

Development of New Antituberculosis Products and Their Application to Medical Practice

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Tuberculosis

**GLOBAL ANNUAL EXPENDITURES FOR
TUBERCULOSIS
PROBLEMS COME TO \$ 12, 000,000 US**

**8.4 MILLION
CASES OF TUBERCULOSIS
ANNUALLY**

**AVERAGE WORLD DEATH-RATE
ON ACCOUNT OF
TUBERCULOSIS IS 23%**

**IN THE COUNTRIES OF PREVALED
HIV-INFECTION THE DEATH-RATE
RUNS UP TO 50%**

Tuberculosis Problem in the Future

**ONE THIRD OF THE EARTH
POPULATION
IS INFECTED WITH TUBERCULOSIS
MICOBACTERIA (ABOUT 2 BILLIONS
PEOPLE**

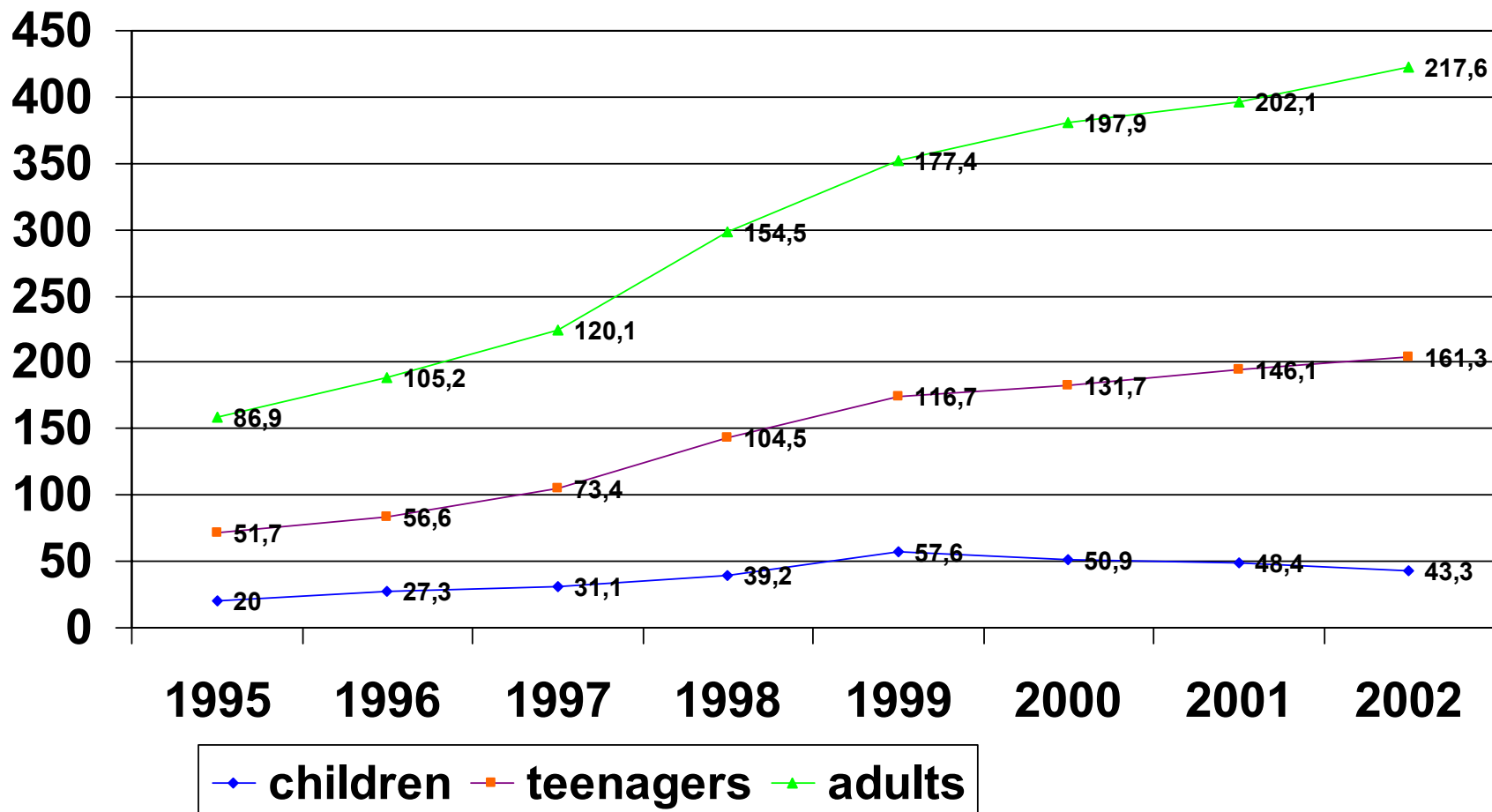
**5-10% OF INFECTED PEOPLE USUALLY
FALL SICK OF SOME TUBERCULOSIS
FORMS DURING THEIR LIFE**

