Donetsk National Medical University named after M. Gorky

DISODERS OF PURINE AND PYRIMIDINE NUCLEOTIDES METABOLISM IN HUMAN GASTROINTESTINAL TRACT CANCER

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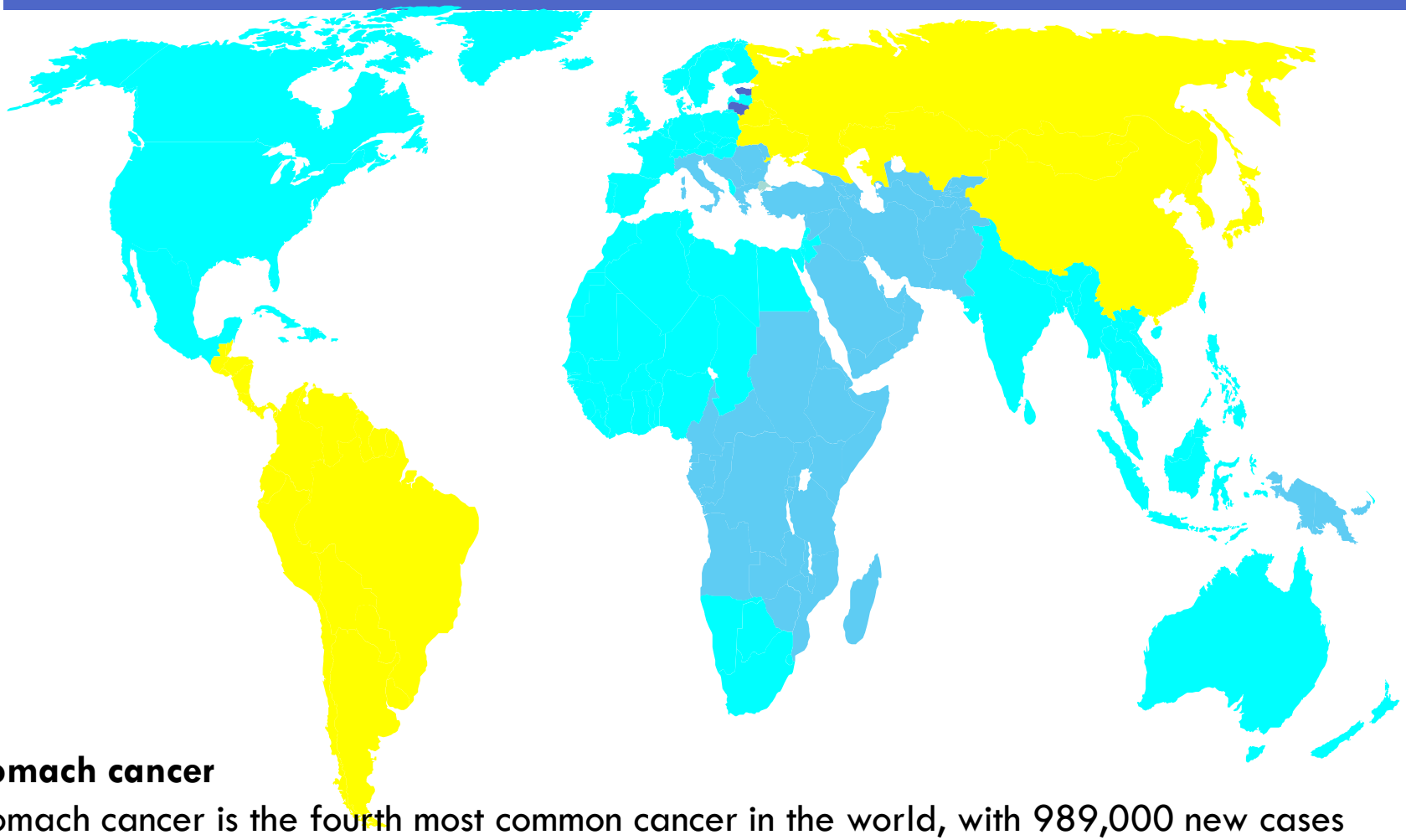
Co-authors: associate prof. Elena Bakurova, assistant Kseniia Mironova

Stomach cancer is the fourth most common cancer in the world

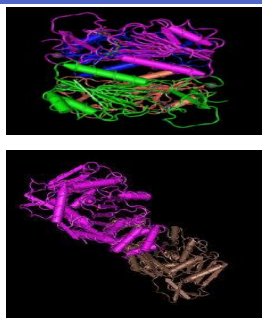


Stomach cancer

Stomach cancer is the fourth most common cancer in the world, with 989,000 new cases diagnosed in 2008 [WCRF International].

Key enzymes of thymidine metabolism

Thymidine kinase (TK; EC 2.1.2.1.)
Thymidine phosphorylase (TP; EC 2.4.2.4.)



TP is similar to the platelet-derived endothelial cell growth factor (PD-ECGF) and hence plays dual role in cell biology

