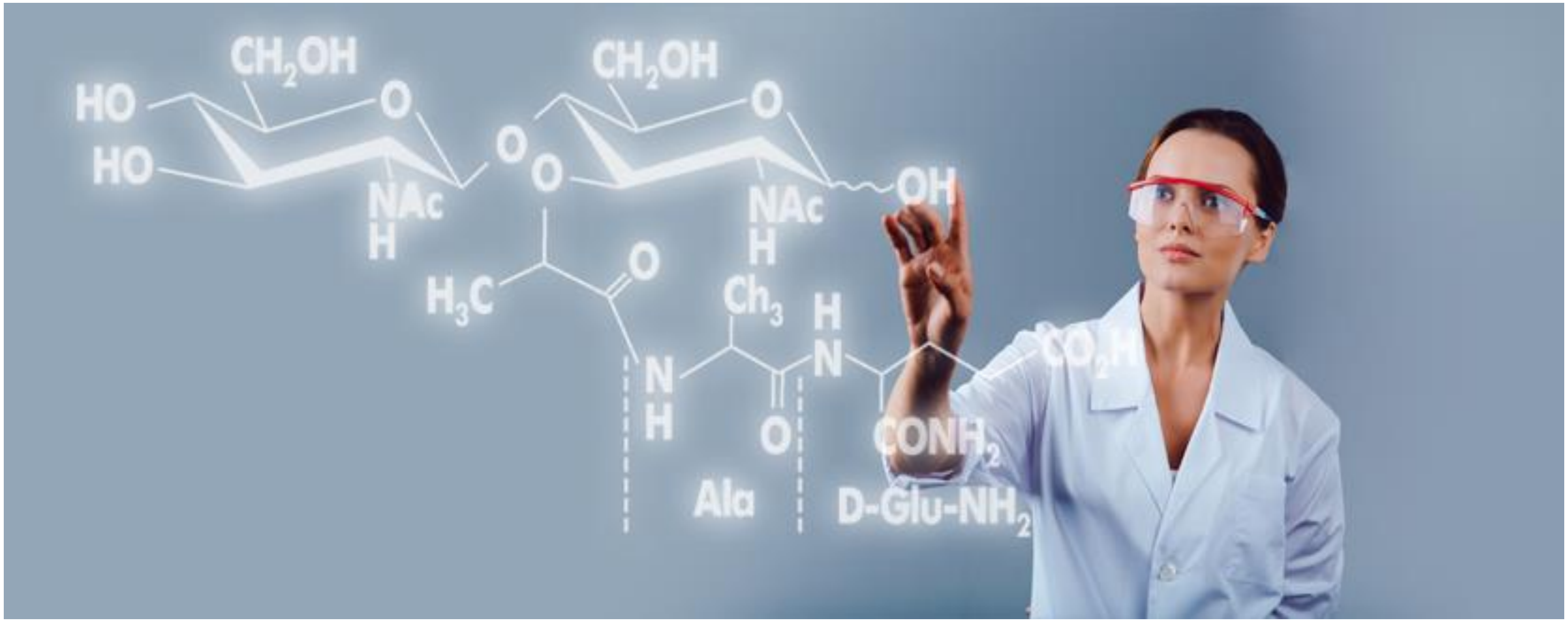
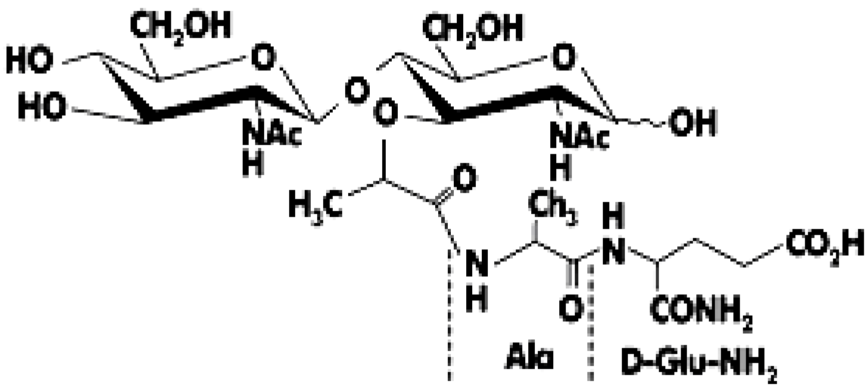
From molecule to drug