**TUBERCULOSIS WITH
PLURAL MEDICINAL
RESISTANCE
INCREASES
CONSTANTLY**

**SPREADING HIV- INFECTION BROUGHT
ABOUT SHARP GROWNT OF
TUBERCULOSIS**

**75% OF PATIENTS
ARE
THE PEOPLE OF ABLE-
BODIED AGE (20-40
YEARS)**

Tuberculosis Sickness Rate in Kazakhstan, per 100,000 Population



Low Efficacy of Anti-TB Therapies

- **Multiresistant forms of Tuberculosis are spreading**
- **Anti-TB therapy has high toxicity**
 - **Hepatitis**
 - **Hearing loss**
 - **Disarray of sight**
 - **Anemia**
 - **Impaired kidney function**
 - **Dyspepsia**
- **Combined medicines are most toxic (50% of patients make a complete recovery, 35% come to chronic form)**
- **Absence of new effective and low-toxic medicines**
- **Many medications were developed more than 50 years ago**

Kazakhstan: in need of new TB therapies

- **According to data from the World Health Organization (WHO) the Republic of Kazakhstan has been the country of highest TB sickness rate among the countries related to the European WHO Bureau and the country with the highest rate of primary TB in the world**
- **Markets for new TB medicines include regional departments of the Kazakhstan Ministry of Health**
- **New Medicines active against plural resistant tubercular forms and against the forms of tuberculosis with concomitant HIV infection will also have an export potential**

Capabilities of “Romat”

- **Romat is the first-rate pharmaceutical company in Central Asia**
- **Kazakhstan manufacturer № 2, it has 4 of 7 pharmaceutical plants in Kazakhstan (tablets, infusion solutions, biomedicines and syringes)**
- **Two plants have been built and now work in accordance to International standards GMP, they are intended to be certificated in 2005**
- **Wholesale net № 1 and retail net №2 in Kazakhstan**

Research Objectives

- **Reduction of toxic-allergic reactions and harmful side effects of Anti-TB therapies**
- **Development of combined products active against drug-sensitive and drug-stable TB micobacteria**
- **Synthesis and study of the new heterocycle compounds with potential Anti-TB activity**
- **Determination the dependency of Activity and Toxicity on structure of Anti-TB compounds**
- **Development, preclinical & clinical study and eventual licensing of promising new Anti-TB medications**

Stages of Planned Research

- **Development of composition and technologies of Anti-TB medicines on the basis of Chitosan**
- **Development of composition and technologies of new combined Anti-TB medicines active against drug-sensitive and drug-stable TB micobacteria**
- **Purposeful chemical modification of pharmaceutical drugs by piperidine derivatives**
- **Synthesis of the new heterocyclic compounds with potential Anti-TB activity**

Biologically Active Substances: Potential basis for new TB therapies

- **Natural stuffs, prolongers and active pharmacological substances permitted for medicine and having the ability:**
 - penetrate through TB micobacteria lipidic cover
 - transport the active substances inside the cell through the cell membrane
 - increase the activity of the main active substances against the drug-stable TB micobacteria
 - long use thanks to low toxicity
- **Current Anti-TB medicines modified by piperidine derivatives**
 - **New compounds with Anti-TB activity on the base of piperidine**

Increasing Efficacy of TB therapies: I

- Chitosan is a powerful enterosorbent of toxic metabolites, it can penetrate through lipidic cover of TB bacteria acidic components
- We have established the moderate bacteriostatic activity of Chitosan against M.tuberculosis H37Rv
- We have developed the modified Isoniazid on the base of Chitosan
 - 6 times less toxic
 - 10 times more active on gram positive bacteria
 - Equivalent to standard Isoniazid in therapeutic action
 - Eliminates negative influence of Isoniazid on intestines and liver microflora

