ON MECHANISM BIOLOGICAL ACTION OF ULTRA LOW DOSES

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A hypothesis of the phenomenon of the physical and chemical factors at ULD was formulated by Viktoria Yamskova and Igor Yamskov in 1999. It was based on the concept of unknown bioregulatory mechanism inherent in all living organisms. Physical and chemical factors at ULD influence on this mechanism.

The most part of experimental data were obtained during 13 years.

The main points of the concept are as follows

1. Physical and chemical factors at ULD have a single mechanism of biological action, which is based on speed or direction changes of the bioregulation processes constantly occurring in living organisms.

2. Distribution of regulatory signals in the tissues is mediated by specific macromolecular structures of the intercellular spaces, one of which is called as "small matrix".

3. First of all “small matrix» acts as adhesive structure, and secondly it provides the structuring of intercellular space water which play a role of "information matrix".

4. The impact of physico-chemical factors perceived by intercellular spaces water through the formation of their certain structures.

5. The phenomenon of ULD is based on restructuring of the spatial organization of intercellular space macromolecular structures, arising under the influence of structurated water. As a result, a new regulatory signal penetrates into the cell by a system of ligand-receptor interactions at the cell surface and the system of secondary messengers.

6. "Small matrix" consists of previously unknown bioregulators, which have a complex structure, namely, they consist of biologically active peptides and proteins that modulate these peptides activity.

Tissue-specific homeostatic membranotropic bioregulators (**TSHMB**) was found in various tissues of animals, plants and fungi. They formed a new separate group due to the similarity of physical and chemical properties and their biological activity.

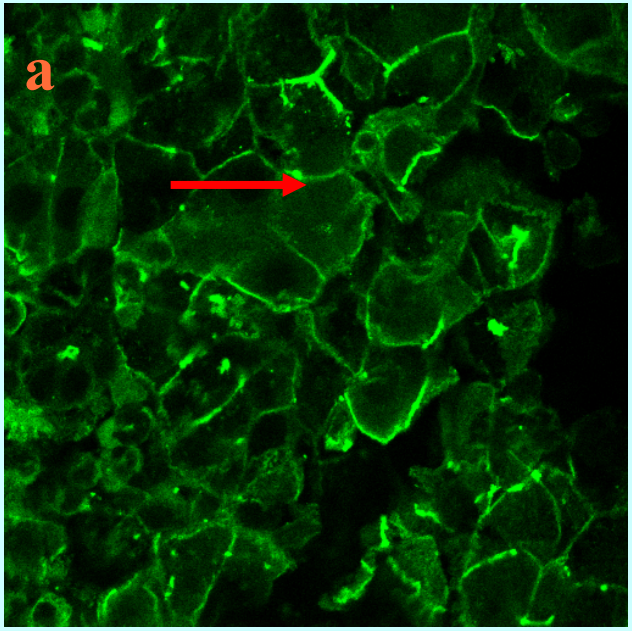
Bioregulators were isolated in a separate group on the basis of :

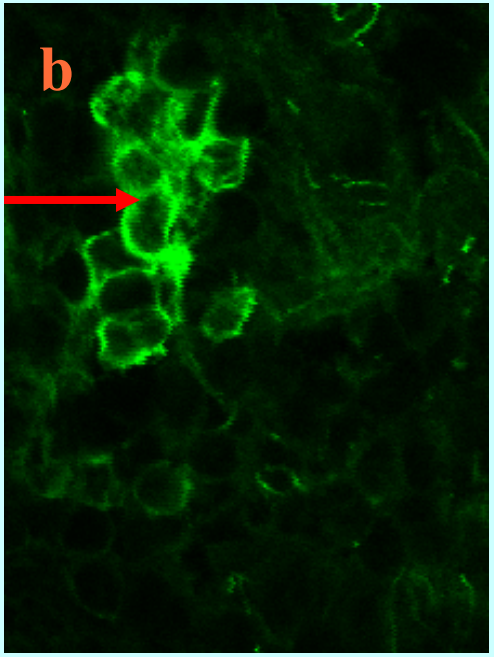
A new experimental approach developed for their identification and investigation (method of isolation from tissue, separation technique, a method of biological testing, methods for studying the specific biological activity).

Similarities of physical and chemical properties.

