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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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A COMPARATIVE REVIEW OF THE USE OF DANIO RERIO (ZEBRAFISH) AS A MODEL OBJECT IN PRECLINICAL STUDIES

Kachanov D.A., Elistratov L.M., Guseinov H.M., Balaeva K.V., Popova N.A.

North-western State Medical University named after I.I. Mechnikov, Ministry of Health of Russia, Piskarevsky Prospect, 47, St. Petersburg, 195067, Russia.

Abstract.

Danio rerio (Zebrafish) as a model object in preclinical studies have been widely used in recent years. This is facilitated by their morphological, physiological, biochemical, genetic, and embryological characteristics, as well as economic benefits and small-time costs of their breeding.

Aim: The aim is to summarize the available data on the use of Danio rerio (Zebrafish) in preclinical studies.

Methods: In this work a review of domestic and foreign articles on the use of Danio rerio in toxicological, pharmacological, embryological, and other research areas was carried out.

Results: Danio rerio (Zebrafish) can be used in many areas of preclinical studies of drugs. Their application in modeling novelty stress and experimental depression is especially interesting.

Conclusions: Danio rerio are a versatile model object that allows cost-effective studies of various pharmacological drugs before they are tested on other models, particularly mammals.

Key words. Danio rerio, zebrafish, model object, preclinical tests.

Introduction.

It is now reliably known that the tropical fish Danio rerio (Zebrafish) is a studied and practical model object of preclinical research. They have a number of advantages over various representatives of this class and even other laboratory animals, in particular rodents. Due to the detailed study of embryogenesis, genome, morphological features and minimal maintenance costs, Zebrafish can be used in biological, genetic, pharmacological research and screening for mutagenesis, teratogenicity assessment and other chemical exposures. Compared to other model objects, such as the fruit fly Drosophila melanogaster and the worm Caenorhabditis elegance, a strong conservative communication. This makes the tropical fish an excellent model for studying complex biological processes such as the development of the nervous, cardiovascular and hematopoietic systems, as well as angiogenesis, apoptosis and toxic effects various factors [1,2]. To date, hundreds of genetic mutants of Danio rerio have already been obtained whose phenotype resembles and can be the clinical equivalent of diseases in humans.

Several chimeric models with human receptors and signaling molecules have also been obtained. Genes encoding certain receptors and signaling molecules are usually associated with the development of cardiovascular pathology, diseases of the hematopoietic and nervous systems, myopathies and myodystrophies, which allows us to analyze the effectiveness of promising drugs [1-3]. In this regard, the use of Danio rerio as an experimental model seems particularly promising in pharmacology.

The purpose of this study is to summarize the available data on the use of Zebrafish in preclinical studies, to establish their advantages and disadvantages in specific laboratory trials and further prospects for work with this model object, which would allow to consider it the first stage of preclinical studies, before they will be carried out, for example, in rodents.

Research methods.

This work involved a review of data from foreign and domestic articles (for the period 2014-2018) on the use of Danio rerio in various preclinical studies.

Results and Discussion.

Danio rerio (Zebrahish) is a small freshwater tropical fish inhabiting mainly rivers and streams of Pakistan, India, Bangladesh, Nepal, Myanmar, and Bhutan. The Zebrafish, well known to aquarium fish enthusiasts, is widely used in laboratory research. Danio rerio has an elongated body shape, the main color tone is silvery with bright blue and yellow-green stripes. Adults in the wild reach a length of 6-7 cm, aquarium inhabitants - 5 cm. Zebrafish are gregarious (at least 7-10 fish), most of the time kept in the upper and middle layers of water. In captivity, they live about three years.

The main advantage of this fish is the presence of a transparent embryo, which allows to fully observe the stages of embryogenesis. This feature has found application in the study of teratogenic, carcinogenic, and other effects of various chemicals and drugs on Danio rerio, which is manifested in the violation of embryonic development stages or the formation of morphological development anomalies. In addition, Zebrafish have a high fecundity and a fast period of embryo maturation. Three days after fertilization, the heart, circulatory and nervous systems begin to function. On the fourth day, the fry is formed, capable of independent feeding and movement. This peculiarity allows accelerating the research process and minimizing costs in the form of funds and time [1].

