In memoriam Sofija Kanopkaitė (1926 – 2024)

MATEMATINIO MODELIAVIMO UŽDAVINYS ONKOLOGIJOJE nr.1

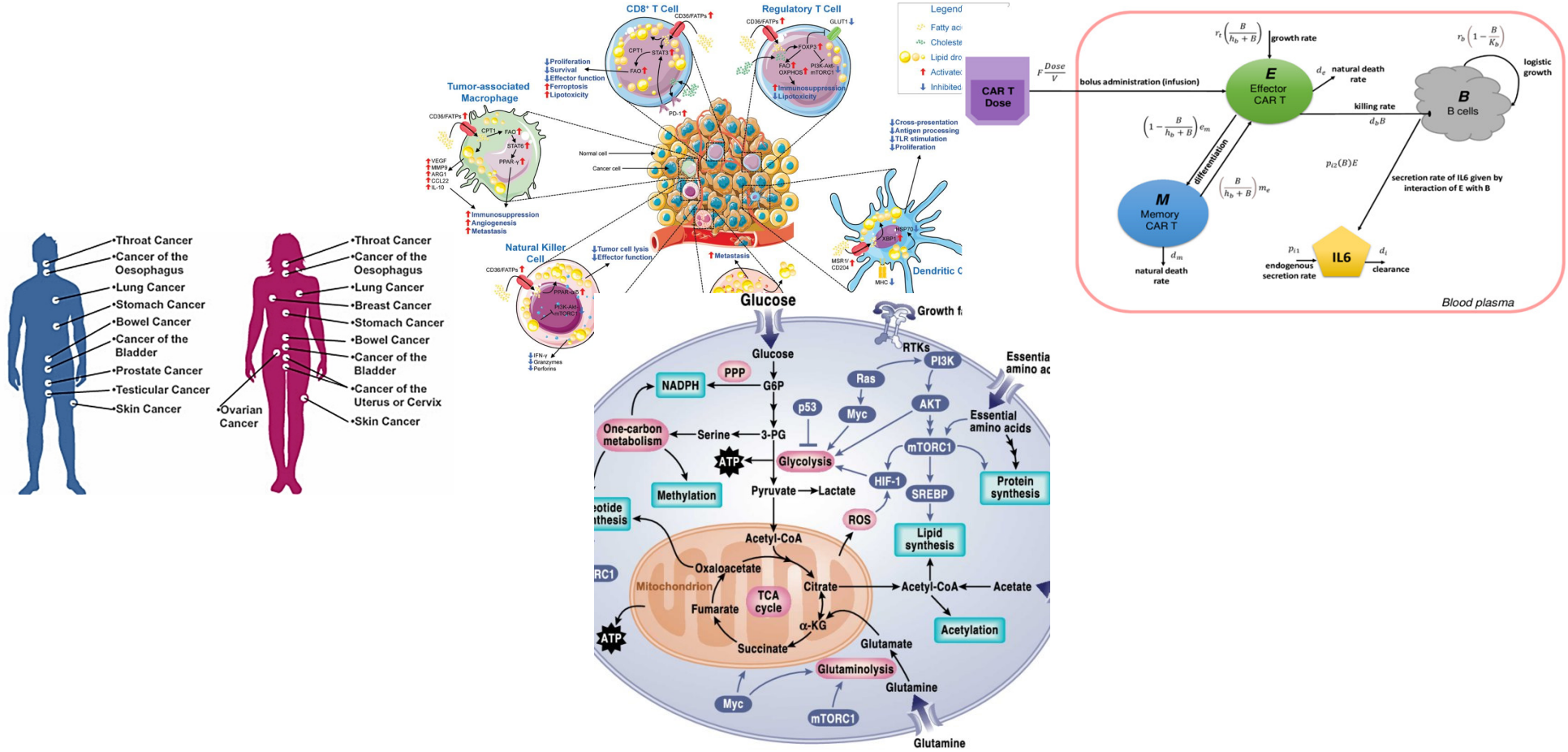
Kęstutis K.Urba

USA NCI - The Ras initiative - international project

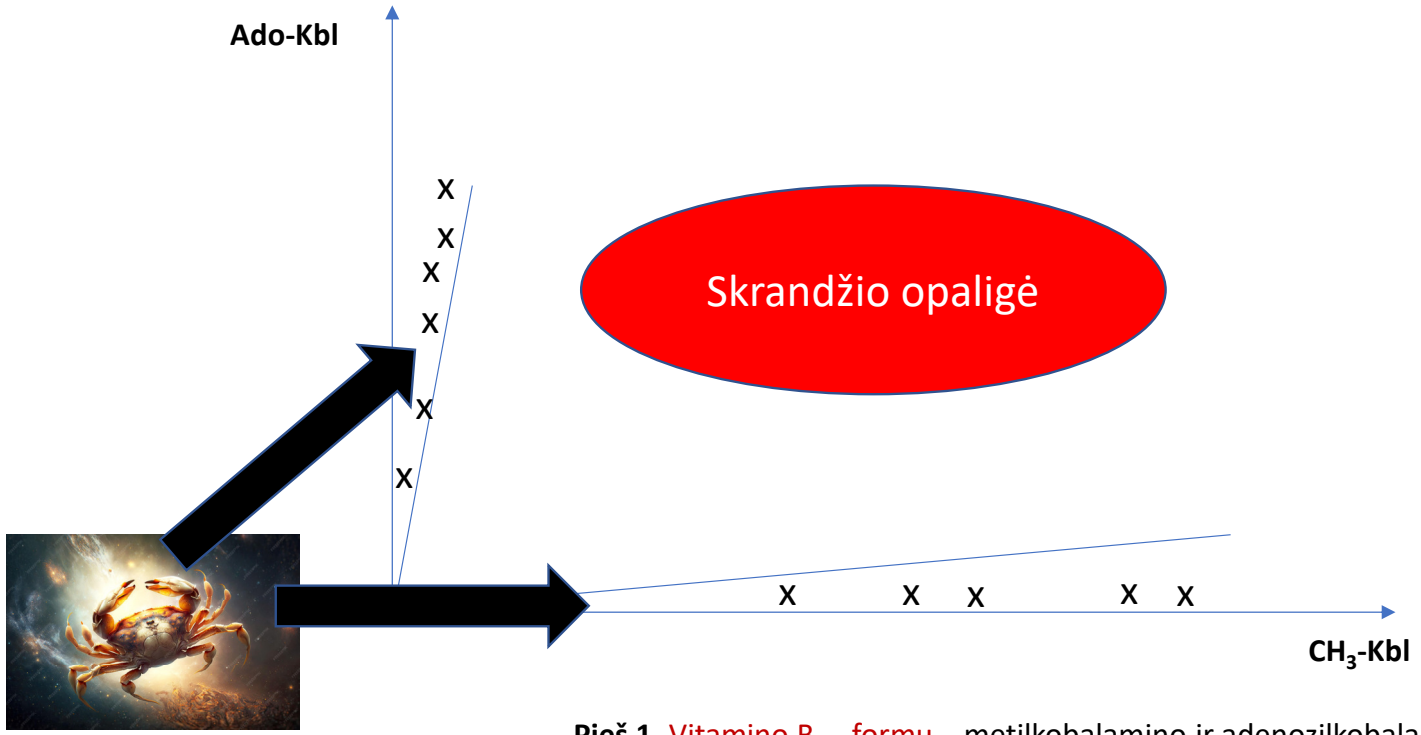
2025 m. rugsėjo mėn. 23 d. VGTU MMK

urbascience@gmail.com

ĮVADAS: modeliuotino objekto sudėtingumas

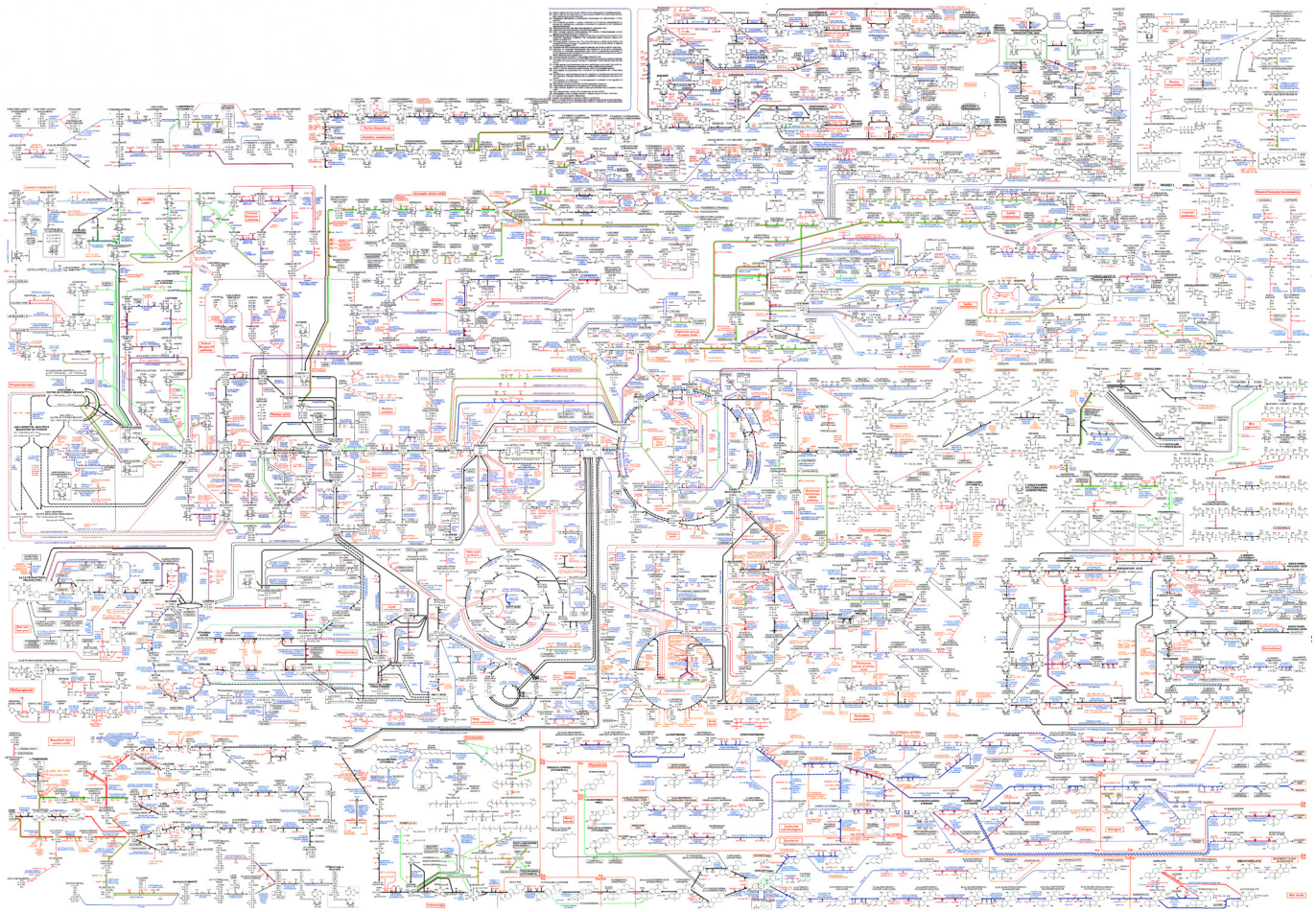


Empirinių duomenų analizės būdu gautas diagnostinis algoritmas - 1989 metai, išradimas 1992 (akad.S.Kanopkaitė ... K.Urba)

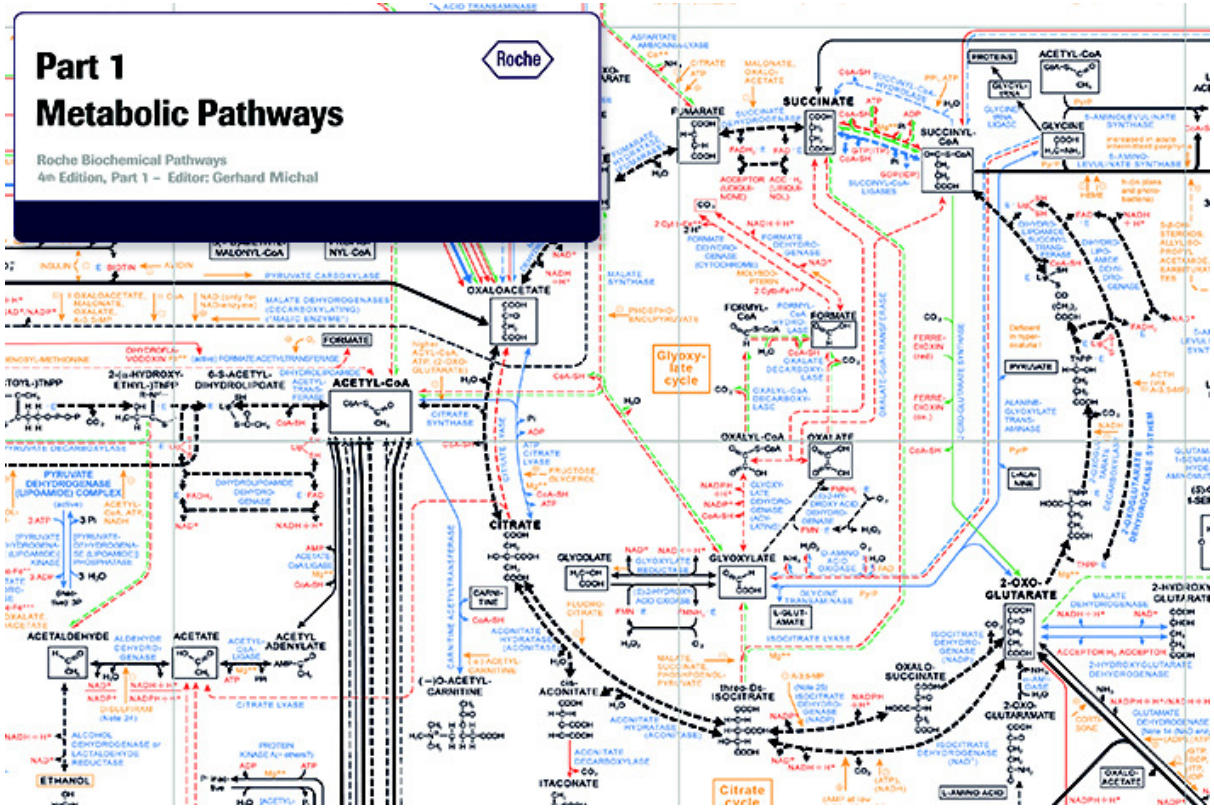


Pieš 1. Vitamino B_{12} formų – metilkobalamino ir adenozilkobalamino kraujo ląstelėse pasiskirstymas žmonių sergančių vėžiu (**x**) bei skrandžio opalige

Medžiagų apykaitos žemėlapis



ROCHE žemėlapis raiškesniame mastelyje



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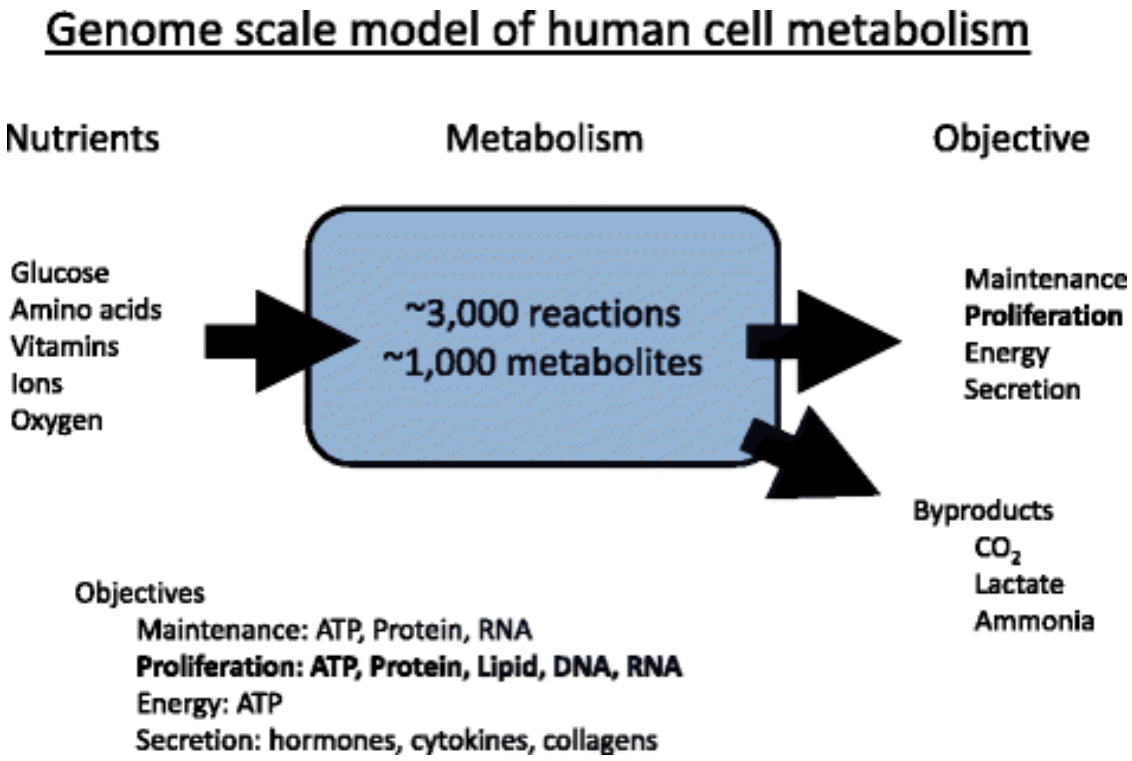
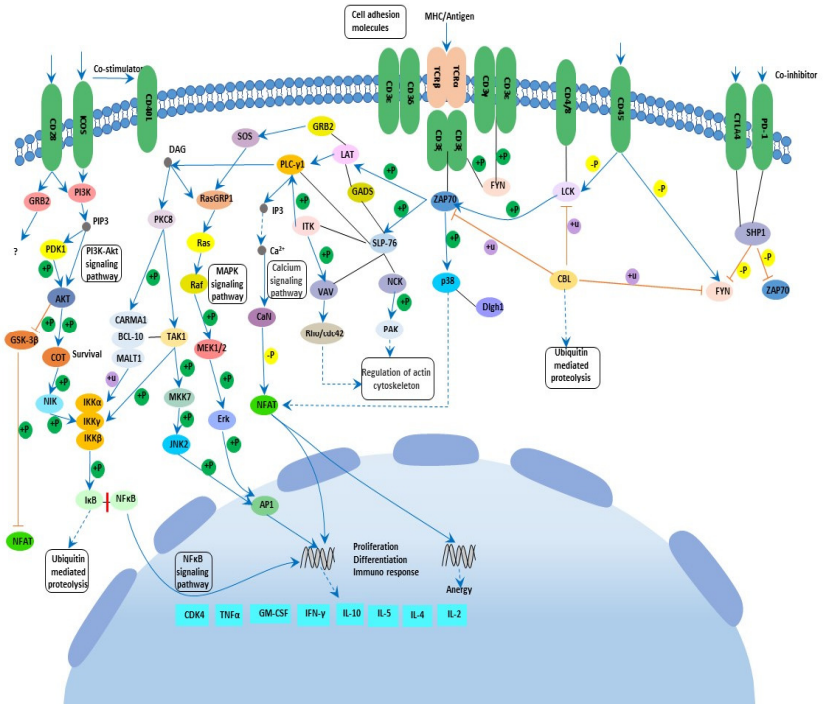
Tyrinėjamos apykaitos apimtys (Elke Katrin Markert, Alexei Vazquez, 2015)



