НЯКОИ ПО-СЪЩЕСТВЕНИ ЦИТИРАНИЯ
В ПОДКРЕПА НА ПРИНОСИТЕ
на чл.-кор. проф. дбн Илза К. Пъжева

ЦИТИРАНИЯ ОТ ОБЩ ХАРАКТЕР

ЦИТИРАНИЯ С ЕКСПЕРИМЕНТАЛНИ ДОКАЗАТЕЛСТВА НА МОДЕЛНИТЕ ИЗСЛЕДВАНИЯ
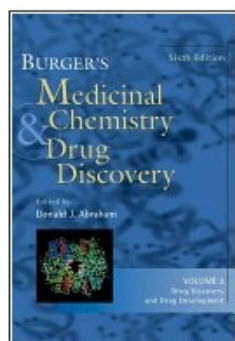
ЦИТИРАНИЯ ОТ ФИРМИ

ЦИТИРАНИЯ В ПОДКРЕПА НА ПРИНОСИТЕ

1. Източник: Burger's Medicinal Chemistry

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"This new edition of Dr. Alfred Burger's internationally celebrated classic helps researchers acquaint themselves with both traditional and state-of-the-art principles and practices governing new medicinal drug research and development. Completely updated and revised to reflect the many monumental changes that have occurred in the field, this latest edition brings together contributions by experts in a wide range of related fields to explore recent advances in the understanding of the structural biology of drug action, as well as cutting-edge technologies for drug discovery now in use around the world."

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160. S. Ekins, B. J. Ring, S. N. Binkley, S. D. Hall, and S. A. Wrighton, *Int. J. Clin. Pharmacol. Ther.*, **36**, 642 (1998).
161. K. R. Korzekwa, N. Krishnamachary, M. Shou, A. Ogai, R. A. Parise, A. E. Rettie, F. J. Gonzalez, and T. S. Tracy, *Biochemistry*, **37**, 4137 (1998).

180. G. A. Bakken and P. C. Jurs, *J. Med. Chem.*, **43**, 4534 (2000).
181. M. Wiese and I. K. Pajeva, *Pharmazie*, **52**, 679 (1997).
182. C. Tmej, P. Chiba, M. Huber, E. Richter, M. Hitzler, K. J. Schaper, and G. Ecker, *Arch. Pharm. (Weinheim)*, **331**, 233 (1998).

Where's the rest of this book?

Откъс от цитата, посочващ разработването на първите тримерни модели на зависимости структура-активност на модулатори на множествената лекарствена резистентност (инхибитори на П-гликопротеина на множественяата лекарствена резистентност).

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vinblastine or ATP, and anticooperative allosteric interactions between ATP, vinblastine, and verapamil (170). Clearly allosteric behavior by multiple substrates, inhibitors, or modulators of CYP3A4 or P-gp complicates predicting the behavior and drug–drug interactions of new molecules *in vivo* and has im-

$CH_2-CH_2-N-CH_2-CH_2$ (179), and linear discriminant analysis with topological descriptors (180). In 1997 the first 3D-QSAR (quantitative structure-activity relationships) analysis of phenothiazines and related drugs known to be P-gp inhibitors was described (181). This was followed by Hansch-type

Цитатите се отнасят до наши резултати от експериментални изследвания на лекарствено-мембранни взаимодействия на катамфифилни съединения - модулатори на множествената лекарствена резистентност в туморни клетки.

Откъси от цитатите:
A major problem in the treatment of cancer is that of multidrug resistance, which remains imperfectly understood, **though in some instances it certainly involves altered membrane transport in tumour cells (Pajeva et al. 2004**; Ferreira et al 2005).

Study of this process in cancer cell lines (Ferreira et al 2005) has been useful, but it is made more difficult by the complicated structures of membranes in vivo, **so for exploring interactions between drugs at the lipid bilayer it can be more informative to use of model membranes of known structure (Pajeva et al 2004)**

Pajeva et al (1996) have likewise stressed that the ability of modulators to reverse resistance in tumour cells is likely to be mediated through their ability to interact with the membrane phospholipids. They concluded from their results that modulators within artificial membranes composed of neutral and negatively charged phospholipids provided a convenient model for screening compounds for their potential ability to reverse multidrug-resistance in tumour cells.

Цитирани работи:
Pajeva I K, Wiese M, Cordes H P and Seydel J K 1996 Membrane interactions of some catamphiphilic drugs and relation to their multidrug-resistance-reversing ability; J. Cancer Res. Clin. Oncol. 122 27–40.
Pajeva I, Todorov D K and Seydel J 2004 Membrane effects of the antitumor drugs doxorubicin and thaliblastine: comparison to multidrug resistance modulators verapamil and trans- flupentixol; Eur. J. Pharm. Sci. 21 243–250.

Цитатите потвърждават концепцията за наличие на „хидрофобен дипол" при модулаторите на MDR.

Откъси от цитатите:
CoMFA and CoMSIA studies were also performed, and the results supported the findings obtained by 2D approaches. The alignment used is based on an overlay of the central aromatic ring, the carbonyl group, and the nitrogen atom (Fig. 5). Molecular interaction fields obtained indicate that there are both steric favorable (in line of the hydroxypropylamino chain) and steric unfavorable regions (orthogonal to the

hydroxypropylamino chain) in the vicinity of the nitrogen atom. **This supports results from Pajeva and Wiese, who also identified lipophilicity as a space-directed property in a 3D-QSAR study of selected propafenone derivatives [14]**.

Цитирана работа
14. I. K. Pajeva and M. Wiese. *Quant. Struct.–Act. Relat.* **17**, 301 (1998)

Източник: Gerhard Koenig, Peter Chiba, Gerhard F. Ecker. Hydrophobic moments as physicochemical descriptors in structure-activity relationship studies of P-glycoprotein inhibitors. Monatsh Chem 139, 401–405 (2008)

Recently, Pajeva and Wiese have shown that for a series of inhibitors of the multidrug efflux pump P-glycoprotein hydrophobicity represents a space directed molecular property rather than a simple overall descriptor [4]. Based on these findings **they also introduced the concept of hydrophobic dipoles and concluded that such descriptors are able to characterize the space directionality of hydrophobicity in the case of multidrug-resistance related drugs and thus provide means to design hydrophobic complementarity [5].**

Цитирани работи:
4. Pajeva I, Wiese MJ (1998) Med Chem 41:1815
5. Pajeva I, Wiese M (2001) Compt Rend Acad Bulg Sci 54:81

Източник: Robert J, Jarry C. Multidrug resistance reversal agents. J Med Chem. 2003; 46(23): 4805-4817.

