ISB[M]

Target prioritization for celiac disease therapy: prediction of therapeutic effect of potential drugs

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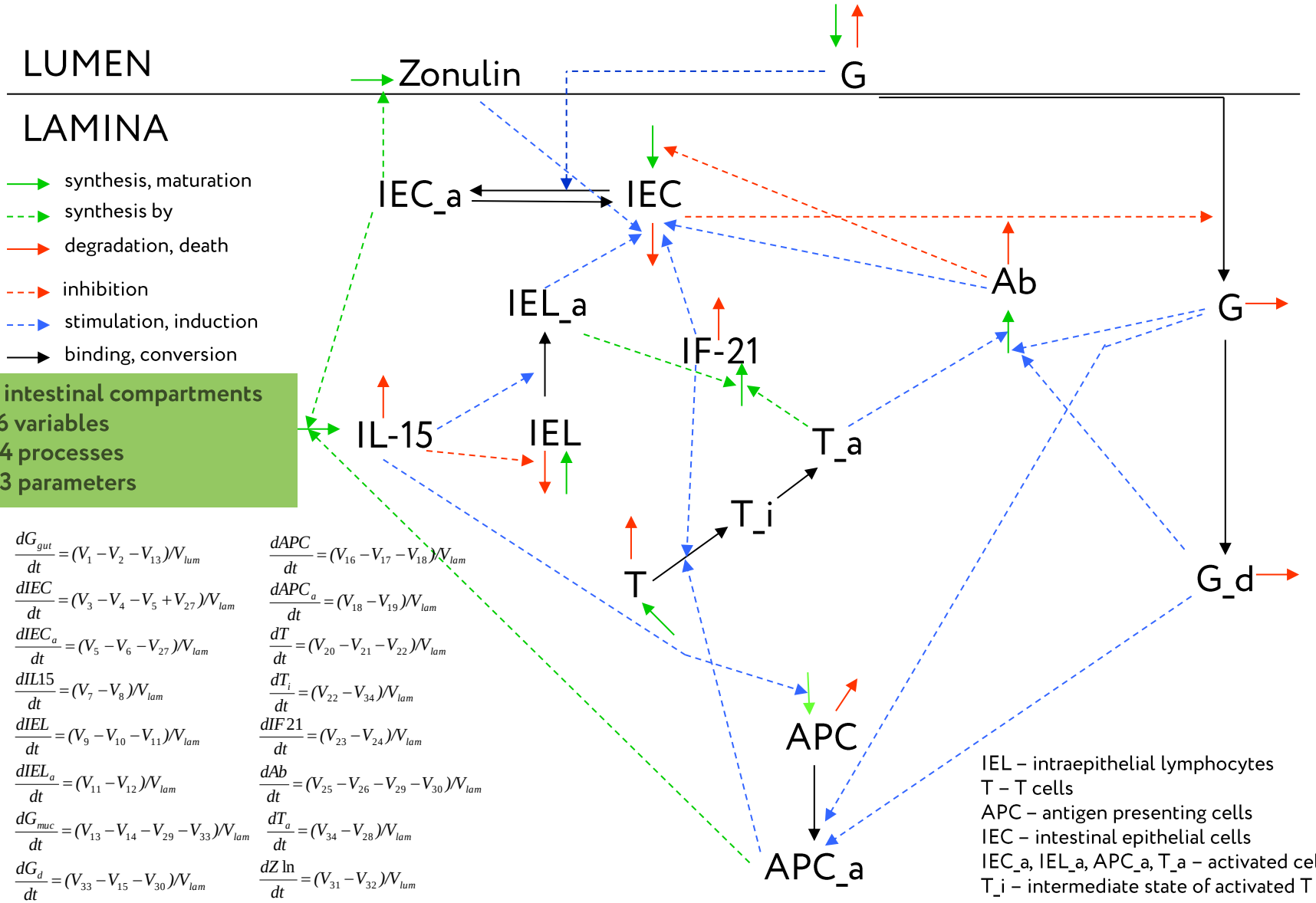
Celiac disease is an autoimmune disorder that occurs in genetically predisposed people. This disease is caused by the reaction to **gluten protein** found in wheat.

In the gastrointestinal tract gluten is breaking up to small peptides. In the small intestine gluten peptides cause an innate immune response which leads to villous epithelial damage.
This allows gluten peptides to enter the intestine's wall (lamina propria). In the lamina, an enzyme called **tissue transglutaminase-2 (TG2)** starts to deamidate this peptides, making them significantly more immunogenic, thus promoting adoptive immune response. The result is antibodies synthesis against TG2 and gluten peptides.

