

Novel Synthetic Immunomodulator “MAK” with Antitumor Activity

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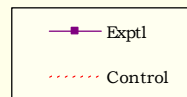
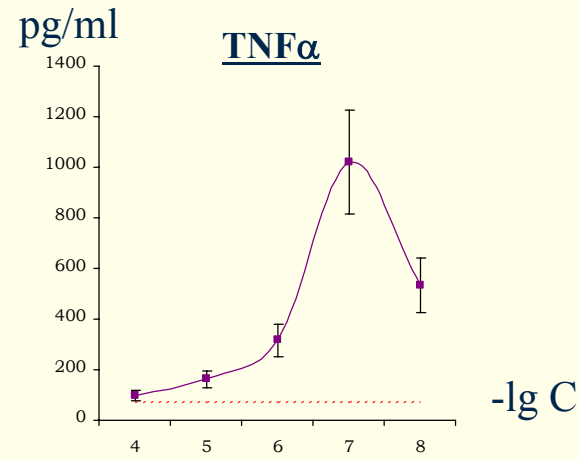
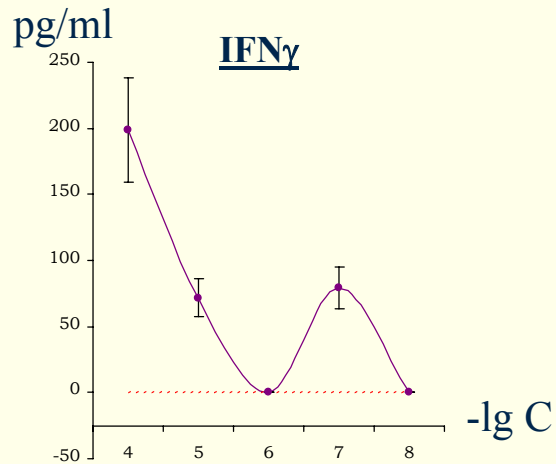
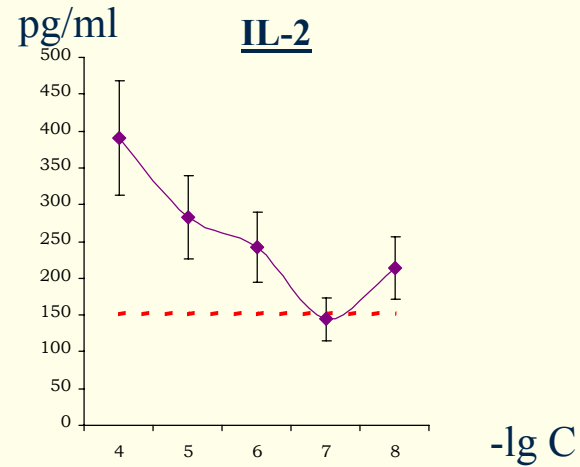
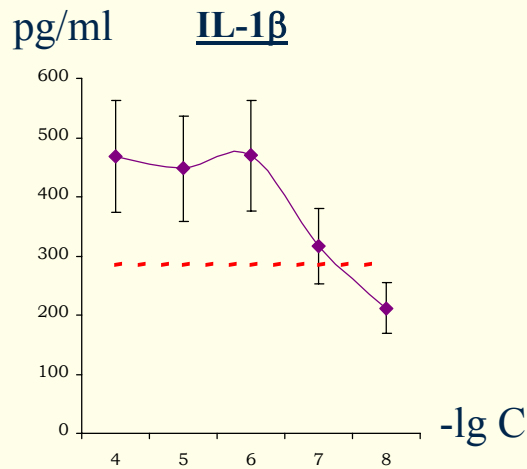
Need for New Immunotherapy Treatments

- In Russia it has been revealed more than 200, 000 malignant tumor patient a year
- 38% of these patients are surgically treated and 28% are treated with chemo-radiation therapy
- Approximately 66% of post-surgery and post chemo-radiation therapy patients require immunomtherapy treatment
- In Russia, the approximate need for immunomotherapy is estimated at 7 Million doses/year
- Current treatments range from \$24 to \$480 USD per dose

