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Dedicated to young endocrinologists and pathophysiologists

Antiandrogens, nanoparticles and bioactive peptides: experimental and clinical issues

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Abstract. The review article contains the main results of experimental studies of the staff of the Laboratory of Neurohormonal Control of Reproduction and the Department of Endocrinology of Reproduction and Adaptation with regard to the biological effects of non-steroidal antiandrogens, metal nanoparticles, bioactive peptides and their implementation in various branches of medicine. The pharmacodynamic effects and pharmacokinetics of niftolide (flutamide) and other androgen receptor antagonists from the group of substituted carboxanilides that had been synthesized locally were studied. On this basis, a new method of functional diagnostics of gonadotropic reserves of the hypothalamic-pituitary-testicular system was proposed and drugs were developed for the treatment of hirsutism, polycystic ovary syndrome, and prostate cancer. Their preclinical studies and implementation in clinical endocrinology, oncology, gynecology, and dermatology have been carried out. The concept of optimal androgen blockade and the method of low-dose estrogen-antiandrogen palliative and neoadjuvant therapies for prostate cancer and its metastases were experimentally substantiated and confirmed by oncourologists. A method for increasing the effectiveness of gonadotropic stimulation of ovulation in cycles of assisted reproductive technologies has been developed and implemented.

Inhibitory effect of a polydisperse colloidal solution of gold nanoparticles (10-50 nm) on the growth of xenografts of androgen-dependent human prostate cancer transplanted under the kidney capsule of mice was revealed. The drug reduced the quantitative ratio of xenograft epithelial cells to stroma, and *in vitro* experiments inhibited proliferation of prostate cancer cells LnCaP and partially blocked the stimulating effect of 5-alpha-dihydrotestosterone on culture growth.

In experiments on aging rats, a stimulating effect of oral administration of cerium dioxide nanoparticles (2-3 nm) on spermatogenesis and testosterone secretion was found.

The influence of the recombinant cytokine, endothelial-monocyte activating polypeptide II (EMAP II), and its nanocomposites on the growth of xenographs of androgen-dependent human prostate cancer in mice was studied. EMAP II injections inhibited the growth of xenografts, and induced a cytotoxic effect and an inflammatory reaction in them. Flutamide augmented the antitumor effect of EMAP II. In experiments on LnCaP culture, the proapoptotic and antiproliferative effects of the drug were observed.

The obtained results of animal studies form the basis for the development of new methods for treatment of androgen-dependent prostate cancer using nanometals and bioactive polymers.

Keywords: niftolide, flutamide, polycystic ovaries, prostate cancer, gold nanoparticles, cerium dioxide nanoparticles, endothelial-monocyte activating polypeptide II, rats.

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The thirty-year anniversary of the Department of Endocrinology of Reproduction and Adaptation, celebrated in 2021, is a good reason to sum up some of the results of research not only for this period, but also for almost twenty antecedent years of work of the team of the Laboratory of Neurohormonal Regulation of Reproduction (Head — Dr. med. sci. A.G. Reznikov). The laboratory was established in 1973 on the initiative of academician V.P. Komisarenko, the founder of the Institute. The Department included the laboratory of neurohormonal regulation of reproduction and adaptation (headed by Dr. biol. sci. N.D. Nosenko) and the newly created laboratory of experimental andrology, which was headed by Dr. med. sci. S.V. Varga, who died untimely in 1994, and later became headed by Head of the Department A.G. Reznikov.

The results of studies on perinatal programming of neuroendocrine functions and hormone-dependent behavior have been recently published [1]. This article presents the results of long-term research by scientists of both laboratories in the field of antiandrogens, bioactive peptides and metal nanoparticles.

