the candidate drug was further compared to TNFα mAb, a currently approved therapy for IBD





A more substantial decrease in MMPs (>20%) can be expected with 75% and higher blockade of the target receptor

CONCLUSIONS

Assuming that **MMPs levels** are associated with **clinical activity**, **the selected dose of the P2X7A candidate** should **antagonize at least 75% of the target receptor**. This approach has apparent translational medical impacts due to **similarities in the pathophysiology of IBD between humans and dogs**

REFERENCES

[1] Arulkumaran N et al. Expert Opin Investig Drugs. 2011
[2] Eser A et al. Inflamm Bowel Dis. 2015
[3] Irurzun-Arana et al. Bioinformatics. 2016

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