    Цитатите се отнасят до оценка на фармакофорния модел, предложен от нас, като много по-информативен за оценка на разпознаваемост на съединения за взаимодействието им с П-гликопротеина, в сравнение с други модели.

Откъси от цитатите:
Finally, a general pharmacophore model was recently proposed by Pajeva and Wiese.[58] It is based on the study of the molecular characteristics of 19 compounds be-longing to different structural classes, some studied in their enantiomeric forms. This was achieved using the GASP software (genetic algorithm similarity program). **The structure proposed for the pattern of recognition by P-glycoprotein is much more complex than the simple hydrogen bond donor model proposed by Seelig[52] and, as a consequence, much more informative for the design of new modulators.**

Цитирана работа: Цитат 58. Pajeva IK, Wiese M. Pharmacophore model of drugs involved in P-glycoprotein multidrug resistance: explanation of structural variety (hypothesis). J Med Chem. 2002; 45(26):5671-5686.

Източник: Leong MK, Chen H-B, Shih Y-H (2012) Prediction of Promiscuous P-Glycoprotein Inhibition Using a Novel Machine Learning Scheme. PLoS ONE 7(3): e33829.

    Цитатът показва коректността на предложените от нас модели и възможността им за използването им като средство за потвърждение на други резултати.

Откъси от цитатите:

In addition, numerous studies have demonstrated the importance of HBD in determining the interaction between inhibitor and P-gp. For instance, Ekins et al. [30] and Pajeva et al. [29], [32] recruited the chemical feature HBD to develop their pharmacophore hypotheses.

More importantly, the discrepancies in feature selections among these four models are consistent with the fact that Hypo A, Hypo B and Hypo C in the PhE also employed different chemical features, suggesting that different chemotypes of inhibitors can interact with P-gp using different chemical interactions, which completely agrees with the observation of Pajeva et al. [29,32].

Цитирани работи:

1. Цитат 29. Pajeva IK, Wiese M (2002) Pharmacophore model of drugs involved in P-glycoprotein multidrug resistance: explanation of structural variety (hypothesis). J Med Chem 45: 5671–5686.
2. Цитат 32. Pajeva I, Globisch C, Fleischer R, Tsakovska I, Wiese M (2005) Molecular Modeling of P-Glycoprotein and Related Drugs. Med Chem Res 14: 106–117.

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7. Източник: Dei S, Coronnello M, Floriddia E, Bartolucci G, Bellucci C, Guandalini L, Manetti D, Romanelli MN, Salerno M, Bello I, Mini E, Teodori E. Multidrug resistance (MDR) reversers: High activity and efficacy in a series of asymmetrical N,N-bis(alkanol)amine aryl esters. EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY 87C: 2014 Sep 30 pg 398-412

Цитатът показва полезността на разработения от нас хомоложен модел на П-гликопротеина.

Откъси от цитата:

Although a high resolution crystal structure of human P-gp is still lacking, fundamental information on its structure and mechanism of action has been collected from the resolution of the 3D-structures of the bacterial homolog Sav1866 [7] and murine P-gp (having 87% of homology with human P-gp) [8] and [9] that has allowed the development of several useful homology models [[10] and therein cited literatures].

Цитирана работа: Цитат 10. Pajeva, I. K., C. Globisch, M. Wiese. Comparison of the inward- and outward-open homology models and ligand binding of human P-glycoprotein. *FEBS J.*, 276 (23)**,** 2009, 7016–7026.

Източник: Pereira de Souza F., M. P. Sabbag, G. C. de Araujo, H. L. P. Cravo, T. P. S. Teixeira, D. E. Gomes, V. Fadel, M. A. Fossey, Interaction Model between HRSV G-Protein and Flavonoids, Int. J. Sciences, 2013, 2(10), 12-19

Цитатът се отнася до използването на разработен от нас пакет AMMOC за пост-докинг оптимизация на белтък-лигандни комплекси.

Откъс от цитата: Most of the flavonoids studied in this work have no three-dimensional structures solved by experimental techniques. For this reason, in silico modeling of these structures was required. FROG2 [Miteva et al., 2010] was used to calculate the three-dimensional structure of molecules through the Monte Carlo method and also through energy minimization via the AMMOS force field [Pencheva et al., 2008].

Цитирана работа: Pencheva T., D. Lagorce, I. Pajeva, Br. Villoutreix, M. Miteva, AMMOS:

Automated Molecular Mechanics Optimization Tool for in silico Screening, BMC Bioinformatics, 2008, 9:438

Източник: Brylinski M., G. L. Waldrop, Computational Redesign of Bacterial Biotin Carboxylase Inhibitors Using Structure-Based Virtual Screening of Combinatorial Libraries, Molecules, 2014, 19, 4021-4045.

Цитатът се отнася до използването на разработен от нас пакет АММОС за пост-докинг оптимизация на белтък-лигандни комплекси.

Откъс от цитата: Next, the best binding pose was selected using non-linear machine learning models; the final docking result was also assigned a binding score and binding affinity. In addition, ligand poses modeled by eSimDock **were refined by molecular mechanics using AMMOS [54]** and thestandard AMMP force field sp5 [55].

Цитирана работа: Цитат 54. Pencheva T., D. Lagorce, I. Pajeva, Br. Villoutreix, M. Miteva, AMMOS: Automated Molecular Mechanics Optimization Tool for in silico Screening, BMC Bioinformatics, 2008, 9:438

Източник: Brylinski M., J. Skolnick, Q-DockLHM: Low-Resolution Refinement for Ligand Comparative Modelling, Journal of Computational Chemistry, 2010, 31(5), 1093-1105.

Цитататите се отнасят до използването на разработен от нас пакет АММОС за пост-докинг оптимизация на белтък-лигандни комплекси, които показват неговата по-добра ефективност в сравнение с други пакети.