Signalų perdavimas transkripcijai nuo membranos



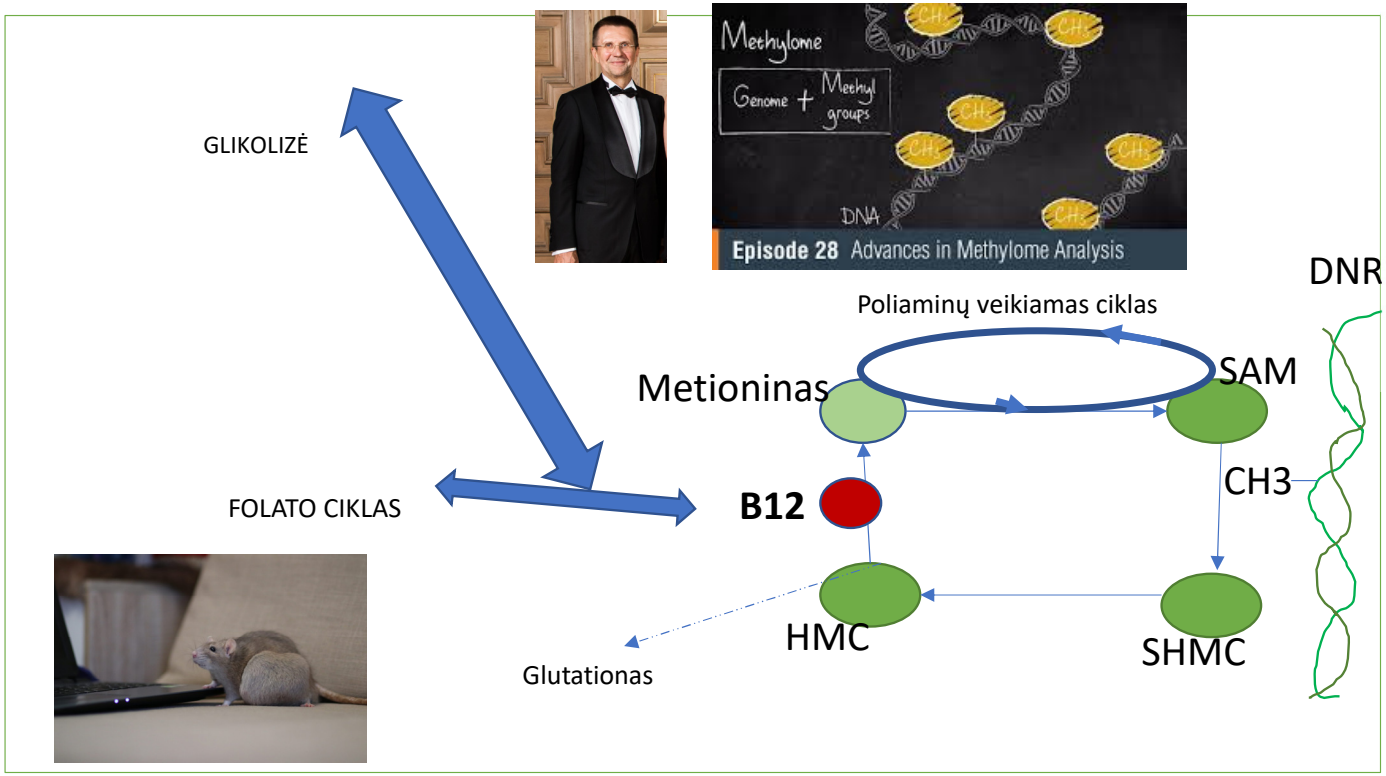
1. Eksposomika (Ex),
2. Genomika (G),
3. Signalomika (S),
4. Cistromika (C),
5. Transkriptomika (TR),
6. Proteomika (P),
7. Lipidomika (L) *(Smirnov D. et al. 2021),*
8. Metalomika (Mtl) (*Zhang Y., et al, 2022*), (*Wolters DA., et al, 2012*)
9. Metabolomika (M)
10. Epigenomika (Ep),
11. Imunomika (Im) *(Nevedomskaya E, Haendler B. 2022*
12. **Fliuksomika** (F)

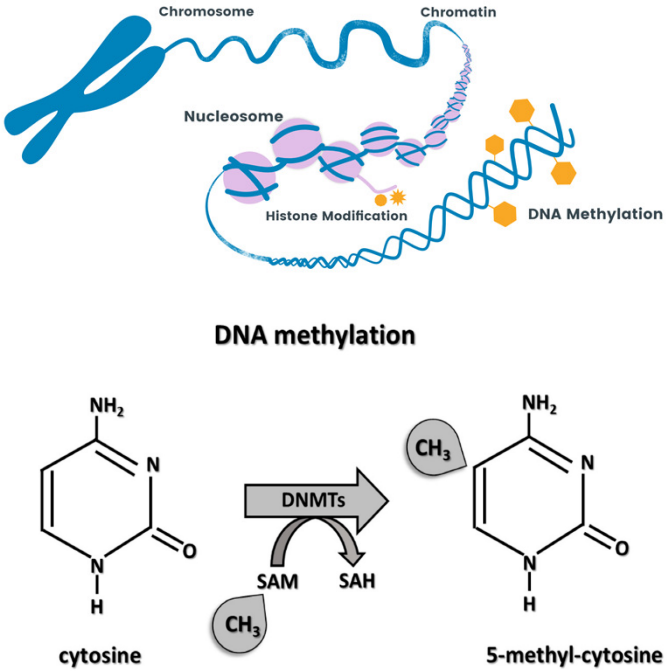
$$\{TUMOR^{OEx}\}_t = U_k Ui_j f_{k,ij}(Ex_{\xi 1}, G(K)_{\xi 2}, S(K)_{\xi 3}, C(K)_{\xi 4}, Tr(K)_{\xi 5}, P(K)_{\xi 6}, L(K)_{\xi 7}, Mtl(K)_{\xi 8}, M(K)_{\xi 9}, F(K)_{\xi 10}, Ep(K)_{\xi 11}, I_{\xi 12})$$

I dalis. Vienanglių fragmentų – „1C“ apykaita ir modeliavimas: Duke universtetas, Kornelio universitetas, Trento (Italija), Bordo (Prancūzija), Brisbenas (Australija)...

1. Ducker GS, Rabinowitz JD. One-Carbon Metabolism in Health and Disease. Cell Metab. 2017 Jan 10;25(1):27-42. doi: 10.1016/j.cmet.2016.08.009. Epub 2016 Sep 15. PMID: 27641100; PMCID: PMC5353360. https://pubmed.ncbi.nlm.nih.gov/27641100/
2. Clare CE, Brassington AH, Kwong WY, Sinclair KD. One-Carbon Metabolism: Linking Nutritional Biochemistry to Epigenetic Programming of Long-Term Development. Annu Rev Anim Biosci. 2019 Feb 15;7:263-287. doi: 10.1146/annurev-animal-020518-115206. Epub 2018 Nov 9. PMID: 30412672. https://pubmed.ncbi.nlm.nih.gov/30412672/
3. Nijhout HF, Reed MC, Budu P, Ulrich CM. A mathematical model of the folate cycle: new insights into folate homeostasis. J Biol Chem. 2004 Dec 31;279(53):55008-16. doi: 10.1074/jbc.M410818200. Epub 2004 Oct 20. PMID: 15496403. https://pubmed.ncbi.nlm.nih.gov/15496403/
4. Reed MC, Nijhout HF, Neuhouser ML, Gregory JF 3rd, Shane B, James SJ, Boynton A, Ulrich CM. A mathematical model gives insights into nutritional and genetic aspects of folate-mediated one-carbon metabolism. J Nutr. 2006 Oct;136(10):2653-61. doi: 10.1093/jn/136.10.2653. PMID: 16988141. https://pubmed.ncbi.nlm.nih.gov/16988141/
5. Ulrich CM, Reed MC, Nijhout HF. Modeling folate, one-carbon metabolism, and DNA methylation. Nutr Rev. 2008 Aug;66 Suppl 1:S27-30. doi: 10.1111/j.1753-4887.2008.00062.x. PMID: 18673484. https://pubmed.ncbi.nlm.nih.gov/18673484/ https://sites.duke.edu/metabolism/files/2015/11/08nutrrev.pdf
6. Duncan TM, Reed MC, Nijhout HF. A population model of folate-mediated one-carbon metabolism. Nutrients. 2013 Jul 5;5(7):2457-74. doi: 10.3390/nu5072457. PMID: 23857220; PMCID: PMC3738981. https://pmc.ncbi.nlm.nih.gov/articles/PMC3738981/
7. Sadre-Marandi F, Dahdoul T, Reed MC, Nijhout HF. Sex differences in hepatic one-carbon metabolism. BMC Syst Biol. 2018 Oct 24;12(1):89. doi: 10.1186/s12918-018-0621-7. PMID: 30355281; PMCID: PMC6201565. https://pubmed.ncbi.nlm.nih.gov/30355281/
8. Kim R, Nijhout HF, Reed MC. One-carbon metabolism during the menstrual cycle and pregnancy. PLoS Comput Biol. 2021 Dec 16;17(12):e1009708. doi: 10.1371/journal.pcbi.1009708. PMID: 34914693; PMCID: PMC8741061. https://pubmed.ncbi.nlm.nih.gov/34914693/
9. Scotti M, Stella L, Shearer EJ, Stover PJ. Modeling cellular compartmentation in one-carbon metabolism. Wiley Interdiscip Rev Syst Biol Med. 2013 May-Jun;5(3):343-65. doi: 10.1002/wsbm.1209. Epub 2013 Feb 13. PMID: 23408533; PMCID: PMC4437664. https://pmc.ncbi.nlm.nih.gov/articles/PMC4437664/
10. Mazat JP. One-carbon metabolism in cancer cells: a critical review based on a core model of central metabolism. Biochem Soc Trans. 2021 Feb 26;49(1):1-15. doi: 10.1042/BST20190008. PMID: 33616629. https://pubmed.ncbi.nlm.nih.gov/33616629/

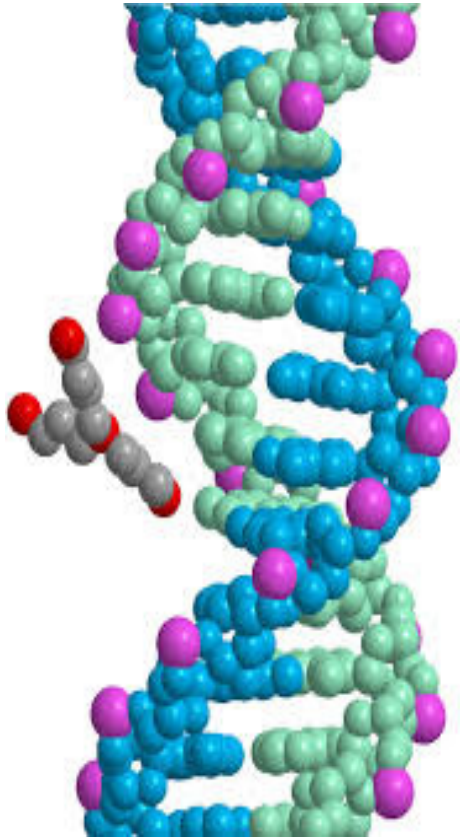
Vitaminas B12-Metionino ciklas: „**One-carbon Metabolism at the Root of Carcinogenesis**“ (Adam Rosenzweig, John Blenis, and Ana P. Gomes, Meyer Cancer Center, NYC. Beyond the Warburg Effect: How Do Cancer Cells Regulate One-Carbon Metabolism?, 2018)



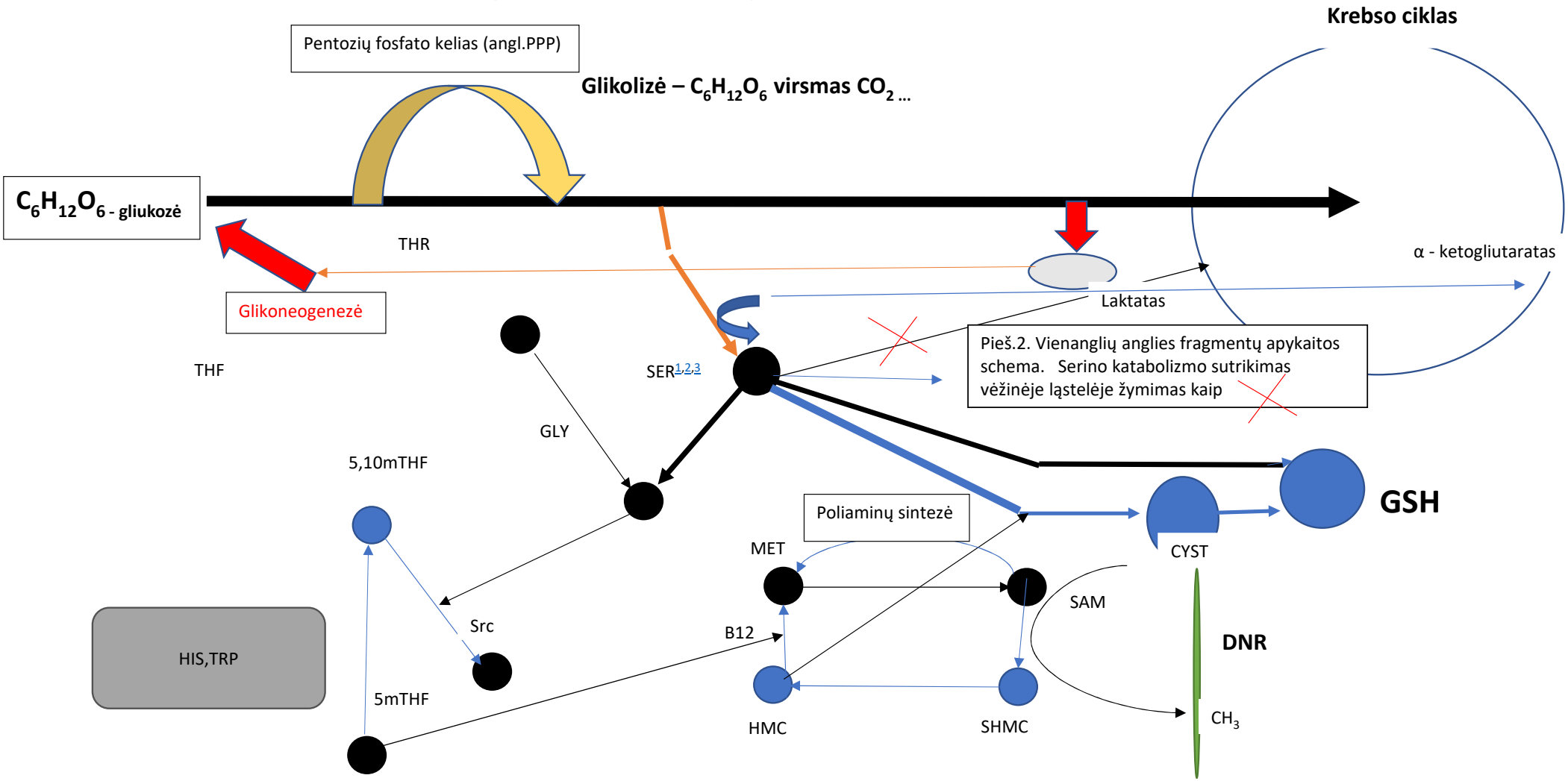


CH3 - Vienanglių fragmentų apykaita. Glikolizės ... metu $C_6H_{12}O_6$ virsta CO_2 arba jos anglies atomas iš β pozicijos nukeliauja iki CH_3