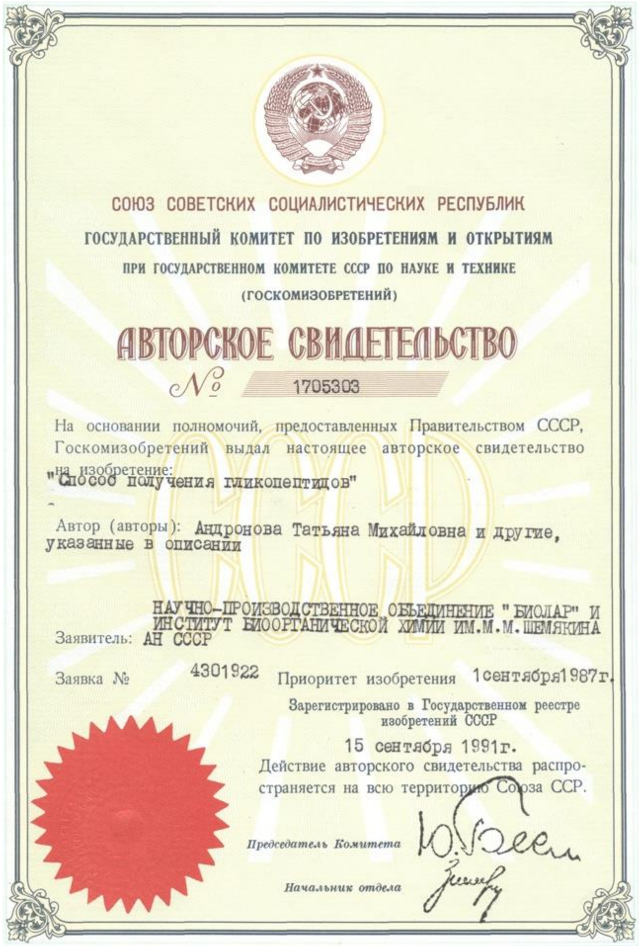


“Peptek” JSC
Moscow, 2018

Identification, Extraction and Synthesis of GMDP



Synthetic glucosaminylmuramyl dipeptide (GMDP) is an analogue of biologically active fragment of peptidoglycane of Gr(+) & Gr(-) bacteria cell wall.
In 1975 it was extracted in the Institute of Bioorganic Chemistry of the Academy of Sciences of USSR.



СОЮЗ СОВЕТСКИХ СОЦИАЛИСТИЧЕСКИХ РЕСПУБЛИК

ГОСУДАРСТВЕННЫЙ КОМИТЕТ ПО ИЗОБРЕТЕНИЯМ И ОТКРЫТИЯМ

ПРИ ГОСУДАРСТВЕННОМ КОМИТЕТЕ СССР ПО НАУКЕ И ТЕХНИКЕ

(ГОСКОМИЗОБРЕТЕНИЙ)

АВТОРСКОЕ СВИДЕТЕЛЬСТВО

№ 1705303

На основании полномочий, предоставленных Правительством СССР, Госкомизобретений выдал настоящее авторское свидетельство на изобретение:
"Способ получения гликопептидов"

Автор (авторы): Андронова Татьяна Михайловна и другие, указанные в описании

Заявитель: НАУЧНО-ПРОИЗВОДСТВЕННОЕ ОБЬЕДИНЕНИЕ "БИОЛАР" И ИНСТИТУТ БИООРГАНИЧЕСКОЙ ХИМИИ ИМ.М.М.ШЕМЯКИНА АН СССР

Заявка № 4301922 Приоритет изобретения 1сентября1987г.

Зарегистрировано в Государственном реестре изобретений СССР

15 сентября 1991г.

Действие авторского свидетельства распространяется на всю территорию Союза ССР.

Председатель Комитета

Начальник отдела

In 1997 set of works “Development and arrangement for the biotechnical production of Licopid® – new immunocorrecting drug” was awarded by the government of the Russian Federation.