Откъси от цитати:
Ligand poses provided by FINDSITELHM as well as low-resolution models generated by Q-DockLHM and transformed into the all-atom representation **were optionally refined by molecular mechanics optimization using AMMOS 50**. AMMOS employs the AMMP molecular simulation package 51 to carry out automatic refinement of the complexes. We used the sp4 force field in all simulations. Using the crystal structures of the receptors, only ligand atoms were permitted to move (AMMOS Case 5), whereas for protein models, protein atoms within a 12 Å sphere around the ligand are allowed to be flexible (AMMOS Case 4).

High resolution refinement using AMMOS applied to ligand poses reconstructed from Q-DockLHM's conformations **removes most of the unphysical contacts**, and similar to AutoDock3 and LIGIN, produces ligand-protein complexes that closely follow the crystal structures with respect to the interatomic distances. **AMMOS was found to be more effective in removing close contacts when applied to ligand poses refined by Q-DockLHM than those provided by FINDSITELHM. This is especially important for subsequent ligand ranking studies**.

Furthermore, we find that the subsequent high-resolution refinement by **AMMOS improves the accuracy of the all-atom conformations reconstructed from low-resolution models** provided by Q-DockLHM to a median RMSD of 4.02 Å.

Цитирана работа: Цитат 50. Pencheva T., D. Lagorce, I. Pajeva, Br. Villoutreix, M. Miteva, AMMOS: Automated Molecular Mechanics Optimization Tool for in silico Screening, BMC

Bioinformatics, 2008, 9:438.

Източник: Yodsoi Kanintronkul, Rattana Worayuthakarn, Nopporn Thasana, Pakorn Winayanuwattikun, Kovit Pattanapanyasat, Rudee Surarit, Somsak Ruchirawat, Jisnuson Svasti. Overcoming Multidrug Resistance in Human Lung Cancer with Novel Benzo[a]quinolizin-4-ones. ANTICANCER RESEARCH 31: 921-928 (2011)

        Цитатът потвърждава идентифицираните от нас структурни признаци, характерни за съединенията, използвани за преодоляване на MDR в туморни клетки.

Откъси от цитати:
Benzo[*a*]quinolizin-4-ones exhibit the common structure of most P-gp inhibitors in having a methoxy phenol group and a basic nitrogen atom, as reported by Pajeva (22).

Цитирана работа:
22 Pajeva IK and Wiese M: Structure–activity relationships of Tariquidar analog as multidrug resistance modulators. AAPS pp. 431-444, 2009.

Източник:Ilić-Stojanović S, Nikolić L, Nikolić V, et al. Semi-Crystalline Copolymer Hydrogels as Smart Drug Carriers: In Vitro Thermo-Responsive Naproxen Release Study. Pharmaceutics. 2021;13(2):158.

        Цитатът се отнася до идентифицирани от нас „слаби" взаимодействия на нестероидното лекарство Naproxen с поливинилпиролидон в твърда фаза като ги потвърждава.

Откъс от цитат:
... The amount of naproxen released depends on the composition of the hydrogel, i.e., its cross-linker content. Analysis indicates that naproxen as a drug is well stabilized by aromatic-aromatic interactions, with the greatest influence (43.2%) attributed to naphthalene-naphthalene interactions [24]. ...

Цитирана работа:
24. Bogdanova S., I. Pajeva, P. Nikolova, I. Tsakovska, B. Müller. Interactions of poly (vinylpyrrolidone) with ibuprofen and naproxen: experimental and modeling studies, *Pharmaceut. Res*., 2005, 22 (5), 806-815.

Източник: Navarro Del Hierro J, Piazzini V, Reglero G, Martin D, Bergonzi MC. In Vitro Permeability of Saponins and Sapogenins from Seed Extracts by the Parallel Artificial Membrane Permeability Assay: Effect of in Vitro Gastrointestinal Digestion. J Agric Food Chem. 2020 Feb 5;68(5):1297-1305.

        Цитатът се отнася до изследванията ни на мембранната пропускливост на флаванолигнани от растението бял трън (Silybum marianum (L.) Gaertn.) с използването на методологията PAMPA; те са класифицирани като изследвания от голям интерес, заради използваната методология.

*Откъс от цитат***:**
The permeability of bioactive flavonoids and iridoids from the extracts of Vitex agnus-castus and Silybum marianum was assessed by PAMPA models and validated through Caco-2 assays, [16,19,20] as well

as furanocoumarins, alkaloids, flavonoid glycosides, and flavonolignans from the extracts of Angelica archangelica, Waltheria indica, Pueraria montana, or S. marianum, respectively. [15,21] These uses of PAMPA are of great interest, suggesting it as a novel, relevant, and interesting tool to be explored for the screening of nutraceuticals or food ingredients with bioactive purpose.

Цитирана работа:
21. Diukendjieva, A.; Alov, P.; Tsakovska, I.; Pencheva, T.; Richarz, A.; Kren, V.; Cronin, M. T. D.; Pajeva, I. In vitro and in silico studies of the membrane permeability of natural flavonoids from Silybum marianum (L.) Gaertn. and their derivatives. Phytomedicine 2019, 53, 79−85.

Същата работа е цитирана по-долу под номер [44] в потвърждение на използваната от нас класификация на биологично-активните съединения на база на тяхната мембранна пропускливост:

Източник: Chi, C.-T.; Lee, M.-H.; Weng, C.-F.; Leong, M.K. In Silico Prediction of PAMPA Effective Permeability Using a Two-QSAR Approach. *Int. J. Mol. Sci.* **2019**, *20*, 3170. https://doi.org/10.3390/ijms20133170

Откъси от цитати:
Compounds collected in this study were classified as having high and low permeability if their log P_e values were $\geq$−6.0 and $<$−6.0, respectively, as suggested by Diukendjieva et al. [44] to verify the observation made by Kelder et al. The analysis of collected compounds indicated that 100% of compounds were poorly permeable and 75% of compounds were well permeable when their PSA values were >120 Å^2 and <60 Å^2, respectively, which is completely consistent with the observation made by Kelder et al. Only 92% of compounds were poorly permeable when the threshold of PSA was set to >110 Å^2, suggesting that the threshold PSA > 120 Å^2 is efficiently enough to characterize the poorly permeable compounds."