Poliaminai suaktyvina „DNR raišką“



VIENANGLIŲ FRAGMENTŲ APYKAITOS SCHEMA



Pieš.2. Vienanglių anglies fragmentų apykaitos schema. Serino katabolizmo sutrikimas vėžinėje ląstelėje žymimas kaip

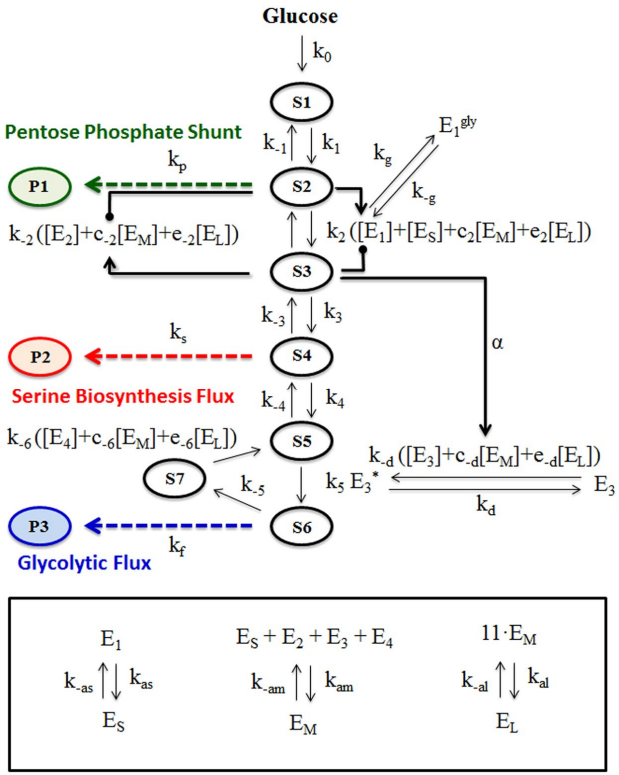
Matematikai modeliuoja biologinius-molekulinius procesus

1. Glikolizės matematinis modeliavimas
https://www.nature.com/articles/s41598-018-20348-7
https://www.nature.com/articles/s41598-019-39901-z
2. Oksidacinio fosforilinimo (tolesnio energijos gaminimo ATF pavidale) modeliavimas
https://www.mdpi.com/2073-4409/11/24/4020
4. Vienanglių fragmentų, apjungiant glikolizės procesą modeliavimas
https://academic.oup.com/jn/article/136/10/2653/4746711
Mathematical Models of Folate-Mediated One-Carbon Metabolism H. F. Nijhout,* M. C. Reed,† and C. M. Ulrich https://sites.duke.edu/metabolism/files/2015/11/08litwack.pdf
5. Metionino ciklo matematinis modeliavimas
https://www.researchgate.net/publication/8991844_A_Mathematical_model_of_the_methionine_cycle
6. Poliaminų sintezės matematinis modeliavimas
https://www.researchgate.net/publication/7071327_Mathematical_Modeling_of_Polyamine_Metabolism_in_Mammals
8. Imuninės sistemos matematinis modeliavimas
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6579737/
9. Biocheminių tinklų matematinis modeliavimas Effect of substrate competition in kinetic models of metabolic networks – ScienceDirect https://ars.els-cdn.com/content/image/1-s2.0-S0014579313004833-mmc1.pdf

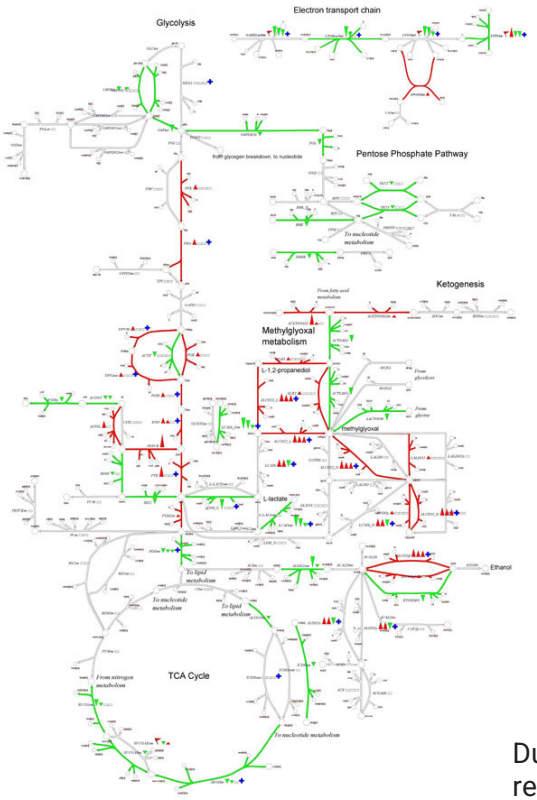
Matematiniai modeliai: tarp įmanomų modelinių uždavinių ir tarp tų, kuriuos reikia spręsti - atskiri reakcijų tinklo fragmentai

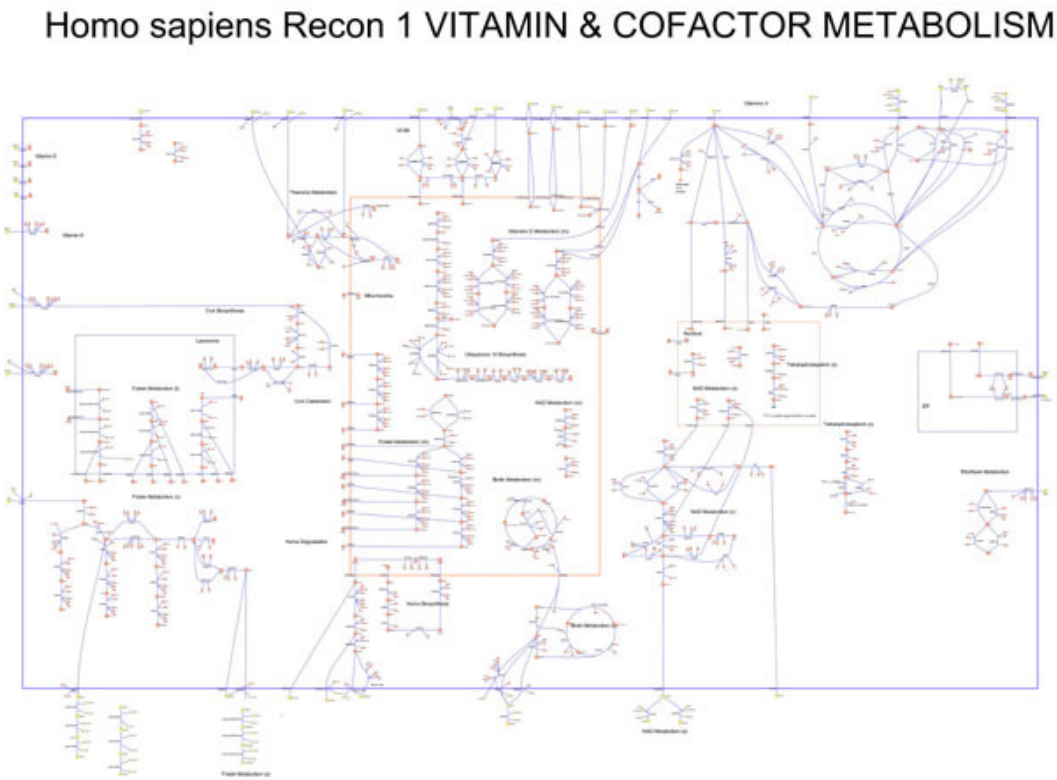
$$dA(t)/d(t) = kAAex - VfA(t)\ KmA + A(t)$$
$$dA1(t)/d(t) = VfA(t)\ KmA + A(t) - VfA1(t)\ KmA\ 1 + B1(t)\ KmB + A1(t)$$
$$dA2(t)/\ d(t) = VfA1(t)\ KmA\ 1 + B1(t)\ KmB + A1(t) - VfA2(t)\ KmA + A2(t)$$
$$dB(t)/d(t) = kBBex - VfB(t)\ KmB + B(t)$$
$$dB1(t)/d(t) = VfB(t)\ KmB + B(t) - VfB1(t)\ KmB\ (1 + A1(t)\ KmA + B1(t)$$
$$dB2(t)/d(t) = VfB1(t)\ KmB\ (1 + A1(t)\ KmA + B1(t) - VfB2(t)\ KmB + B2(t)$$

[1-s2.0-S0014579313004833-mmc1.pdf]



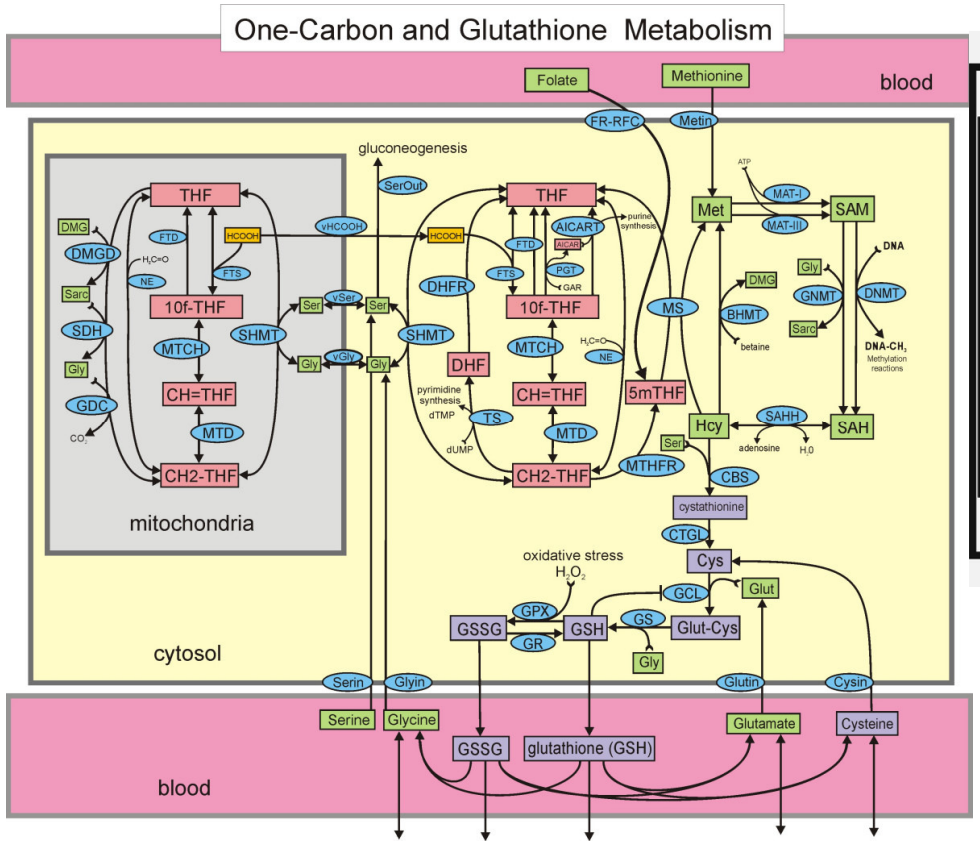
Balanso modelis (Recon1, Recon2)

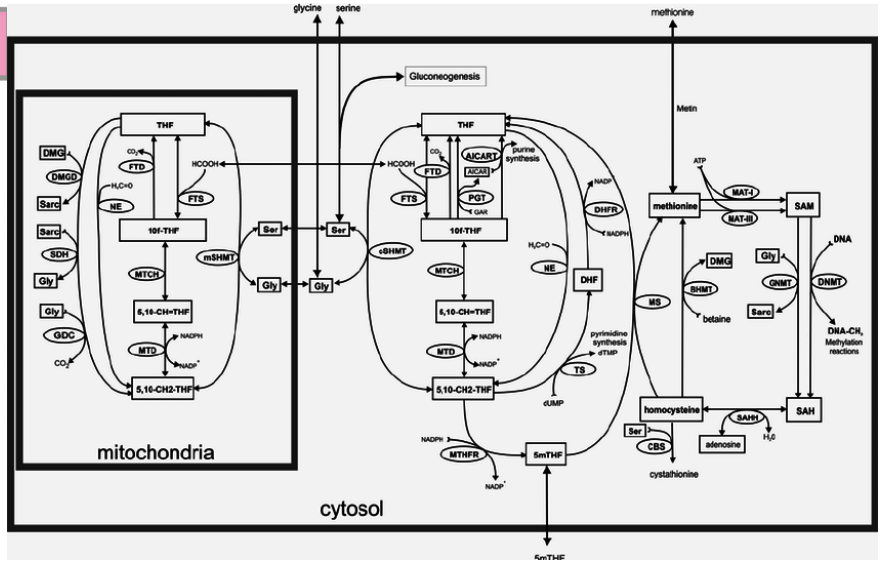




Duarte NC, Becker SA, Jamshidi N, Thiele I, Mo ML, Vo TD, Srivas R, Palsson BØ. Global reconstruction of the human metabolic network based on genomic and bibliomic data. Proc Natl Acad Sci U S A. 2007 Feb 6;104(6):1777-82. doi: 10.1073/pnas.0610772104. Epub 2007 Jan 31.

1C apykaitos modeliavimas folatų, metionino ciklo ir radikalų eliminavimo schemoje

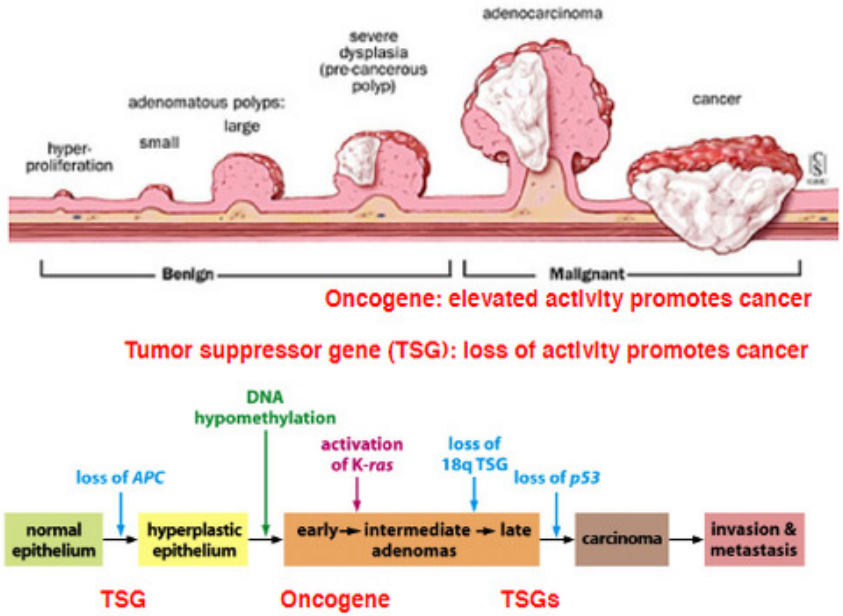


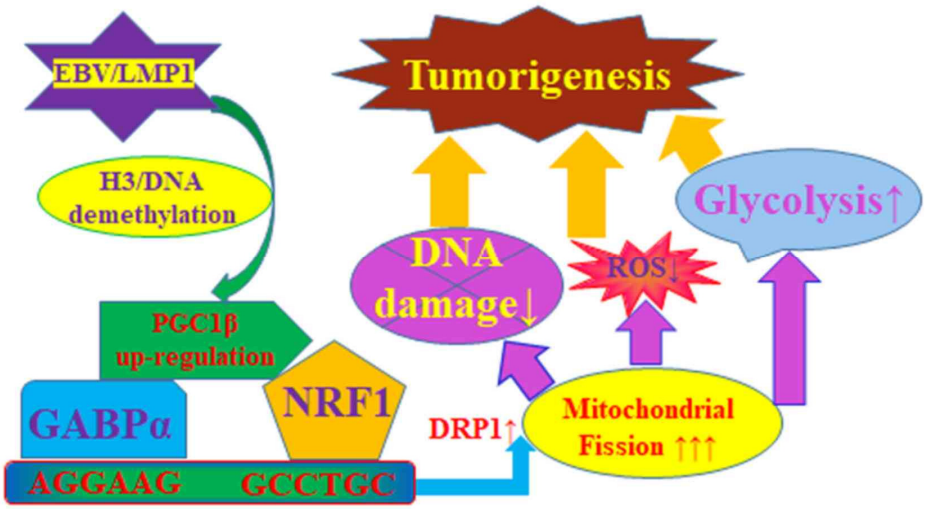


2004-2008 metų modeliai: Nijhout… Reed et al. (2007)

„Įdomu tai, kad vienanglių fragmentų metabolizmo genai *SHMT2* ir *MTHFD2* , koduojantys mitochondrijų serino hidrometiltransferazę ir metilen-tetrahidrofolato dehidrogenazę / ciklohidrolazę, buvo nustatyti tarp 50 dažniausiai didžiausios raiškos genų“