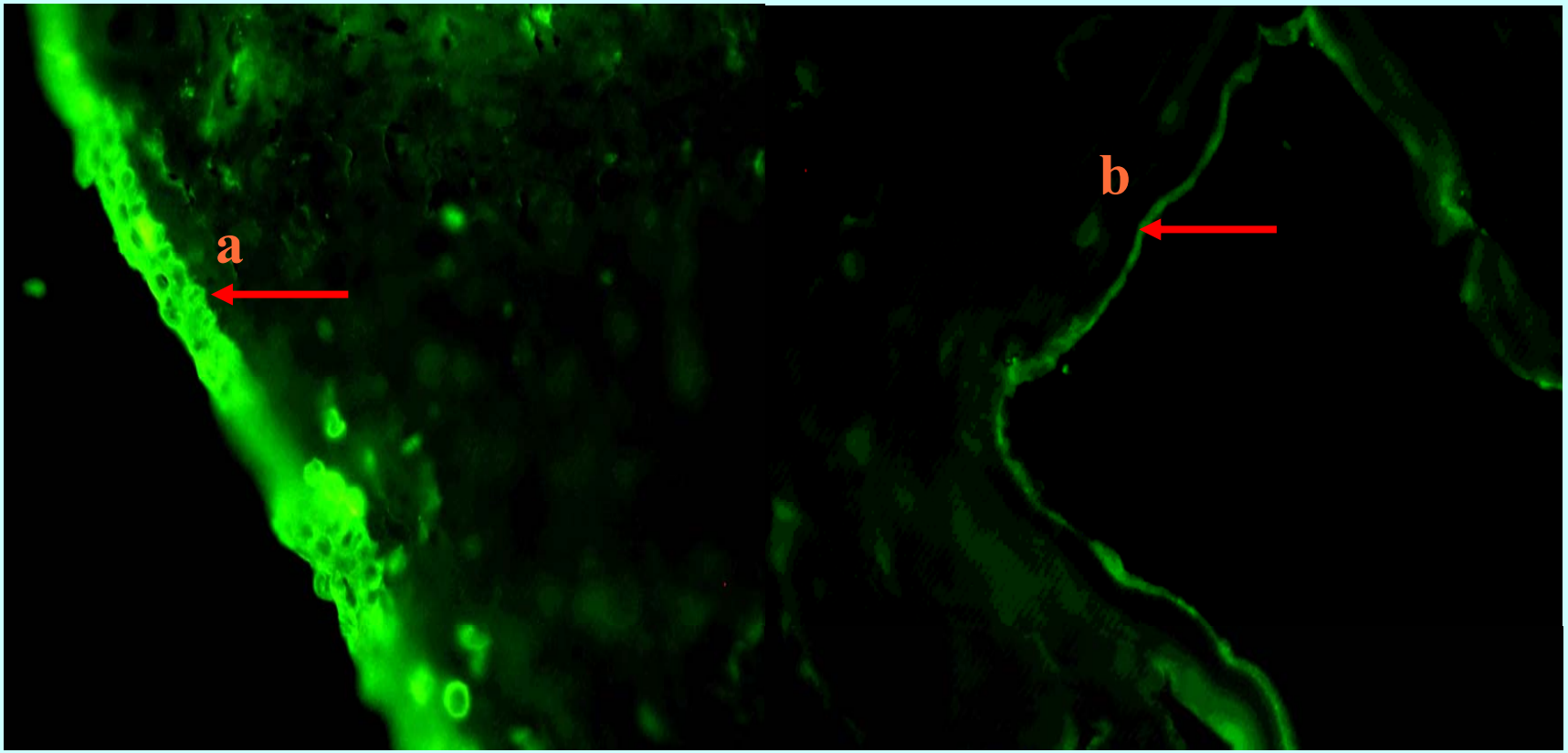
Their ability to be active at ultra-low doses (10^{-7} - 10^{-15} mg/ml).

