

Új gyógyszercélpontok nyomában: gyógyszerkutatás és fejlesztés a múltban, jelenben és jövőben

Dr. Sperlágh Beáta

MTA Kísérleti Orvostudományi Kutató Intézet

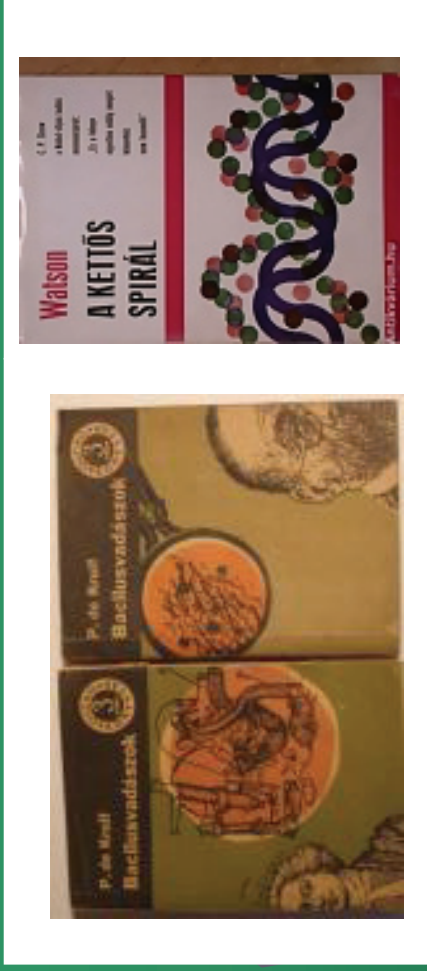
Mottó: „... a helyesen leszűrt és csoportosított elvek nem szűkmarkúan, hanem bőkezűen szolgálják a gyakorlatot és seregestül özönlenek nyomukban az új meg új gyakorlati eredmények... (Francis Bacon)”

Az előadás vázlatja

- Hogyan lesz valakiből gyógyszerkutató?
- Mivel foglalkozik a gyógyszerkutató?
- Hogyan születnek az új gyógyszerek a múltban a jelenben és a jövőben?

Hogyan lettem kutató ? A kezdetek

„Nem vagyok különösebben tehetséges csak szenvedélyesen kíváncsi” (Einstein)

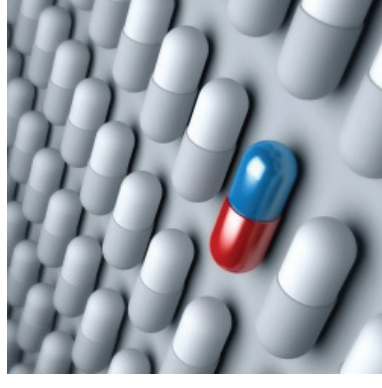
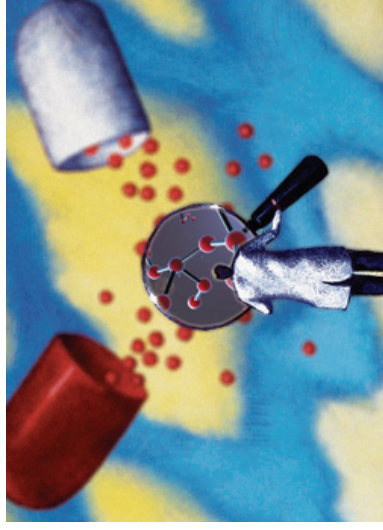
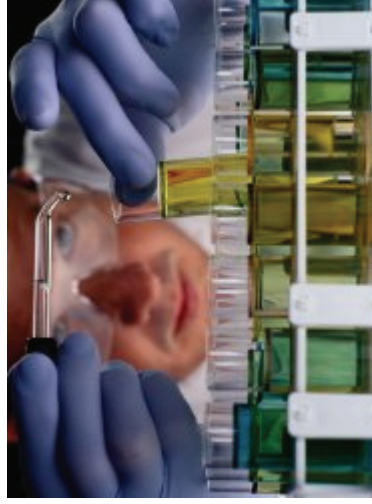


- Kíváncsiság → Kísérletezés !
- Olvasmányok a kutatók életéről



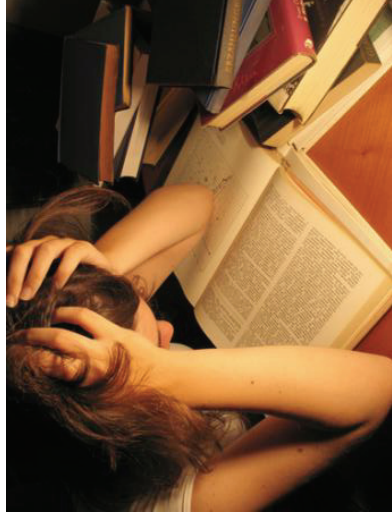
Kiből lehet gyógyszerkutató ? Pályaválasztás

- ▶ Tudományegyetemek: biológus, vegyész szak
- ▶ SOTE, SZTE, PTE, DE: általános orvos, gyógyszerész
- ▶ SZIE: állatorvos, zoológus
- ▶ BME: biológus mérnök, vegyészmérnök



Egyetemi évek

- Tanulni, tanulni, tanulni.....
- Szakterület választás
- Tudományos diákkörözés
- Oktatók, mentorok szerepe



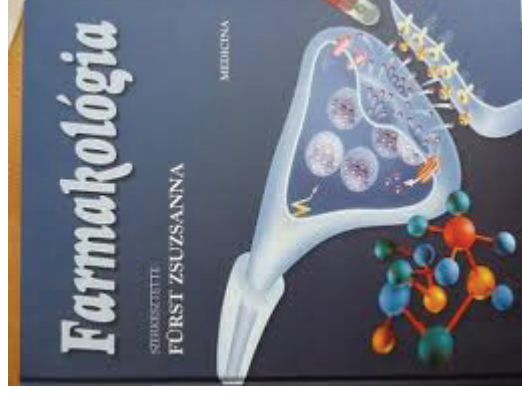
Szentágothai János



Sasvári Mária



Füst Zsuzsanna





A végzés után: hol
helyezkedhet el, aki
gyógyszerkutató
szeretne lenni ?

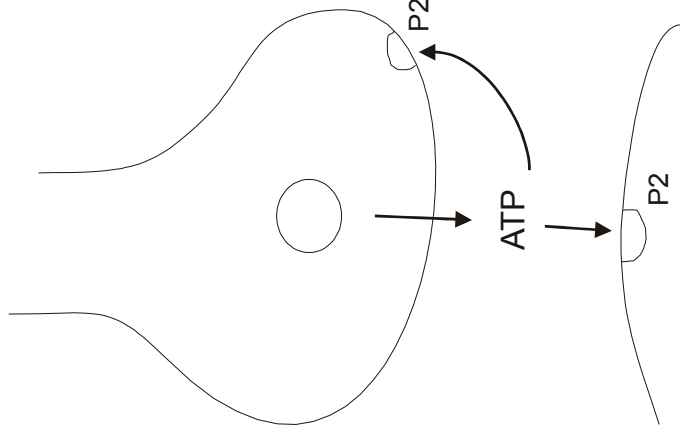
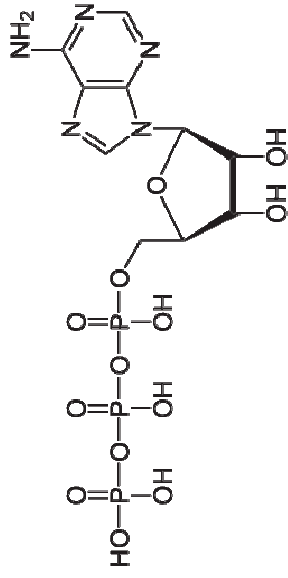


- ▶ egyetemi tanszékek (farmakológia, gyógyszerkémia stb.)
- ▶ akadémiai kutatóintézetek (KOKI, SZBK, KKK)
- ▶ gyógyszergyárak (pl. Richter, EGIS, Pfizer)
- ▶ gyógyszerfejlesztéssel foglalkozó vállalkozások
- ▶ kórházak, klinikák: klinikai farmakológia

Mit csinál egy gyógyszerkutató ? Témaválasztás

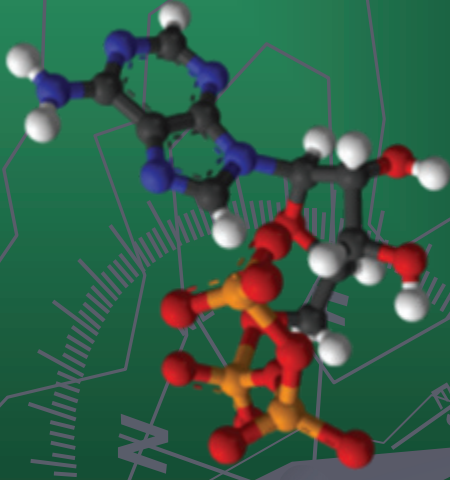
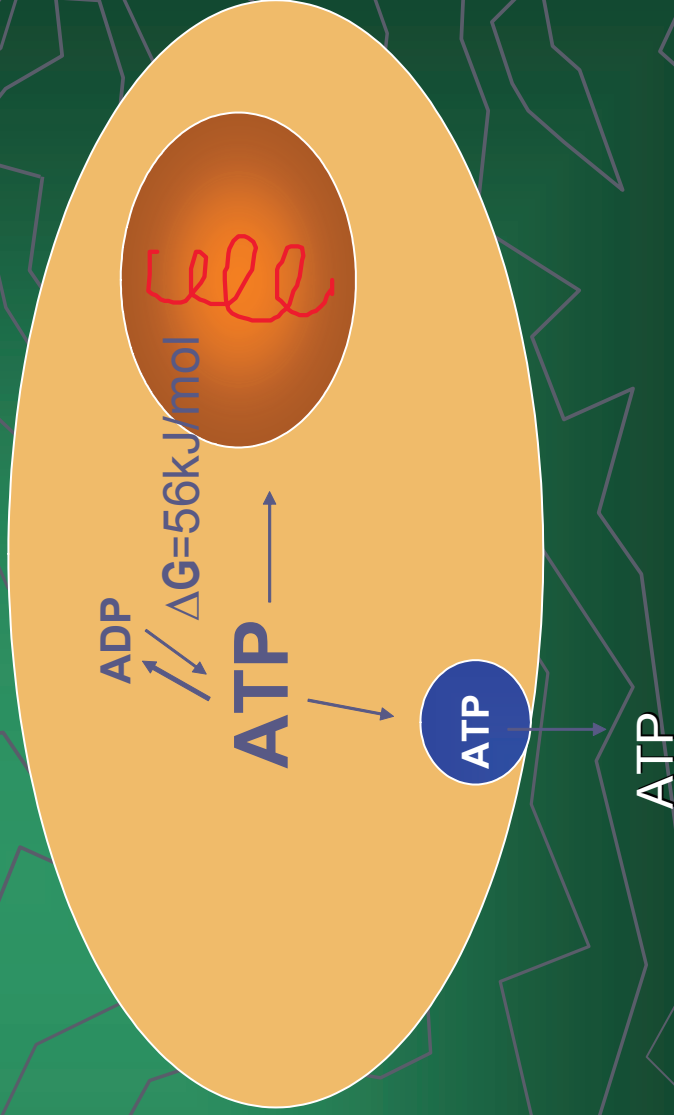
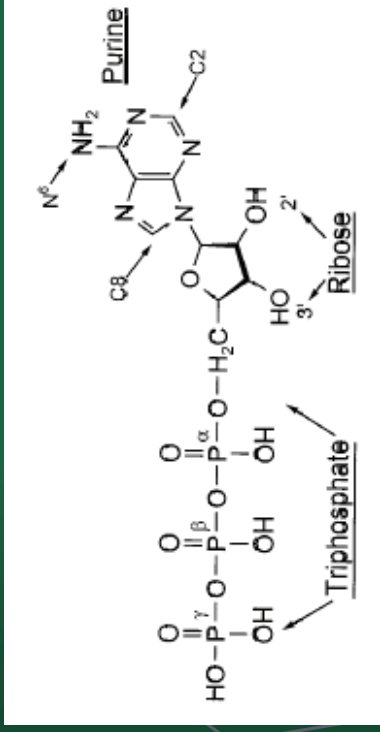