II dalis. TUMORIGENEZĖS MODELIS



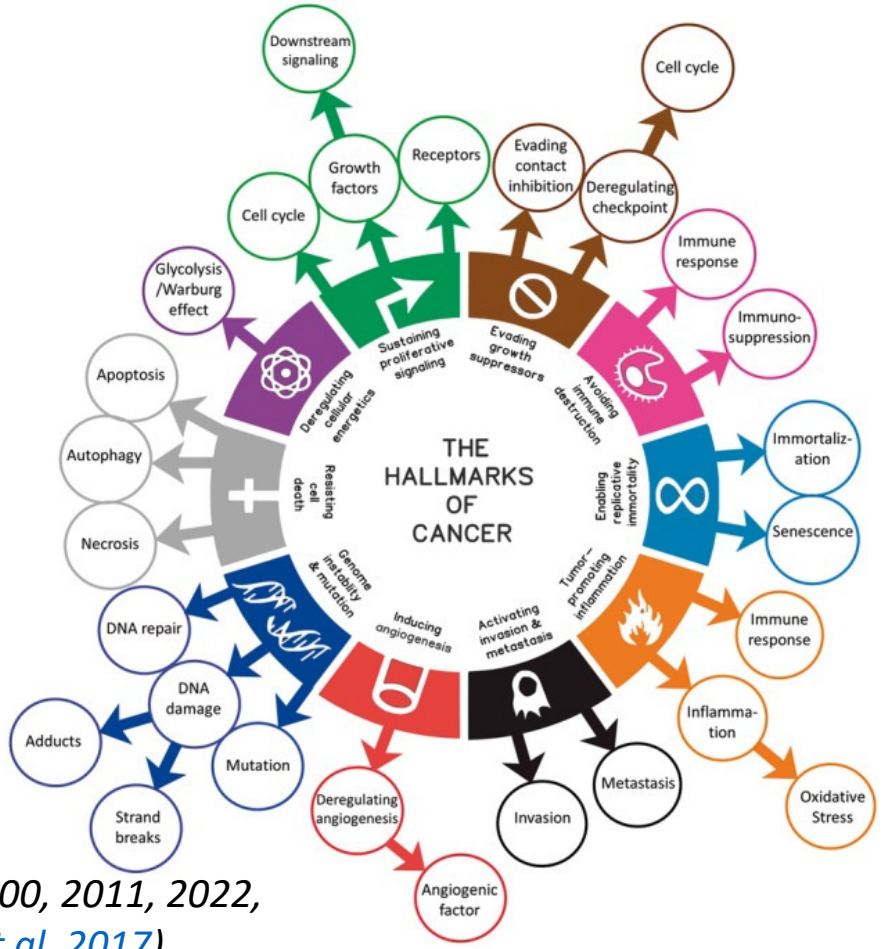


Trys vėžio aprašo terminijos lygmenys

- KLINIKINIS (TNM klasifikacija)
- BIOLOGINIS
- MOLEKULINIS-ELEMENTARIŲJŲ DALELIŲ

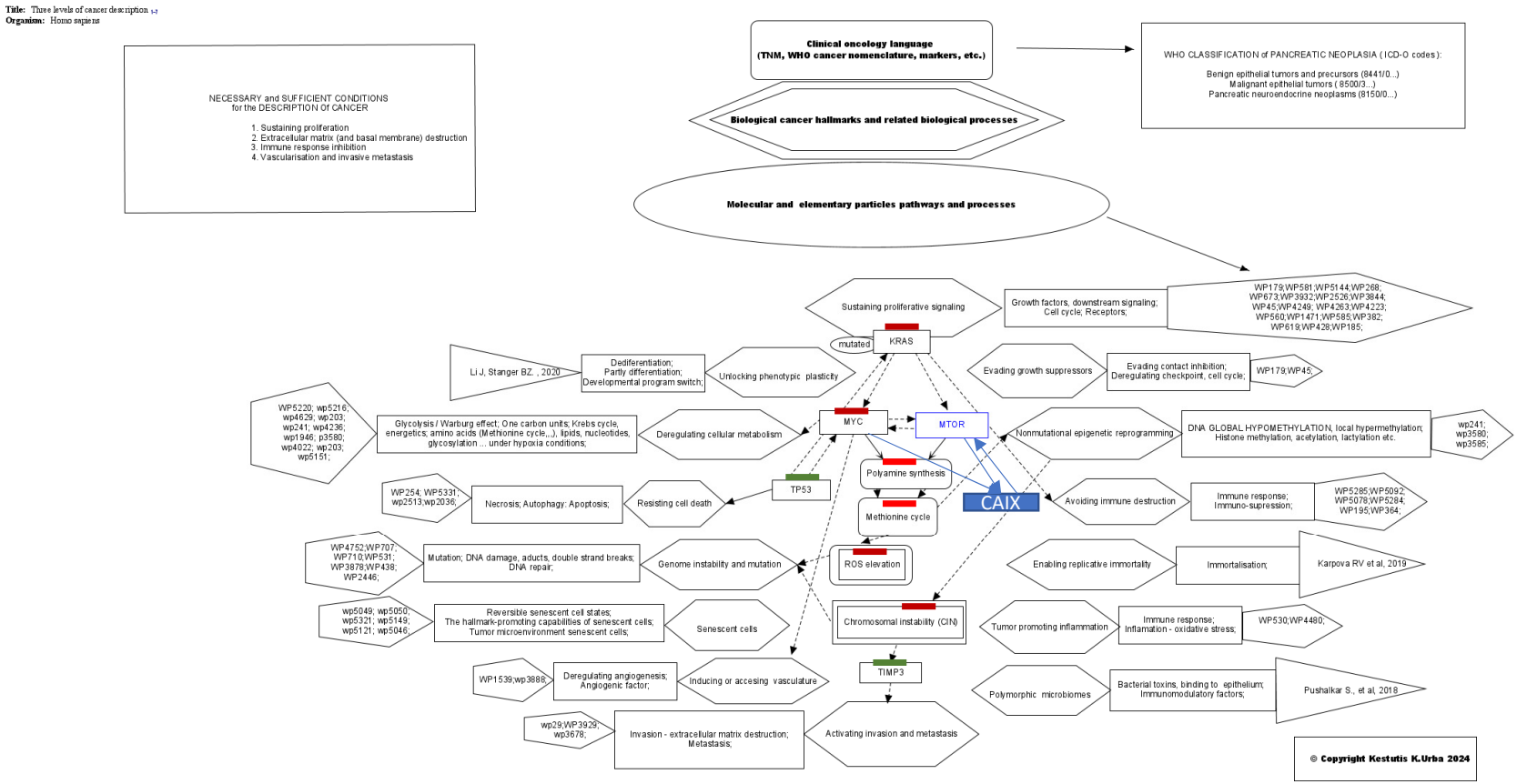
Būtinos ir pakankamos naviko aprašo sąlygos:

I. Spartesnė piktybinių ląstelių sankaupos proliferacija nei aplinkinio audinio
II. Tarpląstelinių jungčių, bazalinės membranos ir ekstraceliuliarinio matrikso griovimas bei ardymas
III. Naviko angiogenezė-kapiliarizacija ir metastazavimas
IV. Imuninio atsako slopinimas

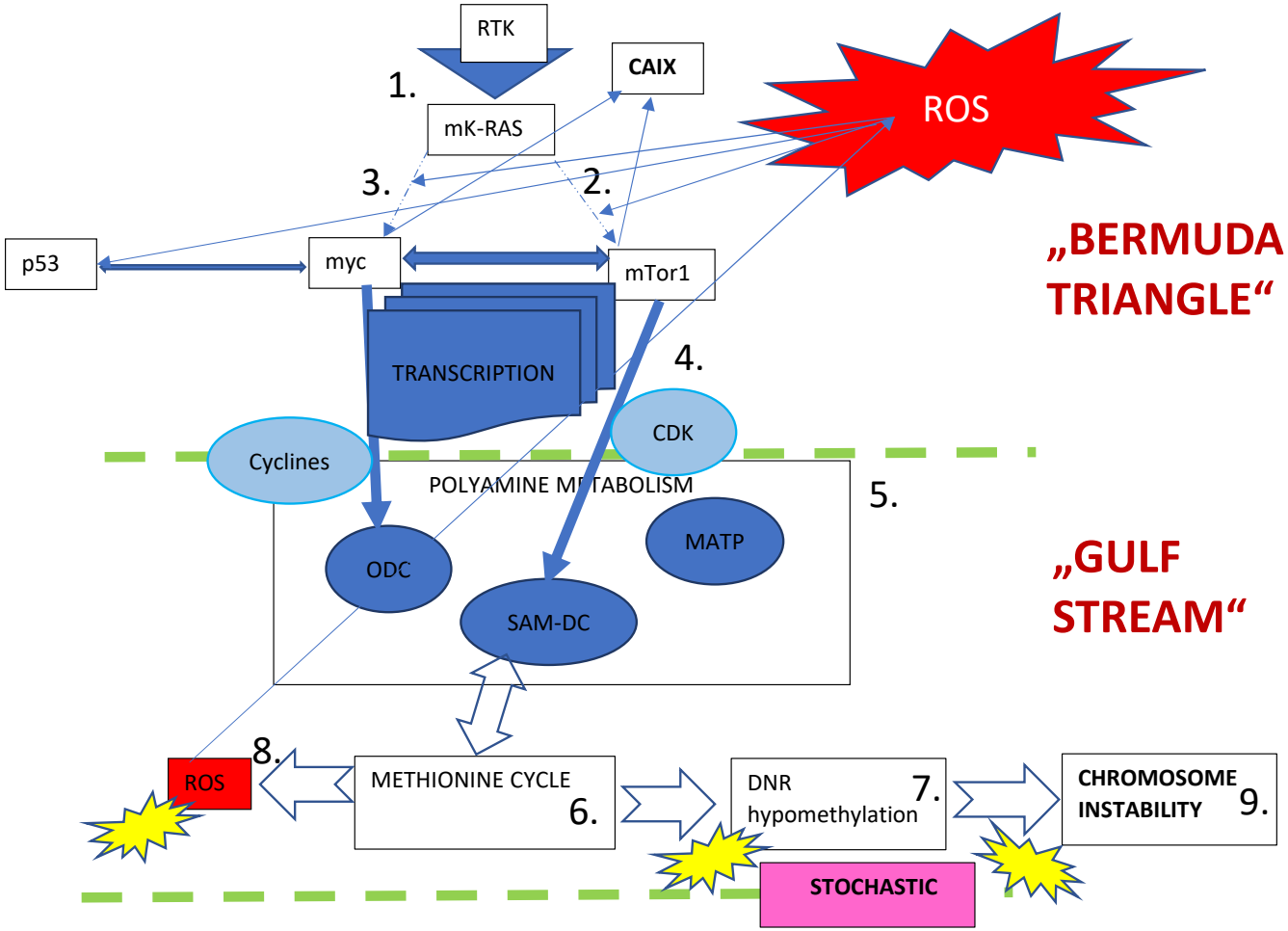


Hanahan-Weinberg 2000, 2011, 2022,
(Baker S, Ali I, Silins I, et al. 2017)

Molekulinio ir biologinio lygmenų sąryšis vėžio apraše



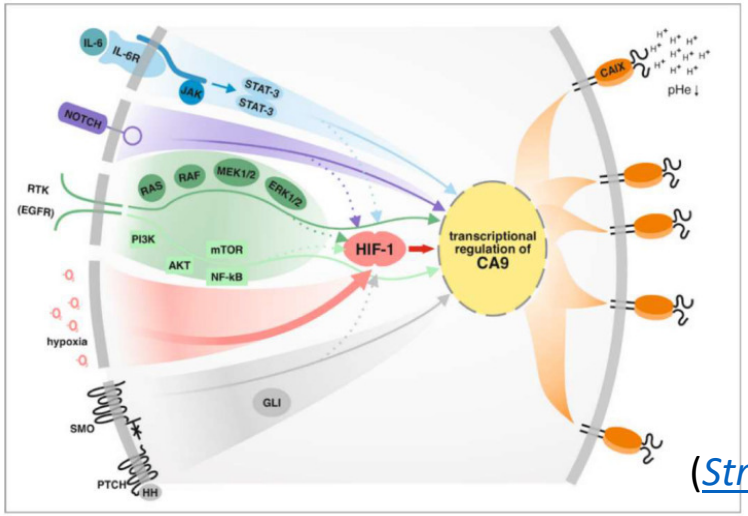
CELL “undruggable” mK-ras INVOLVED CARCINOGENESIS and MALIGNIZATION SCENARIO (K.Urba, 2022, © copyright)



mK-ras is not only „driver“ but long distance long time stochastic „trigger“ too! *Stochasticity*:

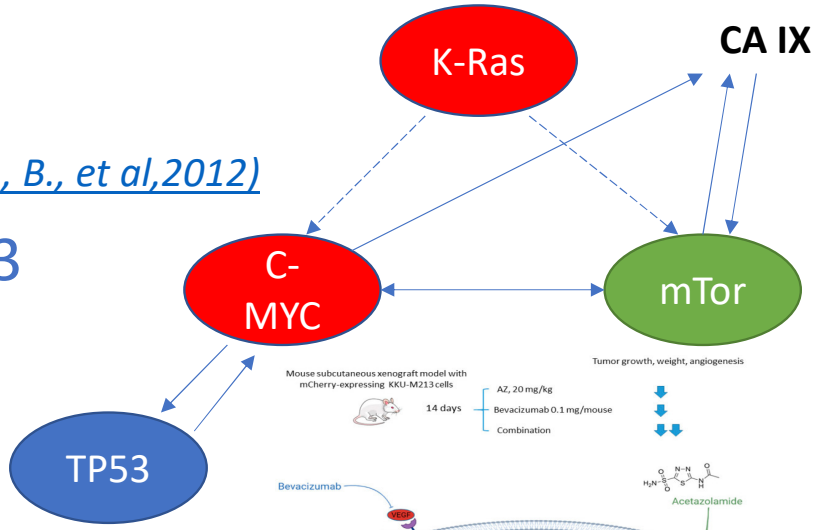
Keletas onkogenų, augimo veiksnių, supresorių

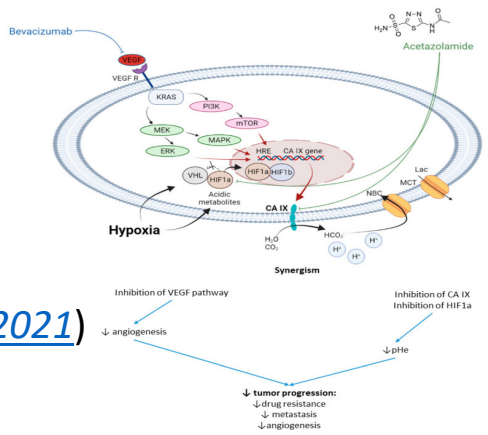
- Onkogenas K-ras
- Onkogenas C-myc
- Onkogenų slopiklis (supresorius) Tp53
- Augimo faktorius kompleksas mTor



(Strapcova S., et al, 2020)

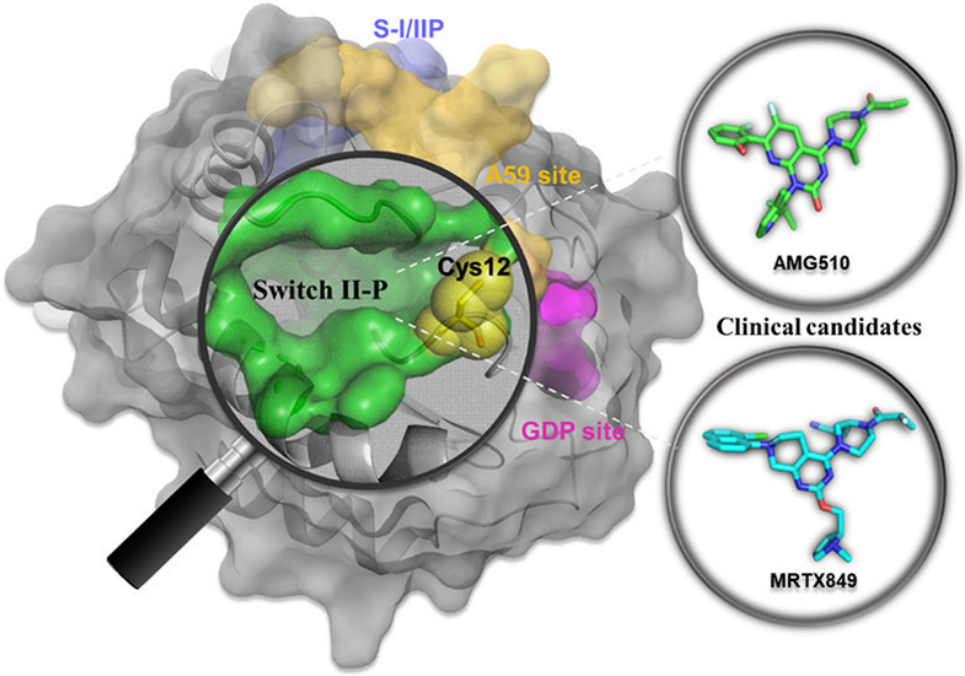
(Kim, B., et al,2012)

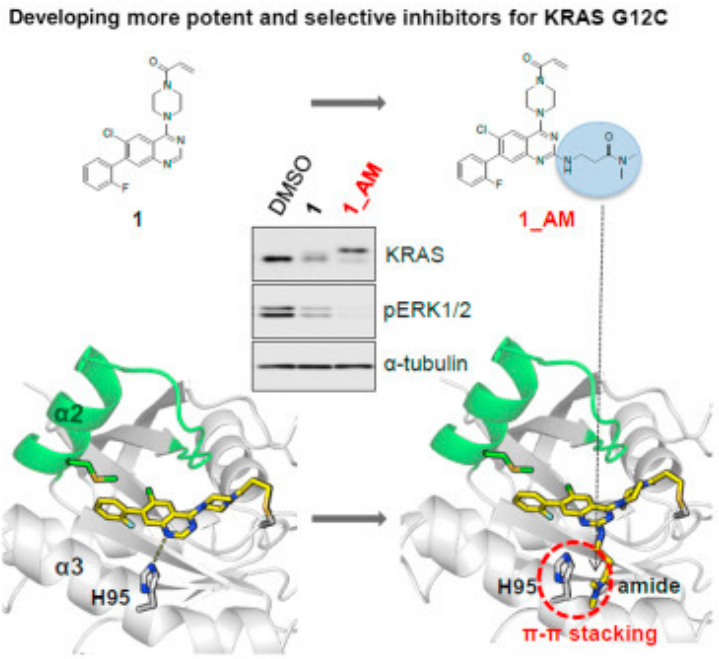




(Kalinin S., et al, 2021)