It is also worth noting that a detailed study of the Danio rerio genome has now been conducted. It has been noted that Zebrafish have 70% homology with the human genome, which allows them to be used as an excellent model for genetic research [1].

Similar biochemical processes with mammals again confirm the feasibility of using Danio rerio as a model for preclinical studies.

A model object for staging stress and depression.

At present, Zebrafish are also actively used as an experimental model for novelty stress and experimental depression followed by exposure to drugs of different pharmacological groups [1-3]. For novelty stress staging, the following technique is used: Danio rerio is first placed in a measuring cup with dissolved substance (or simply with clean water) and then - in a viewing

tank for 6 minutes, where the trajectory of movement, length of path, number of movements to the upper part of the tank, time spent in the lower part of the tank, number and time of "freesing" (immobilization) pattern for each minute of experiment are automatically registered. In response to the novelty of the room, Danio rerio responded by diving to the bottom, increasing freezing, and decreasing the number of movements to the upper half of the aquarium. For example, against the background of phenazepam introduction, the number and time of freesing pattern, as well as the time of staying in the lower part of the aquarium decreased more than 2-fold compared to the control group and a dose-dependent effect was manifested. The novelty stress test is highly sensitive for studying anxiety-phobic reactions in Zebrafish, and this model can be used in preclinical studies [1,2].

Another model can be used to create experimental depression, which consists in separating Danio rerio individuals in pairs in a limited space. This model can be promising for the study of already existing psychoactive substances, as well as in preclinical studies of new drugs [3].

Assessment of toxicity of pharmacological drugs of different groups.

In a study by Sílvia Ribeiro et al., Danio rerio embryos were exposed to drugs from different pharmacological groups: diclofenac, propranolol, simvastatin, and sertraline. Their toxic effects on Zebrafish embryos were evaluated. When evaluating the effect of diclofenac on embryos, significant changes in development were observed: the growth of abnormal cells, disruption of the epiboly stage in embryonic development, as well as abnormalities in the formation of the yolk sac. The most significant developmental abnormalities were observed at the drug concentration of 12.5 mg/l. The number of successfully passed epiboly stages in embryo development decreased from 91% to 82.5% when the diclofenac concentration was increased from 1.25 to 12.5 mg/l.

When exposed to propranolol at a concentration of 12.5 mg/L, the development of pericardial effusion, fin development abnormalities, and a dramatic increase in embryo mortality from 32 to 80 hours of study were detected.

Sertraline at a concentration of 10 mg/L resulted in the death of all embryos by 80 hours of the study. It was also shown a significant decrease in the successful stages of epiboly in embryo development compared to controls (from 90% to 67.5%).

Simvastatin proved to be the most toxic of the studied drugs. A concentration of 5 mg/L was fatal in all embryos from 32 to 80 hours of the study.

At concentrations up to 500 μg/L, this drug caused an increase in the number of abnormal embryos with abnormalities in vision, tail development, and yolk sac, and a discharge developed in the pericardial cavity of the fish.

The study showed that Danio rerio embryos can be used as a model in preclinical studies to assess the toxicity of various new pharmaceutical drugs [3].

In the work of K.V. Zolotareva et al. the adult fish Danio rerio was exposed to Cd and Cu for 4 days, the concentrations of which were equal to MAC (5 mkg/l for both ions) and sublethal concentrations (6.4 mg/l for cadmium and 80 mkg/l for copper).

Based on the results of the experiment, we found markers of the toxic effects of Cd and Cu on the liver and heart muscle (Table 1) [4].