- TSHMB isolated from bovine blood serum is localized in the intercellular space of hepatocytes (a) and hematopoietic cells (b) of the triton *Pl. waltl* liver

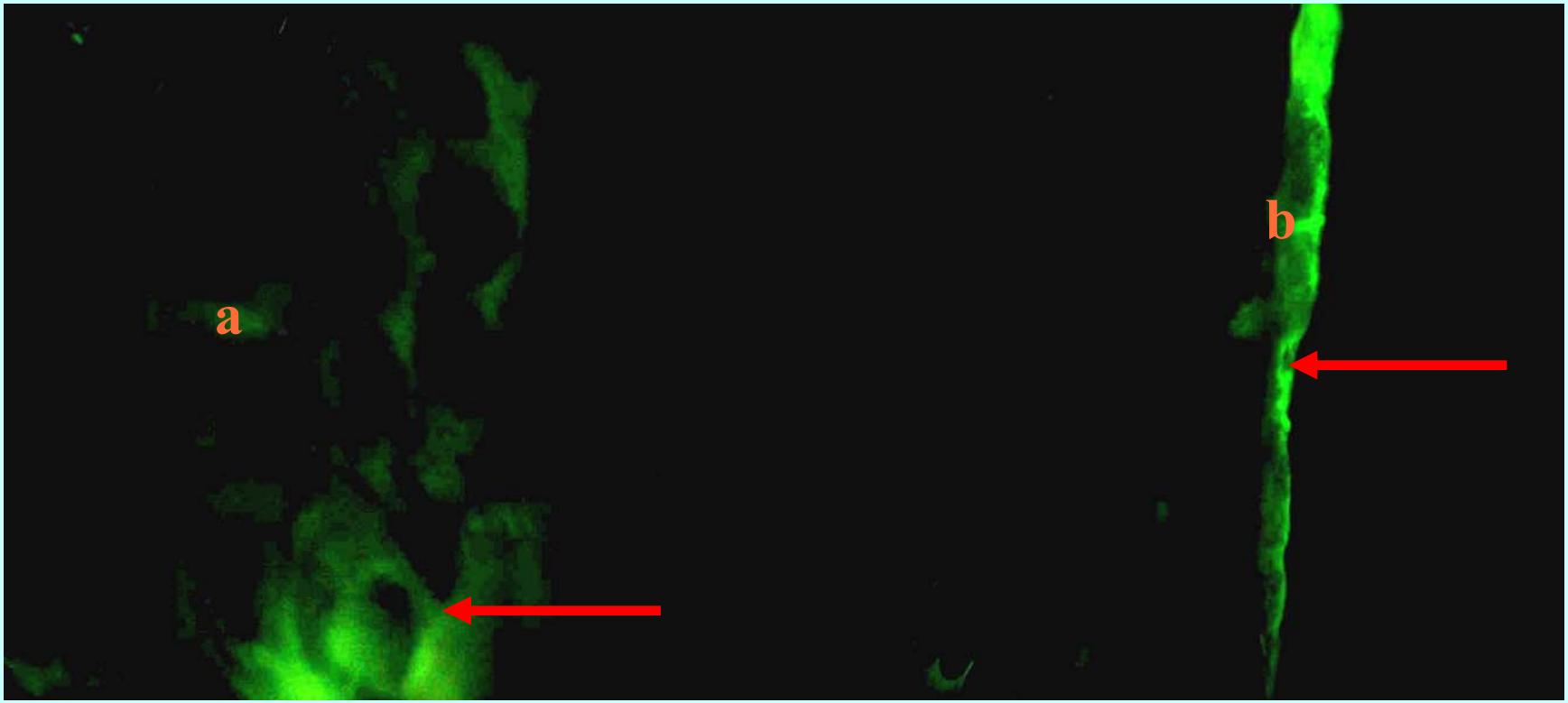




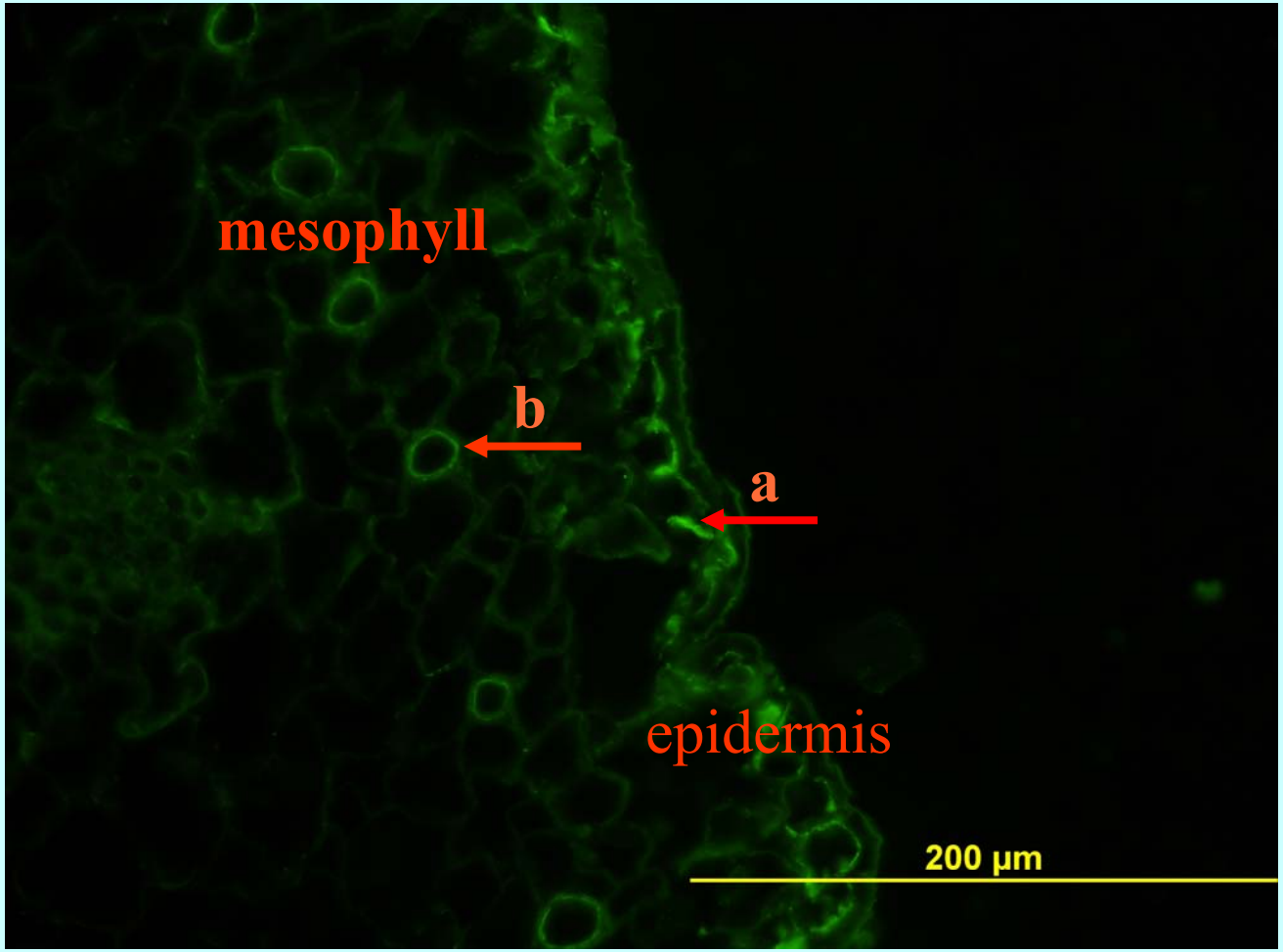
- TSHMB isolated from bovine cornea is localized in the intercellular space of the epithelium (a) and endothelial (b) rat cornea



•TSHMB isolated from bovine cornea is localized in the intercellular space of the epithelium (a) and endothelial (b) triton cornea