Vizi E. Szilveszter

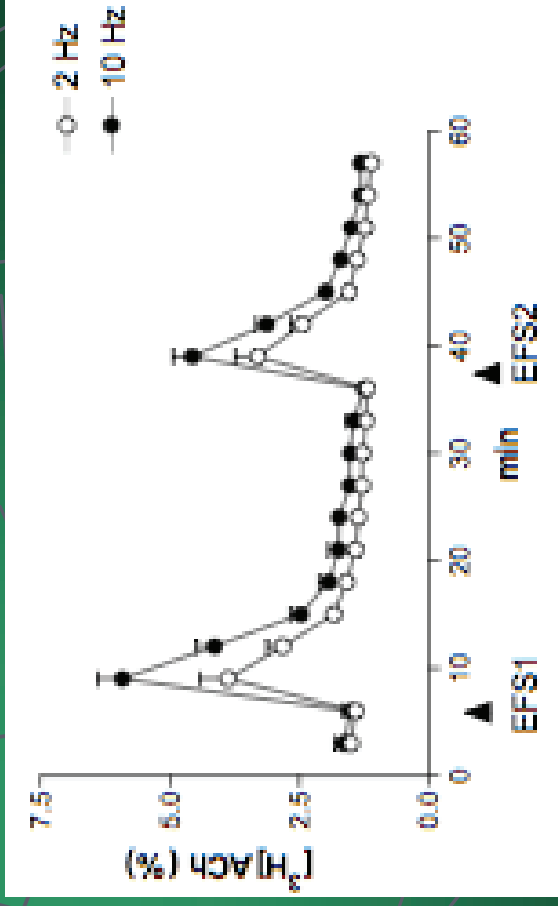
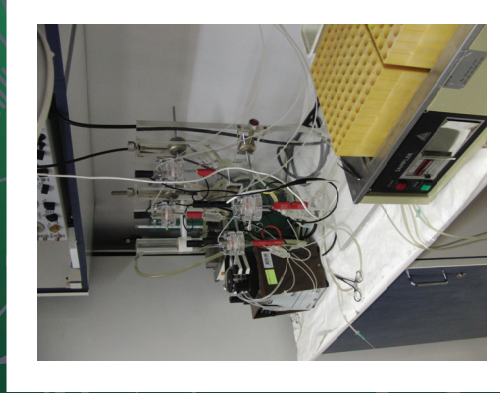
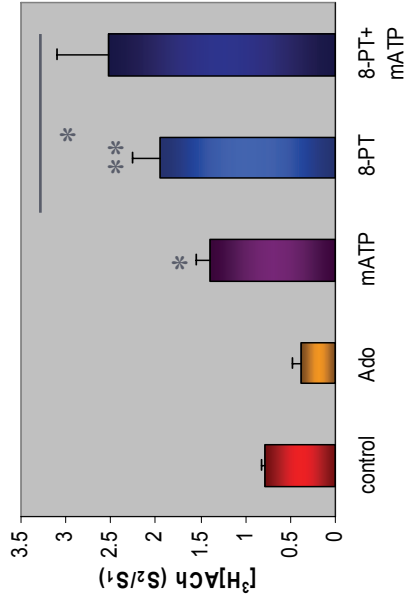
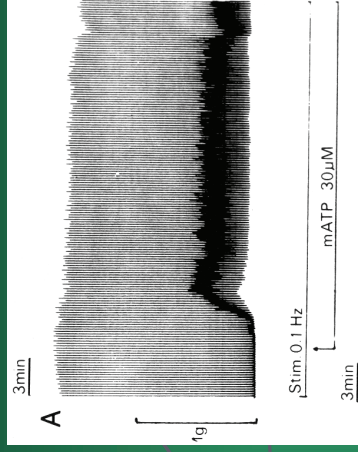
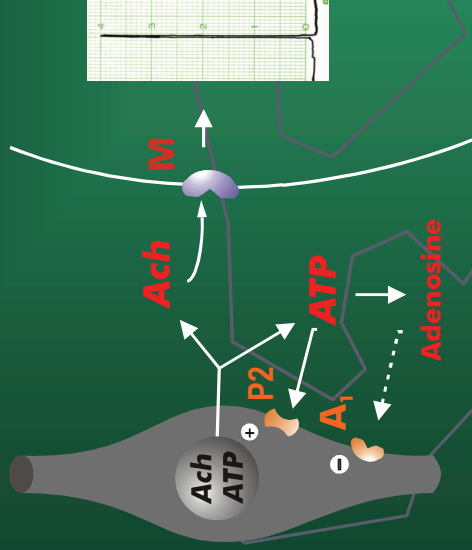


Az adenozin 5'trifoszfát (ATP) biológiai funkciói

1. Energia donor és akceptor
2. Genetikai anyag építőköve
3. Intracelluláris jelátvivő anyag
4. Extracelluláris jelátvivő anyag



Az első mérföldkő: az első publikáció



Effect of Presynaptic P₂ Receptor Stimulation on Transmitter Release

B. Sperlagh and E. S. Vizi

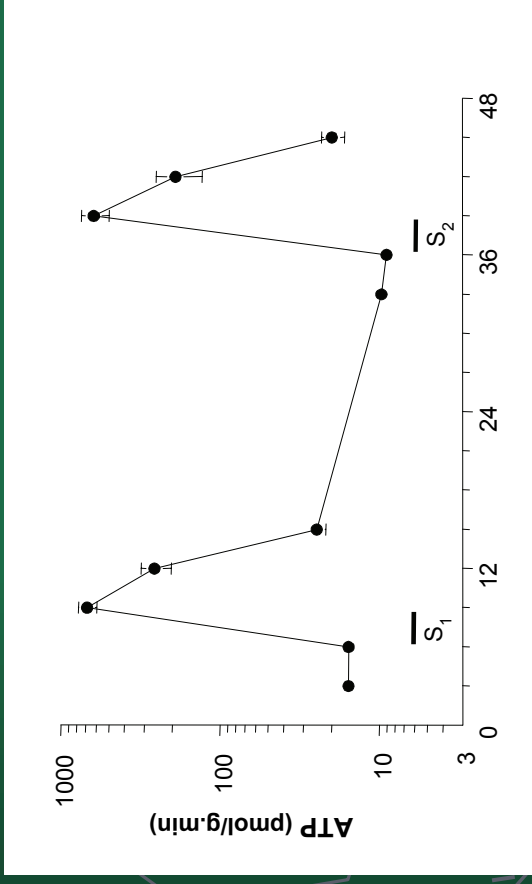
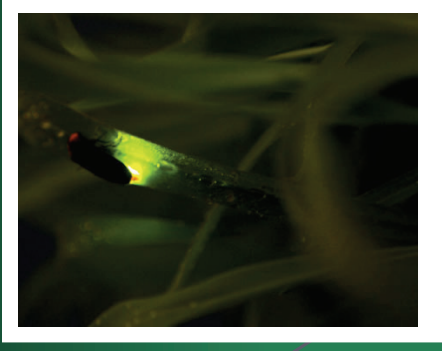
J. Neurochem. 56:1466-1470, 1991

Vándorévek az óperencián túl: ingerlésfüggő ATP felszabadulás patkány habenuzában

Luciferin + ATP -----> Luciferyl adenylate + PP_i

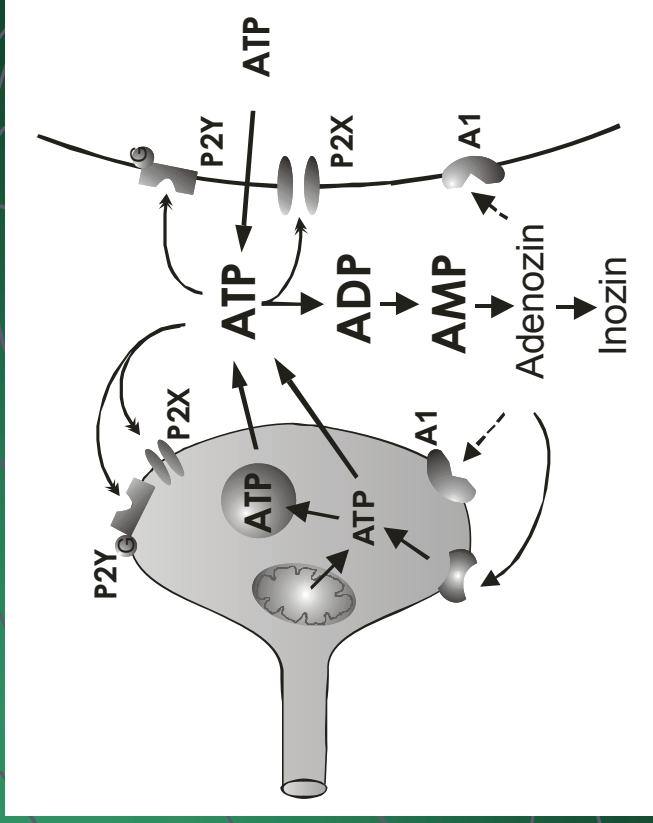
Luciferase

Luciferyl adenylate + O₂ -----> oxyluciferin + AMP + light

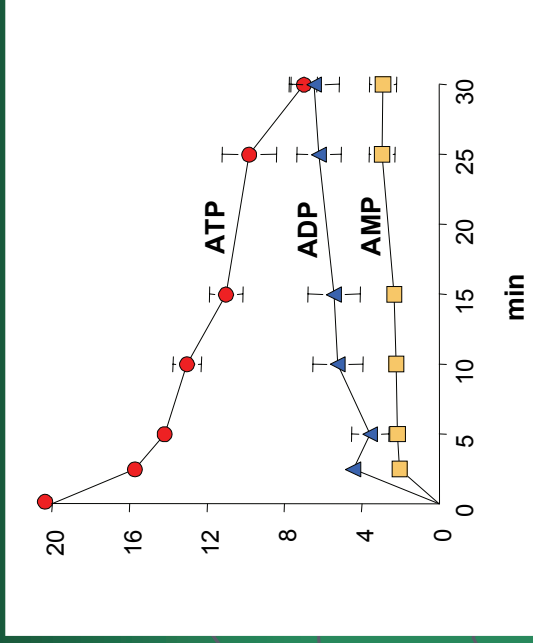
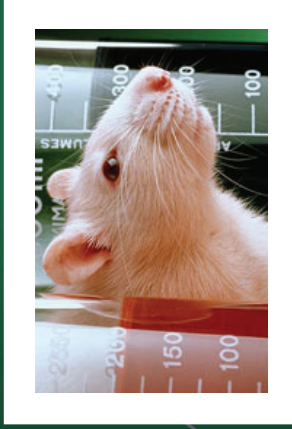


The Nathan Kline Institute
for Psychiatric Research

✓ Szintézis és tárolás az idegvégződésben
 ✓ ingerlésfüggő felszabadulás
 ✓ hatás a posztzinaptikus receptoron inaktivációs mechanizmus