ANTIANDROGENS

Synthesis and study of pharmacodynamic effects of non-steroidal antiandrogens (NSAA)

Androgen receptor antagonists (antiandrogens) of steroid nature have been used for a long time for the palliative treatment of prostate cancer and its metastases. Among them, the most famous is cyproterone acetate. Unfortunately, all steroid antiandrogens have concomitant progestin or estrogenic activity. That is why antiandrogens of non-steroidal structure, which are devoid of hormonal activity, are of particular interest. Antiandrogens are very useful as a tool for studying the mechanism of action of male sex hormones, as a means of pharmacological analysis of the biological role of androgen receptor (AR). The synthesis, study, and clinical use of NSAA were first initiated by us in the USSR in the mid-70s of the last century.

At the beginning of the 70s, the pharmacologists of Schering Plough (USA) had presented experimental data on the selective antiandrogenic activity of a non-steroidal substance from the carboxanilide group 4'-nitro-3'-trifluoromethyl-isobutyranilide (flutamide). Soon, at our request, the resynthesis of flutamide based on the proprietary technology was carried out at the Institute (Ya.G. Balyon) in collaboration with Institute of Organic Chemistry of the National Academy of Sciences of Ukraine (L.M. Yagupolsky, M.O. Lozinsky). By my proposal, this substance was officially named «Niftolide».

In 1988, the first in USSR monograph on antiandrogens by A. Reznikov and S. Varga [2] had appeared. Our team investigated the mechanisms of action and biological effects of Niftolide and several dozen other substituted carboxanilides with their fluorinated derivatives included [3-6]. At the same time, some new properties of Niftolide were discovered, for example, activation of the hypothalamic-pituitary-testicular system. Independently of foreign researchers, the use of Niftolide for the treatment of prostate cancer has been substantiated in preclinical animal studies and implemented in oncological urology. An original ointment has been developed for the treatment of hirsutism, and a method for functional diagnosis of hypogonadotropic hypogonadism using this antiandrogen has been proposed.

Mechanisms of antiandrogen action

The interaction of testosterone (T) and other androgenic hormones with receptor proteins of target tissues is a key event in the mechanism of androgenic regulation in health and disease. AR are found in the organs of the reproductive system, the brain and spinal cord, liver, blood vessels, bone, muscle and other tissues. Like the cellular receptors of other steroid hormones, activated AR functions as transcription factor for the regulation of gene expression.

The result of this is, for example, the inhibition of apoptosis and increased mitotic division and exocrine activity of the epithelium of the acini of the prostate gland under the influence of T and 5alpha-dihydrotestosterone (5α-DHT). Therefore, orchiectomy or pharmacological blockade of AR alters the ratio of the proliferation rate and apoptosis of the secretory epithelium of the prostate gland and causes its atrophy.

We tested the antiandrogenic activity of substituted carboxanilides according to the degree of inhibition of the ability of exogenous T to increase the mass of the ventral lobe of the prostate gland (VLPG) in castrated immature

rats (Herschberger's test). In general, the degree of atrophy of the acinar epithelium corresponded to a decrease in the mass of VLPG, coagulation gland, and seminal vesicles compared with the effect of testosterone administration. Niftolide and its active metabolite, hydroxyflutamide, were the most effective testosterone antagonists, blocking its effect at the AR level in a competitive manner. In addition, antiandrogens prevent 5α-DHT from binding to nuclear AR of the target cells.

The consequence of androgenic blockade is the inhibition of the synthesis of biopolymers: structural and functional proteins, DNA and RNA, as well as RNA polymerase [7, 8]. An additional mechanism of the antiandrogenic action of Niftolide is the inhibition of testosterone metabolism in the prostate gland and liver [9-11]. Niftolide reduces *in vivo* the formation of the active metabolite of testosterone, 5alpha-dihydrotestosterone. In *in vitro* experiments on prostate tissue, Niftolide, in contrast to hydroxylated metabolite of Niftolide, did not have such an effect. This indicates that hydroxyniftolide is an active metabolite of Niftolide.