Същата работа е цитирана в положителен смисъл под номер [19] по-долу, заради голямата извадка от съединения, използвани в изследването за извеждане на модела за мембранна пропускливост.
Източник: Roy, D., Dutta, D., Wishart, D.S. et al. Predicting PAMPA permeability using the 3D-RISM-KH theory: are we there yet?. J Comput Aided Mol Des 35, 261–269 (2021). https://doi.org/10.1007/s10822-020-00364-4

Откъс от цитат:
The biggest data set for modelling: 248 drugs and drug like compounds in the training set [19]

Източник: Kim, H.S., Yang, J.H., Kang, D.S. *et al.* Suggestions for applications of toxicogenomic approaches in the adverse outcome pathway of 2,4-dinitrotoluene. *Toxicol. Environ. Health Sci.* **12,** 109–118 (2020). https://doi.org/10.1007/s13530-020-00054-6

Цитатът потвърждава полезността на QSAR моделите за целите на изчислителната токсикология.

Откъс от цитат:
As such, initiation of the chemical-response pathway starts with exposure to certain materials, which interact with biological components based on their physicochemical properties. Quantitative structure-

activity relationship (QSAR) models are widely utilized by risk assessors for biological effect prediction with an understanding of their properties or kinetic information inside organic systems [17,18].

Цитирана работа:
[18] Al Sharif M., I. Tsakovska, I. Pajeva, P. Alov, E. Fioravanzo, A. Bassan, S. Kovarich, C. Yang, A. Mostrag-Szlichtyng, V. Vitcheva, A. P. Worth, A. N. Richarz, M.T. D. Cronin. The Application of Molecular Modelling in the Safety Assessment of Chemicals: A Case Study on Ligand-Dependent PPARγ Dysregulation, *Toxicology*, 2017, 392, 140-154. doi:10.1016/j.tox.2016.01.009.

Източник: Park JW, Hong S-p, Lee JH, Moon SH, Cho YS, Jung K-H, et al. (2020) [99mTc]-MIBI uptake as a marker of mitochondrial membrane potential in cancer cells and effects of MDR1 and verapamil. PLoS ONE 15(2): e0228848.   https://doi.org/10.1371/journal.pone.0228848

Цитатът се отнася до потвърждение на ролята на катамфифилни съединения като Verapamil за повлияване на мембранната флуидност.

Откъс от цитат:
A possible mechanism for these findings could be the drug's strong hydrophobicity that can influence cytoplasmic membrane fluidity [28,29]. An increase of bilayer fluidity by verapamil has been suggested to facilitate passive diffusion of substrates into cells [30]. Our resultc of reduced PMP by verapamil in a manner that was recovered by FCCP support this possibility.

Цитирана работа:
[30] Pajeva I., D.K. Todorov, J.K. Seydel. Membrane effects of the antitumor drugs doxorubicin and thaliblastine: comparison to multidrug resistance modulators verapamil and trans-flupentixol, *Europ. J. Pharm. Sci.*, 2004, 21(2-3), 243-250.

Източник: Hernandez, D.A., Rodriguez-Zavala, J.G. & Tenorio, F.J. DFT study of antioxidant molecules from traditional Japanese and Chinese teas: comparing allylic and phenolic antiradical activity. *Struct Chem* **31,** 359–369 (2020). https://doi.org/10.1007/s11224-019-01411-z

Цитатът дава висока оценка за обзор на фенолни съединения, изследвани с помощта на молекулно-изчислителни методи.

Откъс от цитат:
... Some recent computational studies have been carried out on hydroxycinnamic acids [4], quercetin, and edaravone (both with DFT benchmark) [11], as well as catechin [12], flavones and flavonids [13], gallic acid [14], myricetin [13], pyranine [15], oxygenated terpenoids [16], and quinazoline derivatives [17]. Likewise, there are excellent reviews written about phenolic antioxidants [18,19]. ...

Цитирана работа:
[18] Alov O., I. Tsakovska, I. Pajeva. Computational Studies of Free Radical-Scavenging Properties of Phenolic Compounds. *Current Topics in Medicinal Chemistry*, 2015, 15(2), 85-104

Изтоник: Kaczor, A.; Nové, M.; Kincses, A.; Spengler, G.; Szymańska, E.; Latacz, G.; Handzlik, J.

Search for ABCB1 Modulators Among 2-Amine-5-Arylideneimidazolones as a New Perspective to Overcome Cancer Multidrug Resistance. *Molecules* **2020**, *25*, 2258. https://doi.org/10.3390/molecules25092258

Цитатът се отнася до предложени от нас места на свързване на субстрати на P-gp (П-гликопротеина), по-специално т.нар. H-място, с което взаимодейства веществото Hoechst33342, известо като субстрат на P-gp. Цитатът подкрепя нашето предложение.

***Откъс от цитат*:**
... Additionally, the ligand was involved in hydrophobic contacts with the amino acids that belong mostly to TM5 (Table S2). The binding mode observed for pose 3 resembled to some extent that proposed by Pajeva for Hoechst 33342, according to which Tyr 307, Asn 721, and Phe 770 were identified as important residues forming a part of the H-site [33]. ...

Цитирана работа:
[33] Pajeva I. , M. Hanl, M. Wiese. Protein contacts and ligand binding in the inward-facing model of human P-glycoprotein, *ChemMedChem*., 2013, 8 (5), 748–762

Същата работа е цитирана по-долу под номер [9], в потвърждение на установените с моделни изследвания контакти между аминокиселините на интерфейса между нуклеотид-свързващия и трансмембранния домени на П-гликопротеина.

***Откъс от цитат*:**
... Even though the mutations described above directly affected the transmembrane region, they also induced changes in the total number of contacts at the ICH-NBD interfaces, suggesting that the TMHs rearrangement is involved in the TMD-NBD communication, in agreement with several experimental 10,126,127 and in silico studies 8,9,45,46 .

Налице са редица цитирания, свидетелстващи за <u>широкото използане на софтуерната платформа със свободен достъп AMMOS</u> и версията й AMMOS2 при изследване на протеин-лигандни комплекси за целите на минимазиция на енергиите на комплкса и за виртуален скрининг.

Цитирана работа:
Labbé C., T. Pencheva, D. Jereva, D. Desvillechabrol, J. Becot, B. Villoutreix, I. Pajeva, M. Miteva, AMMOS2: A Web Server for Protein-ligand-water Complexes Refinement via Molecular Mechanics, *Nucleic Acids Research*, 2017, 45(W1), W350-W355.

