IN SILICO MODELLING FOR *EX VIVO* RELIABILITY

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

CHALLENGES

Health, demographic change and wellbeing

The Industrial Problem

Receptor reserve, an integrative measure of response-inducing ability of an agonist in a receptor system (receptor plus its tissue-dependent signaling), is a useful predictor of the behavior of a candidate in the body. Thus, collection of receptor reserve values is an important tool for drug development. However, the determination of receptor reserve is challenging for agonists with short half-lives, such as adenosine.

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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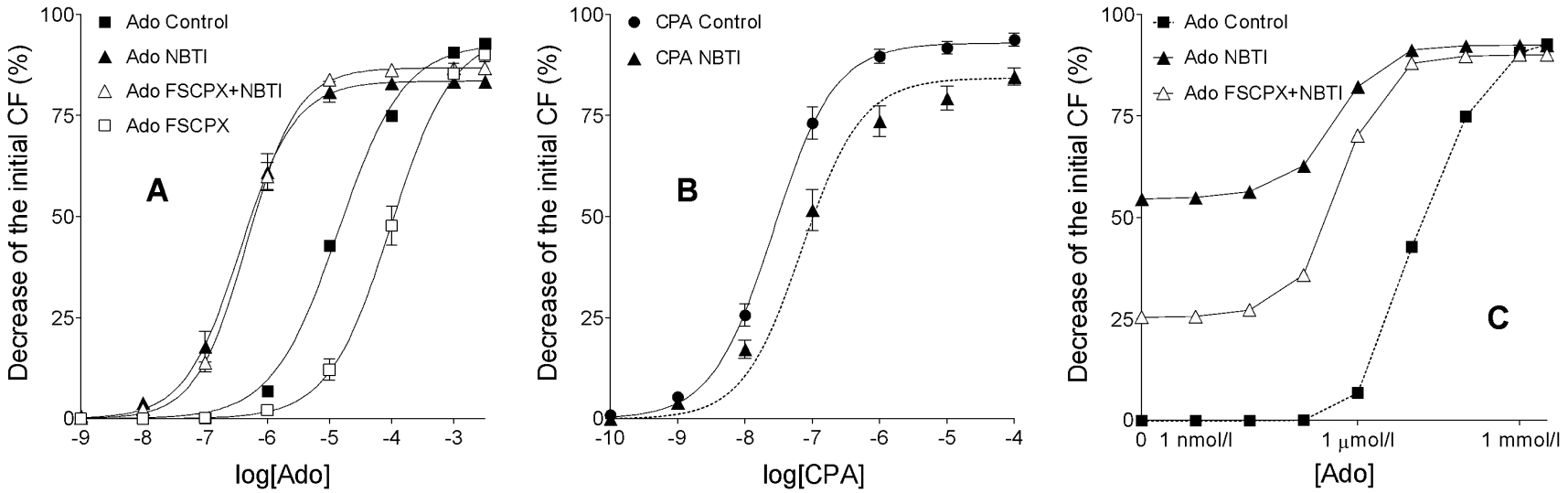
H2020 SOCIETAL CHALLENGES: Health, demographic change and wellbeing

Challenges & Goals

To validate our new method to assess receptor reserve as a possible new tool for drug development



*Concentration-effect (E/c) curves constructed with adenosine (Ado) in the absence and presence of FSCPX and NBTI (**A**), the completive CPA E/c curves (dotted line: the fitted model of RRM) (**B**), and the E/c curves, generated from data of the previous ones, provided by our new method to estimate receptor reserve (together with the control adenosine E/c curve indicated with dotted line) (**C**). In the panel C, the distance between the final parts of E/c curves treated with NBTI and FSCPX+NBTI gives a glimpse of the magnitude of receptor reserve (that is, herein, quite small). The continuous lines in panels A and B represent the fitted Hill model.*

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Mathematical and computational methods and techniques applied