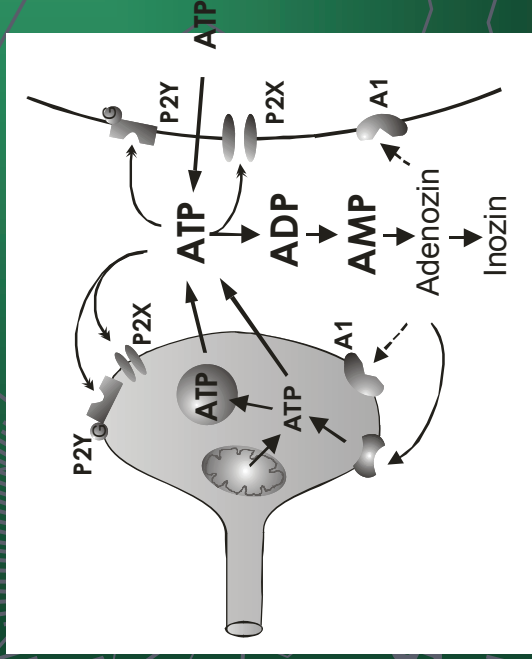


Ekto-ATPáz aktivitás patkány habenuzában

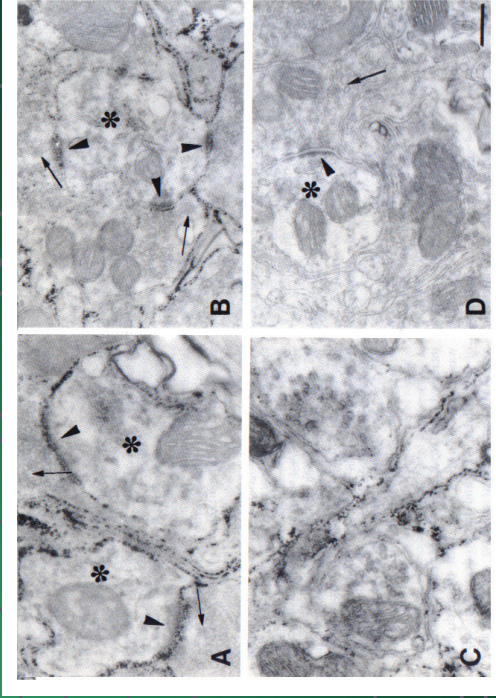


$$K_m = 811.6 \pm 69 \mu M$$

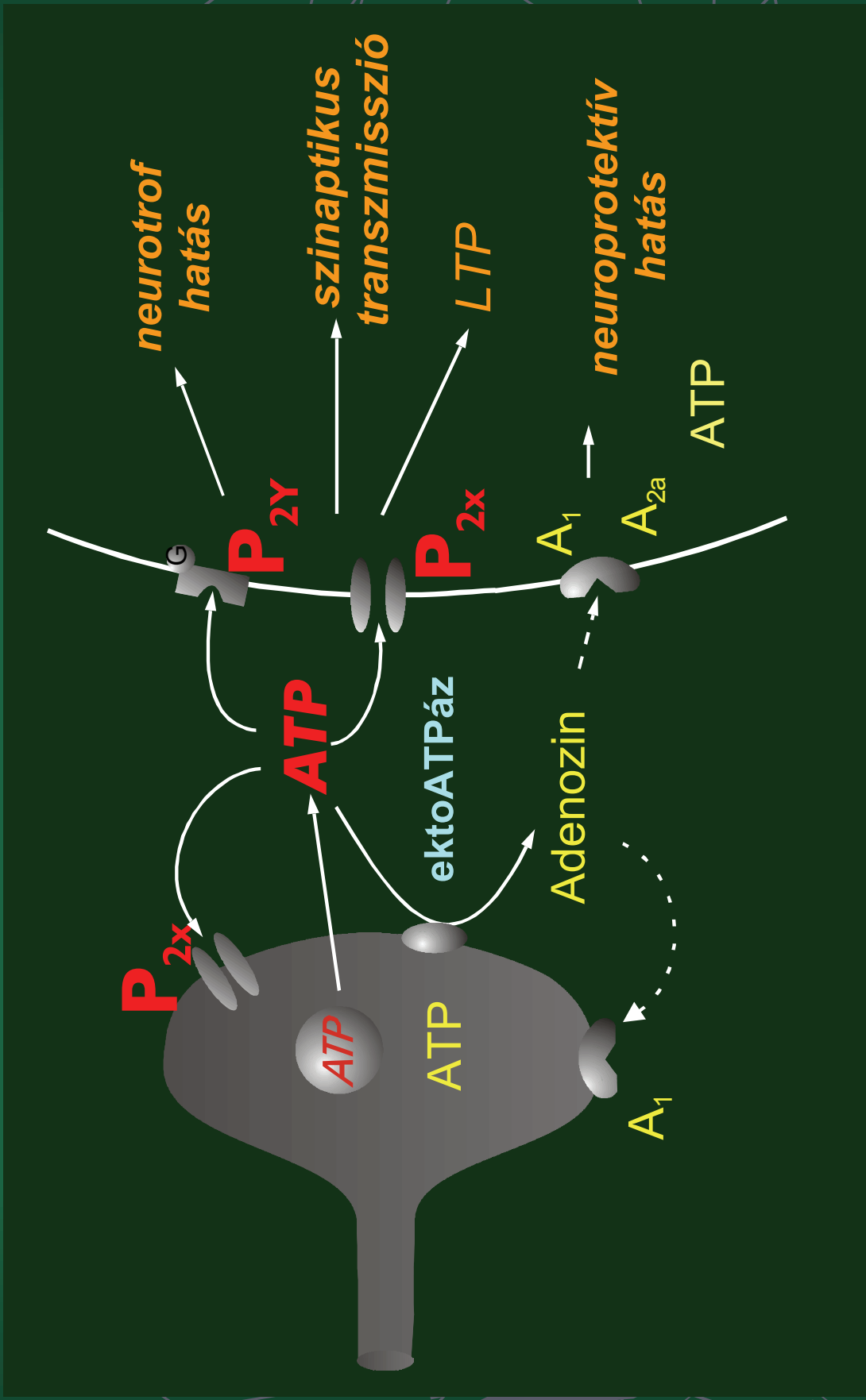
$$V_{max} = 23.1 \pm 2.75 \text{ nmol/min}$$



- ✓ Szintézis és tárolódás az idegvégződésben
- ✓ ingerlésfüggő felszabadulás
- ✓ hatás a posztzinaptikus receptoron
- ✓ inaktivációs mechanizmus



A purinerg jelátvitel alapvető jellegzetességei



Purin receptorok felosztása

Purin receptorok

ATP receptorok

Ionotróp P2X

P2X₁

P2X₂

P2X₃

P2X₄

P2X₅

P2X₆

P2X₇

P2X_{1/2}

P2X_{2/3}

P2X_{2/6}

P2X_{1/5}

P2X_{4/6}

Metabotróp P2Y

P2Y₁

P2Y₂

P2Y₄

P2Y₆

P2Y₁₁

P2Y₁₂

P2Y₁₃

P2Y₁₄

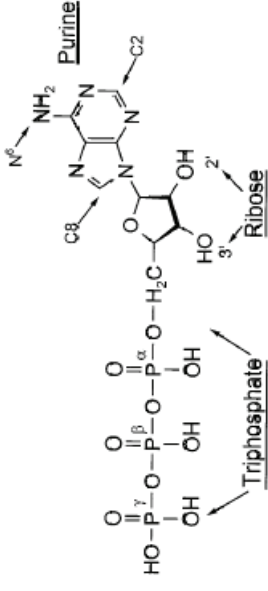
A₁/Y₁

A₁

A_{2a}

A_{2b}

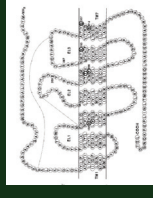
A₃



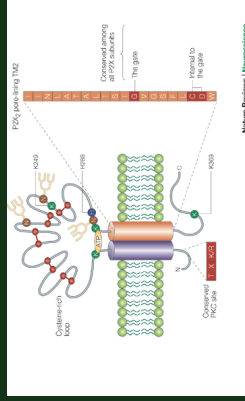
Adenin receptorok

1R

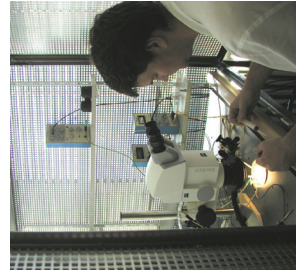
Adenozin receptorok



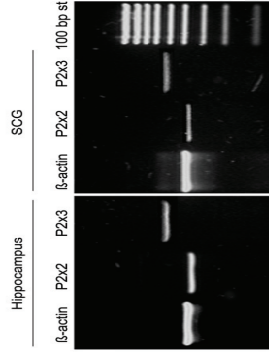
Ap_nA receptorok



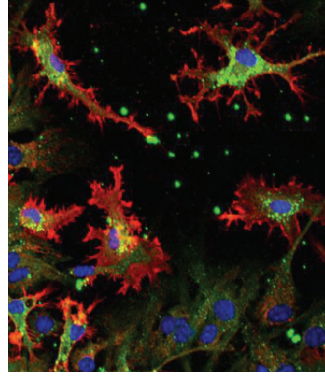
A második mérőföldkő: önálló kutatócsoport indítása



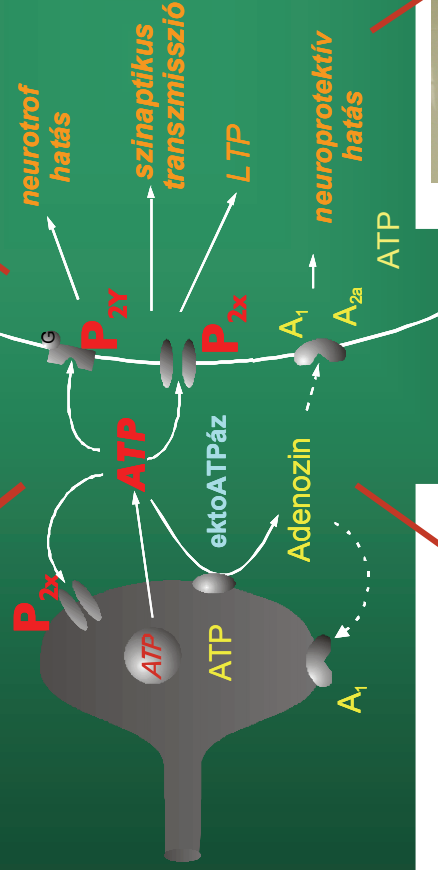
► Mikroelektrod bioszenzor technika



► Molekuláris biológia (real-time PCR, Western blotting, microarray)



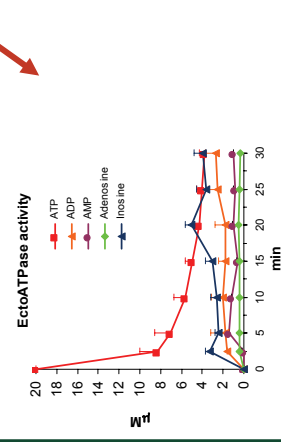
► receptor térképezés (immuncitokémia)



► in vitro sejttes szűrőrendszerek és farmakológia

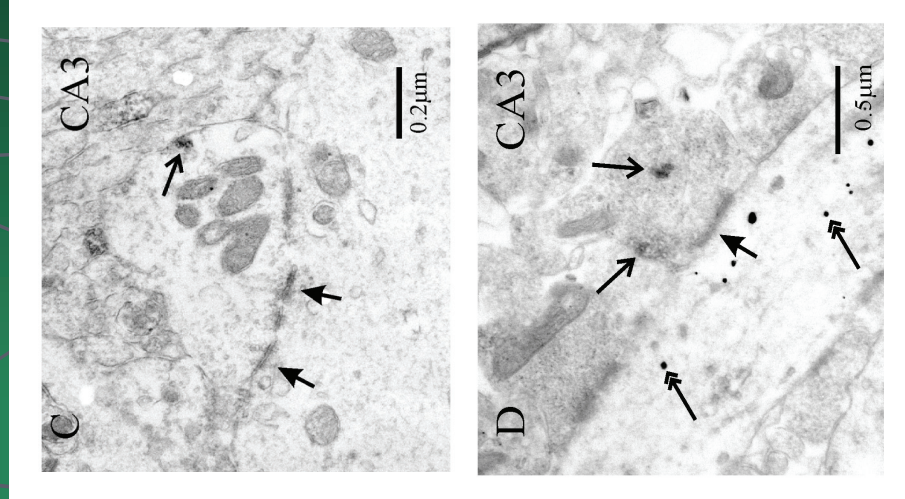
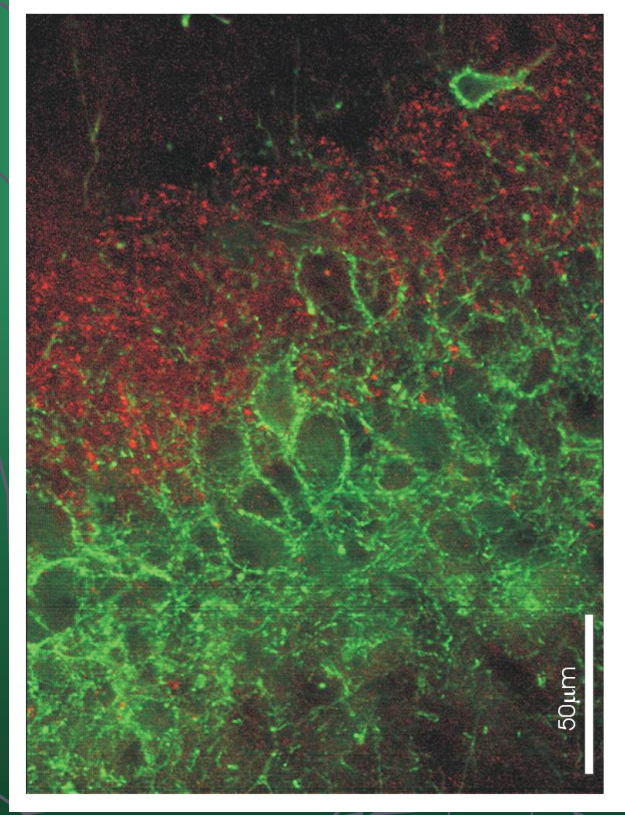
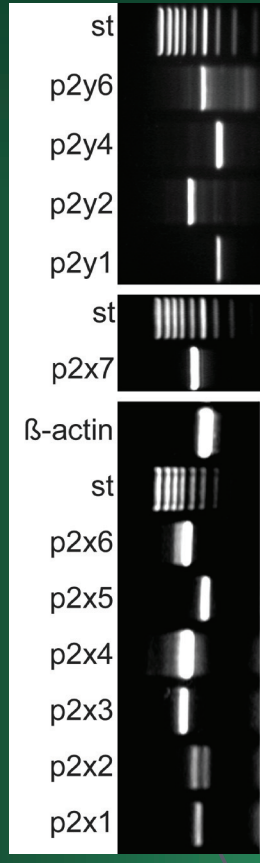
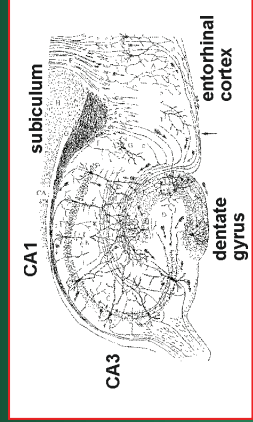
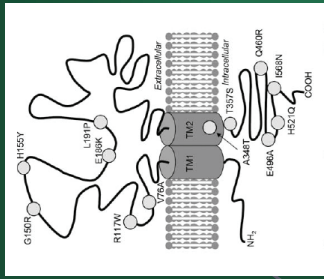