Източник: Zhao Y., Y. Jiao, F. Sun, X. Liu, Revisiting the Molecular Mechanism of Acquired Resistance to Reversible Tyrosine Kinase Inhibitors Caused by EGFR Gatekeeper T790m Mutation in Non-Small-cell Lung Cancer, *Medicinal Chemistry Research*, 2018, 27, 2160-2170.

Откъс от цитата First, both the crystal and modeled structures of EGFR–TKI complexes were subjected to AMMOS2 server (Labbé et al. 2017) for coarse-grained energy minimization to eliminate bad atomic contacts and overlaps, with consideration of kinase side-chain flexibility within 4 Å of inhibitor ligand, followed by a round of dynamics simulations to relax the whole systems (Yang et al. 2015a, 2015b, 2016; Bai et al. 2017).

Източник: Grande F., B. Rizzuti, M. A. Occhiuzzi, G. Ioele, T. Casacchia, F. Gelmini, R. Guzzi, A. Garofalo, G. Statti, Identification by Molecular Docking of Homoisoflavones from *Leopoldia comosa* as Ligands of Estrogen Receptors, *Molecules*, 2018, 23(4), 894.

Откъс от цитата: Refinement of the complex structures was performed by energy minimization using the web server AMMOS2 [48], which employs the universal force field (UFF) potential set [54] and AMBER partial charges [55] with a conjugate gradient optimization.

Източник: Xu Z., H. Chen, F. J. Fan, P. J. Shi, M. L. Tu, S. Z. Cheng, Z. Y. Wang, M. Du, Bone Formation Activity of an Osteogenic Dodecapeptide from Blue Mussels (Mytilus edulis), *Food & Function*, 2019, 10(9), 5616-5625.

Откъс от цитата: The polypeptide was docked by the energy at the position of the original RGD ligand in the crystal structure of the receptor after minimization of energy.[20]

Източник: Liu T., Z. Wang, P. Guo, N. Ding, Electrostatic Mechanism of V600E Mutation-induced B-Raf Constitutive Activation in Colorectal Cancer: Molecular Implications for the Selectivity Difference between Type-I and Type-II Inhibitors, *European Biophysics Journal*, 2019, 48(1), 73-82.

Откъс от цитата: In this way, the complex structures of six investigated inhibitors with B-Raf kinase in six states were obtained, totally resulting in 36 B-Raf–inhibitor complex systems (six inhibitors × six kinase states), which were then submitted to AMMOS2 server (Labbé et al. 2017) for energy minimization to eliminate bad atomic overlaps and contacts, with consideration of protein side-chain flexibility within 4 Å of inhibitor ligand.

Източник: Terali K., B. Baddal, H. O. Gulcan, Prioritizing Potential ACE2 Inhibitors in the COVID-19 Pandemic: Insights from a Molecular Mechanics-assisted Structure-based Virtual Screening Experiment, *Journal of Molecular Graphics and Modelling*, 2020, 100, art. no. 107697.

Откъс от цитата: In order to provide a more realistic description of the predicted proteineligand complexes, successfully docked ligands were refined and subsequently rescored using the AMMOS2Web service [31] (available at http://drugmod.rpbs.univ-paris-diderot.fr/ammosHome.php) in a setting where the ligand and ACE2 sidechain atoms within 4 Å of the ligand were rendered flexible.

Цитира се също и статията, описваща версията AMMOS.
Pencheva T., D. Lagorce, I. Pajeva, Br. Villoutreix, M. Miteva**.** AMMOS: Automated Molecular Mechanics Optimization Tool for *in silico* Screening, *BMC Bioinformatics*, 2008, 9:438

Източник: Song L., C. Zhu, W. Zheng, D. Lu, H. Jiao, R. Zhao, Z. Bao, Computational Systematic Selectivity of the Fasalog Inhibitors between ROCK-I and ROCK-II Kinase Isoforms in Alzheimer's Disease, *Computational Biology and Chemistry*, 2020, 87:107314, DOI: 10.1016/j.compbiolchem.2020.107314.

Откъс от цитата: In the procedure, the molecular structure of Fasudil (in complex with kinase domain) was manually modified to other inhibitors, which were then subjected to the molecular ==mechanics-based AMMOS2 structural minimization for conformational relaxing== (Pencheva et al., 2008; Labbé et al., 2017).

Източник: Li D., C. Li, D. Liu, Analyses of Structural Dynamics Revealed Flexible Binding Mechanism for the Agrilus mali Odorant Binding Protein 8 towards Plant Volatiles, *Pest Management Science*, 2020, , https://doi.org/10.1002/ps.6184

Цитатът се отнася до използването на разработен от нас пакет AMMOC за пост-докинг оптимизация на белтък-лигандни комплекси.

Откъс от цитата: The AMMOS online tool (https://mobyle.rpbs.univ-paris-diderot.fr/cgi-bin/portal.py) was ==used to find the lowest energy conformation of small-molecule compounds.==[35]

Източник: Song L., C. Zhu, W. Zheng, D. Lu, H. Jiao, R. Zhao, Z. Bao, Computational Systematic Selectivity of the Fasalog Inhibitors between ROCK-I and ROCK-II Kinase Isoforms in Alzheimer's Disease, *Computational Biology and Chemistry*, 2020, 87:107314, DOI: 10.1016/j.compbiolchem.2020.107314.

Откъс от цитата: In the procedure, the molecular structure of Fasudil (in complex with kinase domain) was manually modified to other inhibitors, which were then ==subjected to the molecular mechanics-based AMMOS2 structural minimization for conformational relaxing== (Pencheva et al., 2008; Labbé et al., 2017).

Източник: Schneider M., J. L. Pons, W. Bourguet, G. Labesse, Towards Accurate High-throughput Ligand Affinity Prediction by Exploiting Structural Ensembles, Docking Metrics and Ligand Similarity, *Bioinformatics*, 2020, 36(1), 160-168 (Available online 2019).

Цитатът се отнася до използването на разработен от нас пакет AMMOC за пост-докинг оптимизация на белтък-лигандни комплекси.

Откъс от цитата: In addition, other evaluations are performed on the server, such as the model quality of the receptor [QMean (Benkert et al., 2008)] and the evaluation of the ligand conformation [such as LPC (Sobolev et al., 1999) or AMMP energy computed by AMMOS (Pencheva et al., 2008)].