DE NOVO

The activity of the pathway
in norm 90-95%
In tumor ~80% ↓

$NH_3 + CO_2 + ATP$
Asp

Simple precursors

→ ⋯ →UMP → ⋯ → dUMP → dTMP

Thymidine synthase

FU

Total pool

SALVAGE

The activity of the pathway
in norm 5-10%
In tumor ~20% ↑

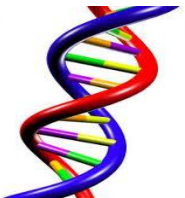
TK

dTDP

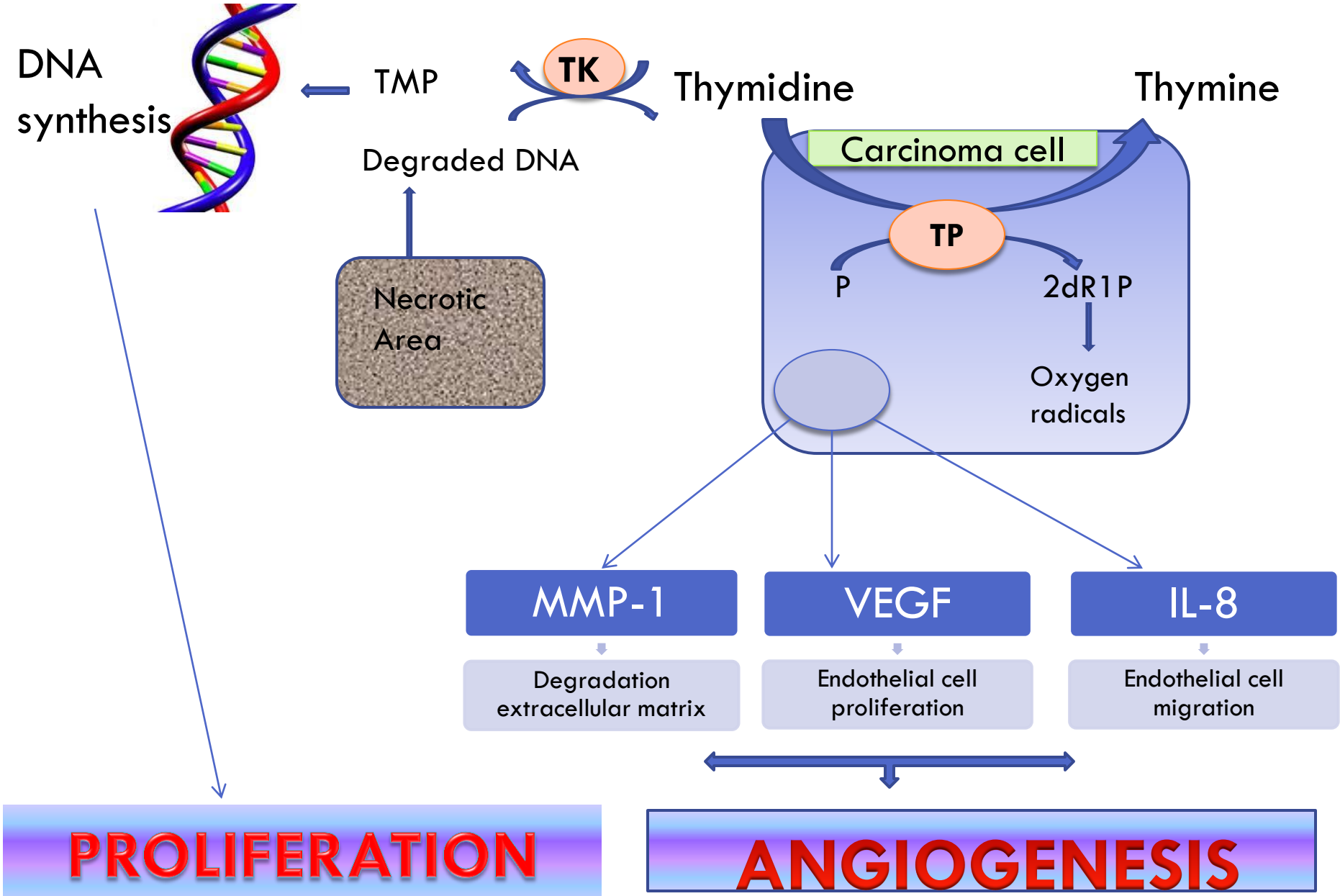
dTTP

TP

Thymine ⇌ Thymidine



Cancer
feed back
mechanism is
absent

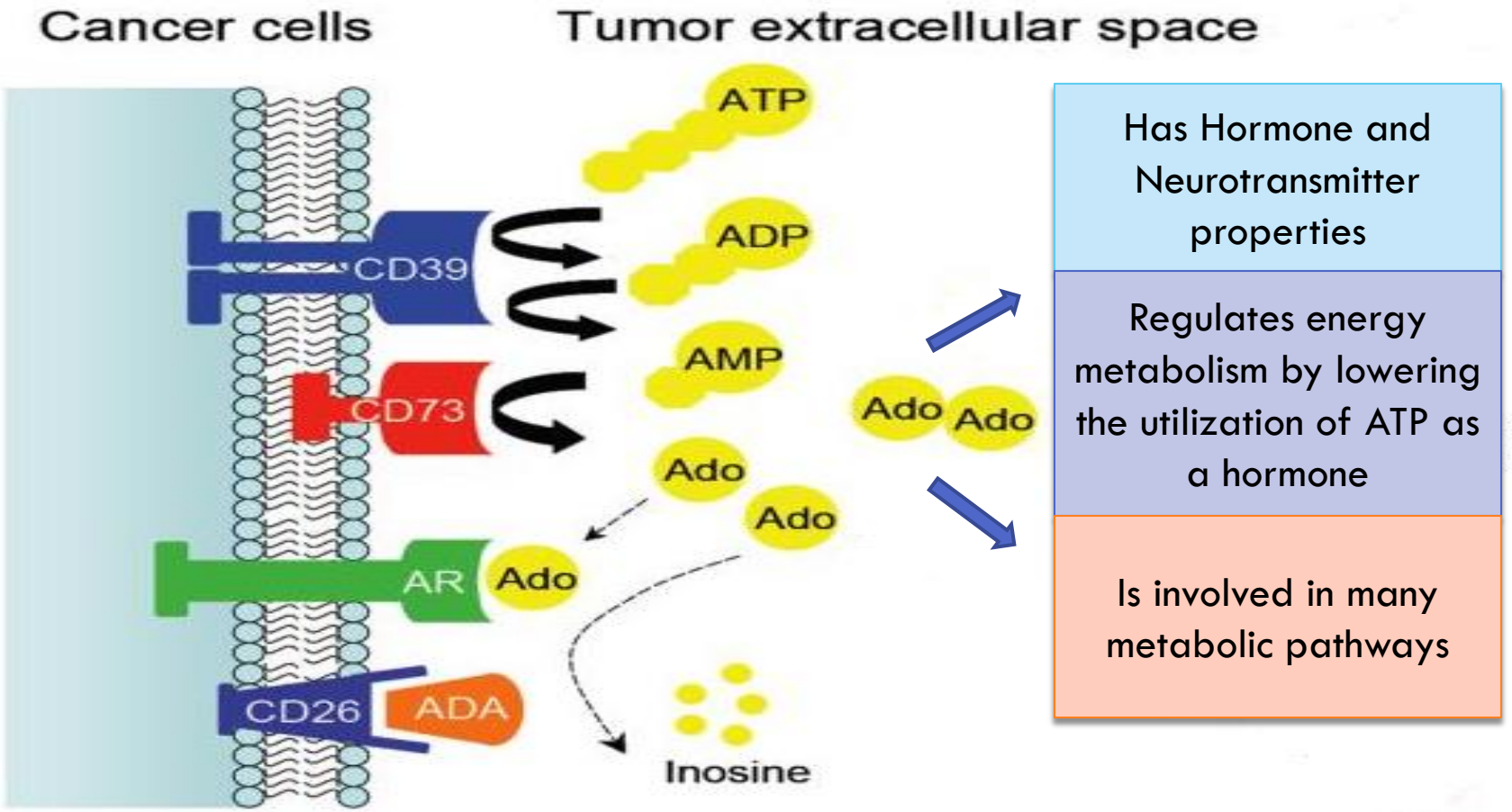

DNA synthesis
TMP
TK
Thymidine
Thymine
Degraded DNA
Necrotic Area
Carcinoma cell
TP
P
2dR1P
Oxygen radicals
MMP-1
VEGF
IL-8
Degradation extracellular matrix
Endothelial cell proliferation
Endothelial cell migration
PROLIFERATION
ANGIOGENESIS

The thymidine salvage pathway enzymes TK and TP compete for thymidine as a substrate and catalyze opposing synthetic and catabolic reactions that have been implicated in the control of proliferation and angiogenesis, respectively.

Key enzymes of adenosine (**Ado**) metabolism

Ecto-5'-nucleotidase (5'-NT AMP) or CD73 (5`-NT: 3.1.3.5)

Adenosine deaminase (ADA: 3.5.4.4)



Has Hormone and Neurotransmitter properties

Regulates energy metabolism by lowering the utilization of ATP as a hormone

Is involved in many metabolic pathways

The aim of this study

is to investigate the DNA precursors metabolism in healthy and patients with gastric cancer $T_{3-4}N_{0-x}M_0$ and to determine the possible role of it`s regulatory enzymes as biomarkers.