► in vivo betegségi modellek (fájdalom, depresszió, neurodegeneratív betegségek)

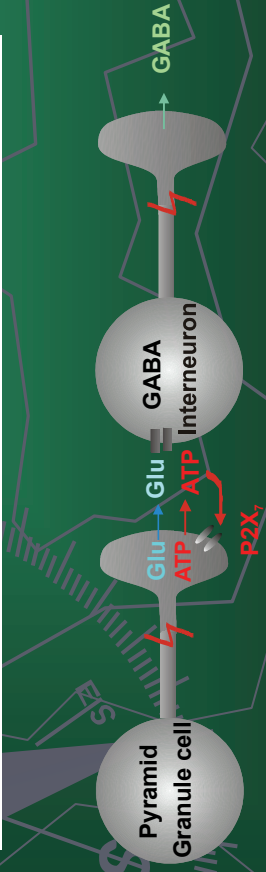


► Neurokémiai laboratórium (HPLC, Luminimetria)

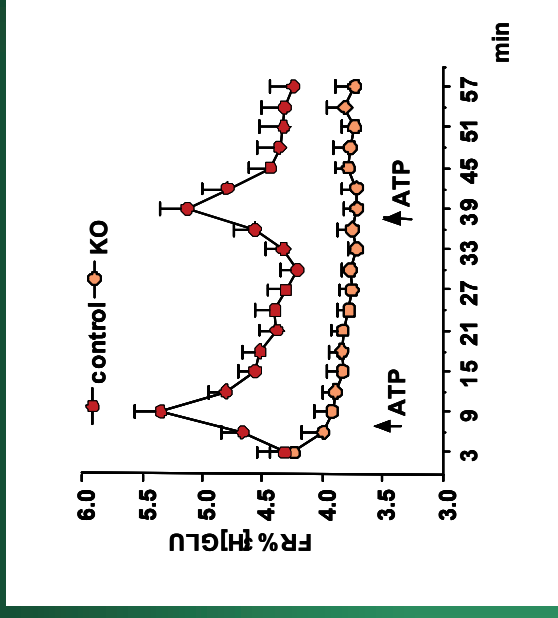
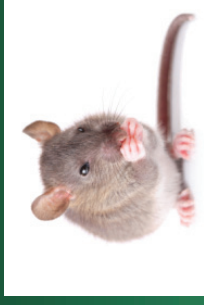
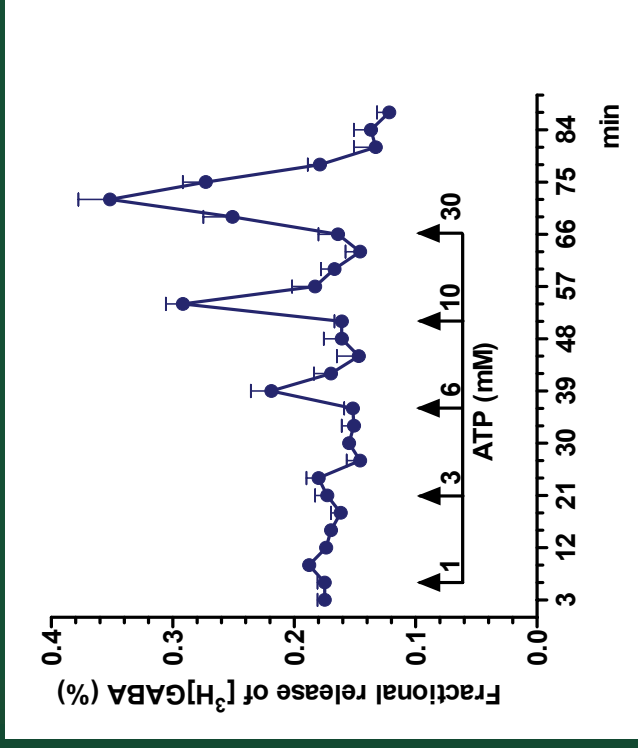
A P2X7 receptor a hippokampuszban a serkentő idegvégződéseken található



- P2X₁
- P2X₂
- P2X₃
- P2X₄
- P2X₅
- P2X₆
- P2X₇**
- P2X_{1/2}
- P2X_{2/3}
- P2X_{4/6}
- P2X_{2/6}
- P2X_{1/5}

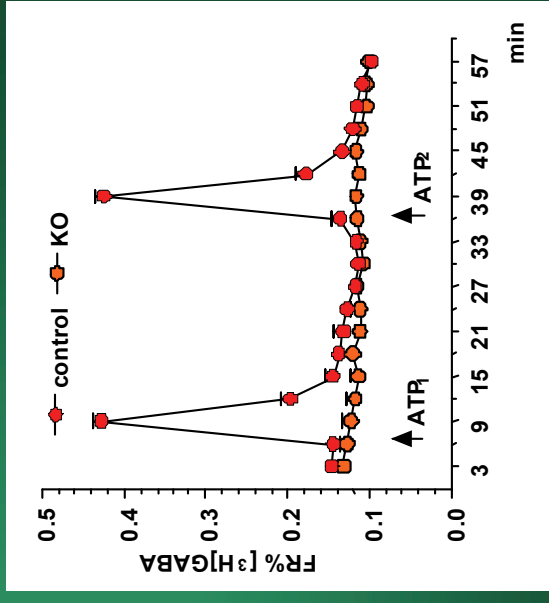
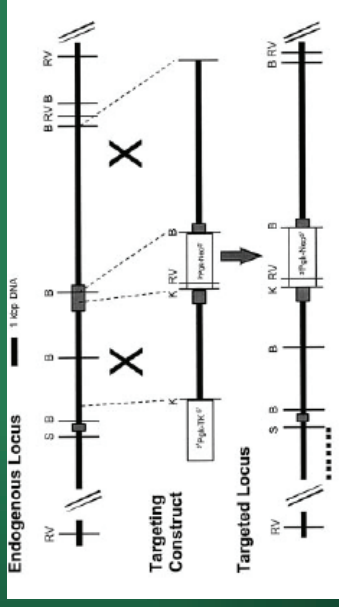
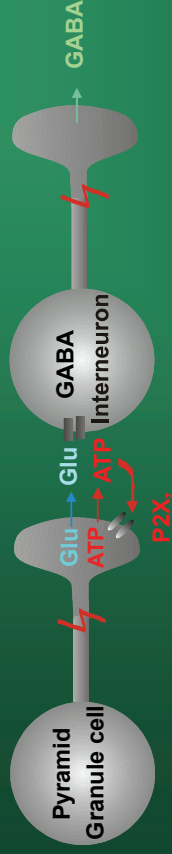


A P2X7 receptorok aktivációja glutamátot és GABA-t szabadít fel a hippocampusban



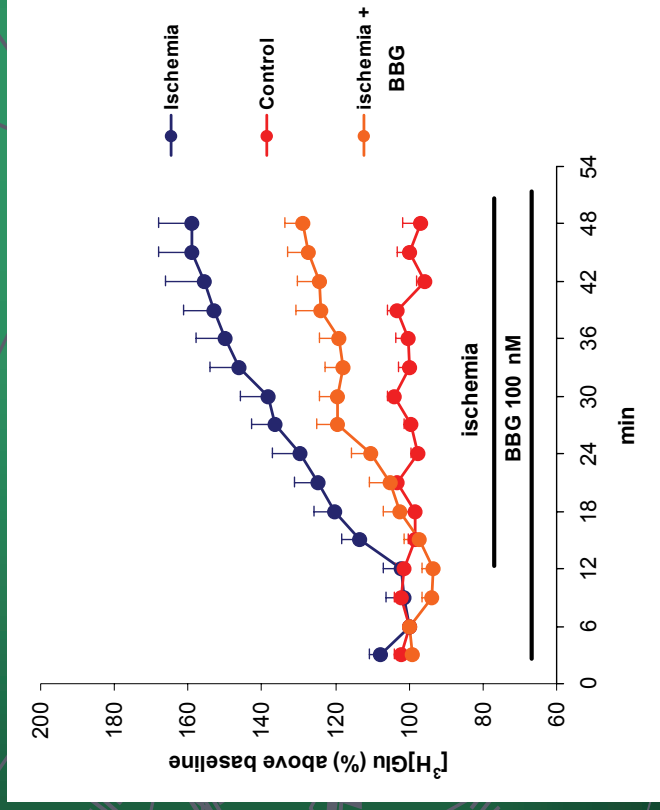
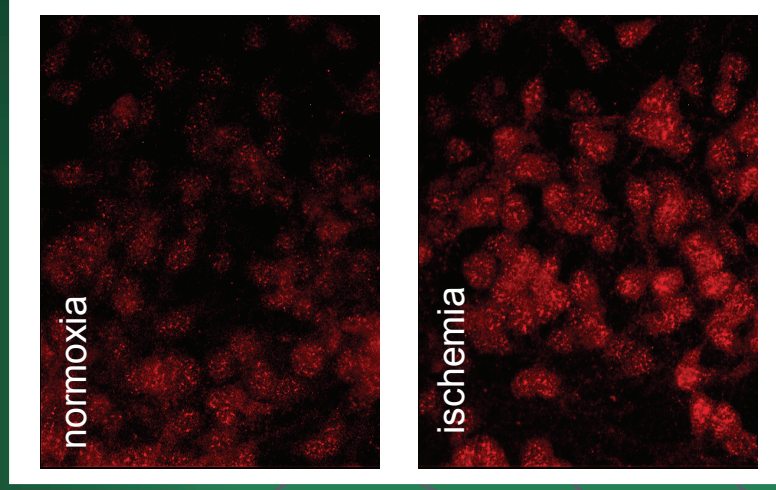
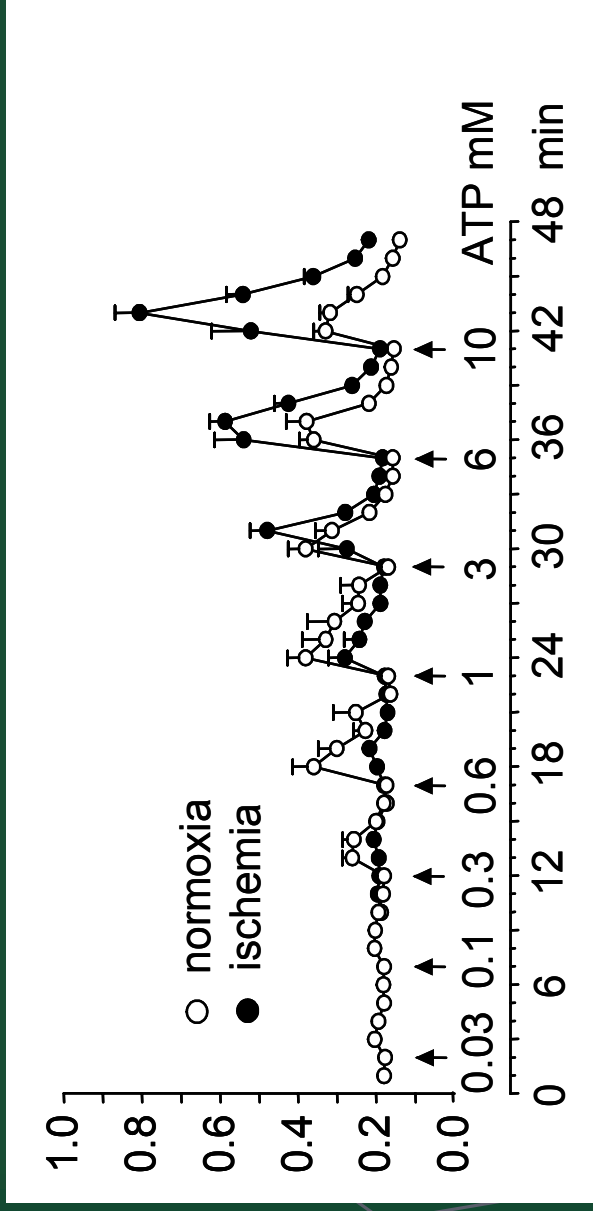
- P2X₁
- P2X₂
- P2X₃
- P2X₄
- P2X₅
- P2X₆
- P2X₇**
- P2X_{1/2}
- P2X_{2/3}
- P2X_{4/6}
- P2X_{2/6}
- P2X_{1/5}