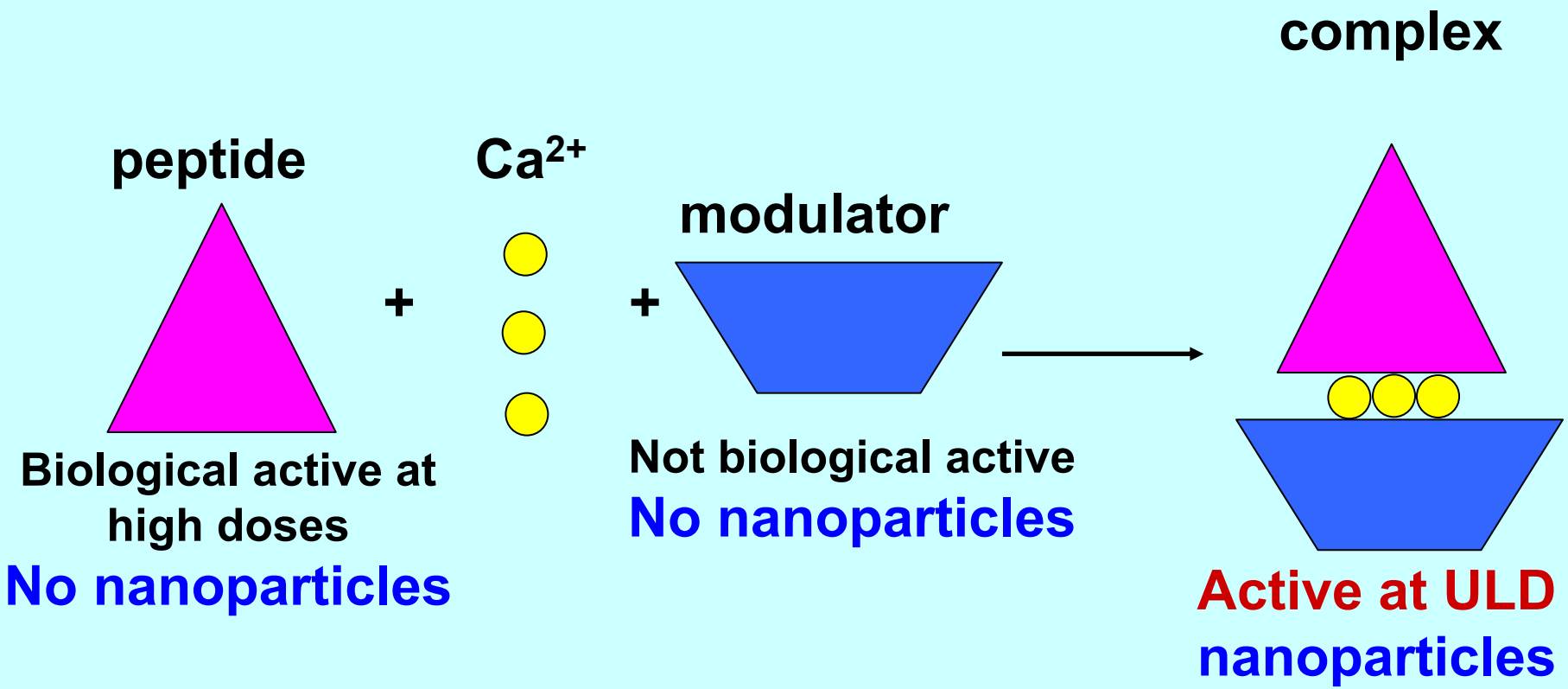


TSHMB isolated from bulbs of garlic (Allium sativum L.), is localized in the leaves of garlic sprouts on the surface of cells of the epidermis (a) and certain rounded cells spongy mesophyll (b).



These and other data indicate the activity of TSHMB has tissue specificity but not species.

The mechanism of formation and functioning of the bioregulators complex based on interaction peptides with their modulators



Peptide composition of bioregulators, isolated from various tissues of the eye.
A list of the mass spectra signals of peptides

