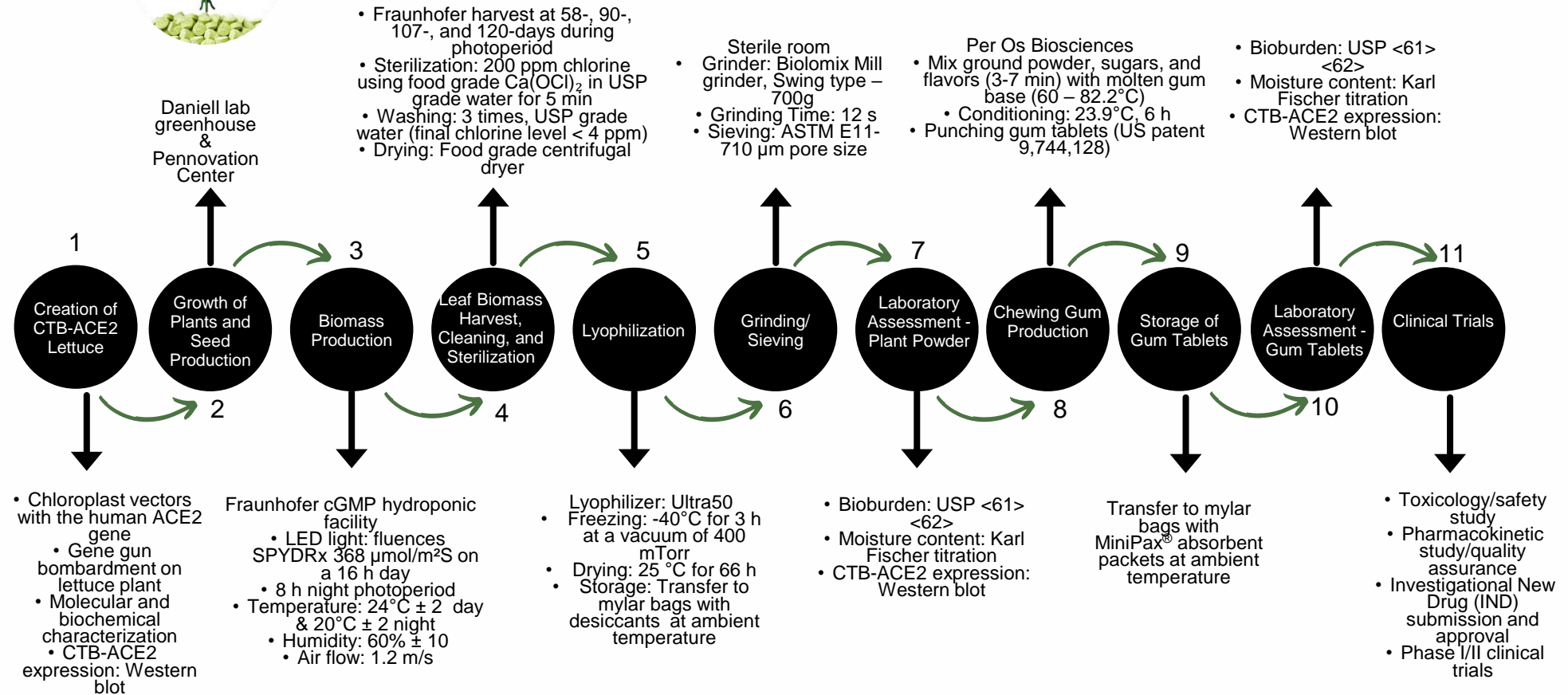
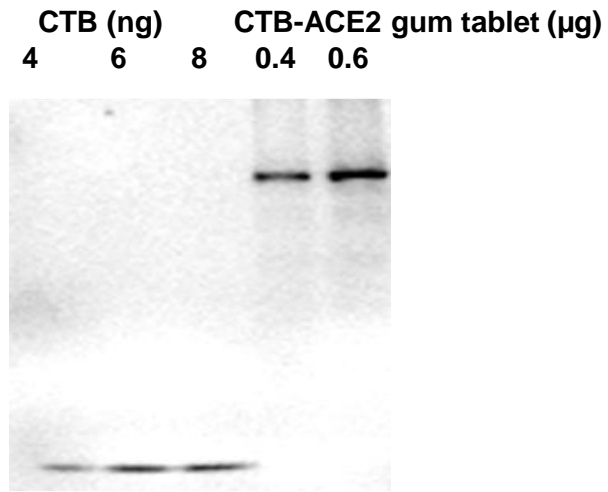
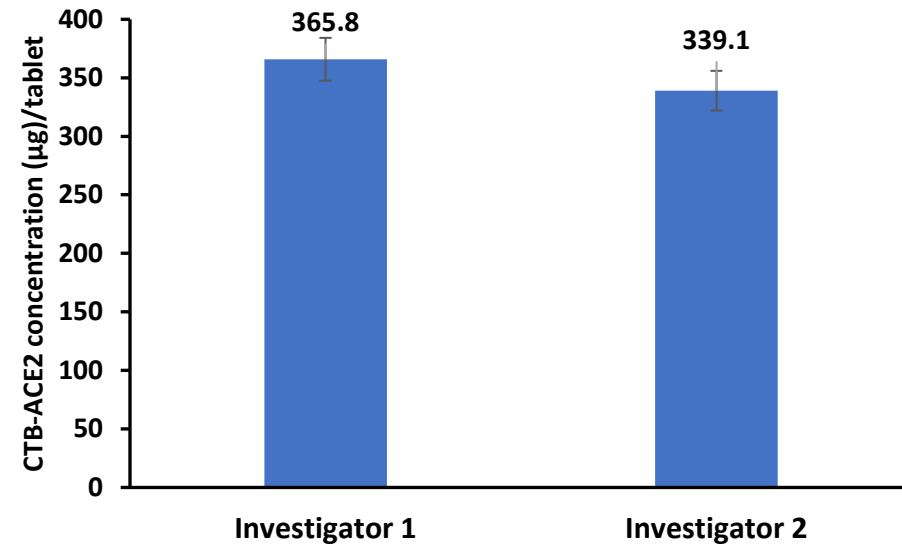
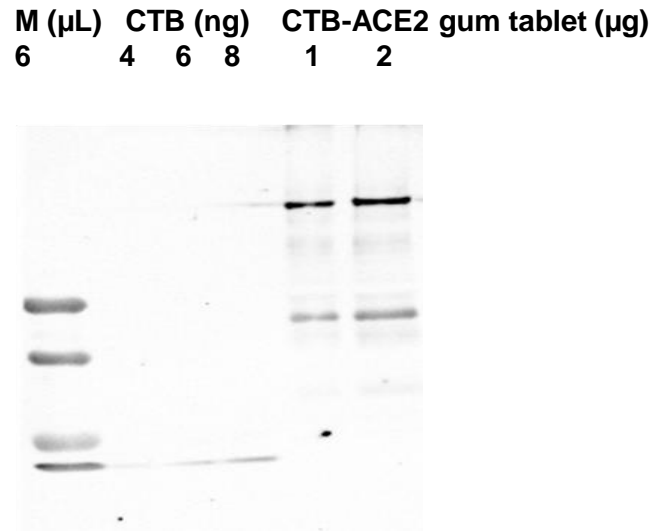
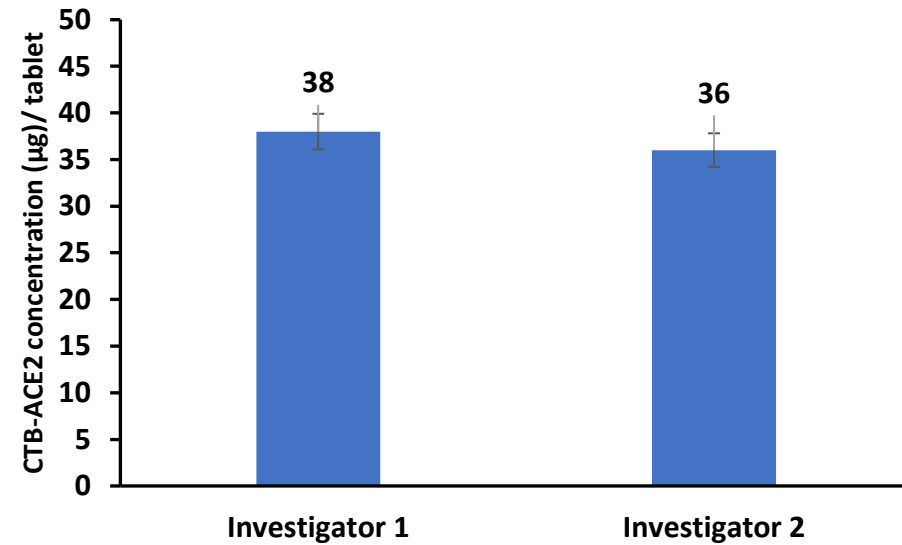




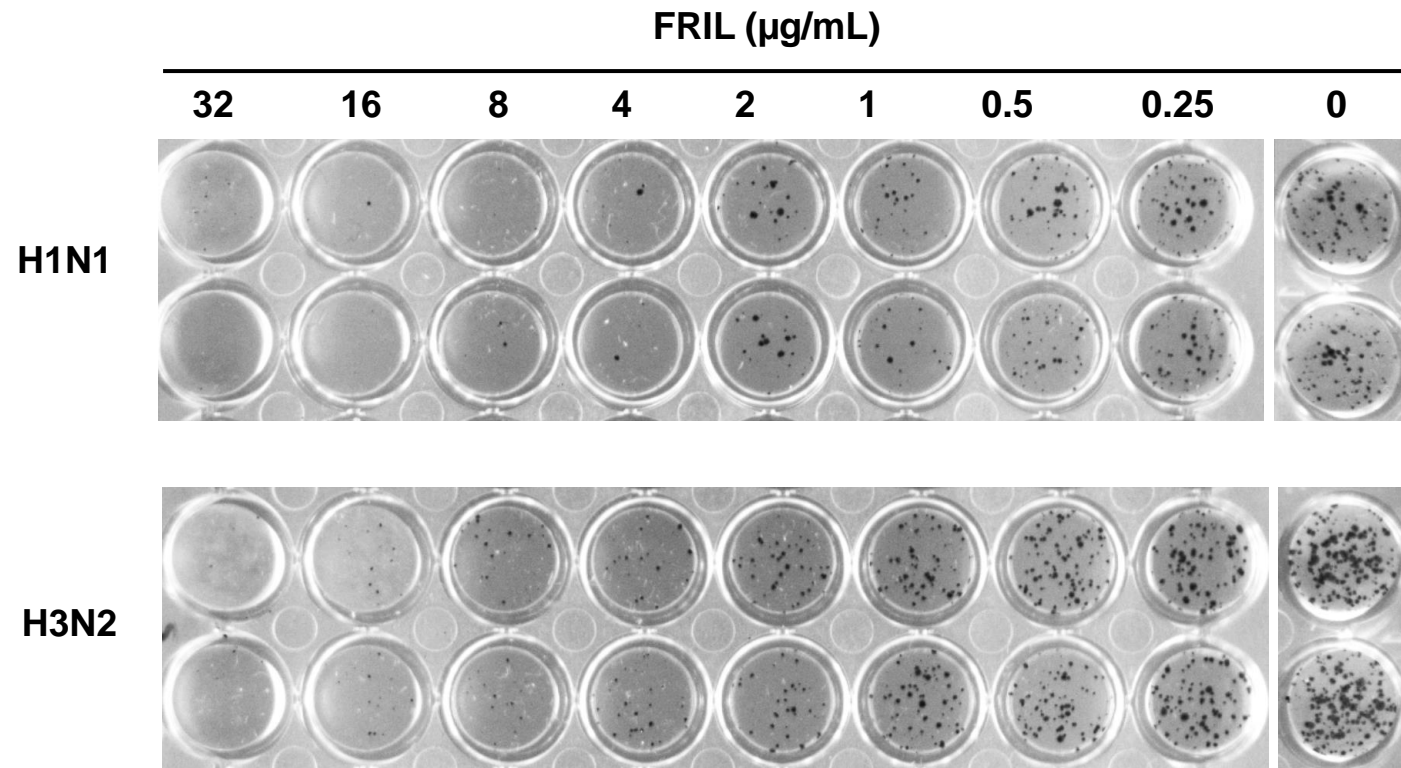