Tiesioginis K-RAS slopinimas

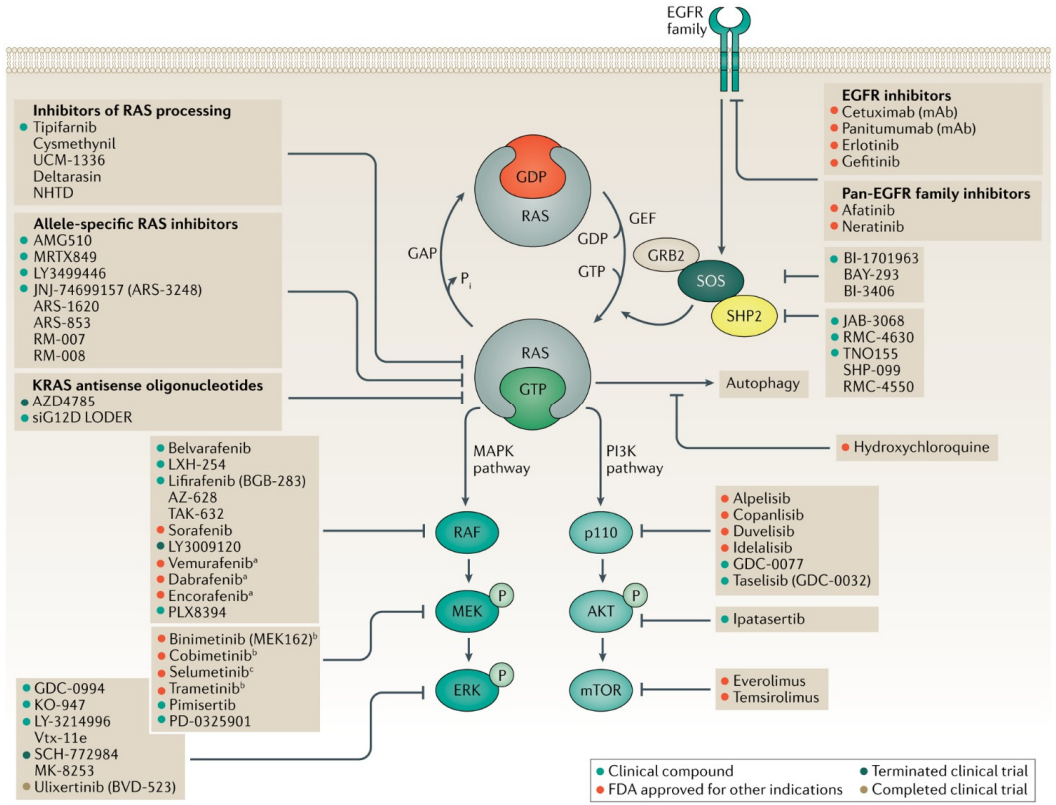


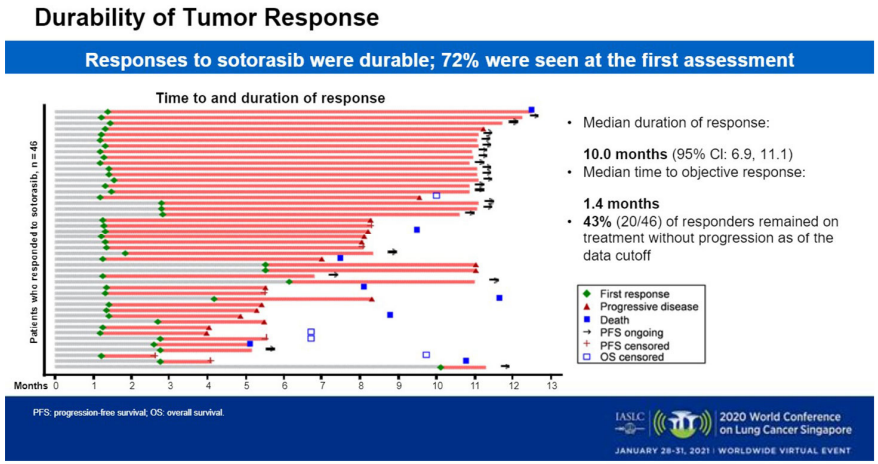


Olivier T, Haslam A, Prasad V. **Sotorasib in KRAS^{G12C} mutated lung cancer: Can we rule out cracking KRAS led to worse overall survival?** Transl Oncol. 2023 Feb;28:101591. doi: 10.1016/j.tranon.2022.101591. Epub 2022 Dec 26. PMID: 36577165; PMCID: PMC9803768.

RAS-targeted therapies: is the undruggable drugged?

Amanda R. Moore, Scott C. Rosenberg, Frank McCormick, Shiva Malek, Nat Rev., 2020





Sotorasib Shows Early Activity Against KRAS G12C Mutant NSCLC

Chris Evelo is the founder and head of the department of Bioinformatics - BiGCaT at Maastricht University; WikiPathways

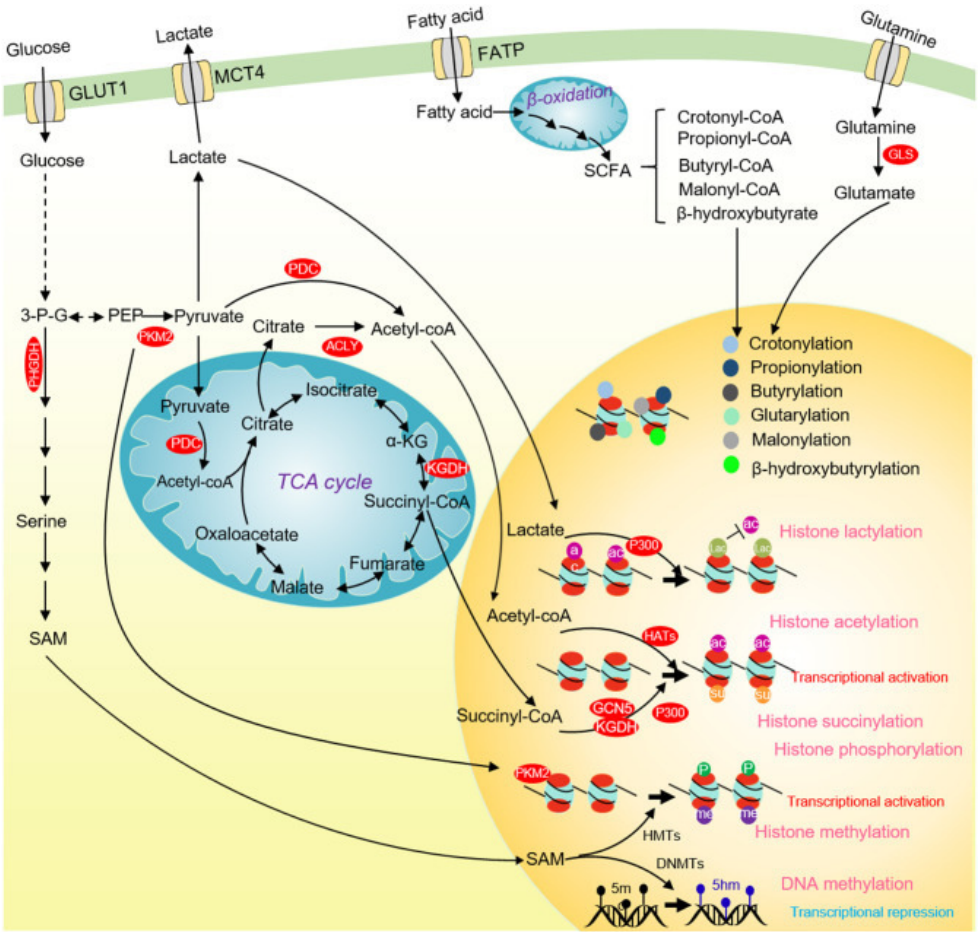
Dear Kestutis,

thank you for your thoughtful email. I agree that targeting MYC as a major downstream effector of KRAS is likely to be effective, as predicted from mouse models using inducible RAS and MYC systems. I had not given much though to the possibility of targeting polyamines and/or ODC, though my PhD thesis focused on regulation of ODC during viral infections. I appreciate your comments and will give these matters more attention.

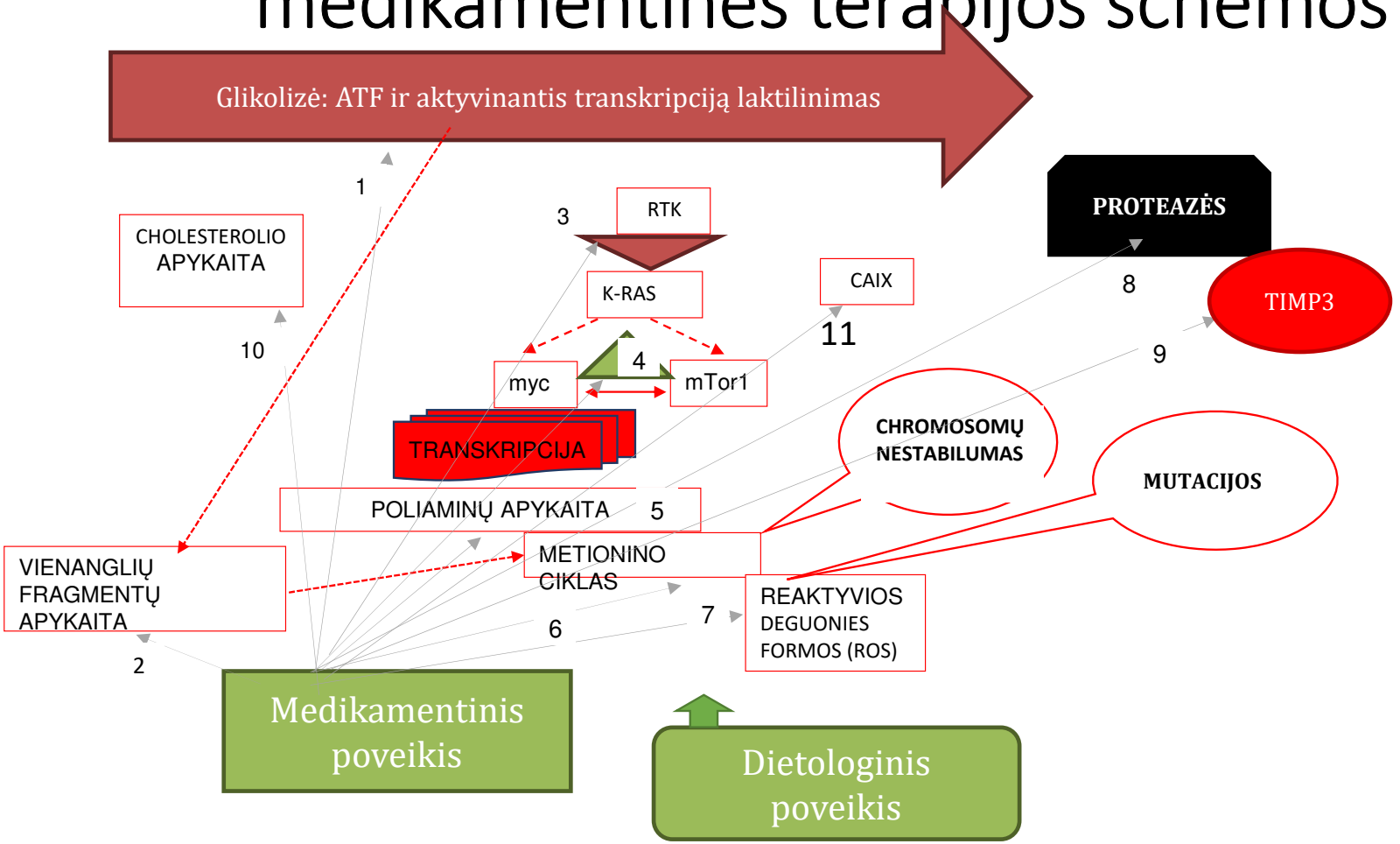
With best regards
Frank

Frank McCormick, PhD, FRS,
UCSF Helen Diller Family Comprehensive Cancer Center,
Room HD-371
1450 3rd Street,
San Francisco, CA 94158-9001
415 218 0155 (Cell phone)

Ma R, Wu Y, Li S, Yu X. **Interplay Between Glucose Metabolism and Chromatin Modifications in Cancer.** Front Cell Dev Biol. 2021 Apr 27;9:654337. doi: 10.3389/fcell.2021.654337. PMID: 33987181; PMCID: PMC8110832



Vienuolika adaptyvios kompleksinės medikamentinės terapijos schemos krypčių



Dinaminių sistemų onkologijoje modeliavimas

- Penkių tipų dinaminiai modeliai pagal apžvalgą *Markert EK, Vazquez A. Mathematical models of cancer metabolism. Cancer Metab. 2015;3:14.*

Published 2015 Dec 22. doi:10.1186/s40170-015-0140-6:

- Genų biologinės raiškos (Proliferacija/audinio Remodeliavimas: „P−/R−, P−/R+, P+/R− ir P+/R+“)

- Srautų balanso (stacionarumas: „metabolitų koncentracija ir biocheminių reakcijų greitis laikui bėgant išlieka pastovūs“) -tik vidurkinės charakteristikos dėl plačių pasikliautinių intervalų riboja prognozių tikslumą, 2007 m.

- Srautų kinetiniai („Pagrindiniai veiksniai yra fermento apykaitos greitis, fermento koncentracija, substrato prisotinimo terminas ir termodinamikos terminas, susiję su fermento savybėmis esant pusiausvyrai“ – gerėja prognozė) 2012-2014 m.

- Difuziniai (jonų, molekulių pernešimo per membranas modeliai su fizikinėmis savybėmis)

- Mechaniniai („Pagrindinis iššūkis - nustatyti ryšius tarp ląsteles charakterizuojančių savybių ir ląstelių-ląstelių sąveikos su naviko mechaninėmis savybėmis“, elastingumas)

Matematinis chemo-imunoterapijos modelis

Nave O. A mathematical model for treatment using chemo-immunotherapy. Heliyon. 2022 Apr 26;8(4):e09288. doi: 10.1016/j.heliyon.2022.e09288. PMID: 35520602; PMCID: PMC9065634.

„Let $\vec{U}$ be the vector of the dynamic variables of the system: $\vec{U}=(D_I,D,D_T,T_N,T_C,T_{CP},T_R,IL_2,IL_{10},C,C_H)$.

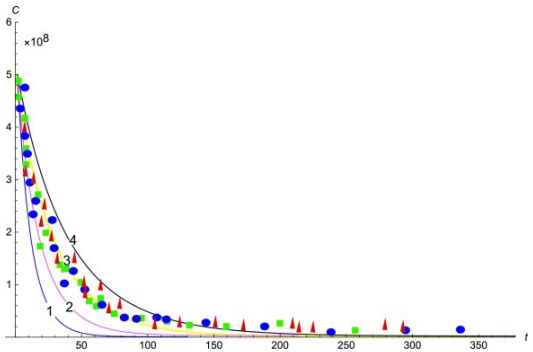
The analytical function F describes chemotherapy treatment, which is a combination of chemotherapy and immunotherapy. The function depends on time *t* and dosage *q*.
The function has the form:

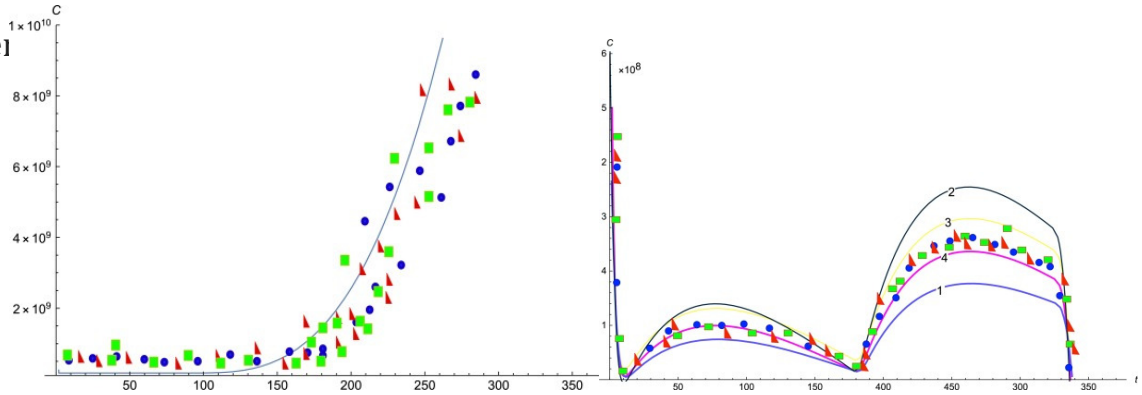
$$F(q,t)=\sum q(t-mk)H(t-mk)e^{t-mk/0.5}$$

The model (*11 netiesinių lygčių*) can be written in abbreviated form as

$$d\vec{U}/dt=\vec{F}(\vec{U}),\ \vec{U}(0)=\vec{U}_0,$$

where $\vec{F}(\vec{U})$ is the vector field of the model; that is, $\vec{F}(\vec{U})=(F_1(\vec{U}),\ldots,F_{11}(\vec{U}))$“





Smegenų auglio ląstelių dinamika be gydymo ir su gydymu kas 28 d. ir kas 7 d.