Niftolide pharmacokinetics

Niftolide is characterized by high bioavailability after oral administration. The maximum concentration of tritiated Niftolide in the blood of rats we observed after 4 h. After 8 h, radioactivity remained quite high (at the level of 70% of the maximum), and the next day was 60% of the maximum. However, 1 h after taking the drug, a significant portion of the isotopic label appears in the composition of hydroxyniftolide. The tissue distribution of radioactivity coincides with the concentrations of the AR (prostate gland, hypothalamus, etc.).

The use of Niftolide in physiological research

In the mid-70s of the last century, we discovered the phenomenon of an increase in the level of testosterone in the blood of male rats and guinea pigs after the administration of Niftolide [12-15]. As a result, the secretion of gonadotropic hormones disrupts, and their concentration in the blood and urine, as well as testosterone in plasma, increases. This was additional evidence of the participation of the brain AR in the negative feedback loop between the testicles and secretion of the pituitary luteinizing hormone [16, 17]. The results of studies on male volunteers have shown that the functional state of the hypothalamic-pituitary-testicular (HPT) axis can be assessed using Niftolide by the degree of increase in testosterone levels in the blood.

The Niftolide test has been successfully applied in a number of animal physiological and pathophysiological studies. In experiments on rats, it was shown that damage of the testes during acute and lasting general overheating is the result of not only structural and functional changes in the gonads, but also disorders of neuroendocrine regulation [18-20]. Morphological and functional changes in the HPT axis of rats under the influence of vibration, noise and their combination have been characterized [21]. Niftolide was used to analyze the role of androgens in the regulation of bile secretion [22] and the heart physiology [23].

Development of drugs and new formulations

Niftolide ointment. The world's first antiandrogen based ointment for the treatment of hirsutism was proposed and investigated by us in the year of 1977 in collaboration with the Kiev Institute for Advanced Medical Studies [24, 25], and then with pharmacists from the Nizhny Novgorod Chemical Pharmaceutical Plant. Clinical trials of two Niftolide ointment formulations in the medical centers of Kharkov, Kyiv, Moscow, Leningrad have shown its effectiveness and safety. After the collapse of the USSR, the Nizhpharm plant, in violation of the agreement on creative cooperation, refused to transfer the industrial regulations for the production of ointments to Ukraine and, ignoring our priority, issued a Russian patent for it [26] and produced this drug for a number of years. Unfortunately, our attempts to interest Ukrainian drug manufacturers in the production of the ointment have not met with a positive response.

Niftolide and Flutafarm tablets. The invention certificate for Niftolide as a treatment for prostate cancer was obtained in 1995 with priority date of 1975 [27]. In collaboration with pharmacists of the Kiev Institute for Advanced Medical Studies (currently the P.L. Shupik National University of Health), a formulation of Niftolide tablets was developed. After our preclinical studies of the efficacy and safety of the drug, as well as clinical trials in the largest clinics in the country, Niftolide tablets were officially approved for the

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treatment of prostate cancer. For some time they were produced by the Experimental Production of the Institute of Organic Chemistry, and then by the Darnitsa Chemical and Pharmaceutical Plant. Niftolide tablets were present at the pharmaceutical market of the Russian Federation with indications in the instructions not only for the treatment of prostate cancer, but also for the differential diagnosis of male hypogonadism. On the basis of the previous experience with Niftolide tablets, new formulation of the domestic flutamide tablets was developed by the specialists of Public joint stock company Farmak, and after our preclinical studies and multicenter clinical trials [28] the drug was approved by authorities. This medication (Flutafarm) is being in use for many years for treatment of prostate cancer in males and hyperandrogenism in women. In terms of therapeutic efficacy in patients with prostate cancer and in terms of pharmacological activity and safety criteria, Flutafarm is equivalent to Flucinom (USA).

Niftolide suppositories. In order to improve the drug delivery to the prostate gland, Niftolide suppositories were developed, and their effectiveness was investigated in experiments on rats [29]. Unfortunately, due to a lack of funding for the study, further work on the suppositories was suspended.

