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Dear colleagues,

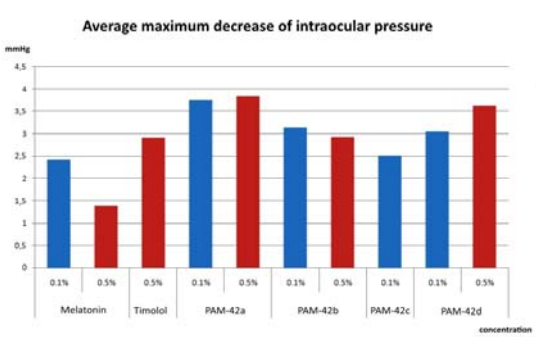
This month, we would like to present to your kind attention a rather prospective molecule PAM-42 “Product for glaucoma treatment”.

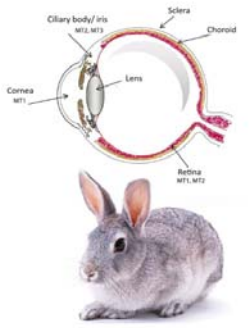
Currently, up to 105 million people suffer from glaucoma worldwide. In Russia glaucoma is the main reason (28%) of ocular disability. The most recent studies have shown that there is a fundamentally new molecular target for glaucoma therapy – melatonin receptors. Hormone melatonin (5-metoxy-3-(2-(acetylamino)ethyl)indole), which is synthesized in the human pineal gland and retinal photoreceptor cells, has a direct effect on ophthalmic tonus. The administration of melatonin or synthetic agonists of melatonin receptors as eye drops or *per os* leads to significant decrease of intraocular pressure (IOP) in mammalians. Moreover, some selective agonists of melatonin receptors reduce IOP more effectively than melatonin.

There are 3 subtypes of melatonin receptors: MT1, MT2 and MT3 in mammalians, including humans. According to numerous studies the anti-oxidant properties of melatonin are provided by low affinity MT3 receptor, which is also known as the enzyme quinone reductase 2 (QR2).

The presence of melatonin receptors in ocular tissues makes them available for locally applied products, such as eye drops or ointments, which decrease possible adverse effects of active compounds and are convenient for patients.

The scientists from the Moscow State University made a target-specific synthesis of the compounds and created a library of type 3 melatonin receptor ligands (MT3 ligands). In the Helmholtz Research Institute of Eye Diseases (Moscow, Russia), the new compounds were tested on rabbits, and as a result four molecules with a stronger IOP decrease activity were selected.





Melatonin and Timolol were chosen as the drugs of comparison. According to the study results, two compounds also showed antioxidant activity exceeding Melatonin antioxidant efficacy.

The acute toxicity studies were carried out for two compounds, which showed the most significant levels of IOP reduction activity. Intraperitoneal administration of the compounds to F1 mice resulted in estimation of LD_{50} values that were 1200 mg/kg for PAM-42a and 2400 mg/kg for PAM-42b.

Currently, we continue the **efficacy studies on PAM-42** in rabbits and **develop the final dosage form** to increase drug action period.

At the end of August we obtained approval from the Ministry of Healthcare of the Russian Federation for **phase I clinical study for the project PAM-3 “Hemoglobin-based Oxygen Carrier”.** We will be happy to present this and other projects in our next issue.

Best regards,
Rakhim Roziev