The history of the discovery of the MDP and GMDP

E. Lederer – synthesis and description of muramyl dipeptide (MDP) molecule

Institute of Natural Compounds Chemistry; Gif-sur-Yvette, Institute of Biochemistry, Faculty of Sciences, Orsay, France

Andronova T.M., synthesis and description of glucosaminylmuramyl dipeptide (GMDP) molecule

INSTITUTE OF BIOORGANIC CHEMISTRY OF THE ACADEMY OF SCIENCES OF USSR,
WELLCOME FOUNDATION LTD, LANGLEY COURT, UK,
BIOKINE TECHNOLOGY LTD, DIRECTOR OF RESEARCH, UK
PEPTECH (UK) LIMITED, DIRECTOR OF RESEARCH, UK

June 8, 1995 – International Birth Date, IBD
Licopid® tablets 1 mg & 10 mg

1989-1996 – organization of the company's branch in the United Kingdom

1996, 2nd August – "PEPTEK" CJSC, Russia

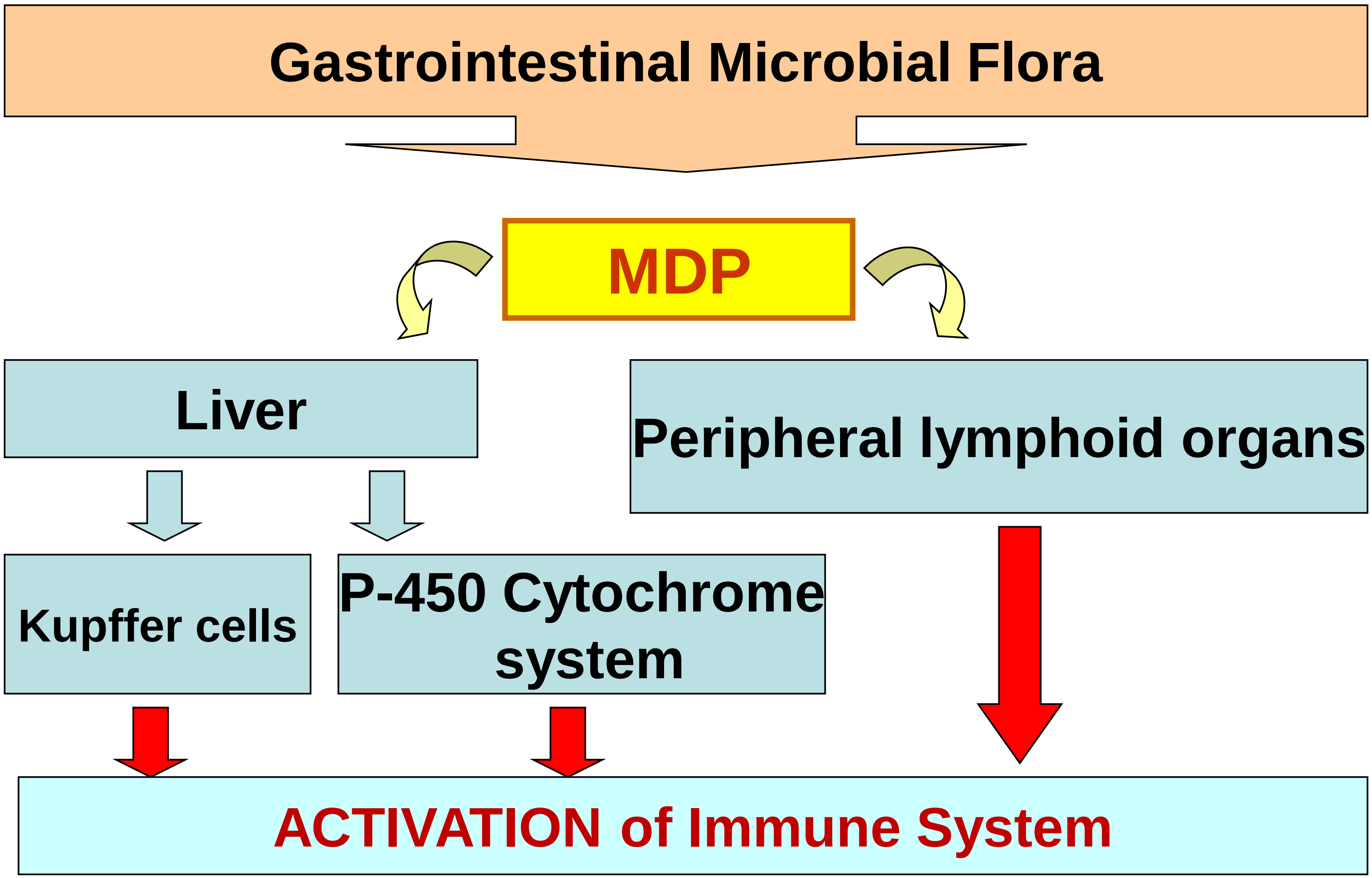
Main areas of application:

- Acute and chronic recurring respiratory infections (adults, children)
- Pyo-inflammatory skin and soft tissue diseases (treatment, prevention of post-surgery complications) (adults, children)
- Herpes Viral infections (adults, children)
- Papilloma viral infection (adults)
- Chronic viral hepatitis B and C (children)
- Psoriasis (adults)
- Tuberculosis (adults)
- Neonantology

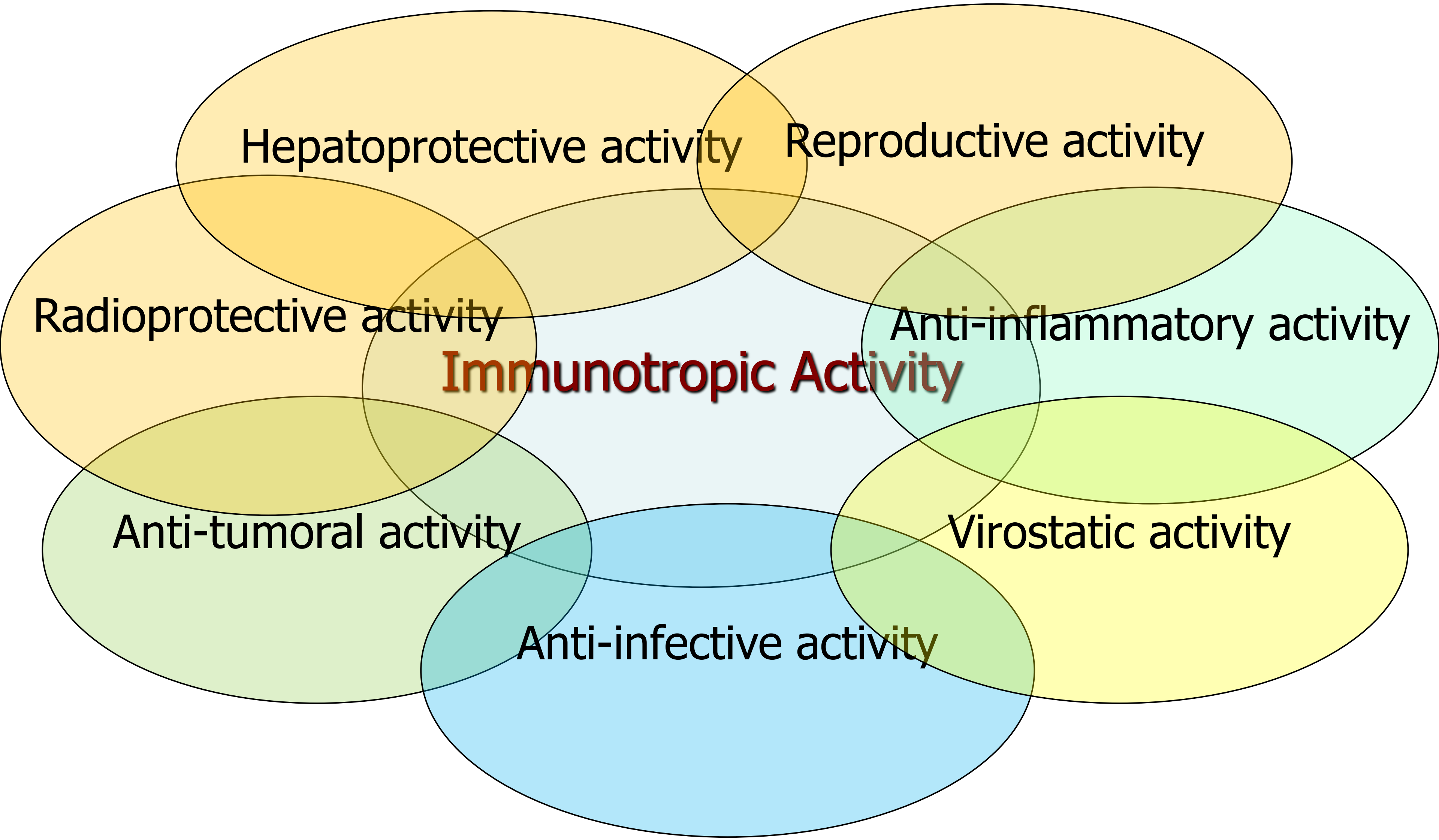
International medical and pharmaceutical
Business Forum «APTEKA»