Clinical use of Niftolide and Flutafarm

Functional Niftolide (Flutamide) test. In the end of 70s of the last century, our laboratory has acquired the status of the Cooperating Center for Human Reproduction of the World Health Organization, and we received a financial grant to develop a method for evaluating the functional reserve of HPT axis based on Niftolide administration. Oral intake of Niftolide by healthy male volunteers caused by 3 and 5 days significant increase of testosterone level in the blood. Thus, the results of animal research were applicable to a human being [13, 19]. After that, method of differential diagnosis of primary and secondary hypogonadism, as well as secondary hypogonadism and delayed sexual maturation in human males, were developed and successfully applied in clinical practice [30-33]. This functional test proved informative in assessing gonadotropic reserves in men with type 2 diabetes mellitus [34, 35].

Prostate cancer. The concept of maximum androgen blockade dominates in palliative treatment of this disease. The AR antagonists as effective means of androgen deprivation occupy is relevant for the first line of hormonal therapy of prostate cancer and its metastases. They are used in modes of mono- or combined therapy with other hormonal drugs. These drugs displaced traditional treatment with a high dose estrogens, which is associated with the high risk of cardiovascular pathology and other fatal complications.

In our department, a large body of experimental studies was performed on the issue of hormonal regulation of the structure and function of the prostate gland and other reproductive organs [36]. On a normal and malignant prostate, the effects of androgens, estrogen, Niftolide (futamide), luteinizing hormone-releasing hormone (LH-RH) agonist, interferon-alpha, inductors of interferon synthesis, inhibitors of the steroid 5-alpha-reductase in the modes of mono- or combined applications are studied. The concept of optimum androgen blockade in the treatment of prostate cancer are proposed [37].

We discovered the phenomenon of potentiation of the antiandrogenic effect of Niftolide on the prostate with low doses of estrogen [38]. The mechanism of this phenomenon is the ability of low doses of estrogen to inhibit the secretion of pituitary luteinizing hormone (LH). The pronounced antiprostatic activity of the combined administration of flutamide and the LH-RH agonist, Surfagon, to rats has been proven [39]. The most common combination hormone therapy for prostate cancer is the combination of flutamide with LH-RH agonists. The replacement of an expensive LH-RH agonist with a cheaper synthetic non-steroidal estrogens, hexestrol (Synestrol) [40], Chlorotrianisene [41], Honvan (fosfestrol) [42, 43] led to the development of a low-dose estrogen-antiandrogen therapy regimen [44, 45]. This method of prostate cancer therapy is implemented into urological oncology practice by the Institute of Urology of the National Academy of Medical Sciences of Ukraine [46]. The results of these studies are summarized in two monographs [47, 48]. Research carried out by academician A.F. Vozianov and co-workers showed that treatment with flutamide (niftolide, Flutafarm) reduces the volume of the prostate by

an average of one third after 3-month course. The severity of pain syndrome, the volume of bone and other metastases decrease, and the outflow of urine improves. After 3 years, all patients with the stage I of disease at the beginning of treatment remained alive, with the stage II — 81.5% of patients, with the stage III — 73.9%, with the stage IV — 50.0%. According to the Cancer Research Center of the Russian Academy of Medical Sciences, monotherapy with flutamide in the presence of distant metastases ensures the survival of patients for at least 2.5 years.

Hyperandrogenic pathology in women. Functional hyperandrogenism is the most common endocrine pathology in women; it occurs in 10-20% of patients who visit an endocrinologist, gynecologist, dermatologist, and cosmetologist. In the pathogenesis of disorders, the leading role is played by increased secretion of male sex hormones by the ovaries (polycystic ovary syndrome, PCOS) or adrenal glands (21-hydroxylase deficiency), tissue hypersensitivity to androgens, increased activity of steroid 5α-reductase in target cells, decrease in the content of sex steroid binding globulin in blood. Clinical manifestations of hyperandrogenic conditions are anovulatory infertility, impaired folliculogenesis in the ovaries, hirsutism, androgenic alopecia, acne, seborrhea, lipid and carbohydrate metabolism disorders, obesity, insulin resistance, and, in severe cases, virilization of the external genitals.