# From lab to the clinic – CTB-ACE2 chewing gum



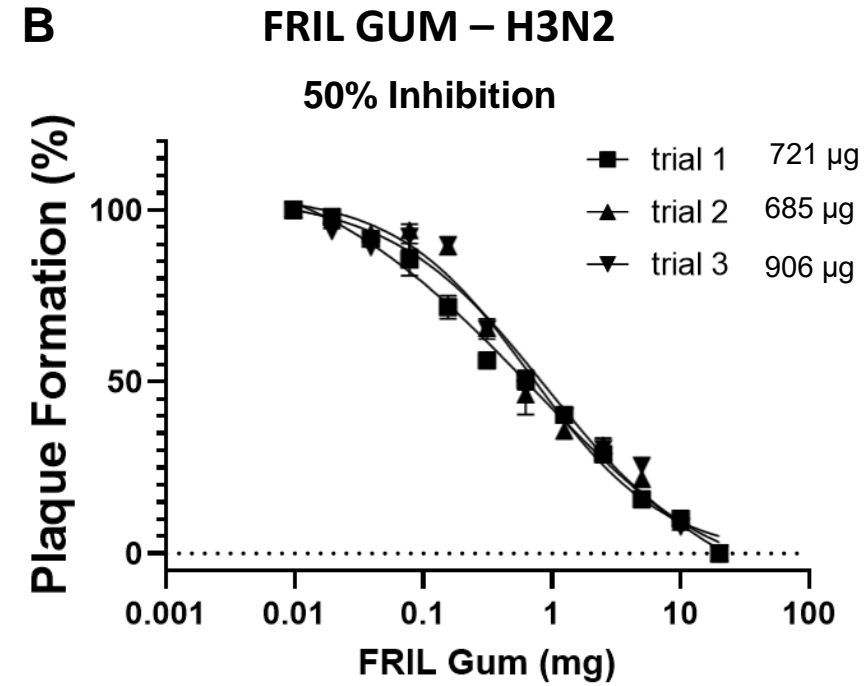
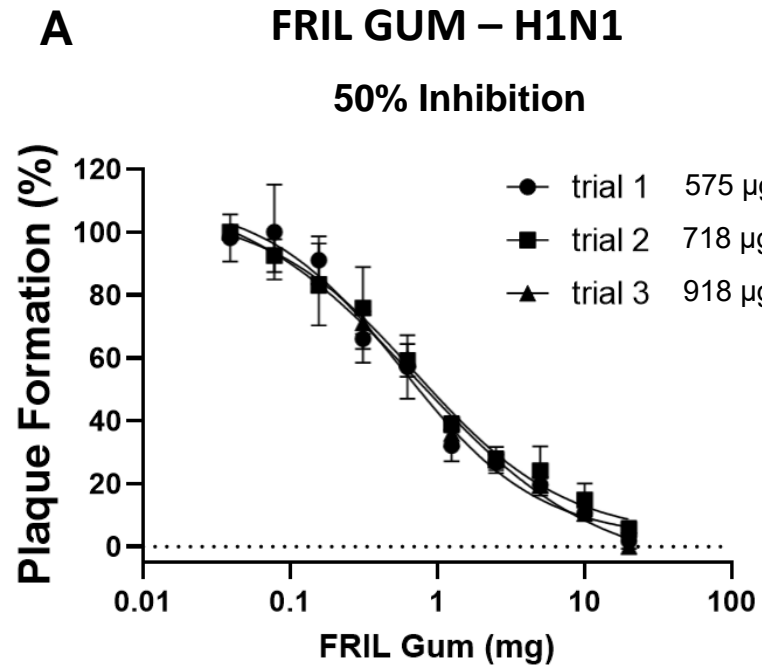
**Fig. S1: Schematic diagram of the process of chewing gum – from lab to the clinic.** The chronological sequence of steps in the chewing gum manufacturing process from creation and characterization of plants expressing CTB-ACE2, production and characterization of the chewing gum and steps towards clinical development. Steps #1 to Step #11 are described in detail in Daniell *et al.* 2020 and Daniell *et al.* 2022 and US patents 11,246,819 (2022) and 10,806,775 (2020). Step #8 is described by Per Os Biosciences in the US 9,744,128 patent.