Increasing Efficacy of TB therapies: II

- **We have developed 5 combined products on the base of pyrazinamide, isoniazide, ethambutol, rifampicin and streptomycin**
 - **The combined products show high antitubercular activity in vitro and in vivo in testing with guinea-pigs regarding drug-sensitive and drug-stable cultures of Tubercular micobacteria**
- **We have received the positive conclusions for giving out the patents of Kazakhstan Republic (5) and Eurasian Patent Authority (5)**

Increasing Efficacy of TB therapies: III

- It is known that piperidine derivatives suppress chronic HIV infection
 - Piperidine derivatives (our original product Richlocain – the derivative of dimethyl piperidine-4-on) activate cytotoxic action of anti-cancer therapies (patented)
 - Richlocain shows high bactericidal activity in concentrations less than therapeutic ones (patented), the action mechanism has been established
 - We have developed the original technology of dimethyl piperidine-4-on synthesis (patented)

Next Steps

- **Study of physico-chemical and toxicological characteristics of new developed medicines**
- **Study of antitubercular activity of the new medicines to choose the most promising ones for the further study**
- **Preclinical study**
- **Clinical study**

This study program for new Anti-TB medicines will correspond to the standards set forth by the United States National Institute of Health and National Institute of Allergy and Infectious Diseases

Seeking Collaborators:

Area of potential collaborators' scientific interests:

- **Experimental pharmacology, toxicology, pharmacokinetics and biopharmacy of antitubercular medicines**
- **Synthesis of nitrous heterocyclic compounds with potentially anti-tubercular properties (thin organic synthesis)**

In the area of production:

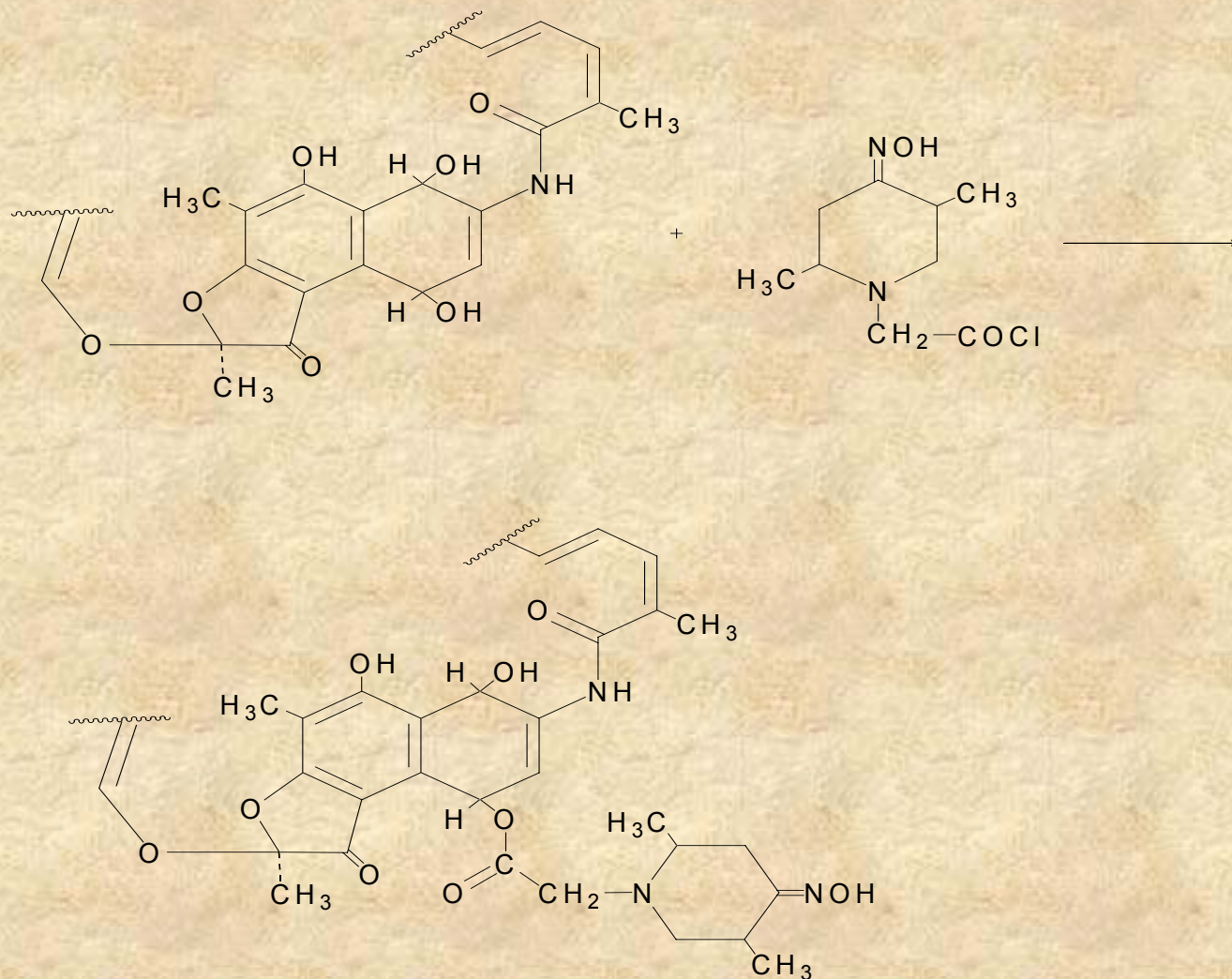
- **Partnership in the organization of drugs & ready products production**