Table 1. *Markers of toxic effects of Cd and Cu on the liver and heart muscle were established in studies on Danio rerio.*

Fabric	**Markers**	
	Cd	**Cu**
Liver	Sulfotransferase 3 family 2, a protective and hydrophilizing enzyme	Eif2s1, subunit 1 of gene translation initiation factor 2. Forms a complex with GTP and initiating t-RNA
	Secretory phospholipase A2, a Ca- dependent phospholipid hydrolysis enzyme	Stat3, a signal-activating protein of gene transcription.
heart	NADN-DH(ubiquinone)	Chaperonin Class 2
		Selenoprotein J, an antioxidant protein.

A model for creating drug transport systems.

Danio rerio is actively used to develop new drug transport systems, which in the future will help in the treatment of various diseases. In particular, the modeling of Zebrafish brain tumor followed by its therapy with doxorubicin and paclitaxel embedded in the exosome is very relevant [6].

Model for assessing the effects of narcotic drugs.

Danio rerio can serve as excellent test-objects for modeling the effect of narcotic drugs on Danio organism and further ways of its pharmacological correction. This is what Eric J. Mercero, Shelby L. Poitra, Ana Espinoza and coauthors were able to prove in their study. When the electrocardiogram of cocaine-exposed Danio rerio fish was measured, an increase in HR in a bell-shaped dose-dependent manner was observed. The maximum increase was evident at a dose of 5 mg/L in most fish compared to the baseline frequency. It is also worth noting that bradycardia was recorded in Zebrafish when exposed to higher doses. Based on this work, a pattern was introduced that the effect of cocaine on heart rate has a dose- dependent effect. This once again confirms the use of Danio rerio as a model system to study the effects of drugs [7].

Using Danio rerio embryos.

Zebrafish embryos are a good model to evaluate the effects of different substances on oocyte development and stimulation.

Previous experiments have shown that eicosanoids (PGF2α or PGE2) are required to stimulate ovulation in bony fish as well as other vertebrates.

In the study of M.N. Skoblina et al. it was shown for the first time that Danio rerio oocytes that have reached a definitive size surrounded by follicular membranes, matured in vitro under the influence of progesterone, ovulate as a result of their treatment with PGF2α and carp cavity fluid (CCF).

In the experiments conducted, treatment of Zebrafish follicles with progesterone and PGF2α (5 μg/ml) after fertilization resulted in 57 to 92% of oocytes ovulating and 17 to 61% of them reaching the hatching larval stage.

Exposure of follicles to 20% FGF2α containing PGF2α revealed that the percentage of oocytes ovulated by Danio rerio stimulated with progesterone and FGF and progesterone and prostaglandin in three out of four females did not differ significantly [5].

A preclinical study of sodium nucleospermatate ("Viruter") on Danio rerio embryos showed that when this drug is added to experimental wells with embryos, their more effective development occurs due to activation of the innate immunity system with further development of a complex of cytokine-regulated pro-inflammatory and anti-inflammatory signals [8].

We can conclude that Zebrafish oocytes are a promising model for studying the role of various compounds in the processes of cell maturation and ovulation.

Studies on hormone preparations.

Thyroid disorders are among the most common disorders of the endocrine system. Thyroid function disorders are common both in children and adults. Lack of synthesis and secretion of hormones at an early age leads to stunting, somatic disorders and oligophrenia (cretinism), at an older age - to a slow metabolism (myxedema). Using Danio rerio fish, it is possible to evaluate the effect of hypo- and hyperthyroidism on the development and survival of eggs before larvae emerge, while recording blood circulation, pigmentation of the eye area, the appearance or absence of various anomalies in body shape development [9].

Using Danio rerio to model human disease.

A large number of studies in the Danio rerio have identified genes associated with human diseases. Such diseases include Alzheimer's disease, amyotrophic lateral sclerosis, muscular dystrophy, leukemia, thrombosis, cardiomyopathy, diabetes, etc. Different approaches are used to model these diseases on Danio rerio. For example, the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine is used to model parkinsonism in fish, because the mechanism of action of this compound, associated with the destruction of dopaminergic neurons, is the same in Danio rerio and mammals [10].