PATIENTS AND METHODS

- Seventy-four adult patients, 35–80 year old, with gastric cancer were included in this study.
- Patients were staged in the accordance with TNM classification (the 6th edition) as $T_{3-4}N_{0-x}M_0$.
- Eighty-two non-cancerous patients of the same age without gastroduodenal zone pathology formed control group and also were examined.
- The study protocol was approved by Ethical Committee permission of M. Gorky National Medical University (Donetsk, Ukraine) for studies with human materials.
- The features of enzymes activity were studied in blood serum and tissues. Activity of tissue enzymes was determined in the surgically removed material in thirty tumors (the mucosa margin of resection distant from the carcinoma had being as a control).

PATIENTS AND METHODS

- TK activity was determined by the radioisotope method. Radioactivity of diethyl-amino-ethyl-cellulose paper disks (DEAE-cellulose disks paper "Limbro" (UK) was counted in a liquid scintillation SL-8 on a biological scintillation counter (CBS-2, Russia). TK activity was given in nanomoles of thymidylate formed within an hour per 1 mg of protein.
- TP, ADA [Fritch], 5`NT [Edwards. Clin. Path. Immunology,1980] activity was determined spectrophotometrically.
- Protein concentration in biological material was determined using the method described by Lowry et al.
- Statistical analysis of results was performed using Medstat software package. On significance of differences was analyzed by parametric and nonparametric methods.

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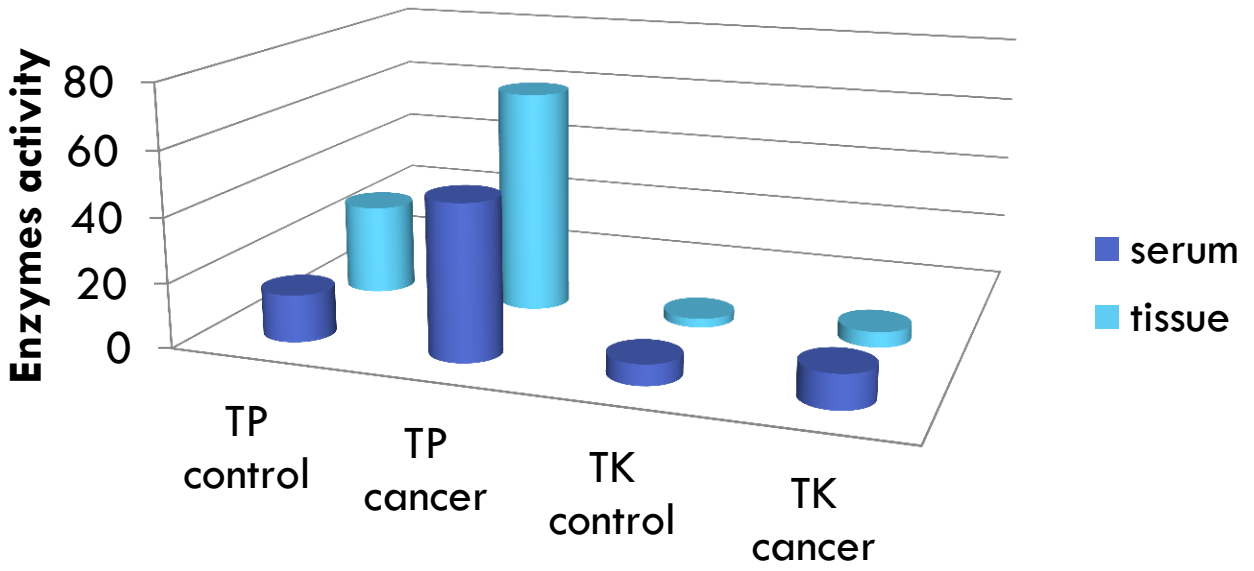
TP and TK activity in the serum of control group, patients with gastric cancer and in tissues, nmol/mg▪min and nmol/mg▪h, respectivly

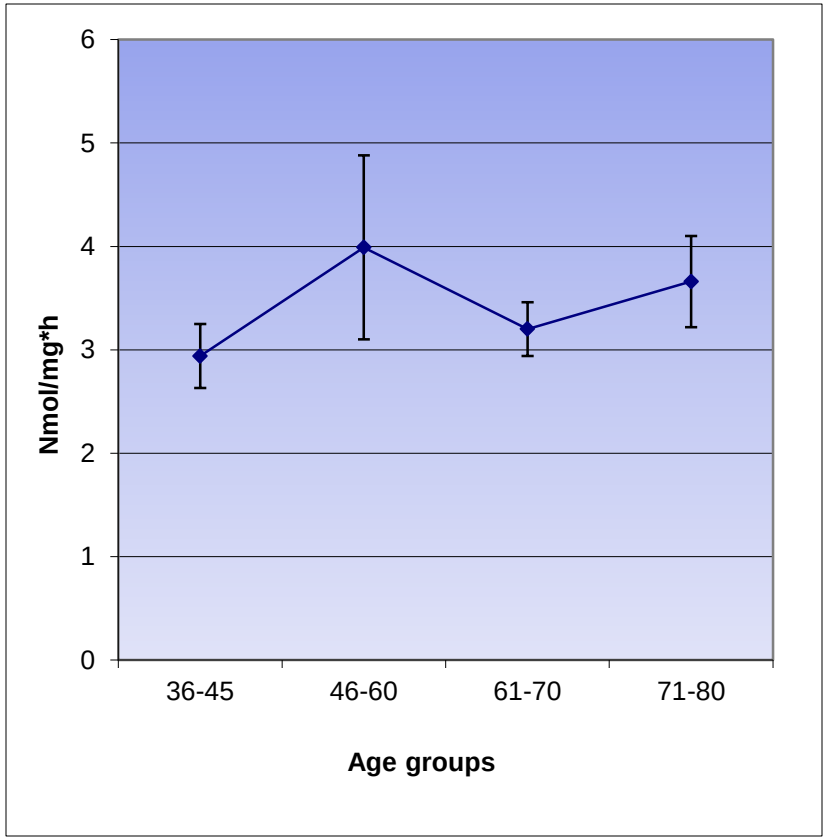


B.G. Borzenko, E.M. Bakurova, Yu.A. Popovich, et all. Activity of thymidilate "salvage pathway" enzymes in human gastric cancer and blood serum: correlation with treatment modalities// Exp.Oncol. – 2013. – Vol. 35, №1. – P. 37 – 40