Kompleksinis TUMORIGENEZĖS matematinis modelis Nr.1 turi susidėti iš:

RTK – K-ras, MAPK, PI3K, tp 53 sąveikos bloko

Erickson KE, Rukhlenko OS, Posner RG, Hlavacek WS, Kholodenko BN. New insights into RAS biology reinvigorate interest in mathematical modeling of RAS signaling. Semin Cancer Biol. 2019 Feb;54:162-173
Sulaimanov N, Klose M, Busch H, Boerries M. Understanding the mTOR signaling pathway via mathematical modeling. Wiley Interdiscip Rev Syst Biol Med. 2017 Jul;9(4):e1379. doi: 10.1002/wsbm.1379. Epub 2017 Feb 10. PMID: 28186392; PMCID: PMC5573916.

Poliaminų apykaitos modelio

Rodríguez-Caso C, Montañez R, Cascante M, Sánchez-Jiménez F, Medina MA. Mathematical modeling of polyamine metabolism in mammals. J Biol Chem. 2006 Aug 4;281(31):21799-21812. doi: 10.1074/jbc.M602756200. Epub 2006 May 18. PMID: 16709566.

Bao K, Liang G, Tian T, Zhang X. Mathematical modeling of combined therapies for treating tumor drug resistance. Math Biosci. 2024 May;371:109170. doi: 10.1016/j.mbs.2024.109170. Epub 2024 Mar 11. PMID: 38467302.

Chen T, Ali Al-Radhawi M, Sontag ED. A mathematical model exhibiting the effect of DNA methylation on the stability boundary in cell-fate networks. Epigenetics. 2021 Apr;16(4):436-457.

Glikolizės, Serino sintezės Folato – B12, B6, Metionino ciklo modelio (1c apykaita)

Saa PA, Nielsen LK. Construction of feasible and accurate kinetic models of metabolism: A Bayesian approach. Sci Rep. 2016 Jul 15;6:29635. doi: 10.1038/srep29635. PMID: 27417285; PMCID: PMC4945864

Kompleksinės vaistinės terapijos

Imuninės terapijos

Pereira EJ, Smolko CM, Janes KA. Computational Models of Reactive Oxygen Species as Metabolic Byproducts and Signal-Transduction Modulators. Front Pharmacol. 2016 Nov 29;7:457. doi: 10.3389/fphar.2016.00457. PMID: 27965578; PMCID: PMC5126069

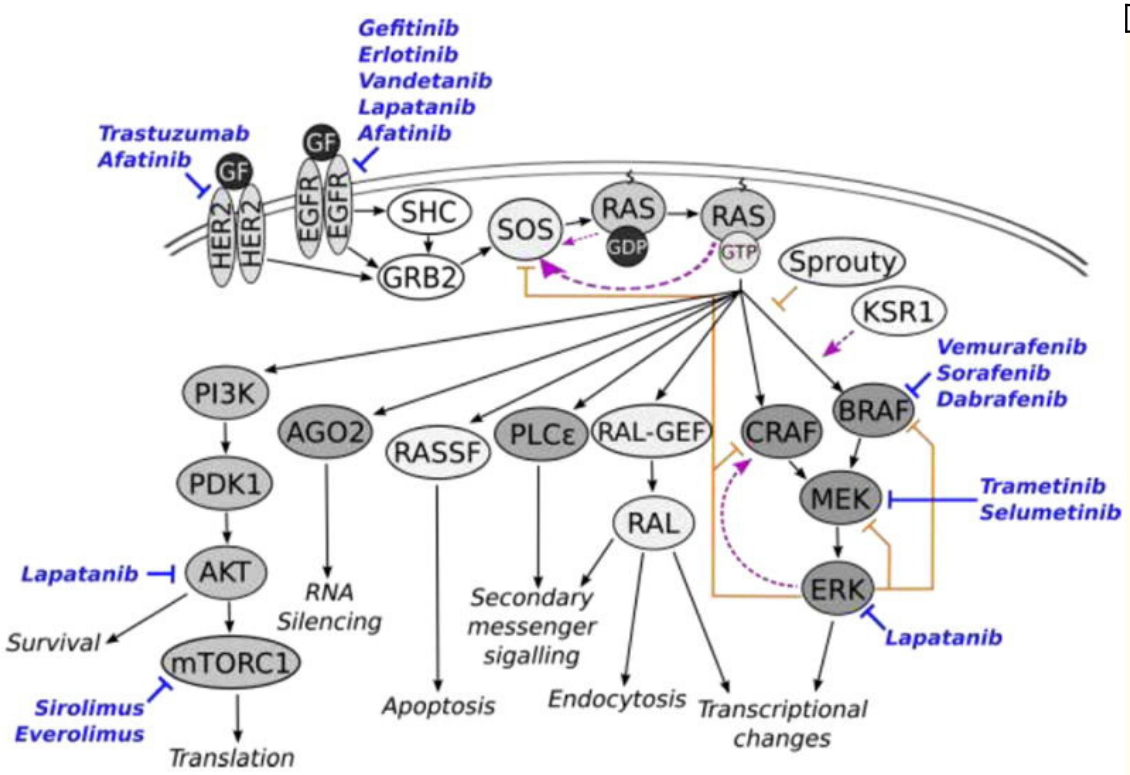
Radikalų eliminavimo – ROS sistemoje GSH

Genominio – chromosominio nestabilumo

Ekstraceliuliarinio matrikso ardymo ir angiogenezės

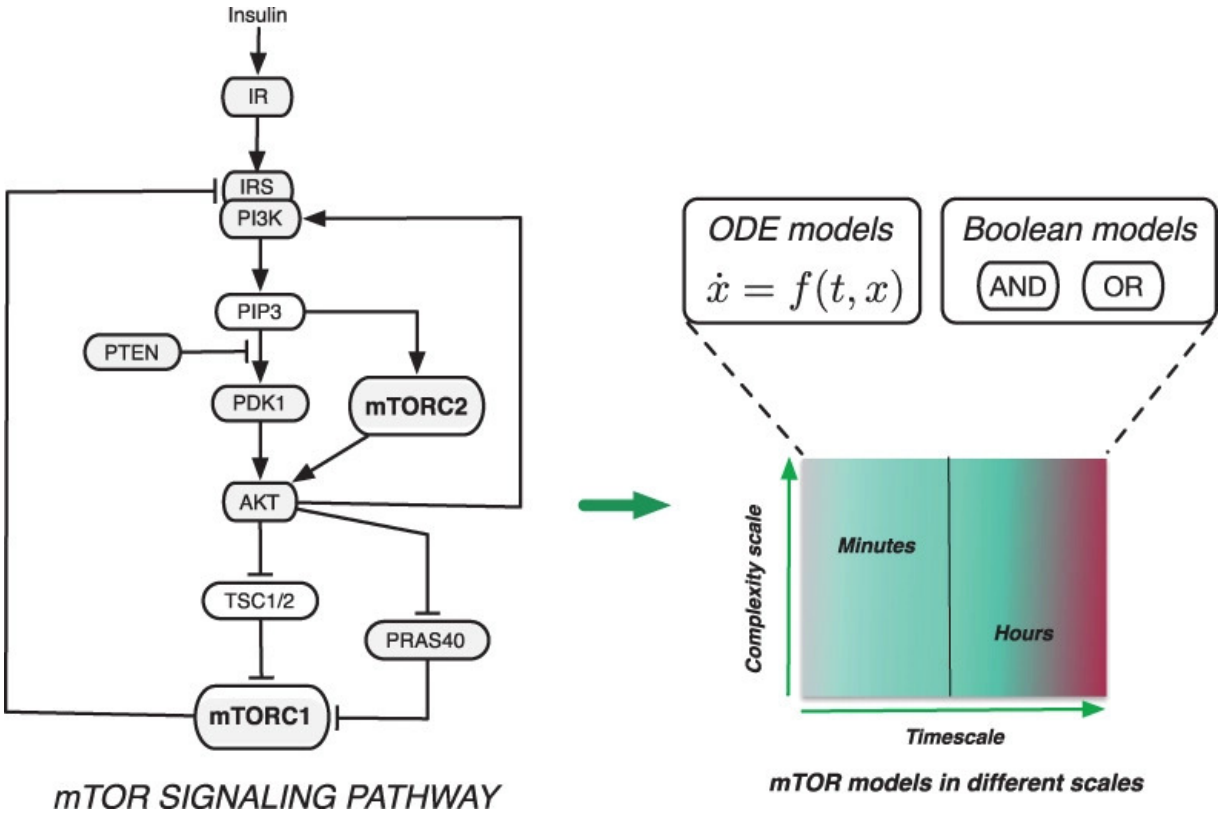
Lynch AR, Arp NL, Zhou AS, Weaver BA, Burkard ME. Quantifying chromosomal instability from intratumoral karyotype diversity using agent-based modeling and Bayesian inference. Elife. 2022 Apr 5;11:e69799. doi: 10.7554/eLife.69799. PMID: 35380536; PMCID: PMC9054132.

1. Erickson KE, Rukhlenko OS, Posner RG, Hlavacek WS, Kholodenko BN. New insights into RAS biology reinvigorate interest in mathematical modeling of RAS signaling. Semin Cancer Biol. 2019 Feb;54:162-173



	$k_{a,GTP}$ (1/M/s)	$k_{d,GTP}$ (1/s)	$k_{a,GDP}$ (1/M/s)	$k_{d,GDP}$ (1/s)	k_{hyd} (1/s)				
	None (WT)			*2.05E-4*	[37]			*6.33E-5*	[48]	*1.47E-4*
RAS Mutation			1.00E-4	[174]			4.20E-4	[174]	3.40E-4	[174]
			2.00E-3	[175]			**2.00E-3**	[175]	**6.80E-4**	[175]
	1.40E8	[174]	*9.00E-5*	[176]	5.10E7	[174]	*1.20E-4*	[176]	*2.10E-4*	[176]
	2.20E6	[173]	*2.50E-4*	[177]	*2.30E6*	[173]	*1.08E-4*	[177]	*3.49E-4*	[177]
			2.33E-4	[180]			**3.00E-5**	[38]	**9.30E-3**	[38]
							2.17E-4	[180]	**2.17E-4**	[180]
							1.60E-5	[173]		
G12A				**200E-3**	[175]			**2.00E-3**	[175]	**1.30E-5**
G12C				**2.00E-3**	[175]			**2.00E-3**	[175]	**4.90E-4**
G12D				5.00E-4	[174]			2.00E-4	[174]	1.50E-4
			2.00E-3	[175]			**2.00E-3**	[175]	**1.90E-4**	[175]
	4.80E8	[174]	*9.50E-4*	[176]	7.00E7	[174]	*1.60E-4*	[176]	*1.40E-4*	[176]
	7.54E6	[30]	*1.25E-3*	[30]	*3.16E6*	[30]	*5.16E-5*	[30]	*1.40E-4*	[30]
G12E										
G12R				**2.00E-3**	[175]			**2.00E-3**	[175]	**1.80E-5**
						6.17E-3	[181]			

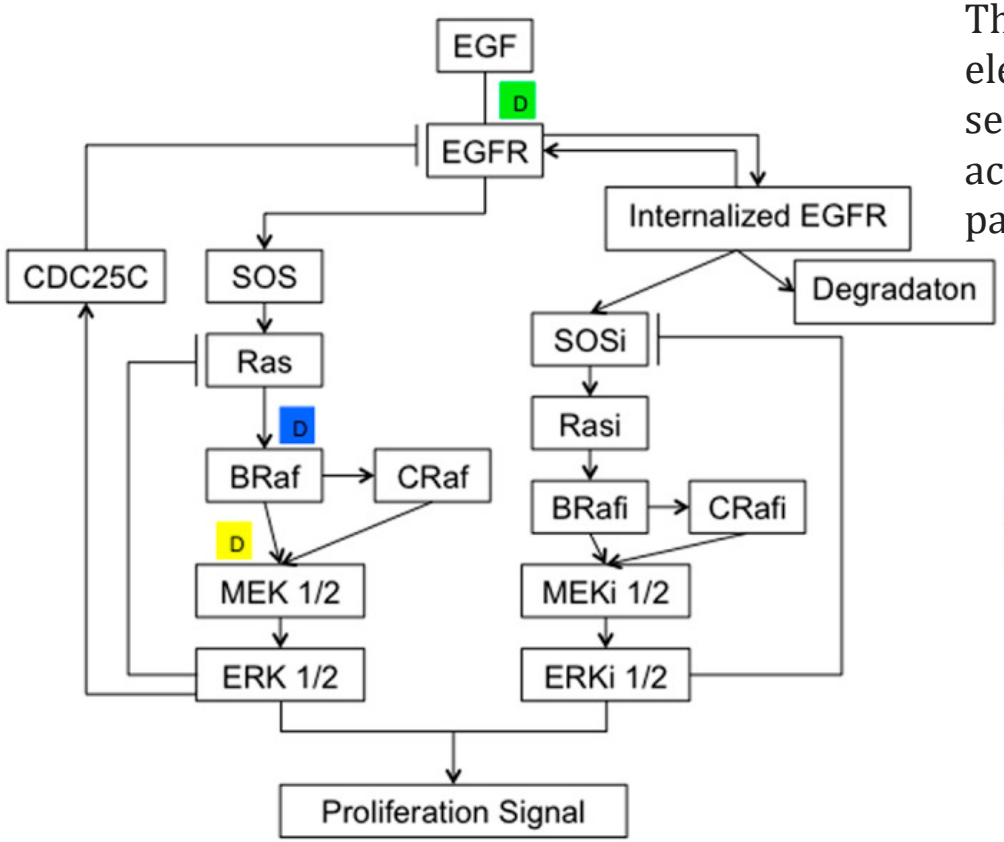
2. Sulaimanov N, Klose M, Busch H, Boerries M. Understanding the mTOR signaling pathway via mathematical modeling. Wiley Interdiscip Rev Syst Biol Med. 2017 Jul;9(4):e1379. doi: 10.1002/wsbm.1379. Epub 2017 Feb 10. PMID: 28186392; PMCID: PMC5573916.



23 publikacijos, pradedant 2002 m. iki 2017 m., skirtos mTor kelio matematiniam modeliavimui. Po to dar 19 citavimų...

mTOR Models	Biological Context	Model Type	Model Size	Timescale
Dalle Pezze et al.[43]	Mechanisms of mTORC2 regulation	ODE	25–33	0–120 min
Sonntag et al.[44]	mTOR-AMPK crosstalk	ODE	26–28	0–120 min
Kubota et al.[45]	Decoding insulin signal in the mTOR pathway	ODE	11	0–600 min
Toyoshima et al.[46]	Signal transfer in the mTOR pathway	ODE	3–4	0–120 min
Noguchi et al.[47]	Metabolism regulation by the mTOR pathway	ODE	15	0–480 min
Borisov et al.[48]	MAPK-mTOR crosstalk	ODE	78	0–30 min
Fujita et al.[49]	Signal transfer in the mTOR pathway	ODE	3–8	0–120 min
Jain et al.[50]	BDNF-mTOR crosstalk	ODE	130	0–30 min
Wu et al.[51]	mTOR-MAPK-PKC crosstalk	Boolean	19–22	0–60 min
Hatakeyama et al.[52]	mTOR-MAPK crosstalk	ODE	33–34	0–30 min
Sedaghat et al.[53]	Metabolic insulin signaling	ODE	21	0–60 min
Faratian et al.[54]	mTOR-MAPK crosstalk	ODE	56	0–60 min
Brännmark et al.[55]	Mechanisms of receptor internalization	ODE	5	0–30 min
Brännmark et al.[56]	Mechanisms of insulin resistance	ODE	26–27	0–30 min
Vinod et al.[57]	mTOR regulation via amino acids	ODE	10–13	0–30 min
Araujo et al.[58]	Feedback characterization in the mTOR pathway	ODE	4–5	a.u.
Giri et al.[59]	Input–output characterization in metabolic insulin signaling	Algebraic	22	a.u.
Tian and Wu[60]	Robustness property of the mTOR pathway	ODE	16	a.u.
Wang and Krueger[61]	Bifurcation analysis of the mTOR pathway	Algebraic	2	a.u.
Nguyen and Kholodenko[62]	Feedback regulation in the mTOR-MAPK pathways	ODE	29	a.u.
Kriete et al.[63]	Metabolism regulation by the mTOR and NF-kB pathways	Fuzzy-logic	34	a.u.
Mosca et al.[64]	Metabolism regulation by the mTOR pathway	ODE, Algebraic	25	a.u.

