IN SILICO MODELLING FOR *IN VIVO* SUCCESS

HU-MATHS-IN
Hungarian Service Network for Mathematics in Industry and Innovations

H2020 SOCIETAL CHALLENGES

Health, demographic change and wellbeing

The Industrial Problem

A possibility in drug development is to find out new molecular targets and new effects for well-known drugs. FSCPX (an irreversible A_1 adenosine receptor antagonist) and NBTI (a nucleoside transport blocker), added together, produce an unexpected (apparently paradoxical) effect pattern in *ex vivo* guinea pig atria.

Biomedicine and Health Care

Research group

Pharmacological Work Team
(in: Industrial Mathematics Research Group of the University of Debrecen)

UNIVERSITY of DEBRECEN

An academic work team with a research topic of quantitative modelling of receptor function

Company

Kéri Pharma Hungary Kft.

KÉRI PHARMA® Csoport

A limited company dealing with market and public opinion research, focused on drug development, production and distribution

SZÉCHENYI 2020
MAGYARORSZÁG KORMÁNYA
Európai Unió
Európai Strukturális és Beruházási Alapok
BEFEKTETÉS A JÖVŐBE

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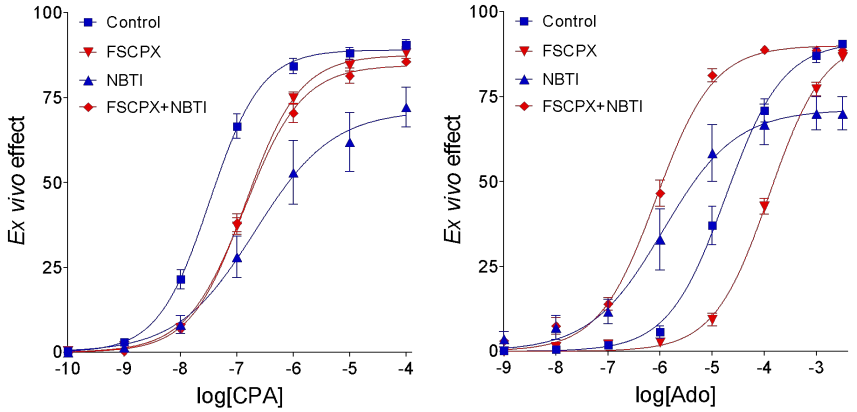
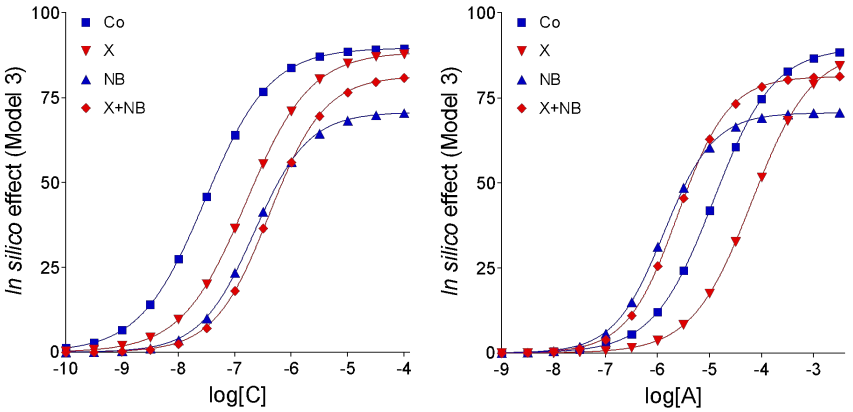
H2020 SOCIETAL CHALLENGES: Health, demographic change and wellbeing

Challenges & Goals

- To reveal and understand the interaction between FSCPX and NBTI, two adenosine analogues
- To explore possible new drug targets and thereby mechanisms of action





The original ex vivo concentration-effect curves (left) and their simulated versions (above) that assume no interaction (reflecting our body of knowledge concerning FSCPX and NBTI until the present investigations). Considerable difference is seen between them.

Mathematical and computational methods and techniques applied

- First, known and hypothesized properties of FSCPX and NBTI were translated into mathematical operations on the parameters of known equations defining the function of the pharmacological receptors
- Then, simple concentration-effect (E/c) curves were constructed by means of the equation of the operational model for one agonist (yellow)
- Next, complex E/c curves were generated using the equation of the operational model for two agonists (blue)
- Afterwards, the complex E/c curves were biased using the equation of RRM (orange)
- Then, all E/c curves were fitted to the Hill equation (purple)
- By means of different combinations of known and hypothesized drug properties, different E/c curves were constructed and then compared to the original *ex vivo* E/c curves

$$E' = 100 - \frac{100 \times (100 - E)}{100 - E_{bias}}$$

$$E = \frac{E_{max}}{1 + 10^{n \times (\log EC_{50} - \log c)}}$$

$$E = E_m \times \frac{(\tau_{test} \times c_{test} \times K_{bias} + \tau_{bias} \times c_{bias} \times K_{test})^{n_{op}}}{(c_{test} \times K_{bias} + K_{test} \times K_{bias} + c_{bias} \times K_{test})^{n_{op}} + (\tau_{test} \times c_{test} \times K_{bias} + \tau_{bias} \times c_{bias} \times K_{test})^{n_{op}}}$$

The equation of the operational model of agonism for the action of one agonist (yellow) and the co-action of two agonists (blue), the equation of the receptorial responsiveness method (RRM; orange), and the Hill equation (purple)

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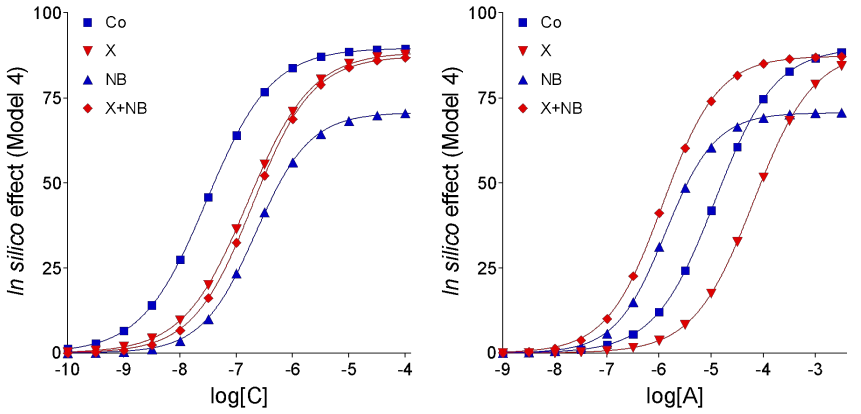
Results & Benefits to the company

- Results
  - the FSCPX should inhibit the effect of NBTI on the interstitial level of endogenous adenosine in the atrium
  - a possible mechanism of this is that FSCPX inhibits an enzyme participating in the interstitial adenosine formation
- Benefits
  - our results provided *in silico* evidence of a new target for FSCPX
  - this opens up a new opportunity for developing drugs that can affect the adenosinergic mechanisms in the heart and possibly throughout the body



The simulated concentration-effect curves with the most appropriate assumptions made to approach the shape of the original curves

A new point of application to influence the cardiac (and possibly other) adenosinergic system(s)

Digital Twin