E. Lederer's Hypothesis:
muramyl peptides - the "vitamins" of the immune system.

MURAMYL PEPTIDES CONSTANTLY GAIN ACCESS TO THE BODY DUE TO DEGRADATION OF BACTERIA CELL WALLS AND ARE PRESENT IN SMALL CONCENTRATIONS IN MANY TISSUES, HAVING VARIOUS NEURO – AND IMMUNE REGULATING EFFECTS, I.E. EXOGENOUS ADMINISTRATION OF DERIVATIVE MURAMYL PEPTIDES REPRODUCES PHYSIOLOGICAL AND EVOLUTIONARY ESTABLISHED IMMUNE RESPONSE MODULATION MECHANISMS.



Pharmacological Effect of Muramyl Peptides

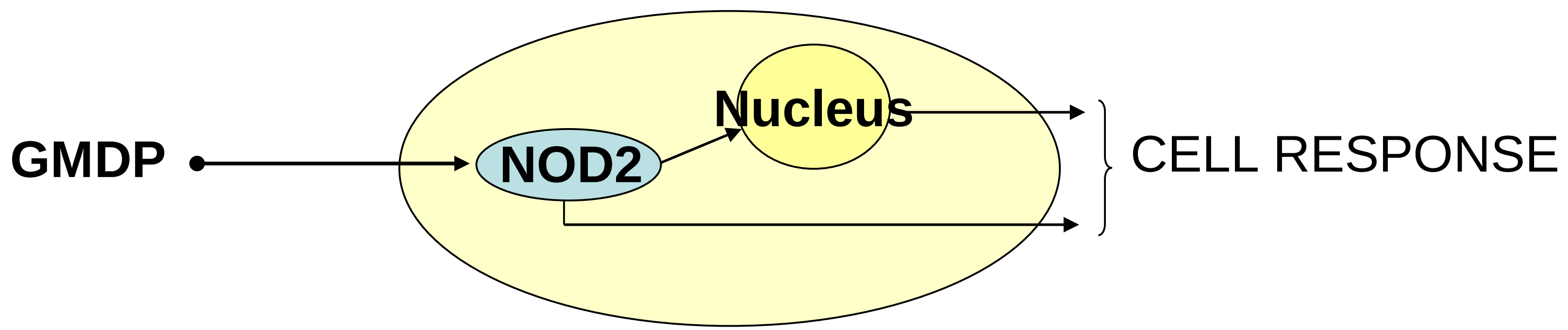


Known and Expected Molecular Mode of GMDP Action (Licopid)