3. Huang L, Jiang Y, Chen Y. Predicting Drug Combination Index and Simulating the Network-Regulation Dynamics by Mathematical Modeling of Drug-Targeted EGFR-ERK Signaling Pathway. Sci Rep. 2017 Jan 19;7:40752. doi: 10.1038/srep40752. PMID: 28102344;

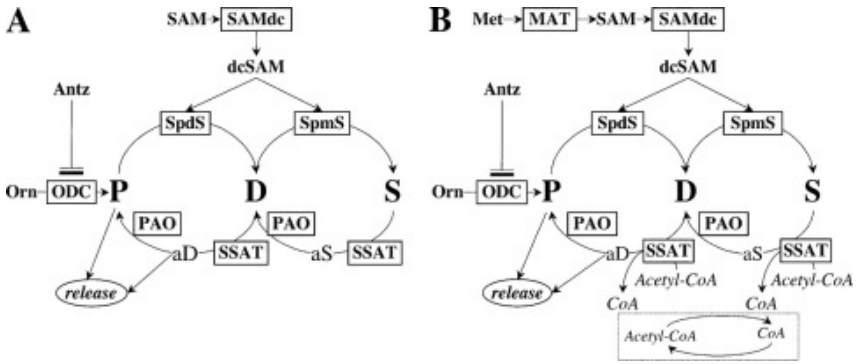


The model contains 126 distinct molecular species, and 190 elementary reactions; these reactions are described as a series of ordinary differential equations based on the mass action law. The model is parameterized by 123 kinetic parameters and 126 initial molecular concentrations.

$$A + B \underset{K_f}{\overset{K_b}{\leftrightarrows}} [A:B]$$

$$\frac{dA}{dt} = K_b \cdot [A:B] - K_f \cdot A \cdot B \qquad (1)$$

4. Poliaminų modeliavimas



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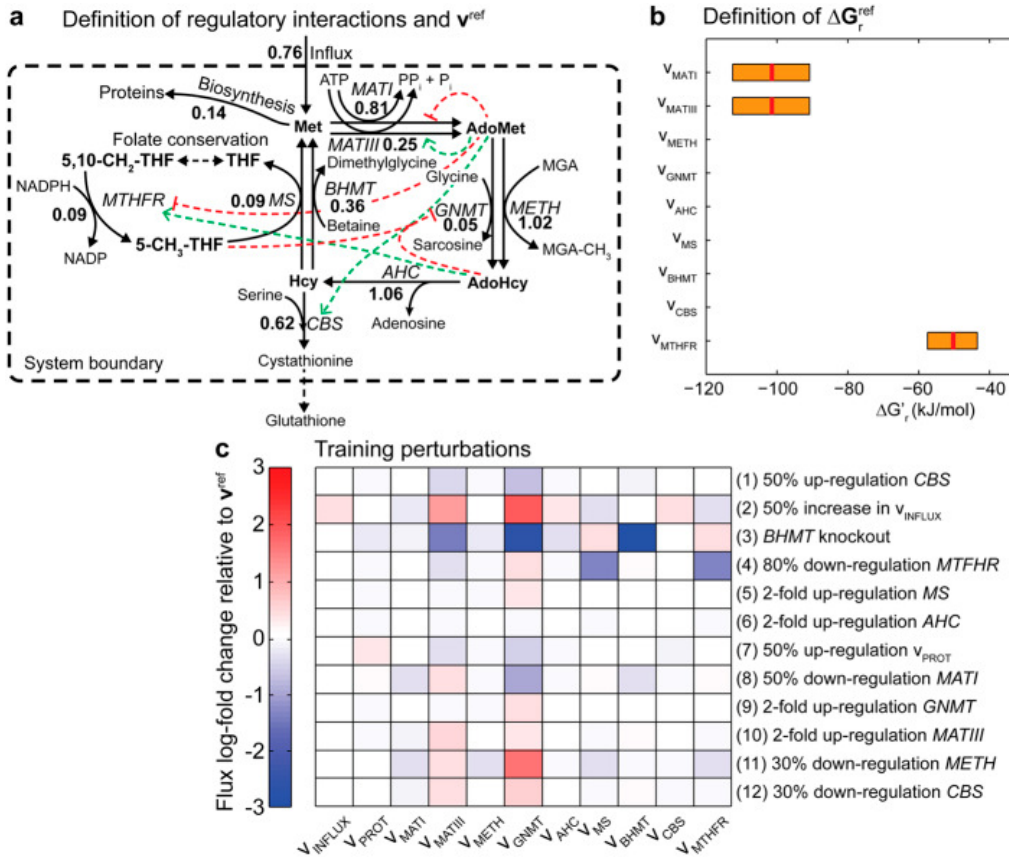
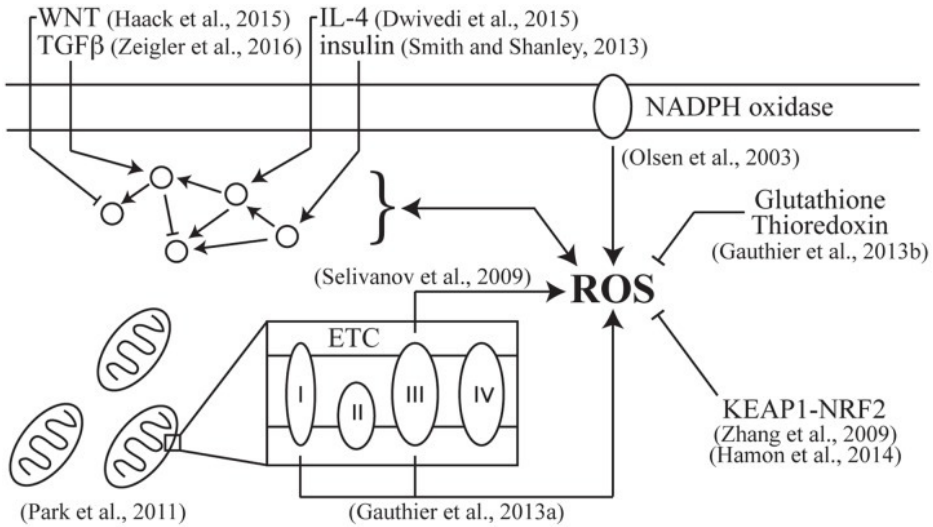
Time-dependent variables	Differential equations
$[P]$	$\frac{d[P]}{dt} = v_{ODC} + v_{PAOxiS} - v_{SpdS} - v_{Pefflux}$
$[D]$	$\frac{d[D]}{dt} = v_{SpdS} + v_{PAOxiS} - v_{SpmS} - v_{SSATD}$
$[S]$	$\frac{d[S]}{dt} = v_{SpmS} - v_{SSATS}$
$[SAM]$	$\frac{d[SAM]}{dt} = v_{MAT} - v_{SAM}$
$[A]$	$\frac{d[A]}{dt} = v_{SAMdc} - v_{SpdS} - v_{SpmS}$
$[aD]$	$\frac{d[aD]}{dt} = v_{SSATD} - v_{PAOxiD} - v_{aDefflux}$
$[aS]$	$\frac{d[aS]}{dt} = v_{SSATS} - v_{PAOxiS}$
$[acCoA]$	$\frac{d[acCoA]}{dt} = v_{acCoA} - v_{CoA} - v_{SSATS} - v_{SSATD}$
$[CoA]$	$\frac{d[CoA]}{dt} = v_{CoA} + v_{SSATS} + v_{SSATD} - v_{acCoA}$
V_{max}^{ODC}	$\frac{dV_{max}^{ODC}}{dt} = k_s^{ODC}\left(\frac{1}{1+\left(K_{eq}^{ODC}([D]+[S])\right)}\right) - k_d^{ODC} \cdot Antz \cdot V_{max}^{ODC}$
$Antz$	$\frac{dAntz}{dt} = k_s^{Antz}\left(1 - \frac{1}{1+K_{eq}^{Antz}([D]+[S])}\right) - k_d^{Antz} \cdot Antz$
V_{max}^{SAMdc}	$\frac{dV_{max}^{SAMdc}}{dt} = k_s^{SAMdc}\left(\frac{1}{1+\left(K_{eq}^{SAMdc}([D]+[S])\right)}\right) - k_d^{SAMdc} \cdot V_{max}^{SAMdc}$
V_{max}^{SSAT}	$\frac{dV_{max}^{SSAT}}{dt} = k_s^{SSAT}\left(1 - \frac{1}{1+\left(K_{eq}^{SSAT}([D]+[S])\right)}\right) - k_d^{SSAT}\left(\frac{1}{1+\left(K_{eq}^{SSAT}([D]+[S])\right)}\right) V_{max}^{SSAT}$

5. Metionino ciklo modelis



6. Saa PA, Nielsen LK. Construction of feasible and accurate kinetic models of metabolism: A Bayesian approach. Sci Rep. 2016 Jul 15;6:29635. doi: 10.1038/srep29635. PMID: 27417285; PMCID: PMC4945864.

6. ROS – reaktyvių radikalų modeliavimas

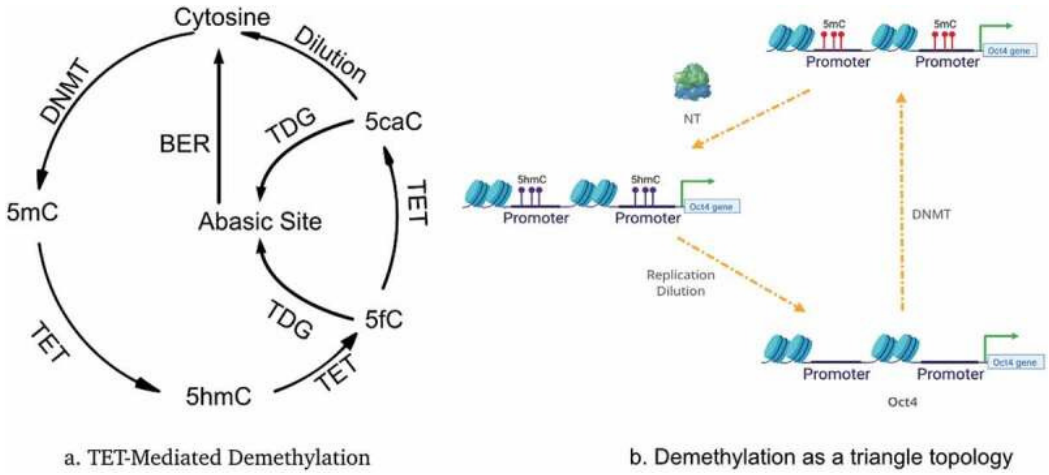


7. Pereira EJ, Smolko CM, Janes KA. Computational Models of Reactive Oxygen Species as Metabolic Byproducts and Signal-Transduction Modulators. Front Pharmacol. 2016 Nov 29;7:457. doi: 10.3389/fphar.2016.00457. PMID: 27965578; PMCID: PMC5126069.

7. DNR metilinimo modeliavimas

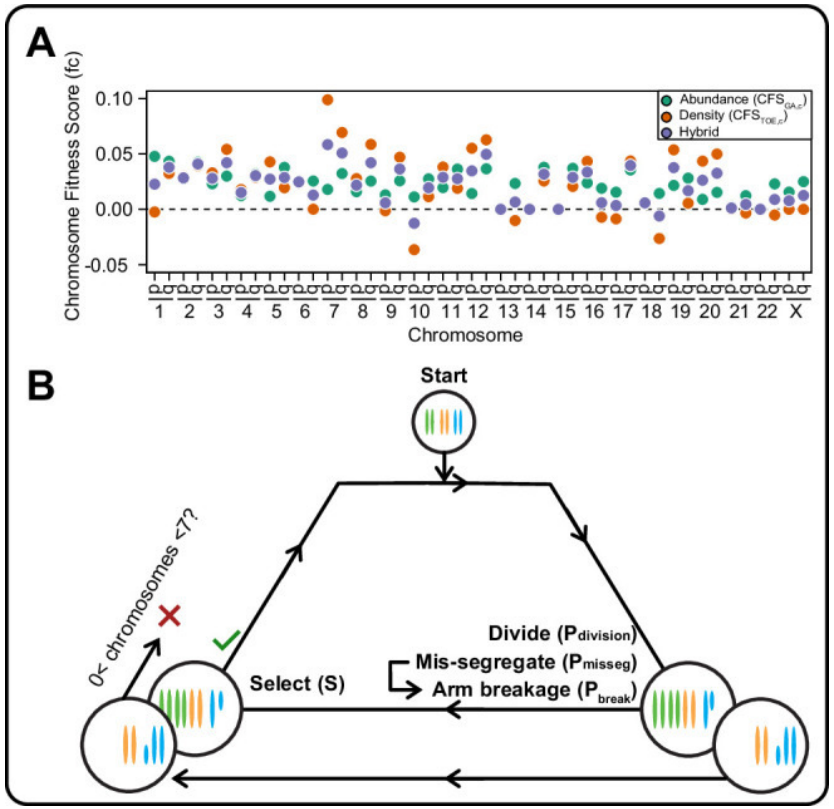
The reduced dynamical system's ODEs can be written as below:

$$dN/dt = m_1 - \delta N + \alpha_N O K_O + O,$$
$$dT/dt = m_2 - \delta T + \alpha_T NTO(NT + K_{nt}K_d)(K_O + O),$$
$$dO/dt = -K_{nt}K_d\delta O_2 - \delta NTO_2 + K_O K_{nt}K_d m_3 + \alpha_O NTO + K_{nt}K_d m_3 O(NT + K_{nt}K_d)(K_O + O)$$
$$+ K_O m_3 NT + m_3 NTO - K_O\delta NTO - K_O K_{nt}K_d\delta O - \alpha_O D_m NTO(NT + K_{nt}K_d)(K_O + O)$$
$$dD_m/dt = -K_O K_{nt}K_{2d}\gamma D_m + K_O K_{nt}K_{2d}\gamma - \theta K_O N_2 T_2 D_m - \theta N_2 T_2 O D_m K_d(NT + K_{nt}K_d)(K_O + O)$$
$$-\theta K_O K_{nt}K_d NTD_m + \theta K_{nt}K_d NTOD_m K_d(NT + K_{nt}K_d)(K_O + O)$$



8. Chen T, Ali Al-Radhawi M, Sontag ED. A mathematical model exhibiting the effect of DNA methylation on the stability boundary in cell-fate networks. Epigenetics. 2021 Apr;16(4):436-457. doi: 10.1080/15592294.2020.1805686. Epub 2020 Sep 22. PMID: 32842865; PMCID: PMC7993226.

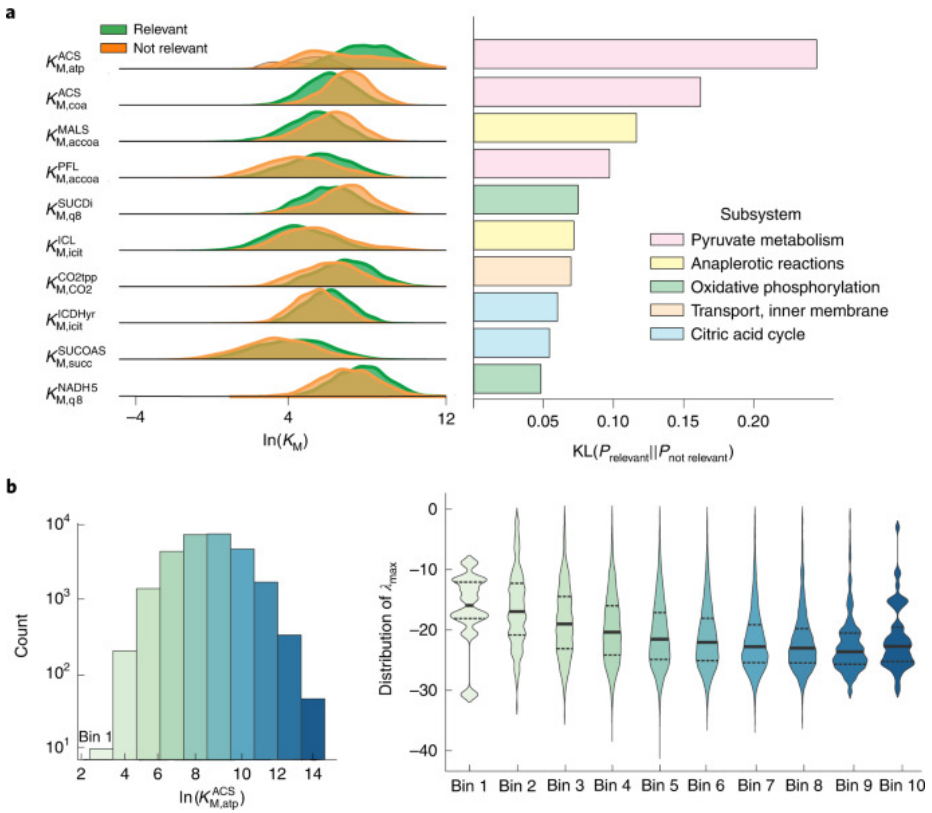
8. Chromosomų nestabilumo modeliavimas



9. Lynch AR, Arp NL, Zhou AS, Weaver BA, Burkard ME. Quantifying chromosomal instability from intratumoral karyotype diversity using agent-based modeling and Bayesian inference. Elife. 2022 Apr 5;11:e69799. doi: 10.7554/eLife.69799. PMID: 35380536; PMCID: PMC9054132.