OBJECTIVES

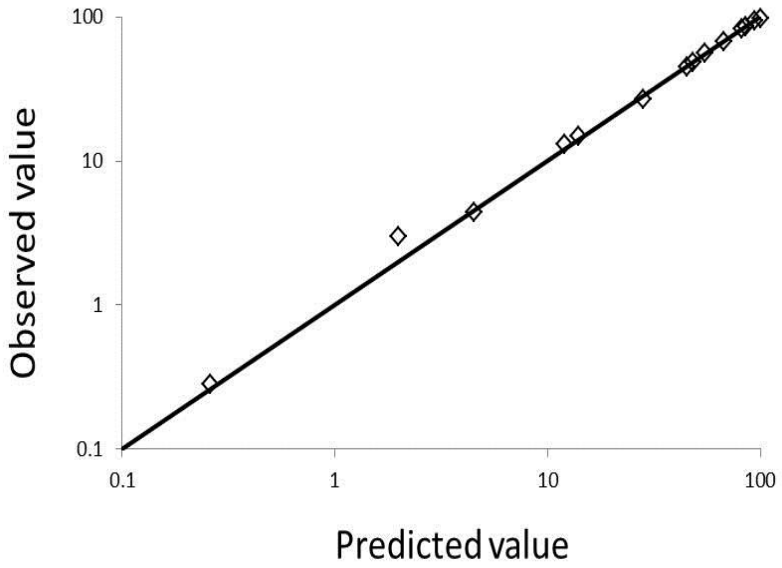
- To develop a QSP model of innate and adoptive immune response in celiac disease, including the impact of different cells and proteins on villous area, the deamidation of gluten peptides and the antibody synthesis.
- To prioritize targets of possible drugs (transglutaminase-2 inhibitor, permeability inhibitor, IL-15 antibodies, IFN-γ antibodies, DQ2-blocking peptides) on the basis of model predicted efficacy for celiac disease treatment expressed in terms of clinically measured endpoints (villous area and antibodies level).