Hyperandrogenism is the main pathogenetic factor of polycystic ovarian syndrome. In our experimental and clinical studies, the role of high blood testosterone level, low sex steroid binding globulin, neuroendocrine disorders, deficiency of steroid aromatase in the ovaries, an increased level of AR in the skin is shown in polycystic ovary condition and hirsutism [49-51]. Regardless of the cause of hyperandrogenism (with the exception of a malignant tumor), the use of AR antagonists is considered a substantiated and effective method of treating its complications. We are the first to propose local (Niftolide ointment) and systemic (Flutafarm tablets) use of flutamide for the treatment of hirsutism and other complications of hyperandrogenism, and conducted appropriate preclinical studies in animals, the results of which were implemented in clinical practice [36, 52].

The use of flutamide (Niftholide and Flutafarm) for the experimental treatment of anovulatory infertility in androgenized rats with implanted Silastic capsules containing crystalline testosterone has been successful. The experimental animals showed restoration of ovulation and estrous cycles, fertility, as well as partial normalization of hormonal, biochemical and morphological characteristics of the reproductive system [53-55]. Further, it was possible to show that Flutafarm reinforces gonadotrophin-induced ovulation in rats with polycystic ovaries [56]. It was shown that the use of Flutafarm before *in vitro* fertilization procedure increases the effectiveness of gonadotropic ovulation inducers, improving the results of the technology in hypofertile women [57].

Especially for women, the Farmak company produces Flutafarm Femina, flutamide tablets with a dose of flutamide adapted for the treatment of hyperandrogenism. Clinical trials have shown the effectiveness of Niftolide ointment in the treatment of hirsutism, Flutafarm and Flutafarm Femina oral tablets in the treatment of hirsutism, polycystic ovary syndrome, infertility, disorders of periods. Against this background, patients with amenorrhea sometimes have spontaneous menses [58-60]. According to Tatarchuk T.F. et al. [61], as a result of treatment, the thickness of the endometrium increased, 76% patients with polycystic ovary syndrome restored regular menstrual cycle, in 36% of them it became two-phase, and luteal bodies appeared in the ovaries. Under the influence of long-term antiandrogenic therapy, free testosterone level in blood plasma, hirsutism number, the gonads size, the number and size of follicles and cysts, and the degree of proliferation of connective tissue decreased.

For the first time, the medical instruction of flutamide tablets included new indications for use: treatment of women with functional hyperandrogenism, accompanied by ovarian-menstrual disorders, hirsutism, polycystic ovary syndrome and infertility. Certainly, antiandrogen use must be combined with reliable non-hormonal contraception.

NANOPARTICLES OF METALS

The last two decades have been characterized by an explosive growth in scientific work concerning the potential applications of metal

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nanoparticles for the diagnosis and treatment of diseases. This problem interested us in two aspects: the effect on the reproductive system and on the growth of androgen-dependent prostate cancer. In these fields of research we cooperated with International Center for Molecular Physiology of O.O. Bogomolets Institute of Physiology, F.D. Ovcharenko Institute of Biocolloid Chemistry of NAS of Ukraine, and with Research Institute of Nanotechnology Industry (Kyiv).

Gold nanoparticles

The experiments were carried out on normal rats and human prostate cancer cells and tissues [62]. We used polydispersed and monodispersed colloidal solutions of gold nanospheres sized 10-50 nm and 20 nm, respectively.