Introducing MAK

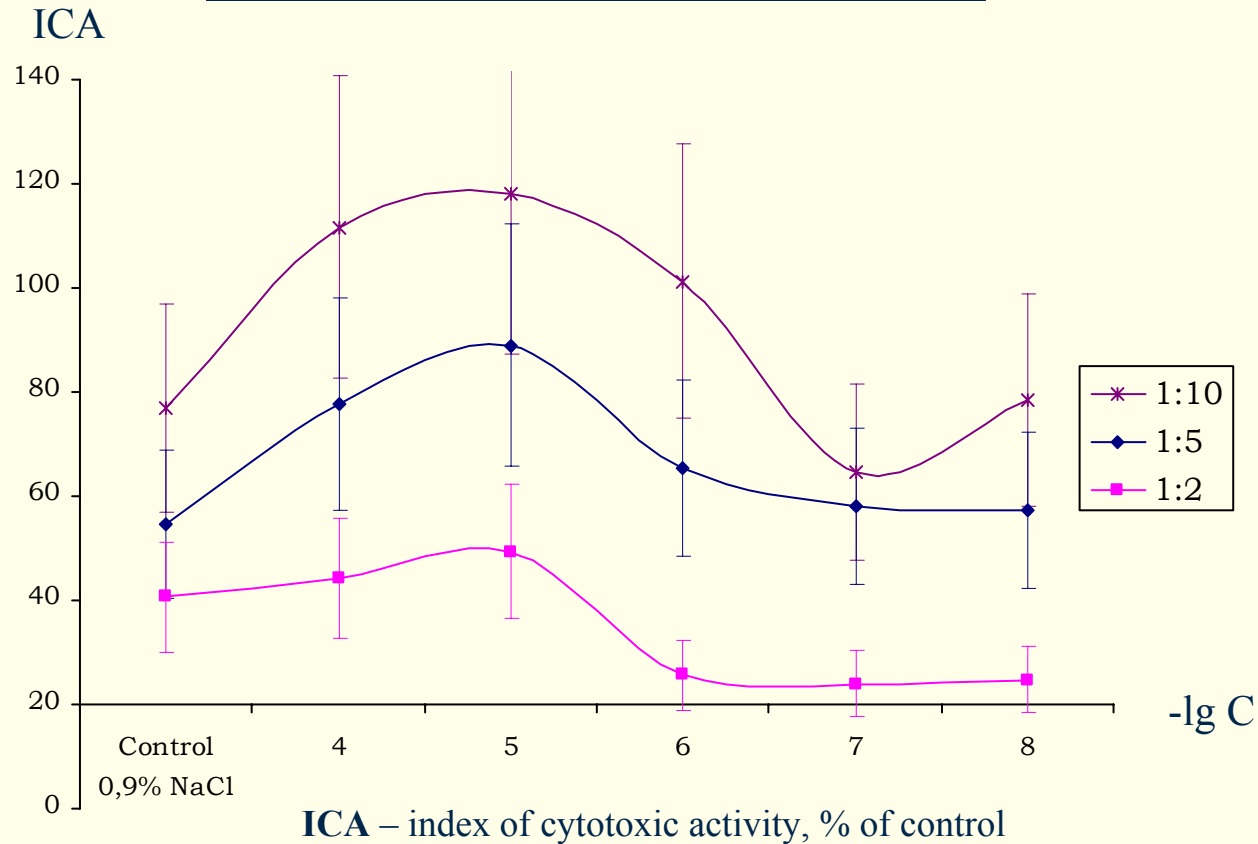
- MAK is a unique synthetic low-molecular-weight substance, designed by and prepared at GosNIIOKhT
- Extremely stable in aqueous solution
- In preclinical tests, MAK exerts biological activity in doses ranging from 0.004 to 0.04 mg/kg, which are 10,000-fold less than the toxic dose.
- MAK is capable of exerting remarkable stimulating effect with respect to antitumor immune defense in humans as shown in experiments *in vitro*.
- MAK activates mononuclear cells to excrete cytokines (IL-2, IL-1 β , IFN γ and TNF α) and stimulates their cytotoxic activity.