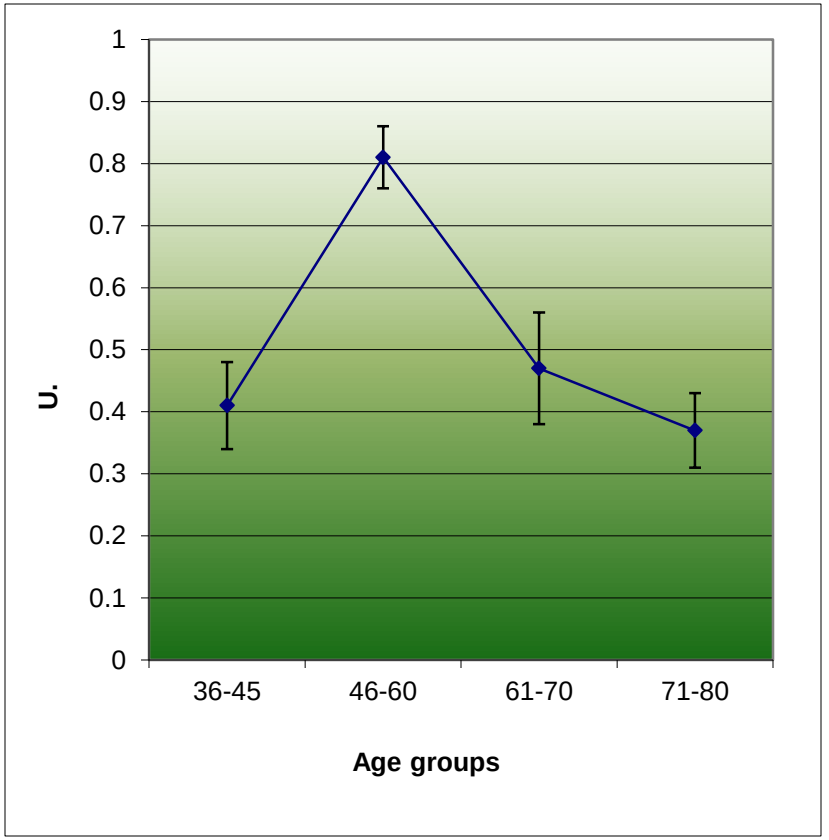
Sho Tabada, Ryuji Ikeda, Masatatsu , Sunii Shimaoka et all. Thymidine phosphorylase activates NFkB and stimulates the exspression of angiogenic and metastatic factors in human cancer cells// Oncotarget. - 2014. - 5(21). – P. 10473 – 85

TK and TP activity in blood serum of control group in dependence of age

The thymidine kinase activity



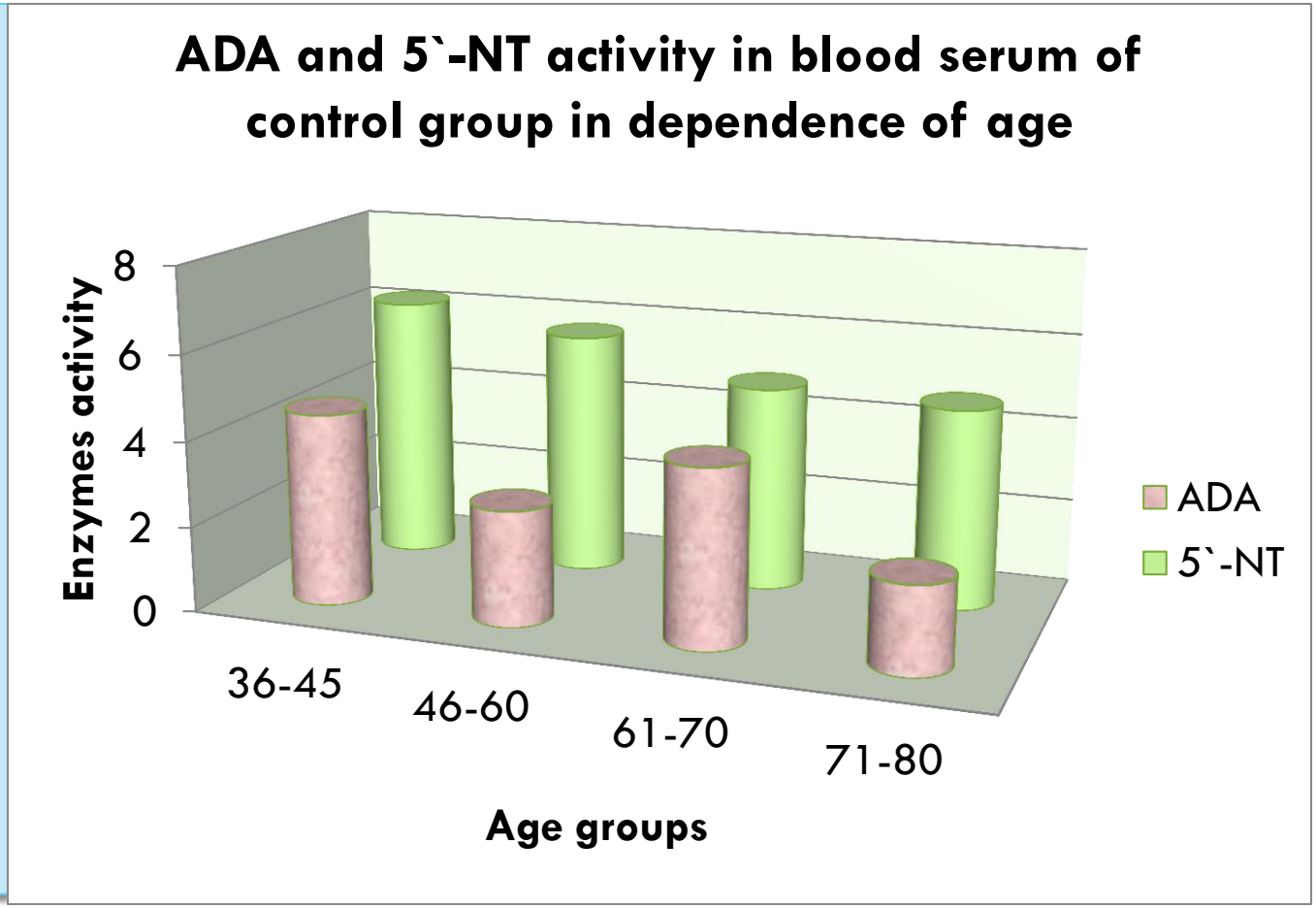
The thymidine phosphorylase activity



The activity of enzymes, which regulates metabolism of adenosine in blood serum of control group and gastric cancer patients

*Regateiro FS, Cobbold SP, Waldmann H. CD73 and adenosine generation in the creation of regulatory microenvironments.
Clin Exp Immunol. 2013. Sir William Dunn School of Pathology, University of Oxford, Oxford, UK.

*Zimmermann H, Zebisch M, Sträter N. Cellular function and molecular structure of ecto-nucleotidases.Purinergic Signal. 2012 .Institute of Cell Biology and Neuroscience, Molecular and Cellular Neurobiology, Biologicum, Goethe-University Frankfurt, Max-von-Laue-Str. 13, 60438, Frankfurt am Main, Germany.