Contact Information

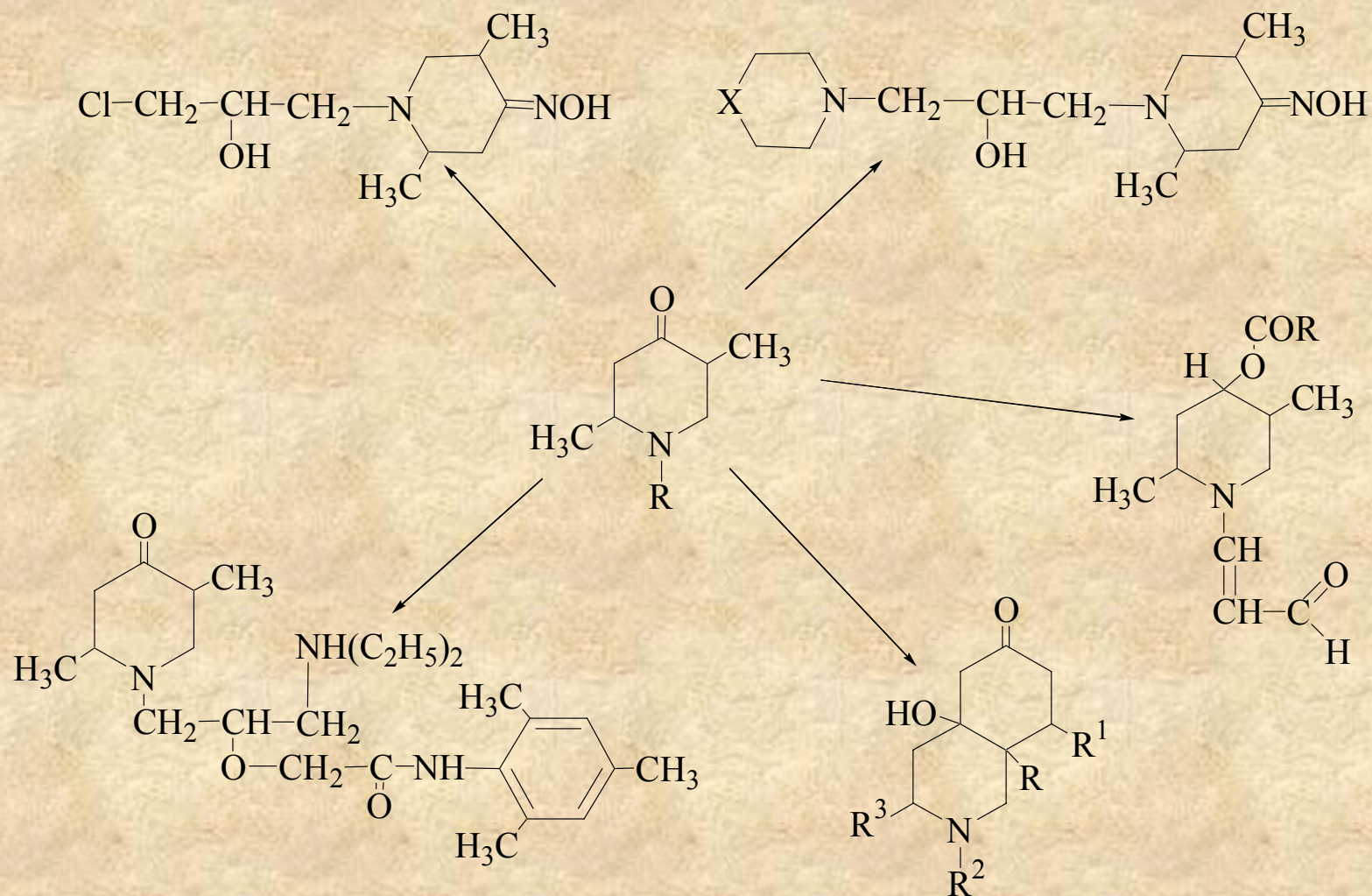
Principle Investigator:

- ❖ **Kunnaz Murzagulova, Dr. of Chemistry**
- ❖ **Vice President of Pharmaceutical Company
“Romat”**
- ❖ **Prof. of Chemical Technologies
Department,
Pavlodar State University named after S.
Torajgyrov**
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Appendix 1



Appendix 2



Minimal Suppressing Concentrations of Some Local Anesthetics

Kind of bacteria Novocaine Lidocaine Bupivocaine Richlocaine

	Вид микроорганизма	Новокаин	Лидокаин	Бупивокаин	Рихлокаин
1	<i>B. cereus v. mycoides</i> LC	>1.0	>1.0	0.2	0.12
2	<i>B. licheniformis</i>	>1.0	>1.0	0.2	0.12
3	<i>Bacillus subtilis</i> 720	>1.0	0.2	0.2	0.12
4	<i>Bacillus subtilis</i> 1.2	>1.0	0.3	0.08	0.08
5	<i>Corynebacterium ulcerans</i>	>1.0	0.5	0.08	0.08
6	<i>Enterobacter aerogens</i> *	>1.0	>1.0	0.2	0.12
7	<i>Enterobacter faecalis</i> 18417*	>1.0	>1.0	0.2	0.12
8	<i>Enterobacter faecalis</i> 18471*	>1.0	>1.0	0.2	0.12
9	<i>Escherichia coli</i> C 600 ^{mf}	>1.0	>1.0	0.2	0.12
10	<i>Escherichia coli</i> J 53	>1.0	0.5	0.2	0.12
11	<i>Escherichia coli</i> K 12	>1.0	0.5	0.2	0.12
12	<i>Klebsiella pneumoniae</i> R 56	>1.0	>1.0	0.2	0.2
13	<i>Proteus mirabilis</i> *	>1.0	>1.0	0.25	0.2
14	<i>Pseudomonas aeruginosa</i> 47	>1.0	>1.0	0.2	0.12
15	<i>Pseudomonas aeruginosa</i> 18570*	>1.0	>1.0	0.8	0.6

16	<i>Pseudomonas aeruginosa</i> 18788*	>1.0	>1.0	>1.0	0.6
17	<i>Pseudomonas aeruginosa</i> 1.1	>1.0	>1.0	0.25	0.3
18	<i>Salmonella typhimurium</i> 79	>1.0	0.5	0.2	0.12
19	<i>Serratia marcescens</i> *	>1.0	>1.0	0.12	0.12
20	<i>Shigella sonnei</i> P-9	>1.0	0.8	0.2	0.12
21	<i>Staphylococcus aureus</i> 209 P	>1.0	>1.0	0.2	0.12
22	<i>Staphylococcus aureus</i> 505*	>1.0	>1.0	0.2	0.12
23	<i>Staphylococcus aureus</i> 831*	>1.0	>1.0	0.2	0.15
24	<i>Staphylococcus aureus</i> 1015*	>1.0	>1.0	0.2	0.12
25	<i>Staphylococcus epidermidis</i> *	>1.0	>1.0	0.2	0.12
26	<i>Staphylococcus epidermidis</i> 170*	>1.0	>1.0	0.2	0.08
27	<i>Staphylococcus epidermidis</i> 1182*	>1.0	>1.0	0.2	0.12
28	<i>Staphylococcus epidermidis</i> 1598*	>1.0	>1.0	0.2	0.12
29	<i>Streptococcus agalactiae</i> 19057*	>1.0	0.3	0.08	0.08
30	<i>Streptococcus edui</i> 18935*	>1.0	0.5	0.12	0.08