Use of Danio rerio (Zebrafish) in experimental nephrology.

Previously, an arsenal of different rat and mouse lines with various genetic defects leading to kidney disease has been studied, in which researchers tried to understand the mechanisms of pathology and more thoroughly develop approaches to assess the glomerular filtration rate [1,3]. However, the process of using different substances, such as inulin or yohexol, in laboratory animals is laborious and involves anesthesia, blood and urine collection with further laboratory analysis. In addition, the use of different mammalian species requires sound ethical review, and limited funding may be another obstacle in the planning and design of these studies [1].

Pathological conditions that affect the development and functioning of the nephron (glomerulonephritis, acute kidney injury, polycystic kidney disease, etc.) have been successfully reconstructed and analyzed in Danio rerio fish [11,13]. The paired excretory organ in Danio rerio eggs, the pronephros, is a useful object for biomedical studies, not only within 2-5 days after fertilization, but also beyond this period due to its anatomical "simplicity" associated with the presence of only two nephrons originating from one diseased glomerulus located along the midline of the embryo [11]. Clobular filtration begins as early as 48 hours after fertilization, and full maturation and selective filtration capacity of the glomerulus occurs on day 4 after fertilization, when podocytes and endothelial cells are already well developed [13]. The pronephrotic tubule is divided into separate segments: proximal and distal. All these features have common structural and functional similarities with nephrons of other mammals, including human kidneys, and it makes it possible to use Danio rerio fish as a model object for studying filtration capacity of glomeruli in various diseases, as well as their regenerative abilities [11-14].

There are quite a few mutant lines of Danio rerio fish that are used to study renal function. For example, the Tg(wtIb:EGFP) line provides fluorescent imaging of the proximal tubules and glomerular nephrons using green fluorescent protein and is used to assess the importance of Wilms' tumor protein (WT1) in Danio rerio nephrogenesis (pronephros and glomerular development). This is similar to its role in tumorigenesis in humans, since WT1 also plays a key role in renal development in mammals, and its mutations can lead to the formation of nephroblastoma (Wilms' tumor) [11].

Given the importance of the urinary system, the presence of edema in mutant Danio rerio may be an indirect indicator of impaired renal function. An obligatory caveat of this model is the difficulty of detecting changes in urine and estimating the clearance of various substances, because excretion in fish is carried out in water, and it is not possible to obtain directly clean urine. This fact may limit the use of Danio rerio in modeling various kidney diseases [11-14].

Studies with fluorescent substances make it possible to study the rate of glomerular filtration in Danio rerio fish. Fluorescent "indicators" are injected into fish embryos and traced their passage in the region of interest under a microscope [11,13]. "Indicators" with a large molecular weight are retained by the intact renal barrier and thus allow evaluation of glomerular function. Researchers developed a transgenic line to express vitamin-D-binding protein labeled with green fluorescent protein (VDBP-GFP). When this line is crossed with another line in which podocyte damage can be induced, the "double" transgenic embryo shows accumulation of VDBP-GFP in the proximal tubules, indicating damage to the glomerular filtration barrier [13,16,17]. In addition, a comprehensive study of the rate of disappearance of low molecular weight fluorescent "indicators" in fish can be used as an approximate marker of the glomerular filtration rate. Disruption of this function will lead to delayed "indicators", which can be visualized and measured [4,11,13].

Conclusion.

A large number of laboratories around the world are now using Zebrafish in their research. These small fish have undoubted advantages over rodents: relatively low cost of work, small time costs and ease of breeding. This model object contributes not only to the creation of new drugs, but also allows on the basis of the created models of human diseases to study their pathogenesis

in more detail, as well as their impact on organs and systems. The Danio rerio model does not replace classical mammalian models; it can be the first stage of preclinical studies before they are carried out, particularly on rodents.

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