In vitro, a polydispersed solution at a concentration of 10 μg/ml of culture medium inhibited by 40% the growth of the androgen-dependent human prostate cancer cell line LNCaP [63]. At the same concentration, gold nanoparticles halved the increase in the number of cells in culture stimulated with 5-alpha-dihydrotestosterone. Unlike the polydispersed solution, the monodispersed solution did not affect the growth of cancer cells. Probably, the inhibitory effect of the polydispersed solution is due to smaller nanoparticles capable of interacting with cancer cells and their compartments. Massive necrosis of the cells and visible impairments of their morphology were not seen. Apparently, the change in the number of cells in the culture under the influence of polydispersed colloidal solution was caused by inhibition of the cell proliferation.

The antitumor properties of gold nanoparticles were demonstrated *in vivo* on xenografts of androgen-dependent human prostate cancer transplanted under the capsule of the mice kidney [64, 65]. Subcutaneous injections of a polydispersed solution of gold nanoparticles stopped the growth of cancer grafts. The antitumor effect of the drug is aimed mainly at malignant epithelial cells of the prostate, which is confirmed by the corresponding changes in the epithelial-stromal ratio.

Polydispersed and monodispersed colloid solutions did not cause damage effects on the reproductive organs of male rats, except for the inflammatory process in the ventral lobe of the prostate [66, 67]. We concluded that the reproductive toxicity of gold nanoparticles larger than 10 nm was insignificant.

Cerium dioxide nanoparticles

Interesting results were obtained when studying the effect of cerium nanoparticles on the reproductive system [68, 69]. There was established stimulatory effect of ten-day oral administration of cerium nanoparticle sol at size of 2-3 nm, at a dose of 1 mg/kg b.w. on testicular hormonal function and spermatogenesis of aging male rats (18 months). This nanoparticles has been shown to activate the testosterone-producing Leydig cells of the testes, as well as the secretory and proliferative processes in ventral lobe of the prostate gland of rats. Later, the stimulation of decreased testosterone secretion and spermatogenesis by cerium dioxide nanoparticles was demonstrated in a rat model of streptozotocin diabetes [70]. The mechanism of this phenomenon is not entirely clear. One of the assumptions is that it is due to the antioxidant properties of cerium dioxide nanoparticles [71].

ENDOTHELIAL MONOCYTE-ACTIVATING POLYPEPTIDE-II (EMAP II)

One of the new approaches in the treatment of oncological pathology is the use of drugs based on proteins and polypeptides. In search of new treatments for hormone-dependent prostate cancer, we studied the antitumor activity of recombinant EMAP II synthesized at the Department of Protein Engineering and Bioinformatics headed by O.I. Kornelyuk, Corresponding Member of NAS of Ukraine, at the Institute of Molecular Biology and Genetics (Kyiv).

EMAP II is the extracellular cytokine-like derivative of the auxiliary protein p43 which is associated with tyrosyl-tRNA synthetase complex in mammalians. This polypeptide is produced intracellularly in tumor tissues due to proteolytic cleavage of endogenous p43. EMAP II possesses a number of cytokine-like activities. It exerts proapoptotic, proinflammatory effects, endothelial-dependent coagulation and antiangiogenic effects [72]. Based on these properties, positive results of *in vivo* EMAP II treatment of some malignant tumours have been demonstrated in animal researches [73, 74].

We hypothesized, that *in vivo* administration of EMAP II might inhibit growth of prostate cancer. Indeed, we were lucky to be the first to find retardation of growth of androgen-dependent

human prostate cancer xenografts implanted subcapsullary to the male mouse kidney. Histopathological study revealed significant degenerative changes and necrotic death of many tumor cells, stimulation of apoptosis (significant increase in number of apoptotic bodies), an enlargement of necrotic areas and an enhancement of the leukocyte infiltration in the transplants exposed to EMAP II [75]. A few days later, after the publication of this article, we received information that it was included in the international information base Drug Discovery.

EMAP II did not affect the level of testosterone in the blood plasma of mice. The dependence of used cancer xenografts on endogenous androgens was confirmed by the absence of its growth in previously castrated recipient mice. Flutamide enhanced effect of EMAP II on the growth of xenografts [76].