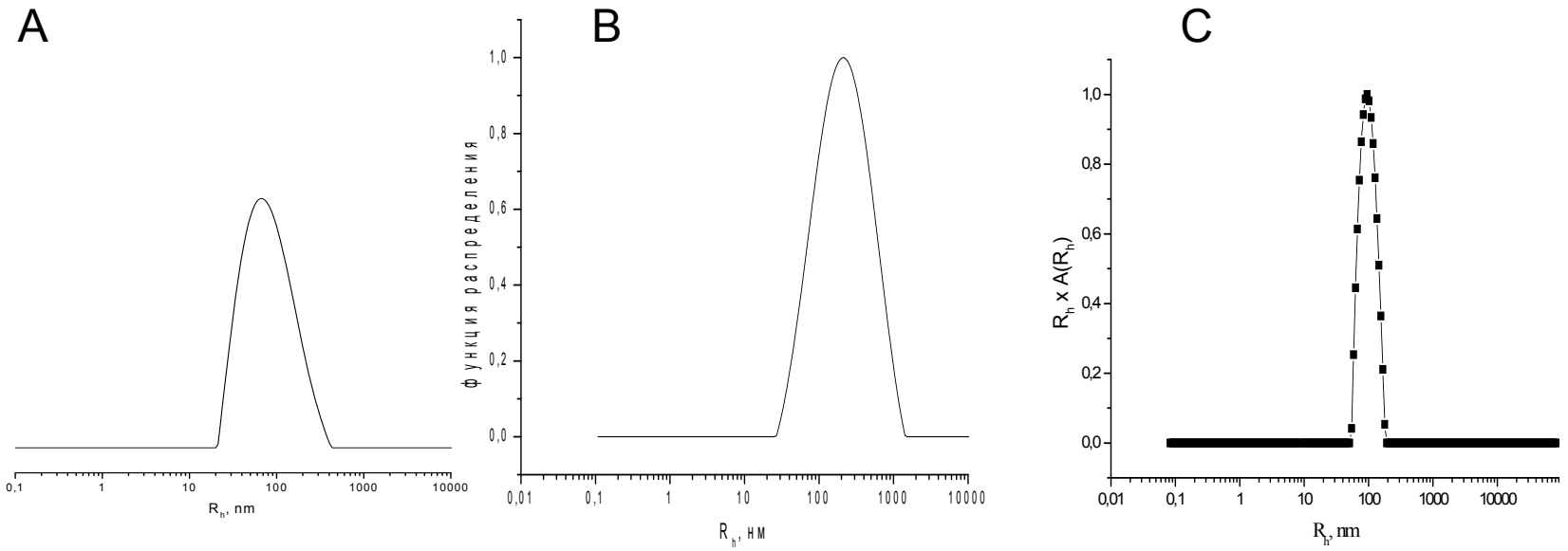
№№	Source	M(m/z)
1	Bovine retina *Bos taurus taurus*	4302, 4528, 4819, 8603
2	Bovine lens *Bos taurus taurus*	4302, 4529, 4817, 8604
3	Bovine vitreous body *Bos taurus Taurus*	4300, 4370, 4420
4	Bovine iris *Bos taurus taurus*	3944, 4301
5	Bovine ciliary body *Bos taurus taurus*	4301
6	Bovine retinal pigmented epithelium *Bos taurus taurus*	4303, 4532, 4819
7	Bovine sclera *Bos taurus taurus*	4171, 4302, 4531, 4819
8	Bovine cornea *Bos taurus taurus*	1442, 3376, 3973, 4302, 4418, 4531, 4817, 8604

The secondary structure of bioregulators

Source of isolation of TSHMB	α-spiral, %	β-sheet (antiparallel) %	β-sheet (parallel) %	β-turn, %	Random coil, %
retinal pigmented epithelium of eye	7,6±0,5	37,4±0,5	5,7±0,5	18,9±0,5	30,4±0,5
retina	7,4±0,5	40,0±0,5	5,2±0,5	18,4±0,5	31,0±0,5
lens	6,8±0,5	40,4±1,0	5,2 ±0,5	18,5±1,0	30,8±1,0
serum	8,0±0,5	40,1±0,5	2,0±0,5	16,9±0,5	33,0±0,5
lung	2.2±0.5	48.1 ± 0.5	3.7 ± 0.5	16.7 ± 0.5	29.3 ± 0.5
liver	2,2±0,5	48,1±0,5	3,7±0,5	16,7±0,5	29,3±0,5
bile	2,2±0,5	48,3±0,5	3,7±0,5	16,7±0,5	29,1±0,5
milk	6,2±0,5	45,7±0,6	3,6±0,8	16,0±1,1	28,5±3,2
prostate	6,4±0,1	47,1±0,2	3,7±0,3	14,1±0,1	28,7±1,5

The laser dynamic light scattering of solutions containing TSHMB isolated from: A) milk (Rh = 87,8 ± 10,1 nm), B) pigmented epithelium (Rh = 205,5 ± 11,3 nm), C) of the cornea (Rh = 130,5 ± 12,4 nm).