B. Sperlágh, A. Köfalvi, J. Deuchars et al., J. Neurochem. 81:1196-1211., 2002

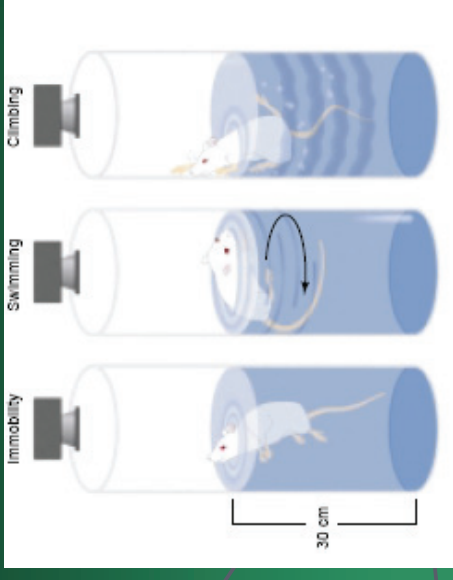


L. Papp, E. S. Vizi, and B. Sperlágh, Neuroreport 15:2387-2391, 2004

A P2X7 receptor expressziója és funkcionális válaszkészsége fokozódik „in vitro iszkémia” hatására

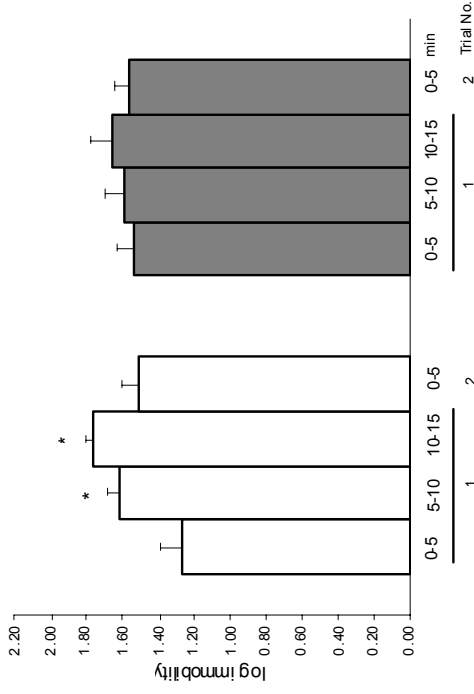


A P2X7 receptorok genetikai deléciója antidepresszáns fenotípust eredményez



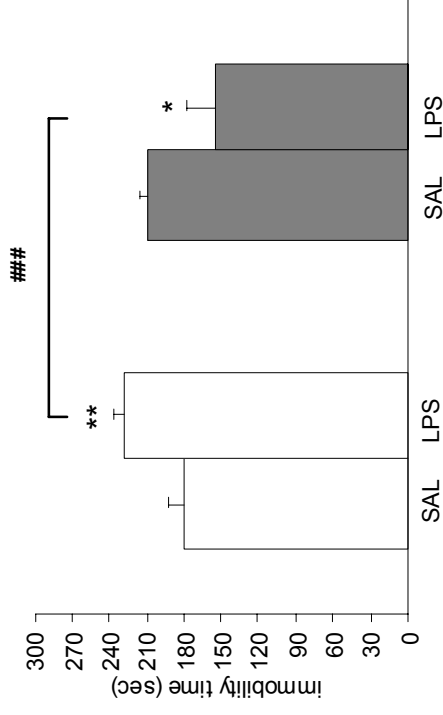
□ P2rx7 +/+
■ P2rx7 -/-

FST

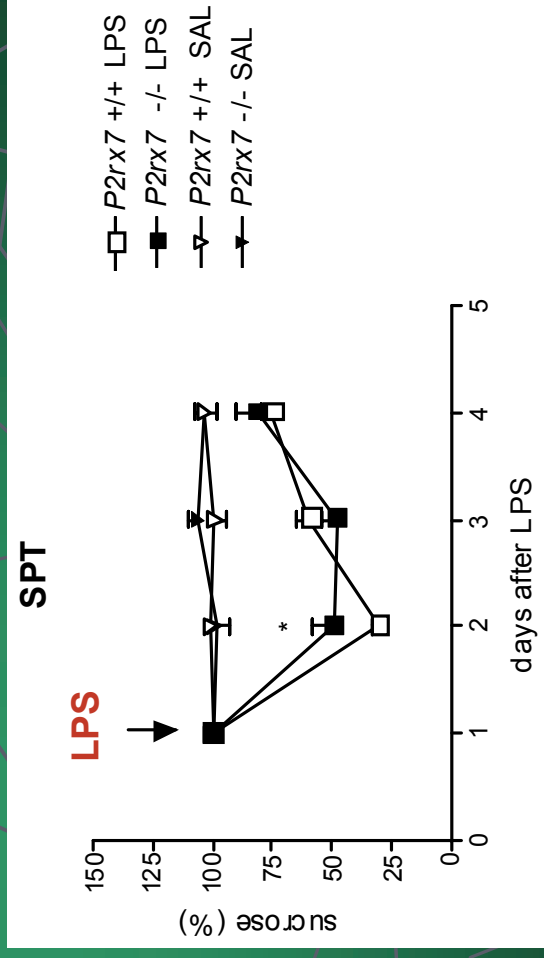
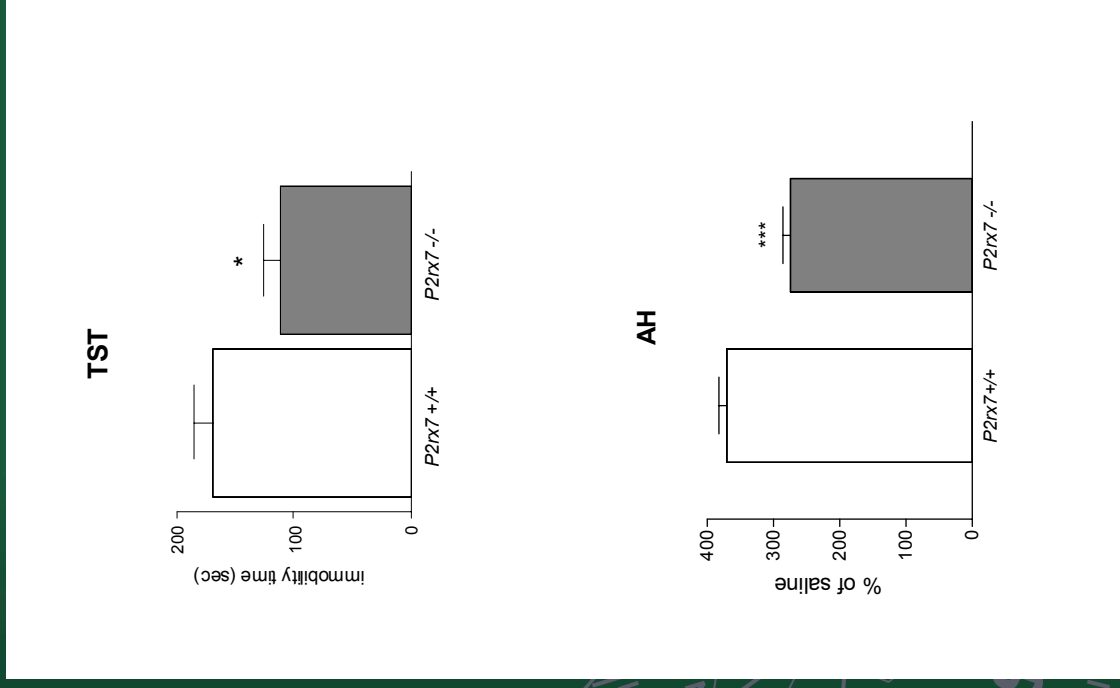


FST

□ P2rx7 +/+
■ P2rx7 -/-



A P2X7 receptorok genetikai törlése hangulatstabilizáló hatást eredményez



FOR

Human Molecular Genetics, 2006, Vol. 15, No. 16 2478-2485
 doi:10.1093/hmg/ddl166
 Advance Access published on July 5, 2006

P2RX7, a gene coding for a purinergic ligand-gated ion channel, is associated with major depressive disorder

Susanne Lucae^{1,2}, Doris Salyakina^{1,2}, Nicholas Barden³, Mario Harvey³, Bernard Gagne³, Michol Labby³, Elizabeth B. Binder^{1,2}, Manfred Uhr¹, Marcelo Pace-Pereira², Inge Sillaber³, Marcus Kling¹, Tanja Brückl¹, Rosekind Lieb¹, Florian Holsboer¹ and Bertram Müller-Neynsok^{1,4}

Molecular Psychiatry (2006), 11, 7
 © 2006 Nature Publishing Group. All rights reserved. 1359-4104/06/1107-0000
 www.nature.com/mp

ORIGINAL ARTICLE

Case-control studies show that a non-conservative amino-acid change from a glutamine to arginine in P2RX7 purinergic receptor protein is associated with both bipolar- and unipolar-affective disorders

A McQuillin¹, NJ Bass¹, K Choudhury¹, V Puri¹, M Kosmin¹, J Lawrence¹, D Curtis¹ and HMD Gurling¹

P2RX7 Gln460Arg polymorphism is associated with depression among diabetic patients

Geza Nagy^a, Zsolt Ronai^b, Aniko Somogyi^a, Maria Sasvari-Szekely^b, Omar Abdul Rahman^b, Attila Mate^a, Timea Varga^a, Zsófia Nemoda^{b,*}

^a Semmelweis University, 2nd Department of Internal Medicine, Budapest, 1083, Széchenyi tér, 46, Hungary
^b Semmelweis University, Department of Medical Chemistry, Molecular Biology and Pathobiochemistry, Budapest, 1088, Pusztai ut, 9, Hungary

The *FASEB Journal* article fj.09-150862. Published online April 1, 2010.

The *FASEB Journal* • Research Communication

Two haplotypes of the P2X₇ receptor containing the Ala-348 to Thr polymorphism exhibit a gain-of-function effect and enhanced interleukin-1 β secretion

Leanne Stokes,* Stephen J. Fuller,* Ronald Slyter,**† Kristen K. Skarratt,* Ben J. Gu,**† and James S. Wilkey**†,‡

American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 141B:374-382 (2006)

Analysis of Single Nucleotide Polymorphisms in Genes in the Chromosome 12Q24.31 Region Points to P2RX7 as a Susceptibility Gene to Bipolar Affective Disorder

Nicholas Barden,¹ Mario Harvey,¹ Bernard Gagne,¹ Eric Shink,¹ Monique Tremblay,¹ Catherine Maynard,^{1,2} Miro Labby,¹ Anne Villeneuve,^{1,2} Jean-Yves Lajeunesse,¹ Lise Borgeleau,¹ Herbert Stadler,¹ Florian Holsboer,¹ and Bertram Müller-Neynsok

BRIEF RESEARCH COMMUNICATION

AMERICAN JOURNAL OF
medical genetics
 Neuropsychiatric Genetics

Association Between Depression and the Gln460Arg Polymorphism of P2RX7 Gene: A Dimensional Approach

Kisztina Hejjas,¹ Anna Szekely,² Eszter Domonkos,³ Zsuzsa Halmaj,² Gabriella Balogh,³ Boglarka Schilling,⁴ Andrea Sarosi,³ Gabor Faludi,³ Maria Sasvari-Szekely,³ and Zsófia Nemoda^{1,*}

¹Institute of Medical Chemistry, Molecular Biology and Pathobiochemistry, Semmelweis University, Budapest, Hungary
²Institute of Psychology, Eötvös Loránd University, Budapest, Hungary
³Department of Psychiatry, Kóroktudományi Intézet, Semmelweis University, Budapest, Hungary

Letter to the Editor

Functional significance of P2RX7 polymorphisms associated with affective mood disorders

Single nucleotide polymorphisms that were identified in affective mood disorders affect ATP-activated P2X₇ receptor functions

Sébastien Roger,^{a,*} Zhu-Zhong Mei^{b,1}, Jocelyn M. Baldwin^b, Li Dong^{b,c}, Helen Bradley^b, Stephen A. Baldwin^b, Ammarie Surprenant^d, Lin-Hua Jiang^{b,*}

“...it is so far the most convincing mutation to have been found with a role for increasing susceptibility to bipolar and genetically related unipolar disorders....”