Possibly, effect of EMAP II is mediated, at least partly, with TNFα. In animal research, treatment with EMAP-II of different types of carcinoma induced the sensitivity to TNFα [77]. Our experiments *in vitro* demonstrate direct proapoptotic and antiproliferative effect of EMAP II on the LnCaP cell line growth [78].

The obtained results of experimental studies form the basis for the development of new methods for the treatment of androgen-dependent prostate cancer using nanometals and bioactive polymers.

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Abbreviation

AR — androgen receptor
EMAP II — endothelial-monocyre activating polypeptide II
HPT — hypothalamic-pituitary-testicular
LH — luteinizing hormone
LH-RH — luteinizing hormone-releasing hormone
NSAA — non-steroidal antiandrogens
PCOS — polycystic ovary syndrome
T — testosterone
VLPG — ventral lobe of the prostate gland
5α-DHT — 5alpha-dihydrotestosterone

Антиандрогени, наночастинки та біоактивні пептиди: експериментальні та клінічні питання

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Резюме. Оглядова стаття підсумовує основні результати експериментальних досліджень співробітників лабораторії нейрогормональної регуляції розмноження та відділу ендокринології репродукції та адаптації стосовно біологічних ефектів нестероїдних антиандрогенів, наночастинок металів, біоактивних пептидів та їх імплементації в різних галузях медицини. Досліджено фармакодинамічні ефекти і фармакокінетику ніфтоліду (флутаміду) та інших синтезованих в інституті антагоністів рецепторів андрогенів із групи заміщених карбоксанілідів. На цьому підґрунті запропоновано новий метод функціональної діагностики гонадотропних резервів гіпоталамо-гіпофізарно-тестикулярної системи та створено лікарські засоби для лікування гірсутизму, синдрому полікістозних яєчників, раку передміхурової залози. Проведено їхні доклінічні дослідження та впровадження в клінічну ендокринологію, онкологію, гінекологію, дерматологію. Експериментально обґрунтовані та підтверджені онкоурологічною практикою концепція оптимальної андрогенної блокади та метод низькодозової естроген-антиандрогенної паліативної та неоад'ювантної терапії раку передміхурової залози та його метастазів. Розроблено і впроваджено спосіб підвищення ефективності гонадотропної стимуляції овуляції в циклах допоміжних репродуктивних технологій.

Виявлено пригнічуючий вплив полідисперсного колоїдного розчину наночастинок золота (10-50 нм) на ріст ксенографтів андрогензалежного раку передміхурової залози людини, трансплантованих під капсулу нирки мишей. Препарат зменшував кількісне співвідношення епітеліальних клітин ксенографтів до строми, а в дослідах *in vitro* пригнічував проліферацію ракових клітин простати LnCaP і частково блокував стимулювальний ефект 5-альфа-дигідротестостерону на ріст культури.

У дослідах на старіючих щурах виявлено стимулювальний ефект перорального введення наночастинок діоксиду церію (2-3 нм) стосовно сперматогенезу та секреції тестостерону.

Досліджено вплив рекомбінантного поліпептидного цитокіну EMAP II (endothelial-monocyre activating polypeptide II) та його нанокомпозитів на ріст ксенографтів андрогензалежного раку передміхурової залози людини в мишей. Ін'єкції EMAP II гальмували ріст ксенографтів, викликали в них цитотоксичний ефект та за-

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пальну реакцію. Флутамід посилював протипухлинну дію EMAP II. У дослідах на культурі LnCaP спостерігали проапоптотичний та антипроліферативний ефекти препарату.

Отримані результати експериментальних досліджень створюють підгрунтя для розроблення нових методів лікування андрогензалежного раку передміхурової залози з використанням нанометалів і біоактивних пептидів.

Ключові слова: ніфтолід, флутамід, полікістоз яєчників, рак передміхурової залози, наночастинки золота, наночастинки діоксиду церію, EMAP II, щури.

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