Dirbtinis intelektas kinetinių modelių generavimui

Reconstructing Kinetic Models for Dynamical Studies of Metabolism using Generative Adversarial Networks, Nature Machine Intelligence **volume 4**, pages710–719 (2022)



Perthera

The Precision Oncology Outcomes Company

Comprehensive analysis of KRAS variants in patients (pts) with pancreatic cancer
Clinical/molecular correlations and real-world outcomes across standard therapies

Andrew E Hendifar[1], Edik M Blais[2], Camille Ng[1], Dzung Thach[2], Jun Gong[1], Davendra Sohal[3], Vincent Chung[4], Vaibhav Sahai[5], Christos Fountzilas[6], Sameh Mikhail[7], Gary L Gregory[2], Jonathan R Brody[8], Emily Lyons[9], Patricia DeArbeloa[2], Lynn M Matrisian[9], Emanuel F Petricoin III[2,10], Michael J Pishvaian[2,11]

[1]Cedars-Sinai Medical Center, Los Angeles, CA; [2]Perthera, Inc, Hollston, MA; [3]Cleveland Clinic, Cleveland, OH; [4]City of Hope Cancer Center, Duarte, CA; [5]University of Michigan, Ann Arbor, MI; [6]Roswell Park Cancer Institute, Buffalo, NY; [7]Zangmeister Cancer Center, Columbus, OH; [8]Thomas Jefferson University, Philadelphia, PA; [9]The Pancreatic Cancer Action Network, Manhattan Beach, CA; [10]George Mason University, Fairfax, VA; [11]Johns Hopkins University, Baltimore, MD

Background

Molecular profiling in pancreatic adenocarcinoma (PDAC) has gained traction and we recently demonstrated that targeting actionable alterations can improve patient (pt) outcomes[1,2] using the Perthera Platform's real-world evidence database[4]. Unfortunately, most (~75%) PDAC genomic profiles do not have any actionable targets[1] due to a KRAS mutation frequency of 80-90%. The spectrum of KRAS isoforms vary considerably between tumor types, but the predictive and prognostic implications for specific KRAS variants in PDAC are largely unknown. Further subtyping of PDAC, particularly those with KRAS mutations and without actionable findings, may provide novel insights into optimal treatment sequencing for individual patients. Here, we categorized PDAC tumors by specific KRAS variants and performed exploratory analyses to understand their implications for prognosis or response to standard frontline therapies (Tx) in PDAC.

Acknowledgements

We wish to acknowledge the patients and their families who were involved in this study

This work was supported by donations to the Pancreatic Cancer Action Network (PanCAN)

Conflicts of Interest

Perthera is a privately-held precision oncology company that captures molecular testing data and real-world outcomes

References

1. Pishvaian, et al. Lancet Oncology. 2020; PMID: 32135080
2. Pishvaian, et al. JCO Precision Oncology. 2019
3. AACR GENIE. Cancer Discovery. 2017
4. Madhavan et al., JAMIA Open. 2019; PMID: 32025647

Pancreatic Cancer Cohort

The Perthera Registry's Real-World Outcomes & Multi-Omic Database

Thousands enrolled via partnering physicians/institutions including the Know Your Tumor® program

Patients with Advanced PDAC & NGS Testing Results (n = 1060)

Molecularly-Defined Subgroups

- DDR Deficient*** (16%)
- KRAS G12D (33%)
- KRAS G12V (23%)
- KRAS G12R (11%)
- KRAS G12C (1%)
- KRAS Q61 (4%)
- RAS Other (1%)
- RAS Wild Type (10%)

Enrichment Analysis Benchmark

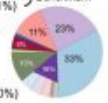
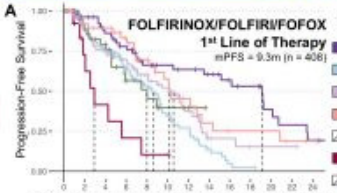
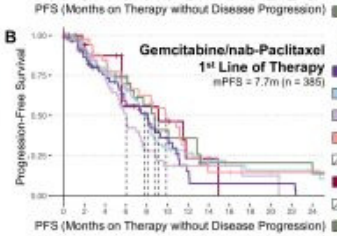


Figure 1: Pts with advanced pancreatic cancer (PDAC) and molecular profiles were analyzed based on specific RAS mutations (or DDR status) for OS/PFS analyses. ***Pts with mutations in DNA damage response (DDR) genes (e.g. BRCA1/2, PALB2, ATM/ATR, etc) were reassigned to the DDR subgroup (see pie chart) due to known implications for platinum-sensitivity[3]

PFS on 1st Line Therapies by RAS Mutational Subgroup



Molecularly-Defined PDAC Subgroup	1st Line PFS median [95% CI]	Enrichment p-value (HR)
DDR Deficient (61)	**19.1m** [13.5-23.4]	0.00023 (0.44)
KRAS G12D (143)	**8.6m** [6.6-9.5]	0.017 (1.51)
KRAS G12V (95)	10.6m [7.1-13.0]	0.42 (0.86)
KRAS G12R (51)	10.1m [8.8-20.8]	0.055 (0.63)
KRAS G12C (4)	10.3m [N/A]	0.91 (0.90)
KRAS Q61 (16)	**2.9m** [2.1-N/R]	0.00053 (3.36)
RAS Other (6)	N/A	N/A
RAS Wild Type (42)	8m [5.8-N/R]	0.80 (1.07)



Molecularly-Defined PDAC Subgroup	1st Line PFS median [95% CI]	Enrichment p-value (HR)
DDR Deficient (60)	8.1m [5.8-10.5]	0.39 (1.18)
KRAS G12D (132)	7.8m [7.1-8.7]	0.32 (0.84)
KRAS G12V (87)	**6.0m** [5.3-7.6]	0.034 (1.5)
KRAS G12R (39)	9.9m [7.2-11.9]	0.32 (0.8)
KRAS G12C (4)	9.4m [5.4-N/R]	0.87 (0.89)
KRAS Q61 (24)	9.1m [5.6-N/R]	0.60 (0.84)
RAS Other (3)	N/A	N/A
RAS Wild Type (43)	8.8m [6.8-13.2]	0.41 (0.83)

Figure 3: Enrichment analyses comparing PFS on 1st line Tx across RAS subgroups. Notable differences between each group and the benchmark subgroups (G12D/V/R) are highlighted (via univariate Cox regression).

Results & Discussion

Novel Insight: Could KRAS Q61 possibly represent a novel predictive biomarker for differential response to SOC in PDAC?

- The KRAS Q61 subgroup had shorter PFS on 5FU-based Tx compared to KRAS G12D/V/R-mutated PDAC (**Figure 3A**)
- No difference was seen for the KRAS Q61 subgroup who received 1st line gemcitabine/nab-paclitaxel (**Figure 3B**)
- KRAS Q61 trend for OS was similar to G12D but not significant for enrichment vs G12D/V/R-mutated PDAC (**Figure 4**)
- Pertinent Caveat: No difference observed in 2nd line where 5FU/nal-Irinotecan is more-common (data not shown)

As expected, the DDR deficient subgroup performed exceptionally well on 5FU-based regimens (**Figure 3A**)

- DDR mutations were excluded from RAS variant-specific subgroupings for this known reason[2]
- Majority received FOLFIRINOX or FOLFOX in the frontline setting (DDR is predictive for response to platinums[2])

Only modest OS/PFS differences were observed between the 3 most common KRAS variant subgroups (**Figures 3 & 4**)

- KRAS G12D was enriched for slightly shorter PFS on 5FU-based therapy compared to KRAS G12V/R-mutated PDAC
  - KRAS G12D also had slightly shorter OS compared to KRAS G12V/R-mutated PDAC (predictive or prognostic?)
- KRAS G12V was enriched for slightly shorter PFS on Gemcitabine/nab-P compared to KRAS G12D/R-mutated PDAC

Additional data are needed to assess the predictive/prognostic implications of uncommon RAS variant subgroups

- KRAS G12C is surprisingly rare (**Figure 2**) in PDAC (1.2% of RAS mutations) limiting our ability to assess OS/PFS trends
- KRAS Q61R/H is found in 5.8% of all PDAC (7% of RAS mutations) and more abundant than G12C in many GI subtypes
- Most other KRAS/NRAS/HRAS mutations are rare in PDAC but other drivers can influence the MAPK pathway in PDAC[1]

KRAS wild type & DDR deficient subgroups had longer OS compared to patients with KRAS G12D/V/R-mutated PDAC

- DDR alterations are predictive markers of response to PARPi/platinums (NOT prognostic in the absence of platinums[2])
- Many patients within the RAS wild type subgroup received targeted therapies[1] for other drivers (e.g. NTRK/ROS1/BRAF)

Co-occurrence and mutual exclusivity analyses were performed on each RAS mutational subgroup

- KRAS G12R-mutated tumors were often found alongside mutations in STK11/PIK3CA; however, KRAS G12R was mutually exclusive with ARID1A mutations (all 3 impact PI3K/AKT/mTOR signaling, relevant for previous studies)
- KRAS Q61 & RAS Other were both enriched for co-occurrence with SF3B1 mutations (dysregulates RNA processing)

RAS Mutation Breakdown by Cancer Type

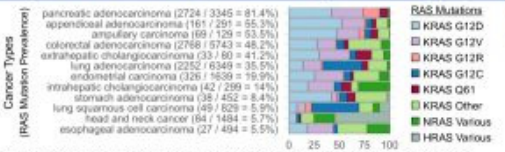


Figure 2: Overview of KRAS variants found in PDAC and other cancer types (broader cohort).

- Prevalence was calculated using data from AACR GENIE[3] & Perthera's real-world registry[4]
- KRAS G12D (43%) and G12V (31%) are the two most common isoforms found in RAS-mutated PDAC
- KRAS G12R is more common in PDAC (17% of RAS mutations) than in lung cancers (1-6%)
- KRAS G12C is surprisingly rare in PDAC (1.2% of RAS mutations) relative to lung cancers (38-47%)
- KRAS Q61H/R is found in 5.8% of all PDAC (7% of RAS mutations) similar to other GI cancer types
- Most other KRAS/NRAS/HRAS mutations are rare in PDAC despite a RAS mutation rate above 80%

Baseline Characteristics

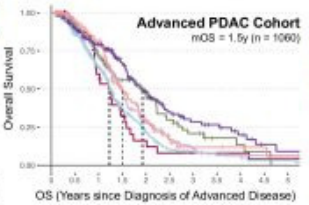
Molecularly-Defined PDAC Subgroup	Age (median [IQR])	Sex (% Female)	Background (% White)
DDR Deficient (175)	62 [55-61]	47%	77%
KRAS G12D (358)	63 [56-62]	47%	84%
KRAS G12V (250)	64 [57-63]	50%	81%
KRAS G12R (120)	63 [57-63]	55%	76%
KRAS Q61 (49)	64 [55-63]	43%	74%
RAS Wild Type (108)	61 [54-60]	46%	91%

Questions? @Perthera or hope@perthera.com

Conclusions & Further Questions

1. Perthera's real-world clinical/molecular datasets may provide novel insights into biomarkers that predict response to standard of care (or lack thereof).
2. Prospective validation may be warranted to optimize treatment sequencing for KRAS Q61 mutations (found in 6% of all PDAC cases).
3. Multivariate analyses are underway to delineate the predictive vs prognostic role of specific KRAS mutations across all lines of therapy.
4. Treatment-specific differences in outcomes motivate the need for a better understanding of tumor biology to support future clinical trial design
5. As expected, DDR-mutated tumors were the most prominent group to benefit from 5FU-based therapy (DDR is predictive for platinum response[2]).
6. Perthera previously demonstrated a 1-year OS benefit for molecularly-matched Tx[1] which likely explains the favorable OS trends for DDR-mutated (independent of RAS status) and RAS wild type tumors (not prognostic)
7. Perthera's outcomes collection efforts for molecularly-profiled patients may begin to support directing specific therapies to certain mutational subgroups

OS in the Advanced Setting by RAS Mutational Subgroup



Molecularly-Defined PDAC Subgroup (n)	Advanced OS median [95% CI]	Enrichment p-value (HR)
DDR Deficient (175)	**1.9y** [1.6-2.4]	0.0000084 (0.58)
KRAS G12D (358)	**1.2y** [1.2-1.3]	0.0035 (1.34)
KRAS G12V (250)	1.5y [1.4-1.6]	0.073 (0.82)
KRAS G12R (120)	1.5y [1.3-1.8]	0.12 (0.81)
KRAS G12C (12)	0.8y [0.5-N/R]	0.69 (0.88)
KRAS Q61 (49)	1.2y [0.9-1.6]	0.45 (1.18)
RAS Other (12)	1.3y [1.3-N/R]	0.88 (1.08)
RAS Wild Type (108)	**1.9y** [1.3-2.2]	0.011 (0.70)

Figure 4: Enrichment OS analyses from advanced diagnosis across RAS subgroups. Differences against the benchmark (G12D/V/R) were noted but do not necessarily suggest prognostic associations[1,2] (see Discussion).

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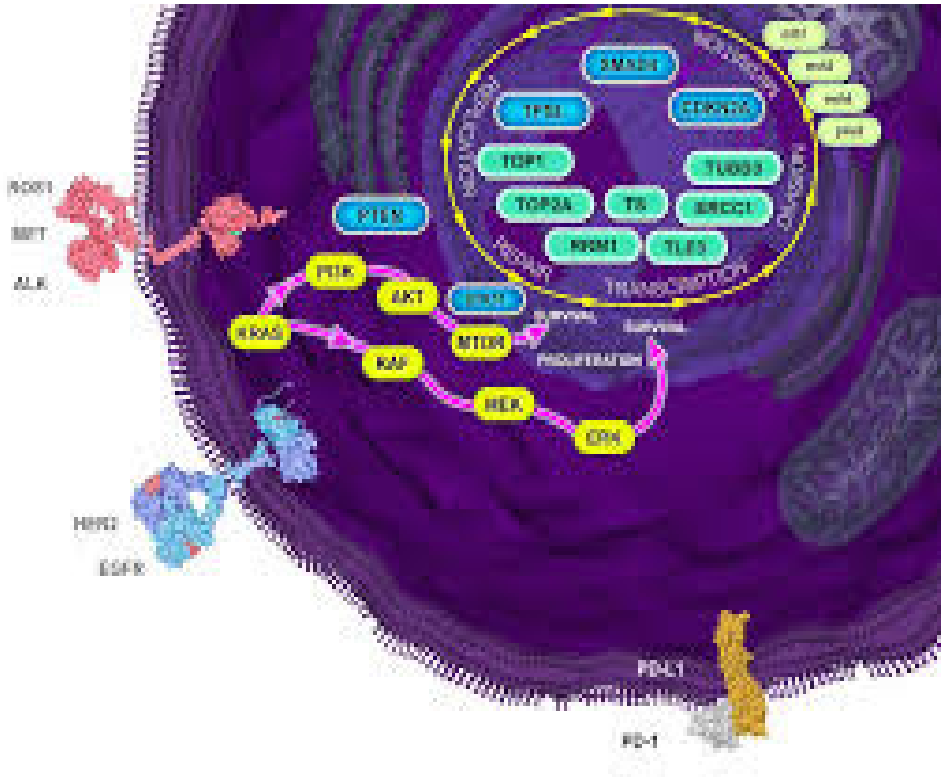

TUMORIGENEZĖ

K-RAS PROBLEMA ONKOLOGIJOJE: SISTEMINIS POŽIŪRIS

Kęstutis K.Urba

VILNIUS 2025

TURINYS

Įvadas

I. Hanahan-Weinberg vėžio modelio patikslinimas ir Warburgo bei Hofmano efektai bei formalus vėžio aprašas
II. K-ras mutacijos, signaliniai keliai, biologinės funkcijos
III. Vienanglių fragmentų apykaita vėžio ląstelėse ir K-RAS
IV. Epigenetinių DNR metilinimo pokyčių modelis – hepatokarcinoma
V. K-RAS ir poliaminų apykaita piktybinėje ląstelėje bei sąryšis su Metionino ciklo ypatumais
VI. K-RAS ir metaloproteinazės, adamlizinai, tarpląstelinės ir matrikso jungtys, angiogenezė, imunitetas
VII. Epigenetiniai chromosomų stabilumo, DNR metilinimo, histonų pokyčiai piktybinėje ląstelėje ir K-RAS
VIII. K-RAS mutacijos ir ląstelės ciklas
IX. Cholangiokarcinomos
X. Skrandžio vėžys
XI. K-ras mutacijos ir kasos, žarnyno, plaučių vėžys
XII. Kasos navikai
XIII. Kolorektaliniai navikai
XIV. Plaučių navikai
XV. Prostatos vėžys
XVI. Melanoma ir K- RAS mutacijos
XVII. Poveikio genai, K-RAS ir vėžio heterogeniškumas
XVIII. Kancerogenezės teorijos, koncepcijos, aiškinimai
XIX. K-ras mutacijų sąlygoti kancerogenezės scenarijai
XX. Imuninė sistema ir K-ras
XXI. Kompleksinė sistematinė adaptyvi orientuota į mK-RAS ir jo betarpišką metabolinę aplinką neo-adjuvantinė bei adjuvantinė medikamentinė taikinių terapija
XXII. Kiekybiniai matematiniai modeliai onkologijoje

LITERATŪRA – apie 1500 publikacijų

Europe’s Beating Cancer Plan will be implemented, enabled and supported using the whole range of Commission funding instruments
with a total of €4 billion

Ursulos von der Leyen palaiminimas Lietuvai

I have passed your report on to my colleagues across the Commission who are working on the development of a comprehensive EU Cancer Plan that will include actions across the entire disease pathway: prevention, early detection and diagnosis, treatment, quality of life as a cancer survivor and palliative care. The proposed actions will aim to ensure that all Europeans will have access to effective prevention and care, respecting the principles of proportionality and subsidiarity.

Currently the Commission is consulting with stakeholders on the potential content and scope of the EU Cancer Plan. Your contribution to the discussion is much appreciated, and your emphasis on prevention, more knowledge, inequities, innovation and avoiding stigmatisation are well noted.

I wish to take this opportunity to thank you for your personal contribution and active role in public health in general and fighting cancer in particular. In times like these, Europe needs health advocates like you and I count on your continued cooperation and involvement in making Europe better and healthier for our people. Related to this, I welcome the initiative to develop a 'Lithuanian flagship Initiative for beating cancer' and the Commission remains available for further support.

Yours faithfully,

Ursula von der Leyen

Ačiū už dėmesį!