A computer simulation was carried out through *in silico* reconstruction of selected *ex vivo* E/c curves describing the direct negative inotropic response to adenosine and CPA, two A_1 adenosine receptor agonists, in isolated and paced guinea pig left atria. As receptor function model, the operational model of agonism was chosen to link the agonist concentration to the effect. Values for concentrations and parameters of the operational model were received from biological measurements or rendered arbitrarily. To transform the *in silico* E/c curves, the known mechanisms of action of chemicals used for the original *ex vivo* experiments were translated into algebraic operations, furthermore, where appropriate, the receptorial responsiveness method (RRM) was applied. The aim of simulation was to position the *in silico* E/c curves to overlap the corresponding *ex vivo* E/c curves as perfect as possible, and, as long as possible, in line with our biological knowledge. When an algebraic operation contradicting this biological knowledge had to be introduced to reach the appropriate overlap, this was followed by making a new biological assumption that could underly the given algebraic operation.

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

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

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

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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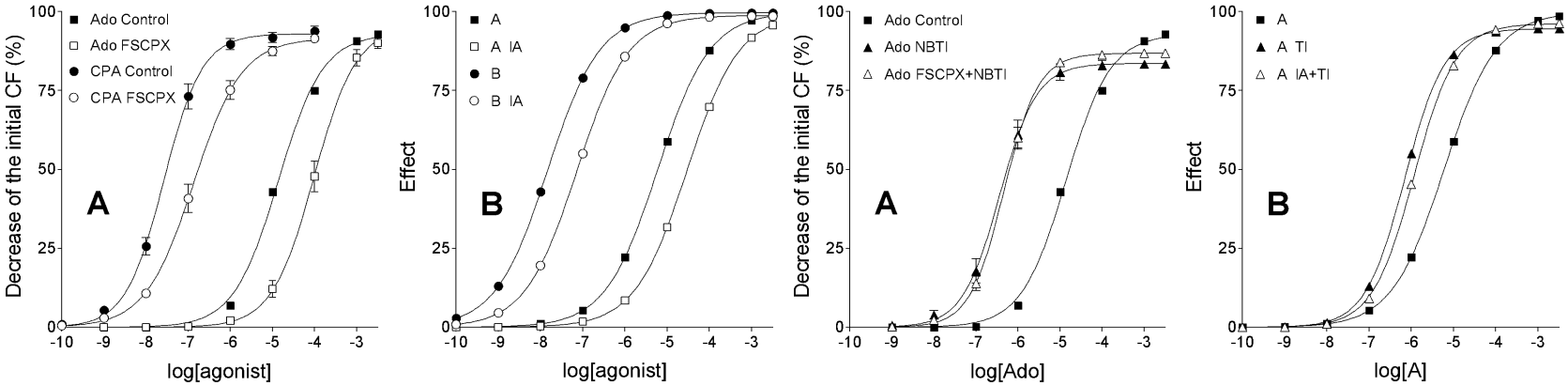
Results & Benefits to the company

- Results
  - Our results provided an *in silico* validation for determining receptor reserve for adenosine, an agonist with short half-life, by means of our recently developed method
  - In addition, our results suggest that FSCPX and NBTI may interact in a way that FSCPX may blunt the action of NBTI
- Benefits
  - Our new method seems to be appropriate to assess receptor reserve for agonists with short half-life
  - Our investigation pointed to the importance of *in silico* validation for *ex vivo* and *in vivo* investigations to disclose or exclude unforeseen interactions between treatment schedules, and, in general, to shine a light on previous results



A panels: ex vivo data to be simulated; B panels: in silico simulated data; Ado: adenosine; A: simulated adenosine; CPA: a synthetic adenosine analogue; B: simulated CPA; FSCPX: an irreversible adenosine receptor blocker; IA: simulated FSCPX; NBTI: an adenosine transport blocker; TI: simulated NBTI; CF: cardiac (atrial) contractile force

A new method to collect data about receptor reserve related to degradable agonists