Cytokine activation effect of MAK



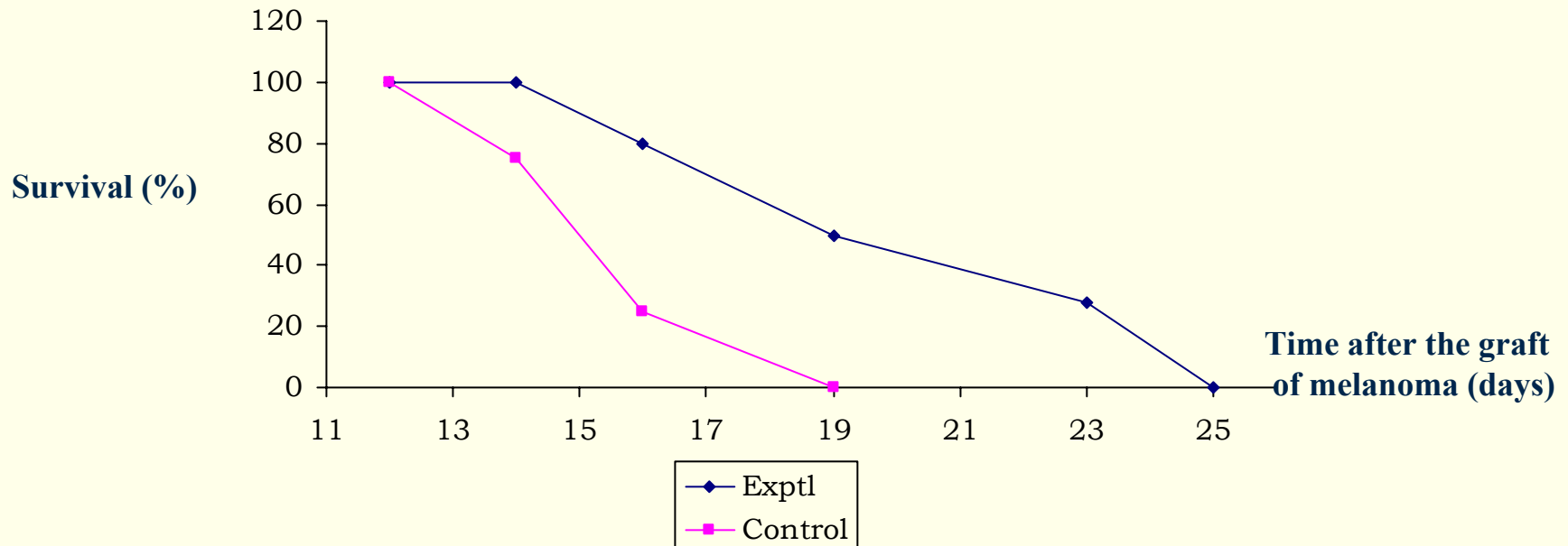
Influence of MAK on cytotoxic activity of natural killers