BRIEF RESEARCH COMMUNICATION

AMERICAN JOURNAL OF
medical genetics
 Neuropsychiatric Genetics

Variation in P2RX7 Candidate Gene (rs2230912) Is Not Associated With Bipolar I Disorder and Unipolar Major Depression in Four European Samples[†]

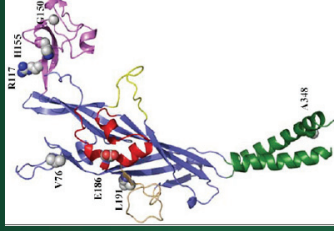
Maria Grigoriou-Serbanescu,^{1*} Stefan Herms,² Thomas W. Mühlisen,² Alexander Georgi,² Carmen C. Diaconu,⁴ Jana Strohmayer,² Piotr Czerski,³ Joanna Hauser,⁵ Anna Laszczyńska-Rodziewicz,³ Rami Abou Jarma,⁶ Julia Babadjanova,⁶ A. Tiganov,⁶ V. Krasnov,⁶ Sofia Kapiletti,⁶ Ana Lulia Neagu,⁷ Jennifer Vollmer,⁷ Rene Breuer,⁸ Marcella Rietschel,³ Peter Propping,⁹ Markus M. Nöthen,^{2,6} and Sven Cichon^{1,2,6}

RESEARCH ARTICLE

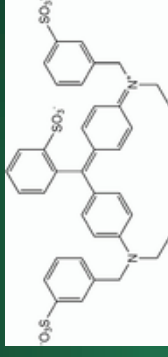
AMERICAN JOURNAL OF
medical genetics
 Neuropsychiatric Genetics

P2RX7: A Bipolar and Unipolar Disorder Candidate Susceptibility Gene?

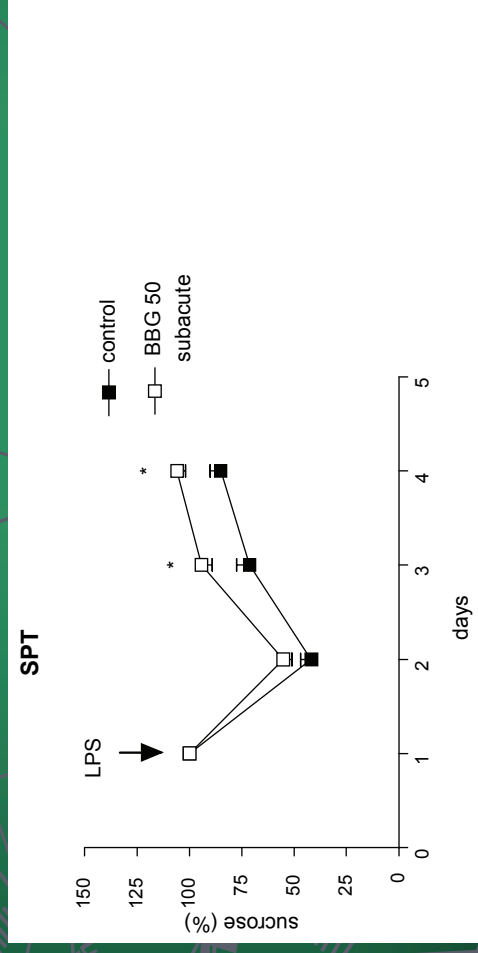
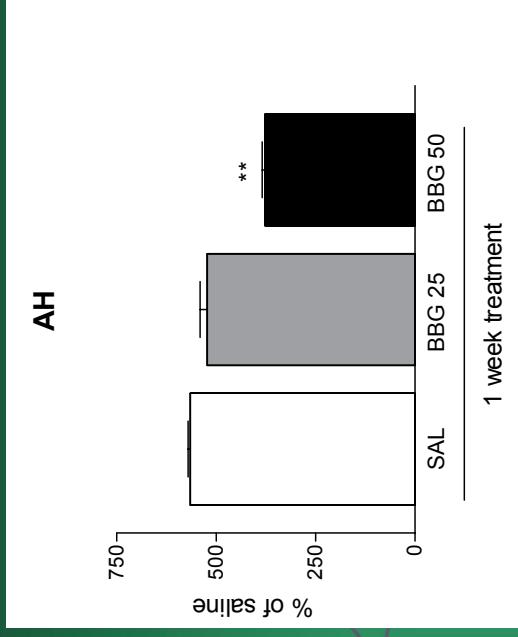
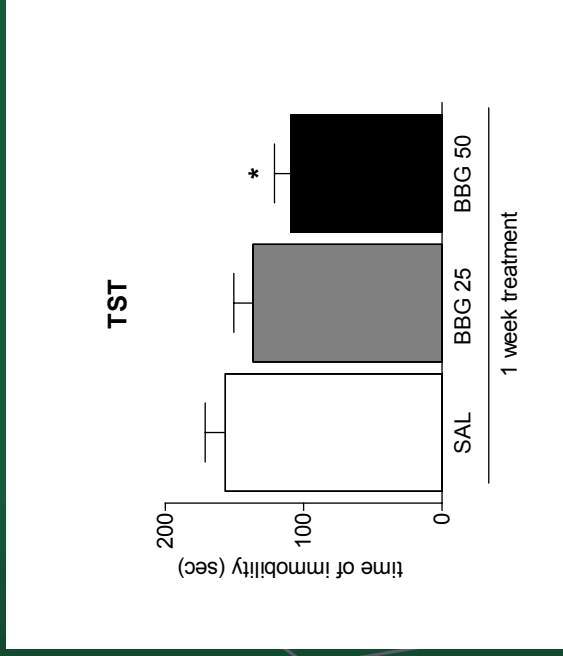
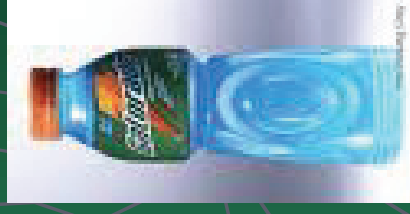
Elaïne K. Green,^{1*} Detelina Grozeva,¹ Rachel Ragboud,¹ Gareth Elvidge,² Stuart Macgregor,³ Ian Craig,⁴ Anne Farmer,⁵ Peter McGuffin,¹ Liz Forty,¹ Lisa Jones,¹ Ian Jones,² Mick C. O'Donovan,¹ Mike J. Owen,² George Kirov,² and Nick Craddock¹



A P2X7 receptor antagonist BBG reprodukálja a géniütés hatását

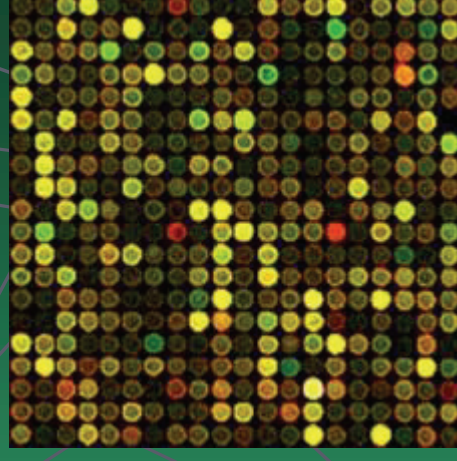
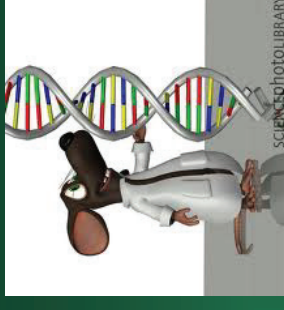


Brilliant blue G

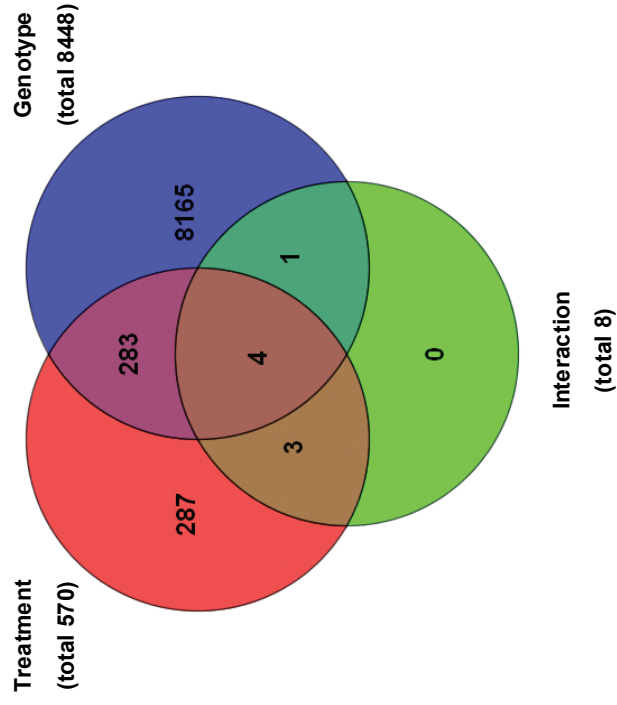


Teljes genom microarray analízis só és LPS kezelt P2rx7 +/+ és P2rx7^{-/-} egerek amygdala mintáin

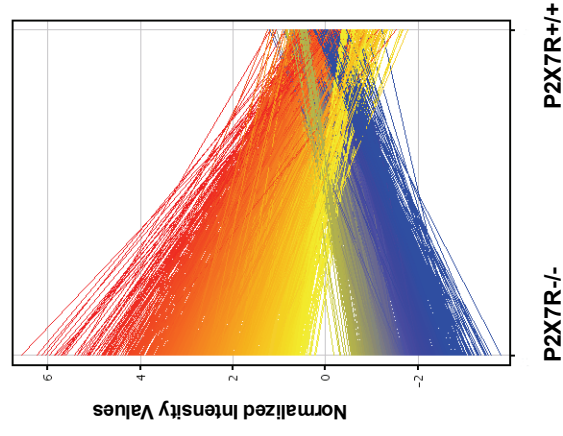
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kezelés: 287
genotípus/kezelés: 283