Източник: Terali K., B. Baddal, H. O. Gulcan, Prioritizing Potential ACE2 Inhibitors in the COVID-19 Pandemic: Insights from a Molecular Mechanics-assisted Structure-based Virtual Screening Experiment, *Journal of Molecular Graphics and Modelling*, 2020, 100, art. no. 107697.

Откъс от цитата: This cut-off was selected on the basis of the ==previously described ability of AMMOS to enrich top 3e5% of an entire compound collection in known bioactive molecules as compared to decoys and unknown binders [33].==

ЦИТИРАНИЯ С ЕКСПЕРИМЕНТАЛНИ ДОКАЗАТЕЛСТВА НА МОДЕЛНИТЕ ИЗСЛЕДВАНИЯ

Представените по-долу цитирания са от експериментални изследвания, които показват коректността на предсказаните от моделите структурни и функционални характеристики на изследваните биологически активни съединения и биомакромолекули.

1. Доказателство за асиметричността на структурата на двете половини на транспортния протеин, показана с модел на П-гликопротеина:

Цитирано е от групата на Суреш Амбудкар (Suresh V. Ambudkar), който е един от най-известните изследователи-експериментатори в областта, от лабораторията по клетъчна биология на Центъра по изследване на рака към Националните институти по здравеопазване на САЩ в Бетезда (Laboratory of Cell Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, United States of America).

Източник: Kapoor, K; Bhatnagar, J; Chufan, EE; Ambudkar, S. Mutations in Intracellular Loops 1 and 3 Lead To Misfolding of Human P-Glycoprotein (ABCB1) That Can Be Rescued By Cyclosporine A, Which Reduces its Association With Chaperone Hsp70. JOURNAL OF BIOLOGICAL CHEMISTRY, 288 (45):32622-32636; 10.1074/jbc.M113.498980 NOV 8 **2013**.

Откъс от цитата:"Pajeva et al also reported the asymmetry in interaction between the two halves of the protein, which is confirmed by our observed differences upon single mutation of Asp164 and Asp805 (28)."

Цитирана работа: Цитат 28. Pajeva, I. , M. Hanl, M. Wiese. Protein contacts and ligand binding in the inward-facing model of human P-glycoprotein, *ChemMedChem*, 2013, 8 (5),748–762.

2. Доказателство за взаимодействия между структурни домени и елементи на П-гликопротеина, показани с моделните изследвания.

Направени са от безспорно най-цитираните изследователи - експериментатори на транспортни проетини в света - учените Тип Лу (Tip Loo) и Дейвид Кларке (David Clarke) (само като информация за тяхната значимост ще спомена, че Тип Лу има около 6000 цитирания, а h-индексът му е повече от 50). Цитатите показват, че предсказаните от модела резултати намират своето експериментално потвърждение.

Източник: Loo, TW; Clarke, DM. Locking Intracellular Helices 2 and 3 Together Inactivates Human P-glycoprotein. JOURNAL OF BIOLOGICAL CHEMISTRY, 289 (1):229-236; 10.1074/jbc.M113.527804 JAN 3 **2014**

Откъс от цитатите:.
"...Molecular dynamic studies, however, predict that IH2/IH3 clamping might inhibit drug-stimulated ATPase activity since conformational changes in IH2 and IH3 during the reaction cycle would alter the relative positions of residues at the IH2/IH3 interface (34, 45).
...
Mutations to Tyr1087 in NBD2 Inhibit Maturation and Activity – In a molecular dynamics simulation study of human P-gp, Tyr1087 was predicted to mediate the key contact between IH3 and NBD2 (34).

To test if Tyr1087 was important for folding or mediating drug stimulation of ATPase activity, we tested the effect of Y1087A, Y1087L, and Y1087F mutations.

....

Molecular dynamic simulation studies of P- glycoprotein predicted that IH2/IH3-NBD2 interactions would be important in driving the necessary conformational changes to couple drug binding to binding and hydrolysis of ATP (34, 45).

......

A detailed molecular simulation study of the IH2, IH3, NBD2 interaction network in human P- gp was recently reported (34). The simulation predicted that rotations of IH2 relative to the adjacent IH3 might be a key feature of the coupling reaction and that a key contact between IH3 and NBD2 was Tyr1087. **In support of these predictions, we found that clamping IH2 to IH3 by oxidative cross-linking of mutant A259C/W803C or mutations to Tyr1087 inhibited activity.** Binding of ATP appeared to influence conformational changes at the IH2/IH3 interface since ATP but not ADP inhibited cross-linking (Fig. 4). Although we previously showed that mutation of the adjacent Phe1086 to Ala also inhibited activity (16), the activity of P-gp was much more sensitive to changes to Tyr1087. For example, mutation of Phe1086 to Leu, Phe, or Trp yielded P-gps with activities similar to the wild- type protein. Mutation of Tyr1087 to Leu severely inhibited activity, while the conservative Y1087F change caused about a 70% reduction in activity. **The molecular simulation study (34) suggested that Tyr1087 interacted with IH3 through a hydrogen bond with Asp805. In support of this prediction** it was recently reported that a P-gp mutant containing the D805C mutation reduced verapamil-stimulated ATPase activity by about 70% but had no effect on the Km for ATP (49).

In this study, we tested our prediction that P-gp requires NBD2 because IH3- NBD2 interactions **(predicted to involve Tyr1087 in NBD2 (34))** are critical for maturation of P-gp during synthesis. In addition, we tested whether cross-linking of IH3 to IH2 would have the opposite effect of cross-linking IH3 to IH1 (16) and cause inhibition rather than stimulation of ATPase activity.

Цитирана работа: (цитат 34). Pajeva, I. K., Hanl, M., and Wiese, M. (2013) Protein contacts and ligand binding in the inward-facing model of human P-glycoprotein. ChemMedChem 8, 748-762.

3. Доказателсто за коректност на идентификация на мястото на свързване на модулатора Tariquidar с П-гликопротеина, направено с моделните изследвания.

Цитатът е в статия, публикувана съвсем наскоро от T. Loo и D. Clarke, известните учени-експериментатори, споменати вече по-горе. Цитирана е работа от 2013 г.