Tumor cells:Natural killers = 1:10, 1:5, 1:2

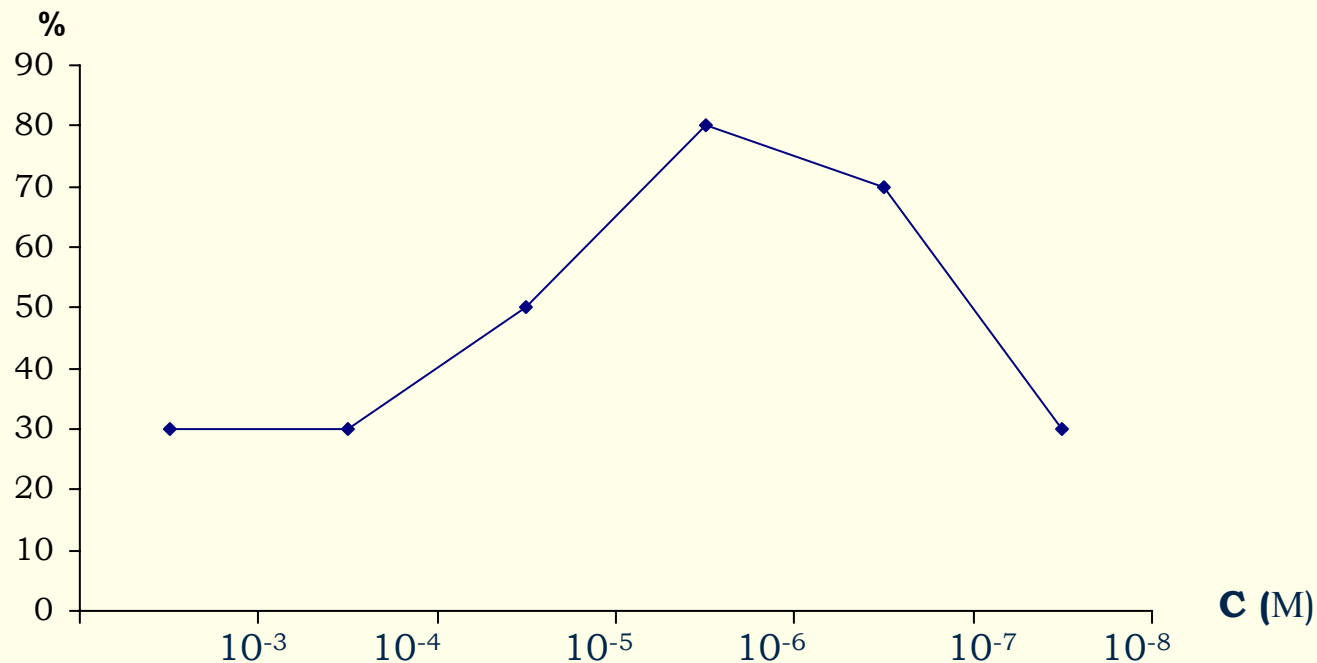


Survival of mice with grafted melanoma B 16 treated with MAK

One injection 0,004 mg/kg everyday during 10 days



Inhibition of tumor growth (melanoma B 16) by MAK



Inhibition of adenocarcinoma (CaO-1) growth by MAK

Dose	Time after transplantation		
	<u>10 days</u>	<u>12 days</u>	<u>15 days</u>
0.005 mg/kg	42 %	43 %	32 %
0.05 mg/kg	45 %	49 %	42 %
0.5 mg/kg	52 %	45 %	40 %

Comparison of MAK vs. Proleukin®: Ehrlich's carcinoma

MAK displays similar immunomodulatory activity to Proleukin®
(interleukin-2) in comparative biomedical assays

Time (Days)	14	15	16	19	20	22	25	26	Survival
Control	6/0	6/1	5/2	3/2	1/0	1/0	1/0	1/0	1
Proleukin®	6/1	5/0	5/0	5/1	4/0	4/0	4/0	4/0	4
MAK	7/2	5/1	4/0	4/0	4/0	4/0	4/0	4/0	4

Acute toxicity of MAK in animal tests

Dose	Mice		Rats	
	Subcutaneous	Per os	Subcutaneous	Per os
LD₅₀, mg/kg	488.9	416.2	420.2	753.5
LD₈₄, mg/kg	690.0	860.0	760.0	1200

Clinical Toxicology: MAK

Object for research	Dose	Result
Blood morphology and biochemistry (rabbits)	0,04 mg/kg, s.c.-5 time	within the limits of norm
	0,4 mg/kg, s.c.–1 time	within the limits of norm
Cumulation (mice)	50-550 mg/kg, s.c.	no cumulation
cardiovascular & respiratory systems (rabbits)	0,05-5 mg/kg	within the limits of norm
Pyrogenesis (rabbits)	0,02 mg/kg, i.v.	no pyrogenic effect
Proallergic and antiallergic action (guinea-pigs)	0,05-0,5 mg/kg, s.c.	no allergic effects and anaphylaxis

MAK: Other Biological Effects

- Increases phagocytic activity (10^{-4} - 10^{-6} M)
- Antiplatelet-aggregation effect (10^{-11} M)
- Bacteriostatic activity (10^{-4} M)
- Cytokine induction by MAK may also suggest application for chronic recidivous viral deseases, such as hepatitis.

MAK: Advantages

- Prominent biological activity
- Stable in solution
- Relatively easy to produce
- **Cost**

Proleukin[®] (Netherlands): \$480 USD/dose

Ronkoleukin[®] (Russia): \$24 USD/dose

Estimated cost of 1 dose of MAK is \$2 USD

Conclusions: MAK

- MAK may have the potential to improve the immune status of patients between the courses of chemo and radiation therapy.
- MAK may be useful for prophylaxis and treatment of purulent and septic complications for post-surgery patients marked by weakening of the immune defense
- MAK could be tested as potential chemo-preventive drug for high-risk persons, supplementary to clinical monitoring for anti-tumor components of the patient's immune system.

MAK: Next Steps

- A procedure for synthesis of MAK has been developed and will be used as a basis for pilot drug manufacturing
- Investigation of chronic toxicity and pharmacokinetics
- Realization of clinical trials

Contact Information

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