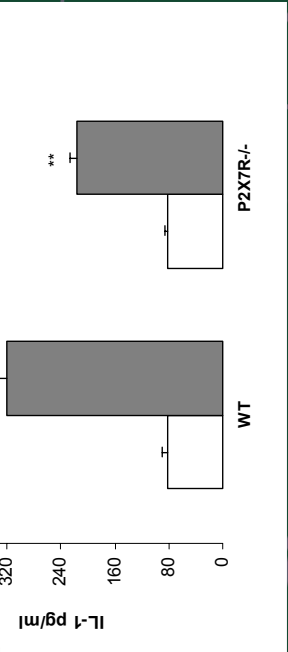
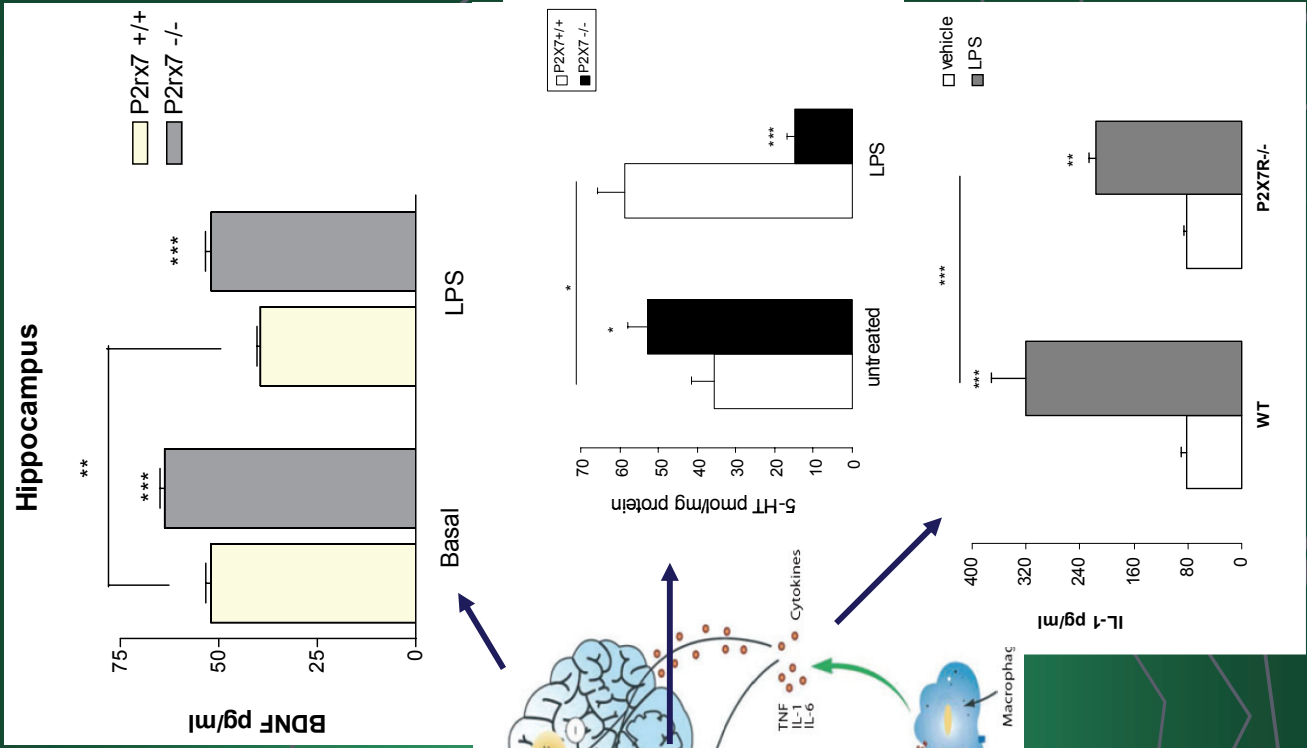
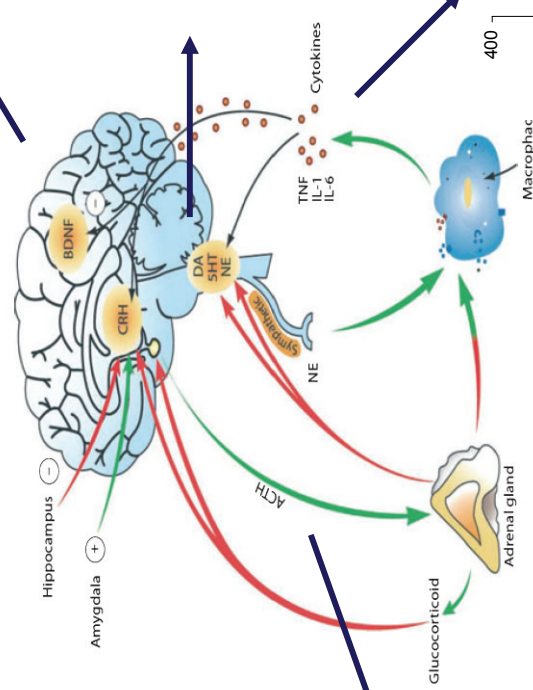
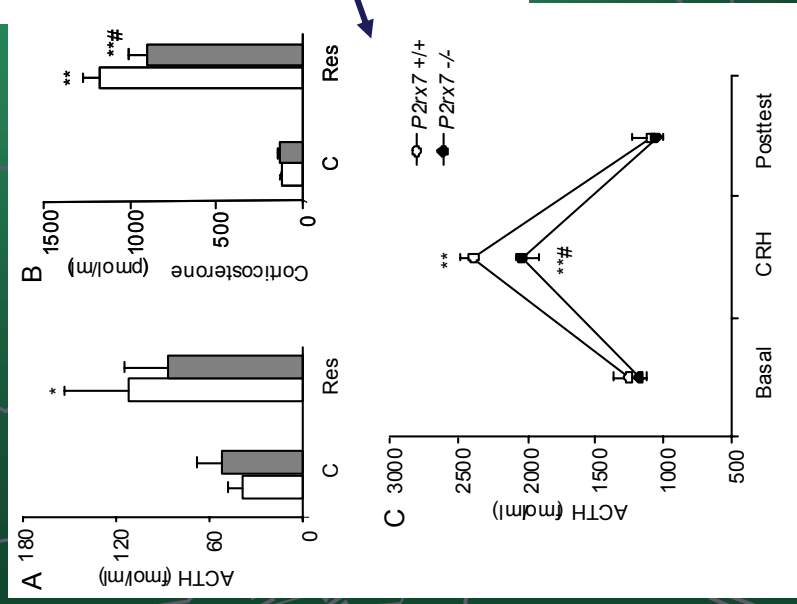
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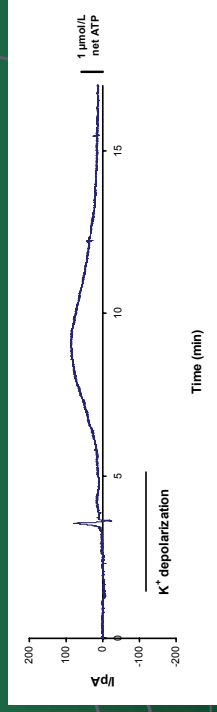
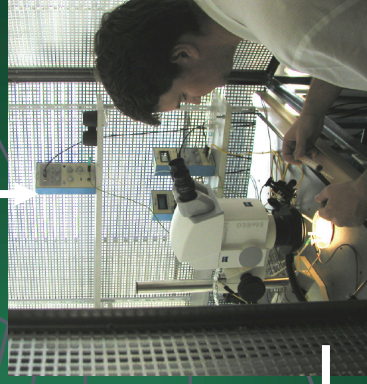
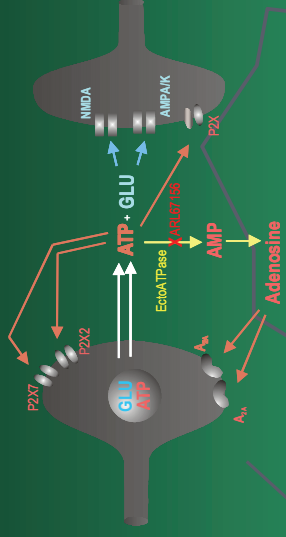
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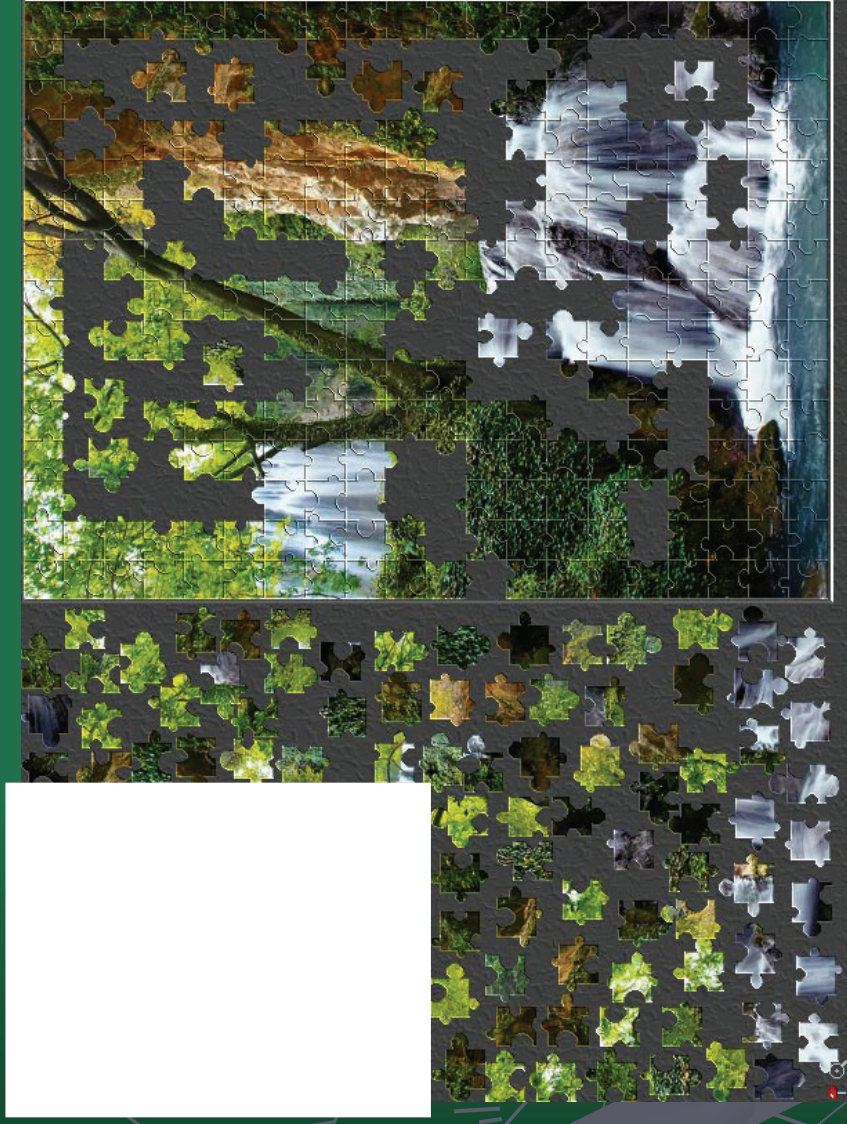
A P2X7 receptor hatásmechanizmus kutatások depresszióban



Mit csinál egy gyógyszerkutató? I.



A felfedezés folyamata



Mit csinál egy gyógyszerkutató? II.



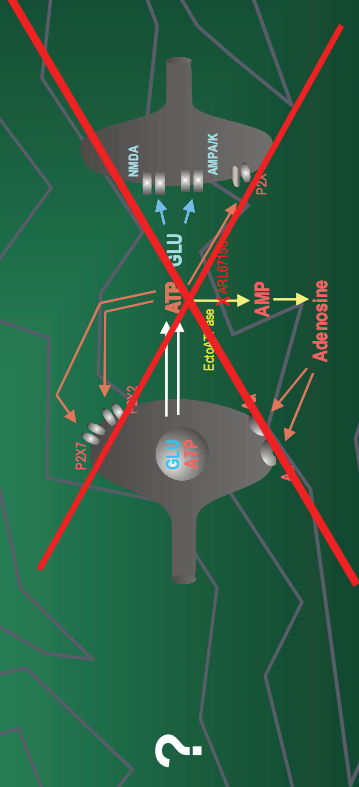
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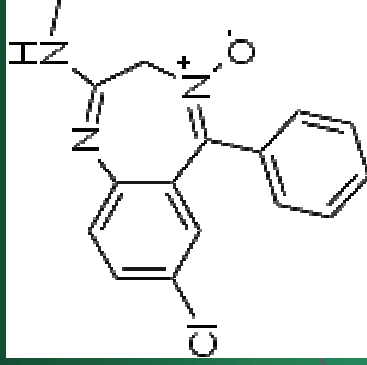
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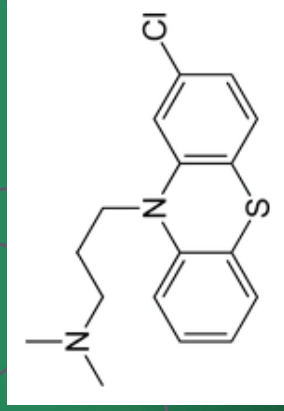
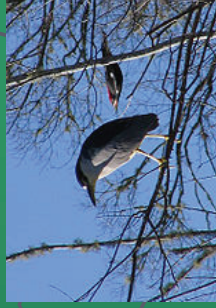
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?



benzodiazepin



fenotiazin



Leo Sternbach



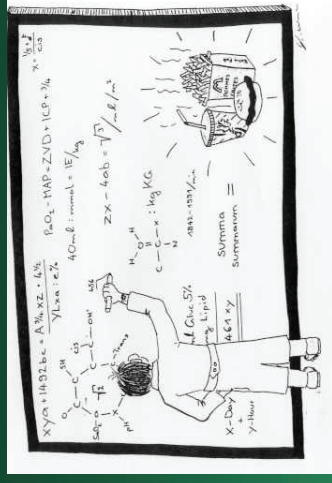
Henry Laborit



Mit csinál egy gyógyszerkutató ? III.



Mit csinál egy gyógyszerkutató ? IV.