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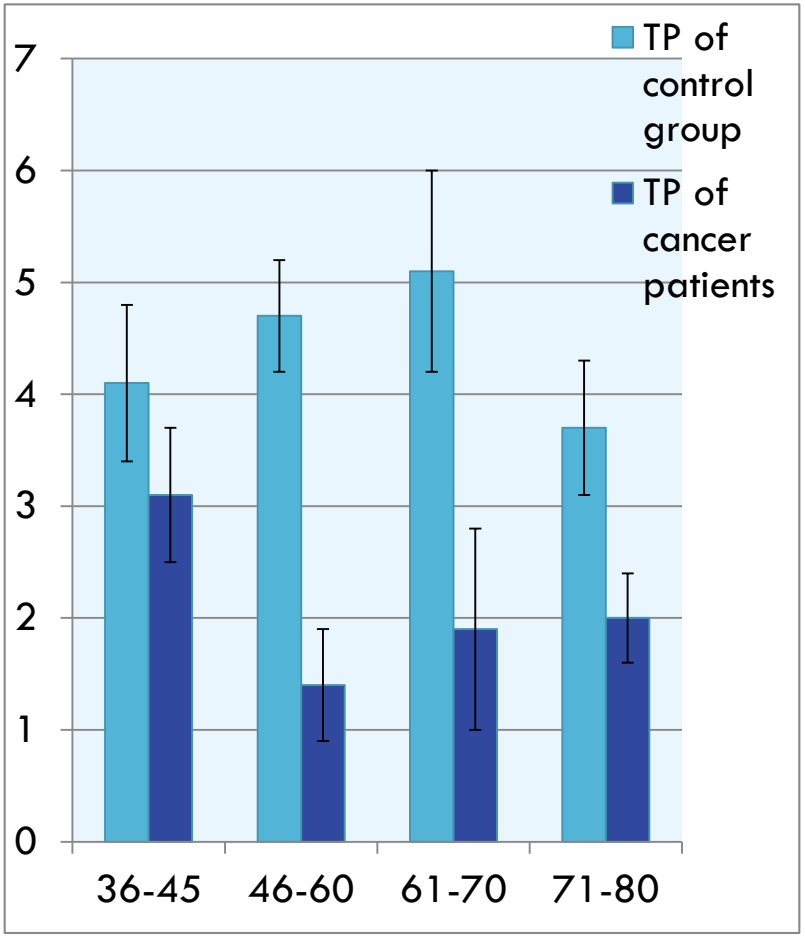
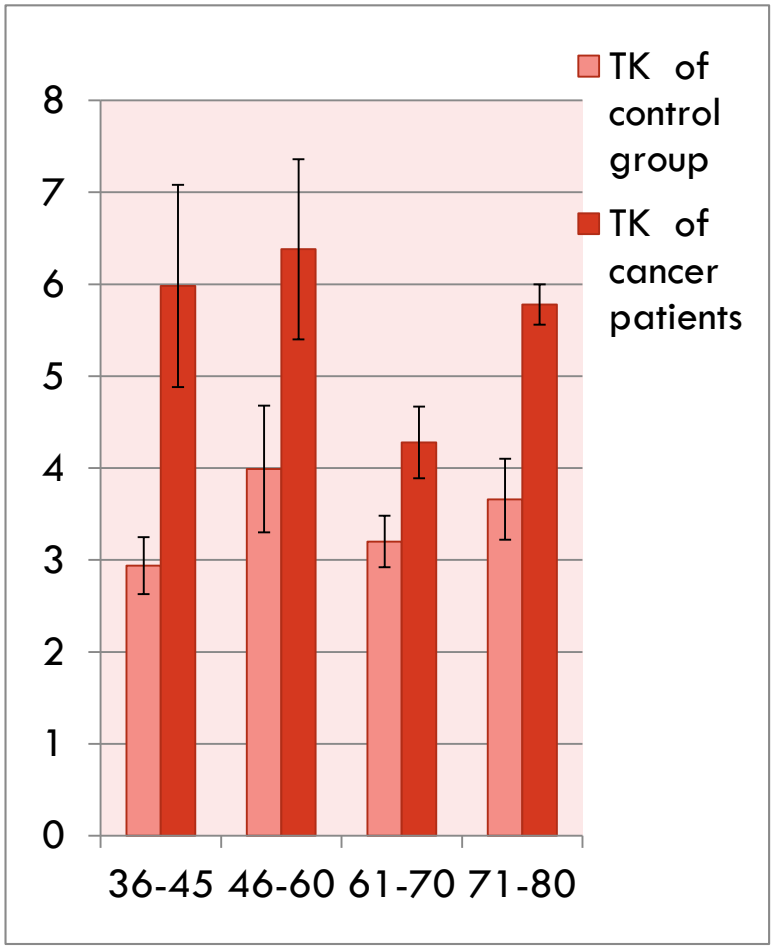
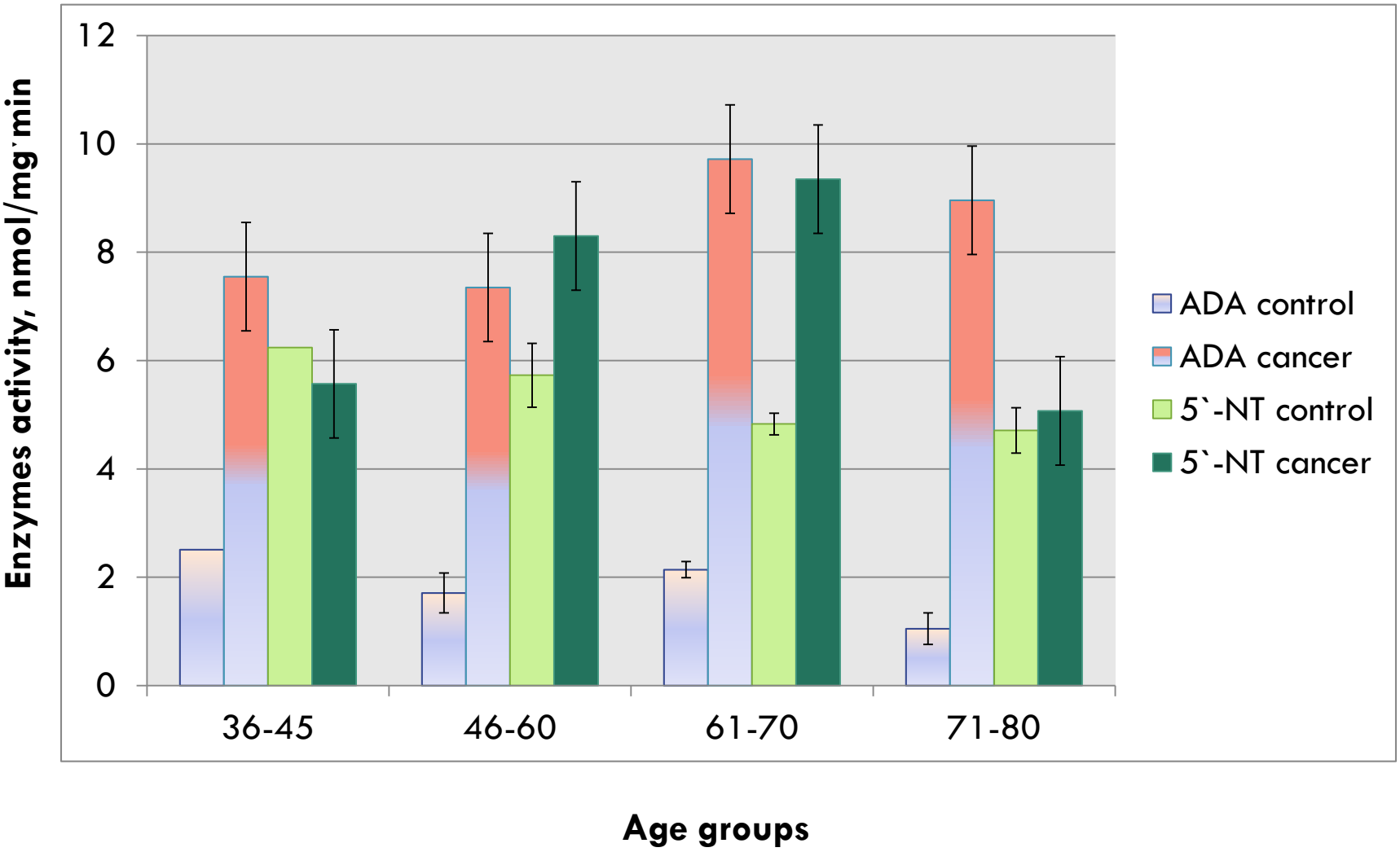
TP and TK activity of gastric cancer patients in different age groups