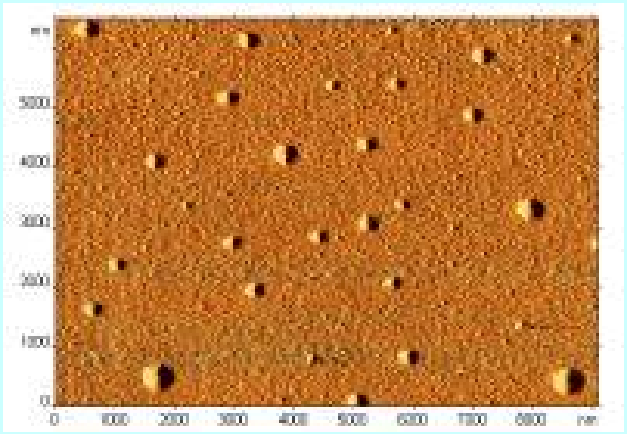
Rh - the value of the hydrodynamic radius of the scattering angle at a value of 0.



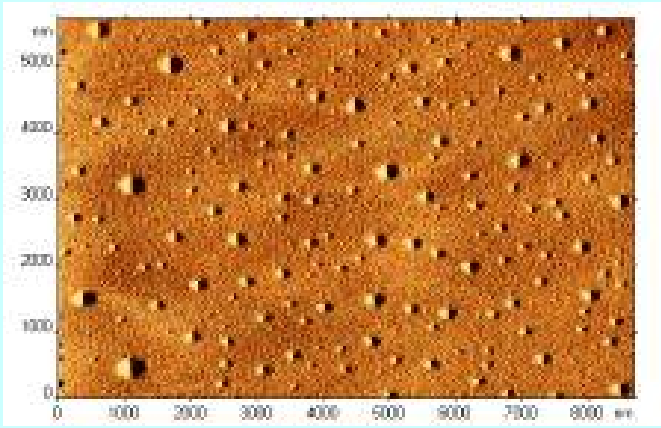
Atomic force microscopy of the TSHMB solutions isolated from: A) lens (110-200nm) and B), pigmented epithelium (150-300nm), C) retina (120-170nm).

A

B



C



Study of physical factors action on biological activity of «imaginary» solution of TSHMB obtained from retinal pigmented epithelium

(10^{-24} mg of protein/ml).

This «imaginary» solution was biological active (membranotropic activity).

Physical factors :

- **High temperature 100 ^{0}C, 20 min**
- **Ultrasound, 100 W, 20 kHz**
- **Microwave, 700 W, 2450 MHz**

- **Membranotropic activity of bioregulator (ULD, an «imaginary» solution) was investigated immediately and in 7 days after physical factors action.**

Membranotropic activity of bioregulator at doses 10^{-7} mg/ml (ULD) and 10^{-24} mg/ml («imaginary» solution) after exposure to ultrasound

Effect of Ultrasound			
ULD		«imaginary» solution	
at once	after 7 days	at once	after 7days
+	+	-	-

Membranotropic activity of bioregulator at doses 10^{-7} mg / ml (ULD) and 10^{-24} mg / ml («imaginary» solution) after 100°C during 20 min.