ELSEVIER

Progress in Neurobiology 78 (2006) 327–346

P2X₇ receptors in the nervous system

Beáta Sperlágh^{a,*}, E. Sylvester Vizi^a, Kerstin Wirkner^b, P

PURINERGIC MODULATION OF GLUTAMATE RELEASE UNDER ISCHEMIC-LIKE CONDITIONS IN THE HIPPOCAMPUS

B. SPERLÁGH^{a*}, G. ZSILLA^a, M. BARANYI^a, P. ILLES^b AND E. S. VIZI^a

A_{2A} receptors rather than the striatal A_{2A} receptors could be an effective ap

Hracsko et al. *Molecular Neurodegeneration* 2011, 6:28
<http://www.molecularneurodegeneration.com/content/6/1/28>



RESEARCH ARTICLE

Open Access

Lack of neuroprotection in the absence of P2X₇ receptors in toxin-induced animal models of Parkinson's disease

Zsuzsanna Hracsko^{1†}, Mária Baranyi^{1†}, Cecília Csöille¹, Flóra Csöböcsé¹, Emília Madarász², Ágnes Kintl¹ and Beáta Sperlágh^{1*}

2004 • The Journal of Neuroscience, March 24, 2005 • 25(12):3274–3284

Cellular/Molecular

Involvement of Cannabinoid Receptors in the Regulation of Neurotransmitter Release in the Rodent Striatum: A Combined Immunochemical and Pharmacological Analysis

Anhila Köföli,^{1,2} Ricardo J. Rodrigues,² Ken Mackie,² E. Sylvester Vizi,¹ Rodrigo A. Cunha,² and Beáta Sperlágh¹

The effect of antiparkinsonian drugs on oxidative stress induced pathological [³H]dopamine efflux after *in vitro* rotenone exposure in rat striatal slices

Milushcheva^{a,b}, Mária Baranyi^a, Eszter Kormos^a, Zsuzsanna Hracsko^a, er Vizi^a, Beáta Sperlágh^{a,*}

BRITISH JOURNAL OF PHARMACOLOGY

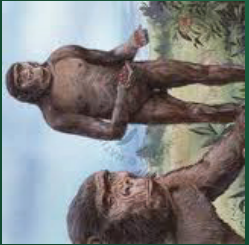
BRITISH PHARMACOLOGICAL SOCIETY

British Journal of Pharmacology (2010), 159, 1108–1117
 doi:10.1111/j.1473-2165.2010.01810.x
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RESEARCH PAPER

A comparative analysis of the activity of ligands acting at P2X and P2Y receptor subtypes in models of neuropathic, acute and inflammatory pain

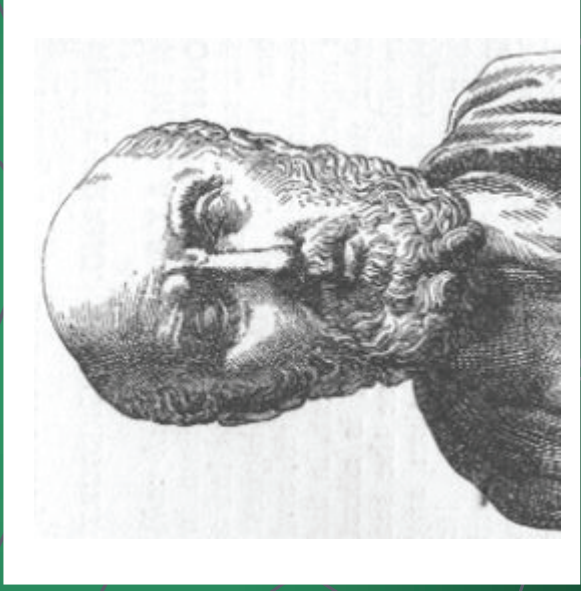
RD Andó¹, B Mészáros¹, K Gyimesi², P Illes² and B Sperlágh^{1,*}



A gyógyszeres terápia kezdetei

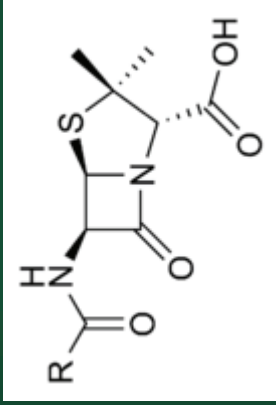
"...MINDEN BETEGSÉGNEK MEGVAN A MAGA TERMÉSZETES JELENTŐS EREJE ÉS NINCSEN OLYAN BETEGSÉG, AMELY LEKÜZDHETTETLEN ÉS GYÓGYSZERREL BEFOLYÁSOLHATATLAN LENNE. A LEGTÖBB EZEK KÖZÜL GYÓGYÍTHATÓ, HA FIGYELEMMEL VAGYUNK EREDETÉRE...."

(HIPPOKRATÉSZ KÖNYVE A SZENT BETEGSÉGRŐL I. E. 465-375)



- Felfogásának lényege a gondos megfigyelésen és feljegyzéseken alapuló tapasztalati tudás nagyrabcsülése

Penicillin



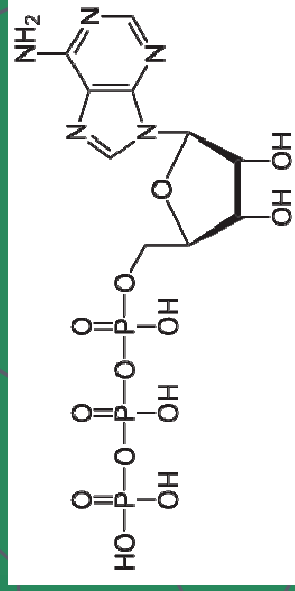
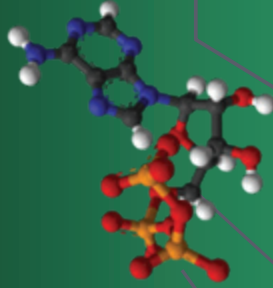
Alexander Fleming



Henry Duchesne



Atriphos



Szent-Györgyi Albert

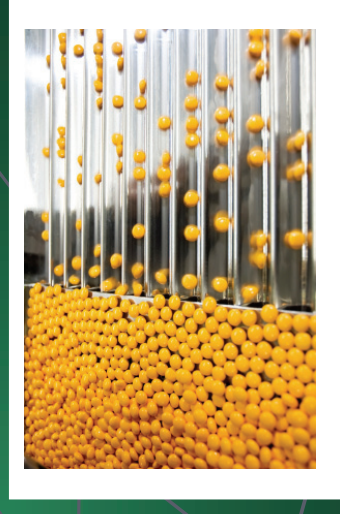
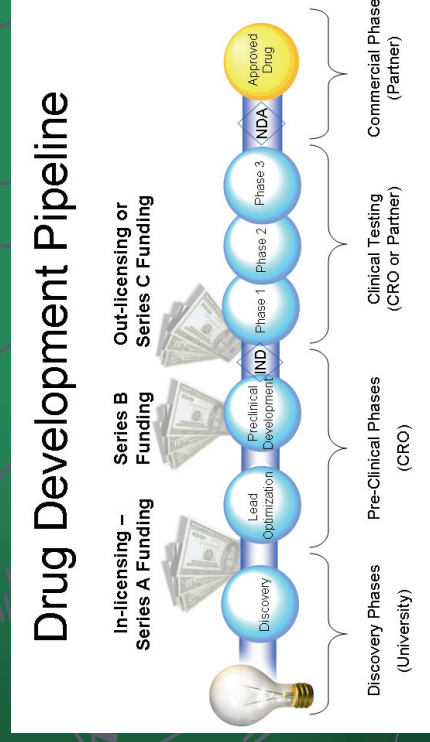
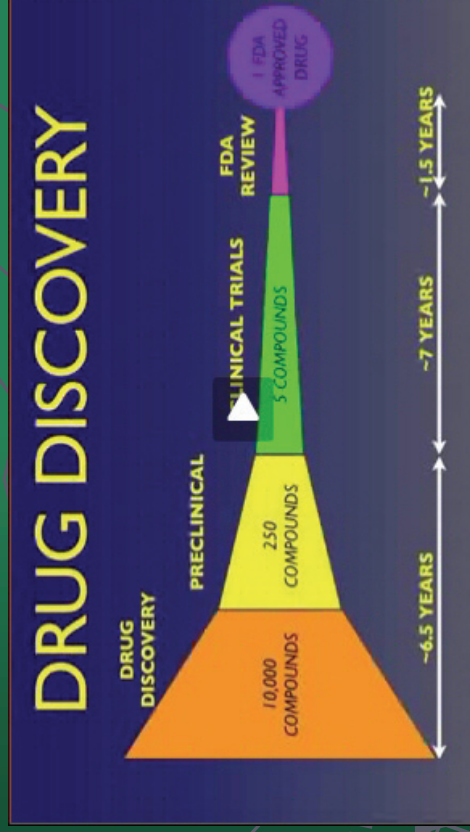


Gedeon Richter

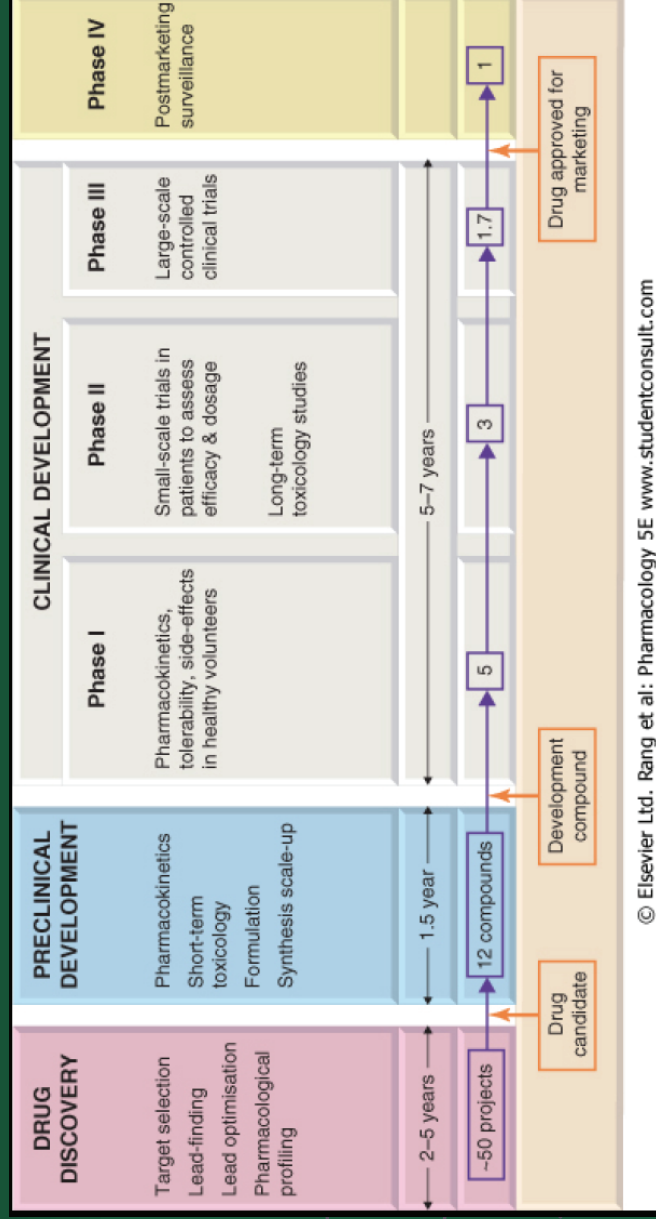
Szent-Györgyi Albert mutatta ki elsőként (1936), hogy az adenozin trifoszfát (ATP) tiszta állapotban erősen tágítja a koronáriákat és a perifériás artériákat. A Richter Rt. gyártmányaként forgalomba került tiszta ATP-oldat (Atriphos) az első kémiailag definiált preparátum volt az értágító organoterapeutikumokkal szemben.

A gyógyszerfejlesztés a XXI. Században I.

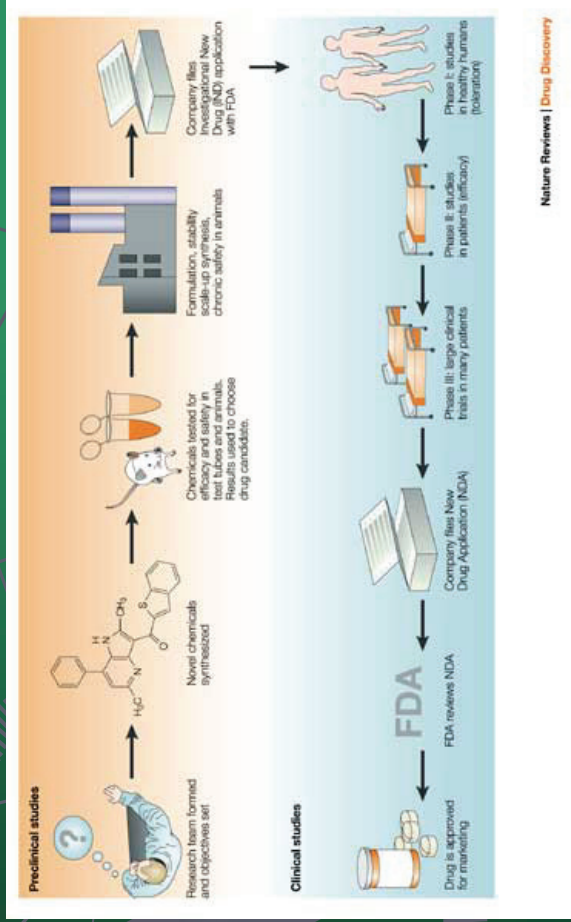
- 10000 molekulából 1 gyógyszer
- 1 új gyógyszer kifejlesztése:
1 milliárd USD
10-15 év



A gyógyszerfejlesztés a XXI. században II.



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