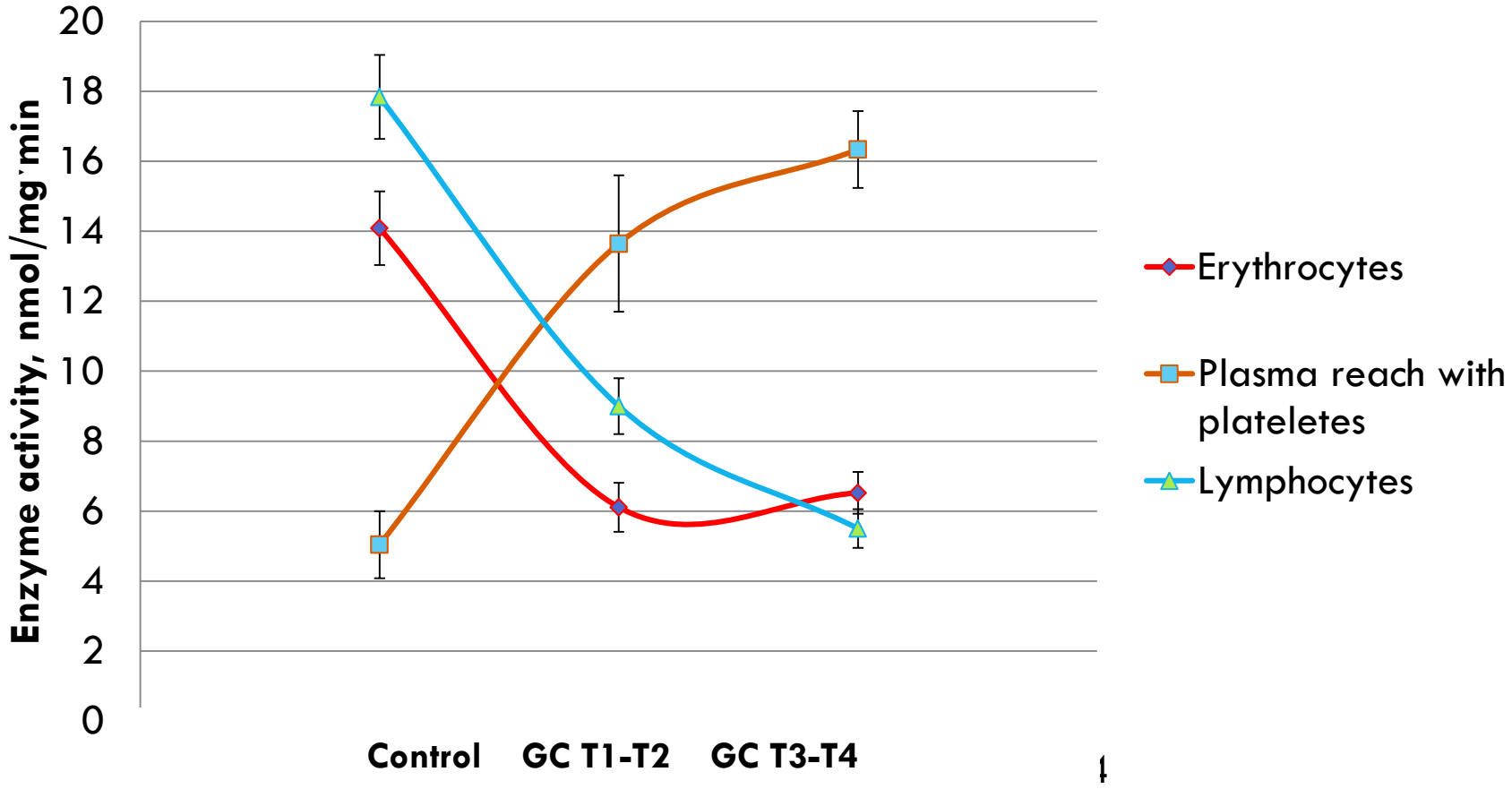




The activity of enzymes, which regulates metabolism of adenosine in blood serum of control group and gastric cancer patients



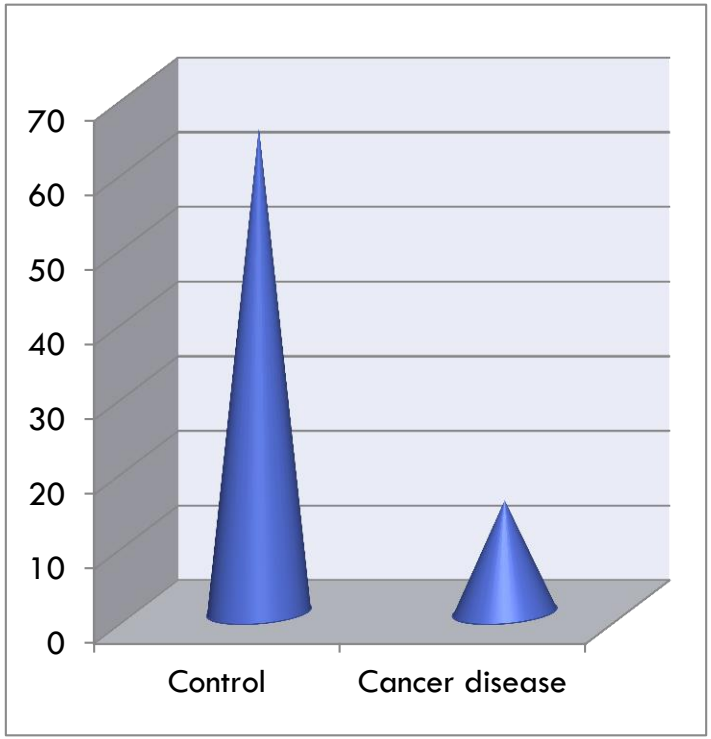
ADA activity in blood cells of gastic cancer patients



Sauer AV, Brigida I, Carriglio N, Hernandez RJ, Scaramuzza S, et.all. Alterations in the adenosine metabolism and CD39/CD73 adenosinergic machinery cause loss of Treg cell function and autoimmunity in ADA-deficient SCID. Blood. 2012.San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), Via Olgettina 58, Milan, Italy