**A****B****C****D**

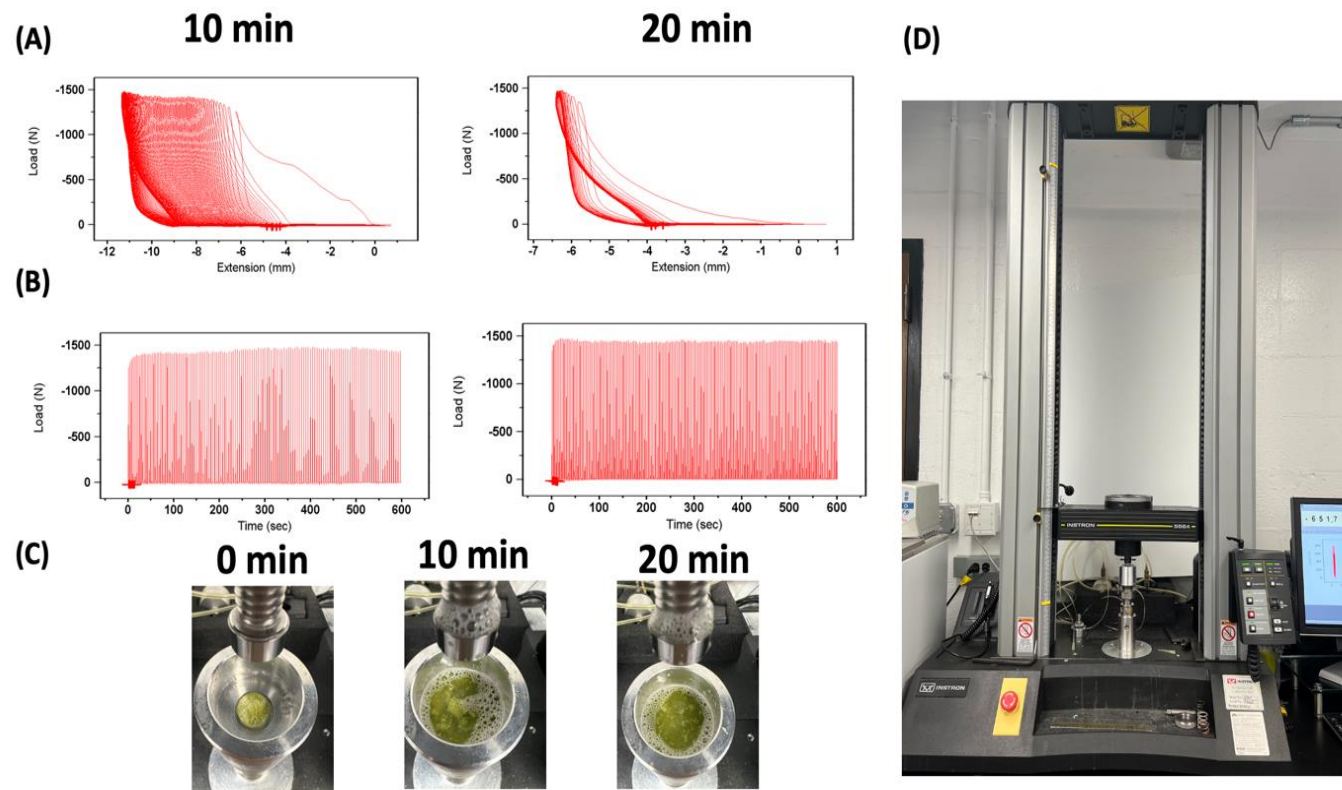
**Fig. S2:** CTB-ACE2 dose quantitation in chewing gums: (A,B) Western blot analysis for CTB-ACE2 after release by sonication. Data present as Mean  $\pm$ SD ; n=4. (C,D) Western blot analysis for CTB-ACE2 immediate natural release without sonication. Data presented as Mean  $\pm$ SD ; n=4.



**Fig. S3: FRIL Plaque Reduction Neutralization Assay:** FRIL inhibition of Vero under infective dose of H1N1 (A/California/7/2009-X181) and H3N2 (A/Singapore/INFMH-16/0019/2016).



**Fig. S4: FRIL Plaque Reduction Neutralization Assay:** FRIL plaque reduction neutralization assay with H1N1 (A/California/7/2009-X181) and H3N2 (A/Singapore/INFMH-16/0019/2016) with FRIL chewing gum and placebo gum. The data represents Mean  $\pm$  SD of plaque numbers from three independent experiments in duplicates. In each experiment different amounts of FRIL gum was evaluated in two duplicates. Plaque formation (%) is normalized among experiments.



**Fig. S5 Cyclic loading data generated by Merlin software for the CTB-ACE2 chewing gum, Instron machine set up and visual observations. (A)** Extension (mm) versus load (N) applied on the chewing gum and the plant extraction buffer (PEB) slurry during different grinding cycles. **(B)** Time (sec) versus load (N) applied on the CTB-ACE2 chewing gum and PEB slurry during different grinding cycles. **(C)** Visualization of the CTB-ACE2 chewing gum tablet (365.8  $\mu\text{g}$  dose) slurry in PEB at different chewing times (0, 10, and 20 mins). **(D)** Experimental set up of the Universal Mechanical Testing Machine with Merlin software (Instron Model 5564) and cup.