Model of the immune response in celiac disease

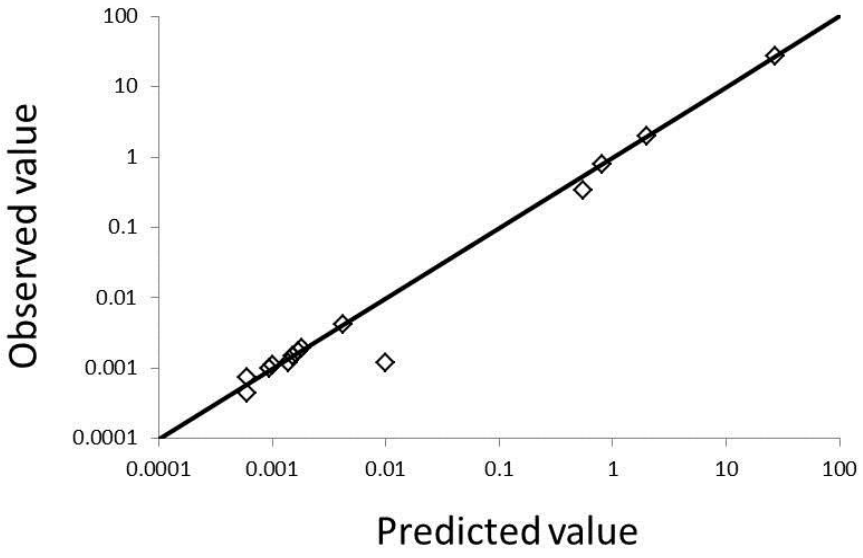


Model verification

Fitting against *in vitro* and *ex vivo* data

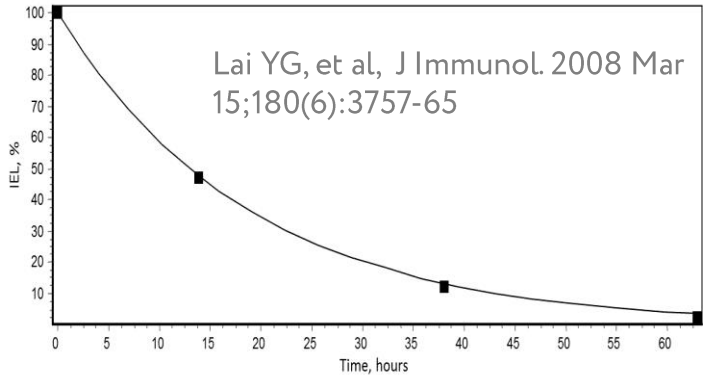


Fitting against *in vivo*

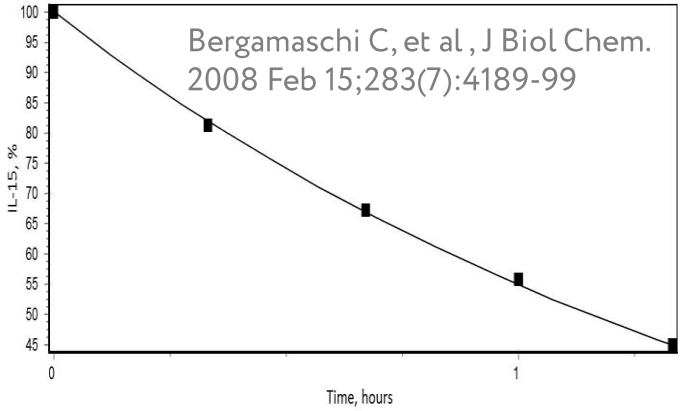


Examples

Fitting against IEL death data



Fitting against *in vitro* IL-15 degradation data



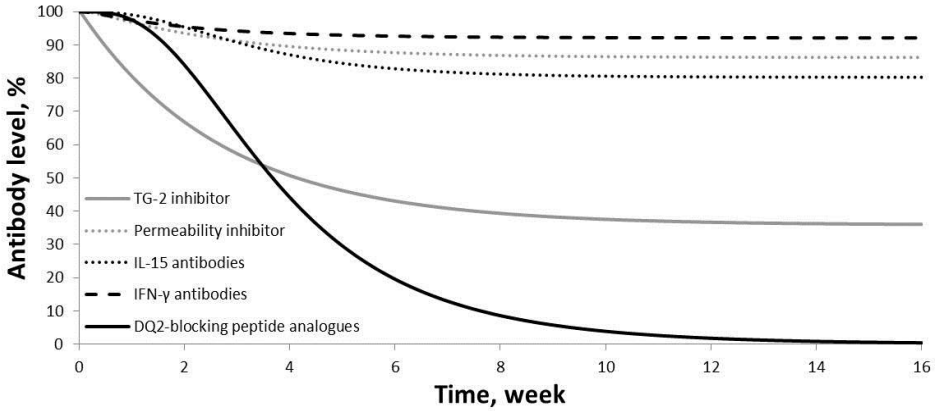
Fitting against *in vivo* steady state concentrations

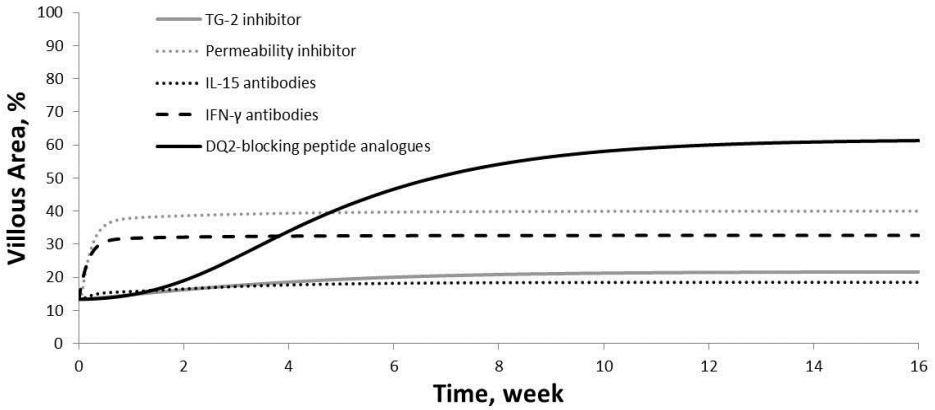
Variable	Gluten-containing diet		Gluten free diet	
	Experimental value	Model value	Experimental value	Model value
Ab	27 μM	27.07 μM	-	-
Zln	2 nM	2.04 nM	-	-
IL15	0.8 pM	0.796 pM	0.56 pM	0.34 pM
IEC	0.0018 pM	0.00186 pM	-	-
IEC_a	0.0006 pM	0.00076 pM	-	-
Total IEC	0.0024 pM	0.00262 pM	0.00425	0.0042
IEL	0.0006 pM	0.00046 pM	-	-
IEL_a	0.0014 pM	0.00125 pM	-	-
Total IEL	0.002 pM	0.00171 pM	0.0017	0.0017
Total APC	0.0015 pM	0.00149 pM	0.001	0.0012
Total T cells	0.001 pM	0.0013 pM	0.00095	0.00098

Simulation of efficacy of various potential drugs

The virtual patient was treated with *gluten-containing* diet.

The drug targets is prioritized in terms of maximal efficacy of corresponding potential drugs. Efficacy is expressed in terms of clinically measured endpoints: **villous** area and **Ab level.**





RESULTS:

- TG-2 inhibitors decrease AB by two times and only slightly increase villous area
- Permeability inhibitors, IL-15 and *IFN-g* antibodies slightly decrease AB level and increase villous area
- Administration of DQ2-blocking peptides allows to decrease AB level to about zero (normal state) and increase villous area to 60% of normal state.

CONCLUSION: among the potential drugs *DQ2-blocking peptide* is most promising one in terms of efficacy of celiac disease treatment.

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