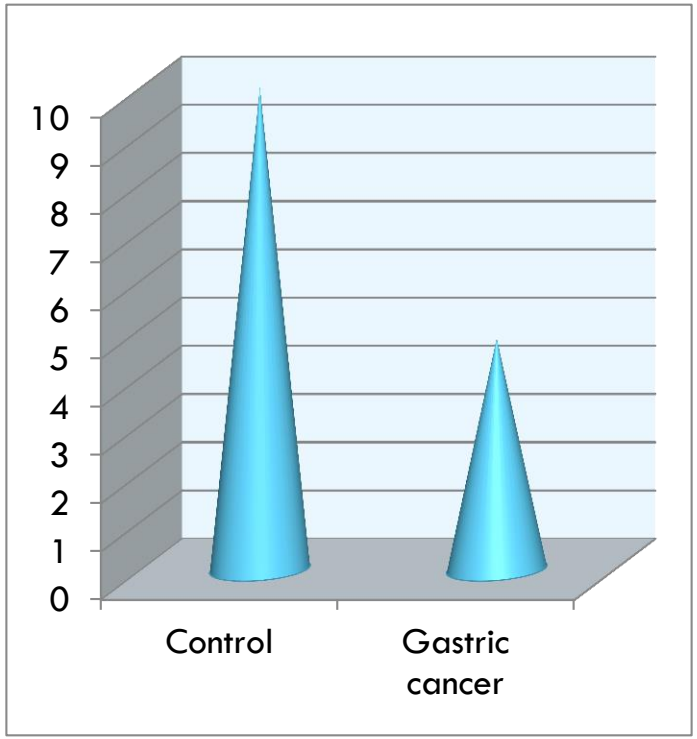
Analysis of lymphocytes and erythrocytes functional power

The blast transformation reactions of lymphocytes



The decline of cellular immune function

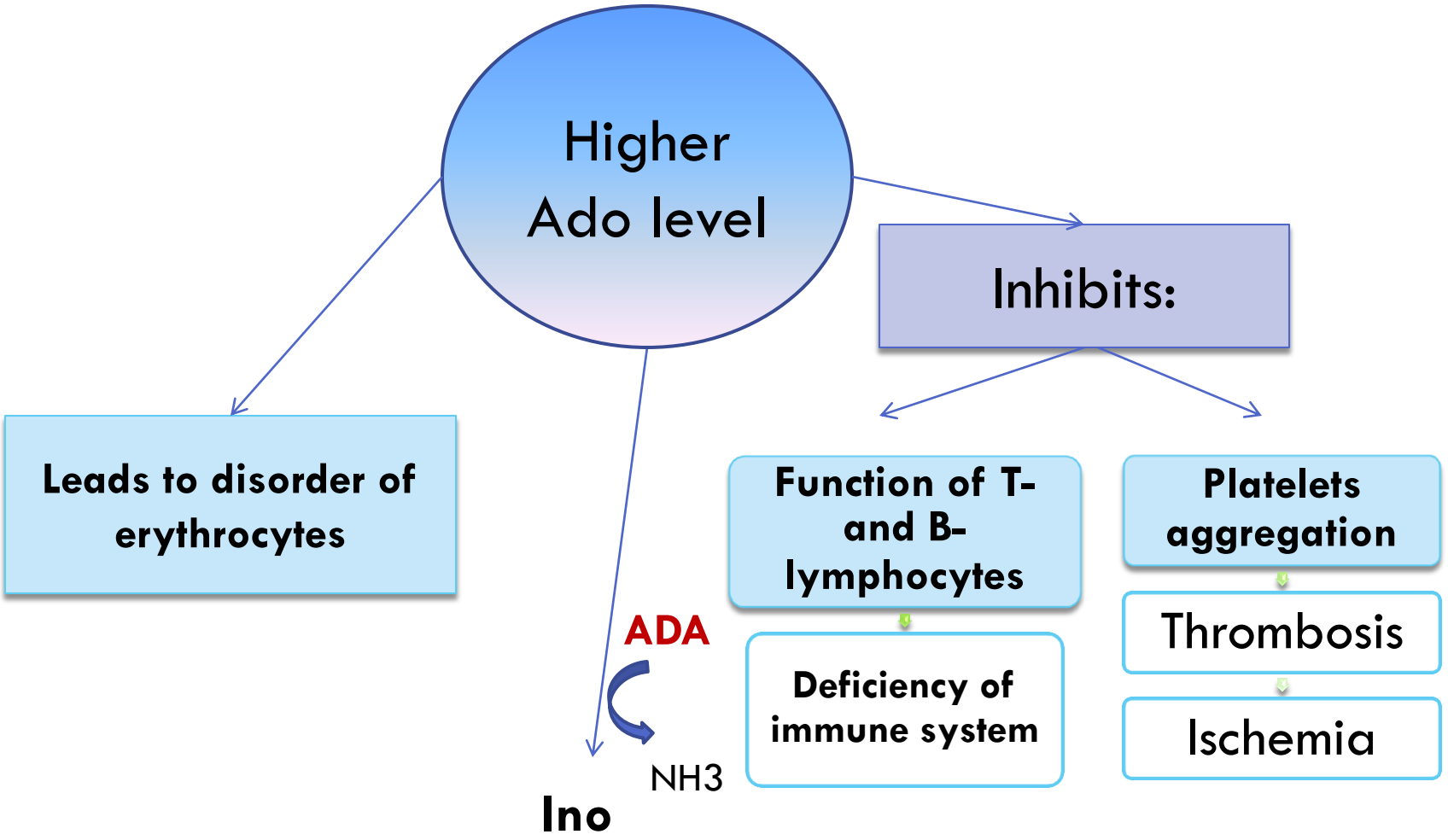
Sorption capacity of erythrocyte membrane



Disorder of transport function of erythrocytes

Regulatory enzymes of adenosine metabolism in blood serum and lymphocytes of gastric cancer patients

Age, years	ADA, nmol/mg*min				5`-NT, nmol/mg*min			
	Healthy		Oncology patients		Healthy		Oncology patients	
	serum	lympho cytes	serum	lympho cytes	serum	lympho cytes	serum	lympho cytes
	men							
36-45	1,83 ±0,14	182,4± 9	6,92 ±0,27	94,2 ±1,1	5,48 ±0,52	50,3 ±3,1	5,2± 0,33	25,4± 0,2
46-60	1,74 ±0,22	178,4± 2,1	9,46 ±2,6	89,6 ±3,6	5,76 ±0,26	48 ±5,7	10±0,5	36,8± 0,9
61-70	2,18 ±0,45	100,7± 7,2	8,98 ±1,2	73,4 ±3,9	5,63 ±0,46	45,1 ±2,1	10,3±0 ,6	29±1,9