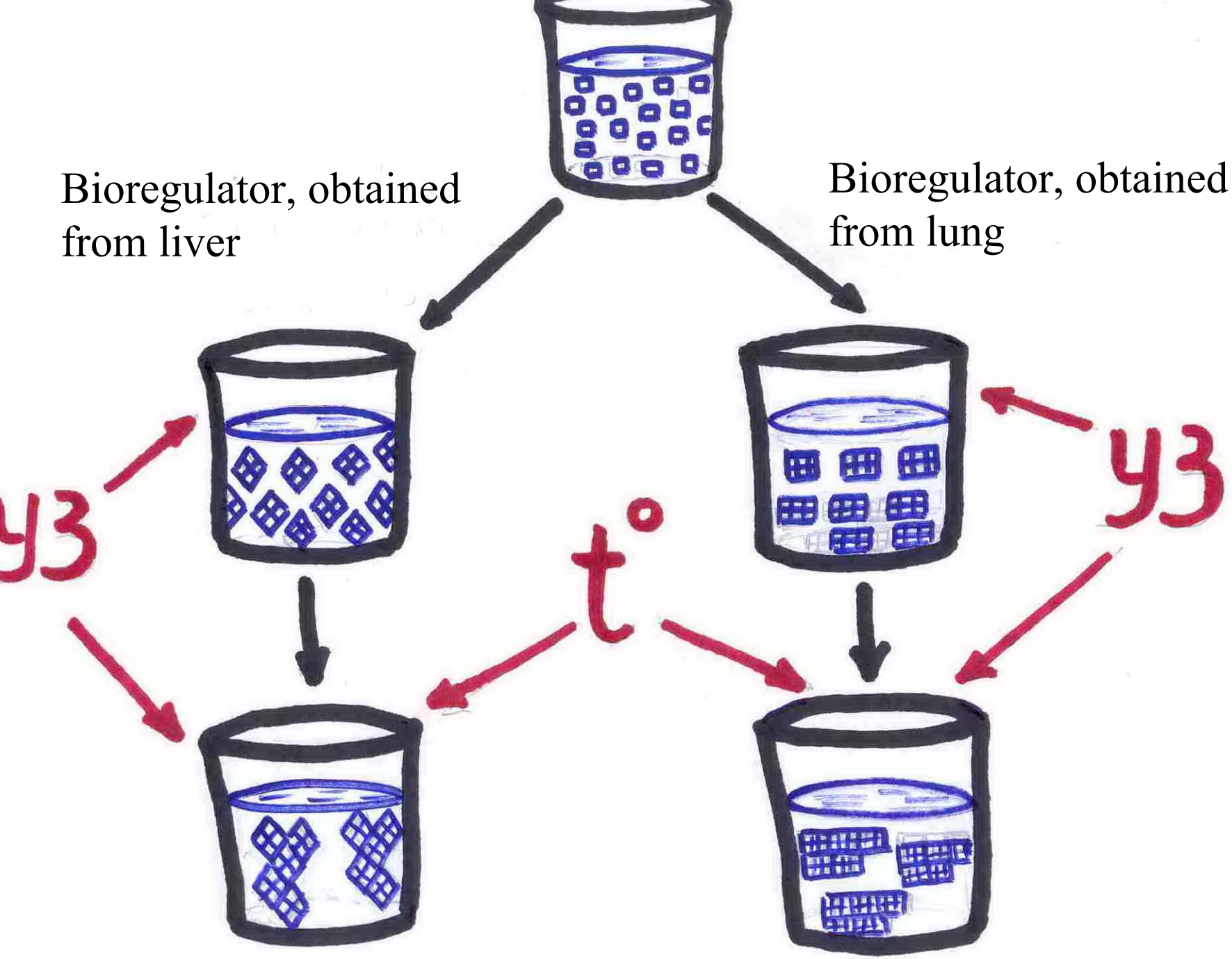
Temperature 100°C			
ULD		«imaginary» solution	
at once	after 7 days	at once	after 7 days
+	+	-	+

Membranotropic activity of PE bioregulator at doses 10^{-7} mg / ml (ULD) and 10^{-24} mg / ml («imaginary» solution) after exposure to ultra-high frequencies

Effect of ultra-high frequencies			
ULD		«imaginary» solution	
at once	after 7 days	at once	after 7 days
+	+	+	+

1) It was formation of water structures by the action of bioregulator;
2) These water structures were biological active; their activity was similar to those of bioregulators.
3) The formation of such structures is carried out at two levels:

- one was destructed at higher temperatures, but it can be restored after some time;
- different level is irreversibly disrupted by ultrasonic treatment of an «imaginary» solution. It is possible that in this case, the specific structure of water like a "broken" and not being restored. These data indicate the existence of tissue-specific associates of water, which are formed under the action of biologically active substances.


Bioregulator, obtained from liver
Bioregulator, obtained from lung
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УЗ

The “imaginary” solutions study for bioregulators extracted from liver and lung tissues performed that water structure formed under these bioregulators action keep not only biological active correspond to origin bioregulator but and tissue specificity character of these activity. It means that different water structures provide different biological activity are formed. These data quite confirm our conception about the water ability to play a role of «information matrix» in living organism. To our opinion the most important TSHMB’s function is to provide water in condition of «information matrix» which allows to fix different kind of physical and chemical actions even at low doses.

The model of experimental mice skin wounds in vivo: a) - the wound was treated with saline solution b) - the wound was treated serum bioregulator at a dose of 10^{-12} mg/ml. × 200.

Thank you for attention!