Източник:Tip W. Loo, David M. Clarke, Tariquidar inhibits P-glycoprotein drug efflux but activates ATPase activity by blocking transition to an open conformation, Biochemical Pharmacology, Available online 22 October 2014, ISSN 0006-2952, http://dx.doi.org/10.1016/j.bcp.2014.10.006

Откъс от цитата:
Tight binding of tariquidar might influence A80C/R741C cross-linking because modeling studies suggest that the tariquidar binding site lies close to residues at the extracellular ends of TM segments 1 and 7 [49]. The extracellular ends of TM segments 1 and 7 extend into ECL1 and ECL4, respectively (Fig. 1). Occupation of the tariquidar-binding site may block movement between ECL1 and ECL4 required for A80C/R741C cross-linking.

The tariquidar-binding site was predicted to overlap the proposed R- and H-binding sites [49]. The R- and H-sites were proposed to be the separate binding sites for rhodamine 123 and Hoechst 33342, respectively [50]. **Both the R- and H-sites were proposed to be at the interface between the TMDs but the H-site was located at the inner end (inner site) of the drug-binding pocket (near the inside of the cell) while the R-site was located at the outer end (outer site) of the drug-binding pocket (near the outside of the cell). The tariquidar-binding site was predicted to overlap both the inner and outer sites [49].**

The overlap of tariquidar with the rhodamine- and Hoechst-binding sites may explain why tariquidar was particularly effective in rescuing P-gp processing mutants. We previously showed that rhodamine and Hoechst had additive effects in promoting rescue of P-gp processing mutants [51]. Perhaps tariquidar acts as a particularly effective pharmacological chaperone to rescue P-gp processing mutants such as F804D (Fig. 4C) because it interacts at both the predicted R- and H-sites to have an additive effect on maturation**.**

*Цитирана работа***:** Цитат 49. I.K. Pajeva, K. Sterz, M. Christlieb, K. Steggemann, F. Marighetti, M. Wiese. Interactions of the multidrug resistance modulators tariquidar and elacridar and their analogues with P-glycoprotein. ChemMedChem, 8 (2013), pp. 1701–1713

4. Доказателства за приложимост на моделите структура-активност на модулатори от 3-то поколение, производни на препарата Тарикидар. Те са послужили за рационален синтез на нови и ефективни аналози от различни изследователски групи:

Цитатът е от учени от Harvard Medical School,САЩ отразено в скоро публикувана статия:

Източник:Sprachman M., A. M. Laughney, R.H. Kohler, R. Weissleder. In Vivo Imaging of Multidrug Resistance Using a Third Generation MDR1 Inhibitor. BIOCONJUGATE CHEM., Just Accepted Manuscript • DOI: 10.1021/bc500154c •Publication Date (Web): 07 May 2014

*Откъс от цитата***:**
It has been established that a hydrogen-bonding accepting moiety such as the amide ortho-to the tetrazole in HM30181 is essential for maintaining MDR1 inhibitory activity.[27] Consistent with established pharmacophore models of third generation MDR1 modulators, this derivative was not active for reversing the phenotype of the paclitaxel -resistant cell lines (Table 1).
Цитирана работа: Цитат 27. Globisch, C, I.K. Pajeva, M. Wiese. Structure-Activity Relationships of a Series of Tariquidar Analogs as Multidrug Resistance Modulators, Bioorg. Med. Chem., 2006, 14(5), 1588-1598

5. Доказателство за локализация на местата на свързване R и H, предложени чрез моделни изследвания
Докзателството е от групата на Джофри Ченг, обявен за най-перспективният млад учен на САЩ през 90-те години и първият публикувал кристална структура на П-гликопротеина.

Източник:Martinez L. Arnaud O., Henin E., Tao H., Chaptal V., Doshi R., Andrieu T., Dussurgey, S., Tod M., Pietro AD., Zhang Q., Chang, G., Falson P. Understanding Polyspecificity Within The Substrate-Binding Cavity Of The Human Multidrug Resistance P-Glycoprotein. FEBS JOURNAL, 281 (3):673-682; 10.1111/febs.12613 FEB 2014

Откъс от цитата:"**Notably, as defined, the H site is bordered by residues F299, Y303 and Y306 (Fig. 4A) which have been proposed to be part of it [12].** When considering the residues forming each H and R pocket (Fig. 4B,C), about half are distinct, in agreement with the competition between each drug at concentrations above 2 lM as previously reported [7]. **A recent study on elacridar and tariquidar-based inhibitors of P-gp reached the same conclusions [20].**

Цитирани работи:
Цитат 12. Pajeva I., M. Wiese. Application of *in Silico* Methods to study ABC Transporters Involved in Multidrug Resistance. In : *In Silico Lead Discovery*, Ed. M. Miteva, Bentham Science, 2011, Vol. 1, 144-162. eISBN: 978-1-60805-142-7
Цитат 20. Pajeva, I., K. Sterz, K. Steggemann, F. Marighetti, M. Christlieb, M. Wiese. Interactions of the multidrug resistance modulators tariquidar and elacridar and their analogs with P-glycoprotein. *ChemMedChem*, 2013, 8 (10), 1701–1713.

6. Доказателство за коректност на роля на предсказани от модели структурни признаци на биологически активни съединения

Доказателството е от международен екип от учени, който усилено работи в областта на изследвания на П-гликопротеина.

Източник: C. Vieira, N. Duarte, M.A. Reis, G. Spengler, A. M. Madureira, J. Molnár, M-J. U. Ferreira, Improving the MDR reversal activity of 6,17-epoxylathyrane diterpenes, Bioorganic & Medicinal Chemistry, Available online 17 October 2014, ISSN 0968-0896, http://dx.doi.org/10.1016/j.bmc.2014.09.041.

Откъс от цитата: These results corroborate the importance of aromatic residues in the lathyrane scaffold but they also are **in agreement with the assumption that this structural feature is not essential for the activity.** [19]

Цитирана работа: Цитат 19. M. Wiese, I.K. Pajeva. Curr. Med. Chem., 8 (2001), p. 685

ДОПЪЛНИТЕЛНИ ДОКАЗАТЕЛСТВА ЗА КОРЕКТНОСТ И ПРИЛОЖИМОСТ НА МОДЕЛНИТЕ ИЗСЛЕДВАНИЯ
(въз основа на резултати от собствени изследвания)

Те са отразени в няколко наши публикации, в които се комбинират моделни с експериментални изследвания на колектива (екип от учени, които синтезират, тестират биоактоивните съединения и моделират). В изброените публикации изведените модели са използвани като база за насочен синтез на нови биоактивни съединения и, по такъв начин, те валидизират получените моделни резултати.