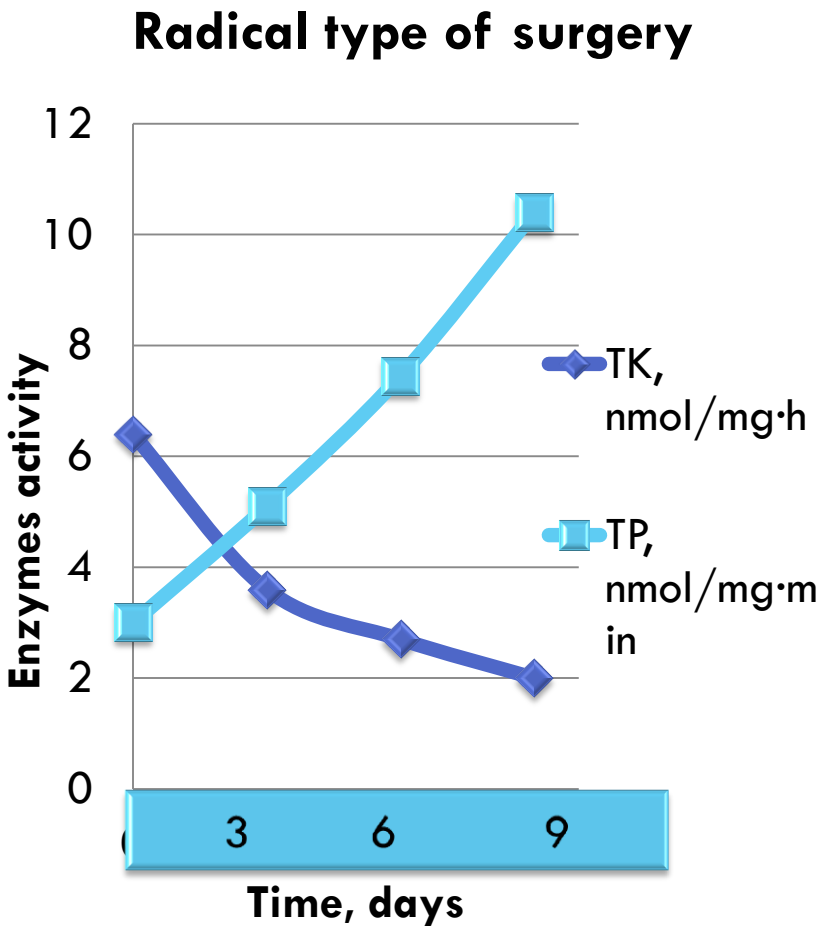

Higher
Ado level
Inhibits:
Leads to disorder of erythrocytes
ADA
NH3
Ino
Function of T- and B- lymphocytes
Deficiency of immune system
Platelets aggregation
Thrombosis
Ischemia

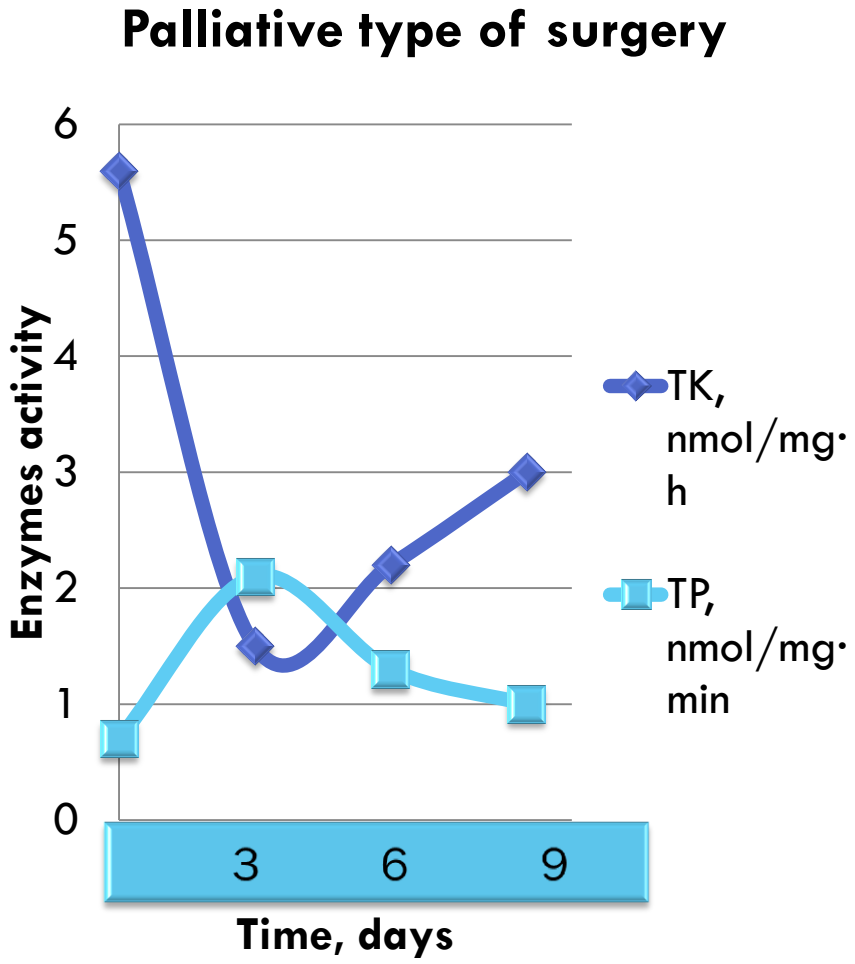
The association between serum enzymes activity and volume of surgical intervention

Enzymes activity	The type of surgery					
	radical		diagnostic		palliative	
	before	after 9 days	before	after 9 days	before	after 9 days
TK, nmol/mg·h	6,29 ± 1,47	3,40 ± 0,58*	6,43 ± 1,76	4,02 ± 0,45	5,50 ± 0,67	1,97 ± 0,20*
TP, nmol/mg·min	15,28 ± 2,1	38,33 ± 1,9**	10,03 ± 2,4	11,43 ± 2,2	13,0 ± 1,8	14,52 ± 1,7*
ADA, nmol/mg·min	7,19 ± 2,9	5,95 ± 0,6	7,45 ± 2,2	6,57 ± 1,3	10,31 ± 2,5	10,96 ± 1,5
5`-NT, nmol/h·mg	63,02 ± 8,1	40,58 ± 6,3*	51,48 ± 2,1	31,52 ± 3,9*	48,62 ± 6,5	38,86 ± 5,2

Note: authentic differences versus previous value: *- $p < 0.05$, ** - $p < 0.01$

Comparative dynamic of thymidine kinase and thymidine phosphorylase activity during treatment





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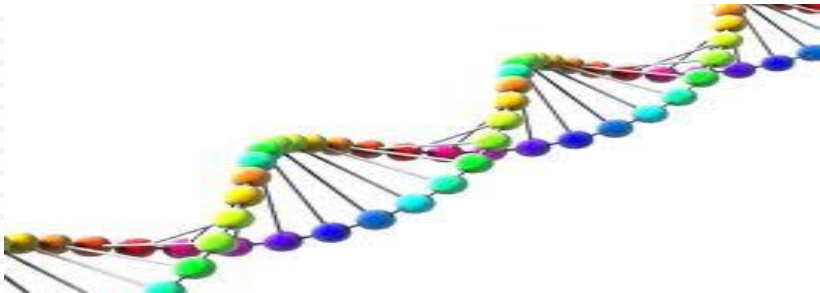
Conclusions

An activity of TK, TP, ADA and 5`-NT has an effect on the tumor disorders.

The control of individual dynamics of this enzymes activity in blood serum of gastric cancer patients may be used as informative tool for monitoring of patients and treatment optimization.



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