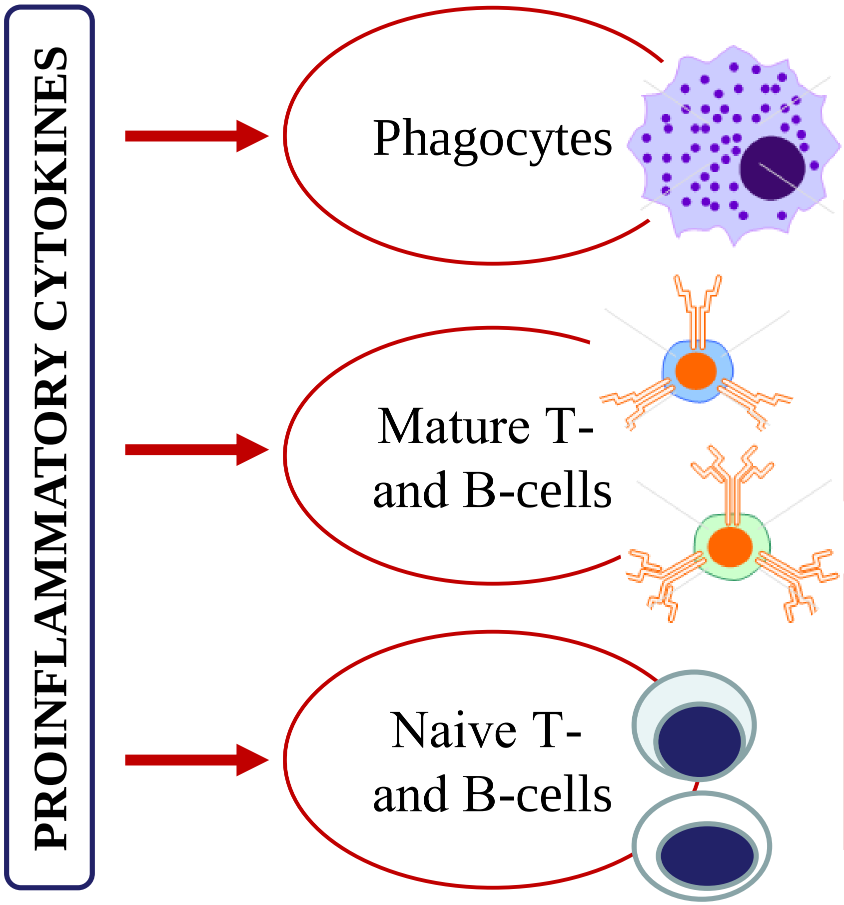
- **1995-2003 –** Search for molecular target of GMDP (Licopid)

- **2003-2007 –** Accurately classified with description of molecular interaction way through the innate immunity receptor - NOD2 receptor Girardin S.E., 2003 (Pasteur's Institute, France); Meshcheryakova E.A., 2007 (Institute of Bioorganic Chemistry of the Russian Academy of Sciences, Russia).

GMDP (Licopid) – ligand of NOD2 receptor



Licopid (GMDP) – NOD2: real activator of innate immunity



Cytokine effect is realized in three directions:

- **Phagocytes**
- **Mature T- and B-cells** – strengthening of functions (increased production of Ig, activation of killers)
- **Naive T- and B-cells** – activation and preparation for immune response

Preclinical & Clinical trials I-III
Peptech, UK&Peptek, Russia

United Kingdom

Preclinical (Toxicol Laboratories Ltd., UK)

Clinical (I phase, The Royal Masonic Hospital, London)

Russia

Preclinical (R&D Institute of Pharmacology of the Russian Academy of Medical Sciences, State Scientific Center at the Institute of Immunology of the Federal Medical and Biological Agency)

Clinical (I-III phase, State Scientific Center at the Institute of Immunology, Russian National Research Medical University n/a Pirogov N.I.)

Latvia

Preclinical (Institute of Organic Synthesis at the Academy of Sciences of Latvia)

Australia

Clinical (II phase, UNSW Department of Surgery and Department of Oncology, Cancer Care Centre, The St. George Hospital, Sydney)

Clinical Trials:

Total: 44 clinical studies, of which:

35 under the protocol of randomized double blind trials with placebo control of

1750 patients

Clinical Trial Bases:

Clinical base	Country	Year	Number of patients
The Royal Masonic Hospital, London (Charterhouse Clinical Research Unit Limited)	United Kingdom	1993	29
UNSW Department of Surgery and Department of Oncology, Cancer Care Centre, The St. George Hospital, Sydney	Australia	1993	26
State Scientific Center at the Institute of Immunology of the Federal Medical and Biological Agency of the Russian Federation	Russia	1992 1993 1994 1995 1996 1997	230 134 20 61 29 253
State Scientific Center , Scientific Center of Dermatovenerology and Cosmetology of the Ministry of Health of the Russian Federation	Russia	1994-1995	139
Clinical Tuberculosis Hospital No. 3	Russia	1993	30
Russian National Research Medical University named after Pirogov N.I.	Russia	1997 1998 1999 2002 2003 2006	60 68 189 90 69 70
First Moscow State Medical University n/a Sechenov N.A.	Russia	1994 1995	30 18
Moscow State Medical University n/a n/a Semashko N.A.	Russia	1993-1994	60
Moscow Research and Development Institute of Eye Diseases n/a Helmholtz	Russia	1993-1994	95
Military and Medical Academy n/a Kirov S.M.	Russia	2009	50
		TOTAL:	1750

Licopid® 1 mg and Licopid® 10 mg
(LS-001438-230911 dated 23.09.2011)

Licopid® 1 mg

Available without prescription

Licopid® 10 mg

Available with prescription

Instruction for Licopid® 1 mg (LS-001438-230911 dated 23.09.2011)

Licopid® 1 mg

	Cost per treatment period:	
Children (from 3 to 18 years old)		
Chronic recurring infections of upper and lower respiratory ways (in the exacerbation and remission phase):	990 ₽	15 $
Acute and chronic pyoinflammatory skin and soft tissues diseases (pyodermatitis, furunculosis and other)	330 ₽	5 $
Herpes viral infections	990 ₽	15 $
	Cost 1 pack:	
	330 ₽	5 $

Instructions for Licopid ® 1 mg (LS-001438-230911 dated 23.09.2011)

Licopid 1 mg	Cost per treatment period:	
Adults		
Chronic respiratory infections	660 ₽	10 $
Acute and chronic pyoinflammatory skin and soft tissues diseases	1320 ₽	20 $
Herpes viral infections	1980 ₽	30 $
	Cost 1 pack:	
	330 ₽	5 $

Instruction for Licopid® 1 mg (LS-001438-230911 dated 23.09.2011)

Licopid 1 mg

Preventive administration (adults):

For prevention or decrease of seasonal ARD incidences, and frequency of aggravation of diseases of ENT-organs, upper and lower respiratory ways

Cost 1 pack:

330 ₽ 5 $

Cost per Treatment Period:

990 ₽ 15 $

Instruction for Licopid® 10 mg (LS-001438-230911 dated 23.09.2011)

Licopid ® 10 mg	Cost per treatment period:	
Acute and chronic pyoinflammatory skin and soft tissue diseases (severe disease, including pyo-septical postsurgical complications)	2000 ₽	30 $
Herpes infections (recurring infection, sever forms):	2000 ₽	30 $
• Ophthalmic Herpes	4000 ₽	60 $
Sexually-transmitted infections:		
• Papilloma Viral Infection	2000 ₽	30 $
• chronic trichomoniasis	2000 ₽	30 $
Psoriasis	4000 ₽	60 $
• severe psoriasis and gross lesion (including psoriatic arthritis)	8000 ₽	120 $
Tuberculosis	2000 ₽	30 $
	Cost 1 pack:	
	2000 ₽	30 $

Recently, Licopid® is registered in 10 countries of the world:

✓ Russian Federation	registration date –1995
✓ Belarus Republic	registration date - 1996
✓ Republic of Kazakhstan	registration date – 2008
✓ Republic of Moldova	registration date – 2001
✓ Armenia	registration date – 1999
✓ Georgia	registration date – 2015
✓ Azerbaijan	registration date – 2001
✓ Uzbekistan	registration date – 2015
✓ Kyrgyzstan	registration date – 2015
✓ Mongolia	registration date – 2015

Health for our Patients

Total number of patients treated by drug Licopid® pills 1 mg and Licopid® pills 10 mg during the period 1999-2018 within the Russian Federation and CIS states:

Total – 7 842 659 patients

1 mg - 6 224 553 patients
of which children – 2 712 270

10 mg - 1 618 106 patients

Advantages of Licopid®:

Natural Origin

Known target cells and intercellular effect mechanism

Sublingual administration

immunomodulators

Compatibility with other drugs