1. Доказателство за коректно прогнозирана активност на съединение с QSAR модел за серия от инхибитори на ензима УДФ-глюкуронозилтрансфераза :

Едно от първите експериментални доказателства на предсказаните от модел зависимости структура-активност е направено от колеги от групата по молекулен дизайн към Института по молекулярна биология - БАН, оглавявана тогава от акд. Е. Головински.

Моделът е публикуван в съвместна статия (номер 11 съгласно приложения списък на публикациите):
11. Naydenova Z.L., K. Grancharov, D. Alargov, E.Golovinsky, I. Stanoeva, L. Shalamanova, I.Pajeva: Inhibition of UDP-glucuronosyltransferase by 5'-O-amino acid and oligopeptide derivatives of uridine: structure-activity relationships, Zeitshrift fuer Naturforschung, 1998, 53c, 173-181.

В статията авторите докладват синтез и резултати от фармакологичен тест на ново съединение с модификация на структурата, предложена въз основа на модела. Тази модификация потвърждава важността на един от структурните признаци в изследваната серия за начина на взаимодействие на съединенията с ензима.

2. Доказателства за приложимост на моделите структура-активност на модулатори от 3-то поколение, производни на препарата Тарикидар. Те са послужили за рационален синтез на нови и ефективни аналози от различни изследователски групи:

Изследванията са направени от колектив от синтетици и фармаколози-експериментатори от Университета в Бон, Гер,мания. Съгласно приложния списък на научните трудове, това са:

36. Mueller, H., I. Pajeva, C. Globisch, M. Wiese. Functional assay and structure-activity relationships of new 3rd generation P-glycoprotein inhibitors. Bioorg. Med. Chem., 2008, 16, 2456-2470.
39. Klinkhammer W., H. Müller, I. K. Pajeva, M. Wiese. Synthesis and biological evaluation of a small molecule library of multidrug resistance modulators, Bioorg. Med. Chem., 2009, 17(6), 2524-2535.
46. Pick, A., H. Müller, R. Mayer, B. Haenisch, I.K. Pajeva, M. Weight, H. Bönisch, C. E. Müller, M. Wiese. Structure-Activity Relationships of Flavonoids ss Inhibitors of Breast Cancer Resistance Protein (BCRP). Bioorg. Med. Chem., 2011, 19(6), 2090-2102.
52. Pajeva I., K. Sterz, K. Steggemann, F. Marighetti, M. Christlieb, M. Wiese. Interactions of the multidrug resistance modulators tariquidar and elacridar and their analogs with P-glycoprotein. ChemMedChem., 2013, 8 (10), 1701–1713.

Цитирания от фирми
1. Accelrys, Inc., 5005 Wateridge Vista Drive, San Diego, CA 92121, USA

Откъс от цитати:

A data set of compounds targeting a specific binding site has been recently reported by Döppenschmitt et al. The IC50 was determined by radioligand-binding assay in which [3H]-verapamil was displaced by other drugs in a concentration-dependent fashion (6). **Based on this data set, Pajeva and Wiese developed a model for drugs that bind to the verapamil binding site on the P-gp (7).** The model was developed with the software GASP. Two of the most rigid members of this set, vinblastine and rhodamine 123, were selected as the templates and a common feature pharmacophore model was generated by aligning the rest of the molecules with the templates.

The top ten hypotheses are clustered and the representative hypotheses from each cluster are shown in Figure 1. For clarity, all the models are mapped onto rhodamine 123. These models are similar. The first and third differs in the relative orientation of the hydrogen bond acceptor and the aliphatic hydrophobe. In one case they point backward and in another case they point outward. This is due to the free rotation of biaryl carbon-carbon bond. The major difference between the second and fourth models is the location of the hydrogen bond acceptor feature. Comparing the third and the fourth models shows that either a hydrogen bond acceptor or a hydrogen bond donor can map to the same amino group. **In their paper, Pajeva and Wiese very insightfully pointed out that the HBD feature can double as an HBA feature if the protonation state of the functional group bearing that feature changes. The current observation is very similar to their results.**

*Цитирана работа:*Цитат 7. I. K. Pajeva and M. Wiese, J. Med. Chem., 2002, 45, 5671.

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2. MedKoo Biosciences, Research Triangle Park, North Carolina, USA

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Description of Tariquidar: Tariquidar, also known as XR9576, is a P-glycoprotein inhibitor undergoing research as an adjuvant against multidrug resistance in cancer. Tariquidar non-competitively binds to the p-glycoprotein transporter, thereby inhibiting transmembrane transport of anticancer drugs. Inhibition of transmembrane transport may result in increased intracellular concentrations of an anticancer drug, thereby augmenting its cytotoxicity. Check for active clinical trials or closed clinical trials using this agent. (NCI Thesaurus). (last updated: 10/06/2014)

Google™ Custom Search
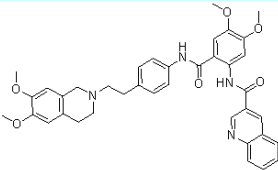Search
(Keyword; CAS#; MedKoo Cat#)

MedKoo Cat#: 202820

Name: Tariquidar

CAS#: 206873-63-4

Synonym: XR 9576; XR9576; XR-9576; D06008.

IUPAC/Chemical name: N-[2-[[4-[2-(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)ethyl]phenyl]carbamoyl]-4,5-dimethoxyphenyl]quinoline-3-carboxamide

Chemical structure	Theoretical analysis

MedKoo Cat#: 202820
Name: Tariquidar
CAS#: 206873-63-4
Chemical Formula: C38H38N4O6
Exact Mass: 646.27913
Molecular Weight: 646.73
Elemental Analysis: C, 70.57; H, 5.92; N, 8.66; O, 14.84

More information about tariquidar

According to news published on 19 May 2003, QLT has discontinued its Phase III trials of tariquidar, licensed from the UK's Xenova, as an adjunctive treatment for patients with non-small cell lung cancer. Tariquidar had been tipped for a launch in 2005, providing all went well with the pivotal trials program, and at one time was forecast to achieve annual sales of $500 million or more at its peak.

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