Activation of the last protein kinases of insulin signaling cascade in peripheral blood mononuclear cells of diabetic patients with different types of cancer

T.S. Vatseba², L.K. Sokolova¹, V.V. Pushkarev¹, O.I. Kovzun¹, B.B. Guda¹, V.M. Pushkarev¹, M.D. Tronko¹

¹ SI «V.P. Komisarenko Institute of endocrinology and metabolism of NAMS of Ukraine», Kyiv
² SHEI «Ivano-Frankivsk National Medical University», Ivano-Frankivsk

Abstract. Akt/mTOR/p70S6K1 signaling pathway plays an important role in the pathogenesis of cancer and diabetes. Macrophages and lymphocytes are involved in the pathogenesis of diabetes, diabetic atherosclerosis, formation of insulin resistance as well as immune response to cancer and tumor maintenance. The aim of the study was to determine the activation of Akt/mTOR/p70S6K1 in peripheral blood mononuclear cell (PBMC) of patients with type 2 diabetes (T2D) and cancer. Results. The level of insulin in the blood of diabetic patients with breast and endometrial cancer was significantly higher compared to control, whereas it did not differ from control in the blood of diabetic patients with colorectal and pancreatic cancer. The highest level of insulin was observed in the blood of patients with T2D solely. Almost the same pattern was observed concerning IGF-1 blood concentration. Akt S473 phosphorylation by mTORC2 was higher than control values in PBMC of breast and endometrial cancer diabetic patients. The level of Akt phosphorylation in PBMC of diabetic patients with colorectal and pancreatic cancer was lower then in control cells that corresponds to insulin and IGF-1 concentrations in the blood. There was no activation of Akt by mTORC2 in PBMC of diabetic patients. There is no activation of mTORC1 in PBMC of patients with cancer and diabetes but there is its significant activation in the cells of patients with T2D only. Probably the Akt activation by mTORC2 is not associated with activation of mTORC1 in the cells of patients with T2D. The decrease in mTORC1 activity occurred in the cells of diabetic patients with all studied types of cancer. It can be assumed, that diabetes-related PI3K/Akt signaling in PBMC is likely to interfere with cancer-related signaling mechanisms. There were the differences in oncological patients

DOI: 10.31793/1680-1466.2019.24-4.302
Protein kinase Akt (v-act murine thymoma viral oncogene homolog) plays a key role in regulation of cell growth, homeostasis, survival, proliferation and metabolism. Akt is activated by PDK1 via T308 phosphorylation in the T-loop of the catalytic domain and by rapamycin-insensitive mTORC2 through S473 phosphorylation in the hydrophobic region on the C-tail. Akt enhances insulin-dependent translocation of GLUT-4 and glucose transport, and activates downstream protein kinases mTORC1 (mammalian target of rapamycin complex 1) and p70S6K, which control protein synthesis [1].

The mTORC1 protein kinase controls cell growth and homeostasis, including protein synthesis, lipogenesis, glucose metabolism, autophagy, biogenesis of lysosomes, proliferation and survival, in response to environmental signals such as levels of amino acids, glucose, energy, oxygen and growth factors [2]. The mTORC1 also includes mLST8/GβL (mammalian lethal with Sec 13 protein 8/G-protein β-protein subunit like), deptor (DEP-domain-containing mTOR interacting protein) and raptor (regulatory-associated protein of mTOR), which is a scaffolding protein that mobilizes substrates for the mTOR kinase, interacting with their TOS (TOR signaling) motifs [3].

The main substrate of mTORC1 is protein kinase p70S6K. The evolutionary conserved kinases of ribosomal S6 protein belong to the family of AGC kinases (PKA, PKG and PKC) and play an important role in regulation of cell growth and metabolism [4]. S6K kinases are mTOR pathway effectors, and activation of the mTOR/S6K axis stimulates protein synthesis and cell growth [5].

The deregulation of the PI3K/Akt/mTOR/p70S6K cascade often leads to serious diseases such as cancer and type 2 diabetes (T2D) [5].

It was established that regulation of insulin/IGF system is often disturbed in cancer. Epidemiological studies have shown that elevated IGF-1 plasma concentrations are associated with a higher risk of developing various malignancies [6].

The peripheral blood mononuclear cell (PBMC) include several types of cells that play a significant role in the development of pathological conditions such as cancer, diabetes and its complications [7-9]. The PI3K/Akt pathway is involved in the activation of macrophages and lymphocytes, secretion of cytokines, initiation of inflammatory processes and immune surveillance failure [10].

The aim of the work was to determine the activation of the last 3 kinases of the PI3K/Akt/mTORC1/p70S6K cascade in PBMC of oncological patients with different types of cancer on the background of decompensated type 2 diabetes.

**Material and methods**

The study was conducted in the diabetology department of IEM and the department of internal medicine № 1, clinical immunology and allergology of Ivano-Frankivsk National Medical University. All patients signed informed consent to conduct further diagnostic and research study. PBMC were obtained from blood as previously described [11]. The PBMC collected were washed in PBS by centrifugation at 200 g to remove platelets and frozen at −80 °C until use.

For determination of the phospho-Akt1/2/3 (p-S473), phospho-PRAS40 (p-T246) and phospho-p70S6K1 (p-T389) ELISA kits 85-86046, КНО0421 and 85-86053 were used respectively (Invitrogen, USA). The cells were lysed in the extraction buffer containing inhibitors of proteases and phosphatases. The measurements were carried out on a microplate reader (Bio-tek Instruments, USA) at a wavelength of 450 nm. The protein concentration in the lysate was determined using BCA protein assay kit (Novagen, USA).
The levels of insulin and IGF-1 in the blood were determined using the automatic analyzer Stat fax 303+ (USA) with the diagnostic kits Insulin ELISA (EIA-2935) and IGF-1600 ELISA (EIA-4140) from DRG (Germany). HbA1c was determined by ion-exchange chromatography, using the Bio-Rad (USA) D-10 analyzer and reagents.

The OD values of samples obtained are located on the calibration curve satisfactorily coinciding with a theoretical lines that indicates no scattering of the data.

All examined patients belonged to the Caucasian race, age was in range from 46 to 72. The patients and a control group were selected with close age and body mass index.

The results of the study are presented as M±SD, n=5-12. To compare the data groups, one-way ANOVA and Student’s t-test were used. Values of P ≤ 0.05 were considered as significant.

Results and its discussion

The following groups were investigated: 1 — control group (n=10) — healthy people, representative by age; 2 — patients with breast cancer and diabetes (n=7); 3 — patients with endometrial cancer and diabetes (n=8); 4 — patients with colorectal cancer and diabetes (n=6); 5 — patients with pancreatic cancer and diabetes (n=5); 6 — patients with type 2 diabetes solely (n=12). Therapy of patients included combinations of glucose-lowering drugs and insulin. The average level of HbA1c in patients was 8.07±0.99% corresponded to the decompensation of diabetes.

Patients with cancer were characterized as belonging to the clinical group II. Blood collection was carried out before specific antitumor therapy (chemotherapy, hormonal therapy, radiotherapy) was assigned.

It is known that in tissues of patients with T2D, as a result of prolonged exposure to high doses of insulin, the activity of Akt and its downstream kinases, mTORC1 and p70S6K, in metabolic tissues is enhanced, resulting in phosphorylation of key adapter protein of insulin cascade — IRS-1 (S307 and other amino acid residues), its degradation, impaired insulin signaling and, consequently, insulin resistance [9]. The level of phosphorylated Akt in PBMC of patients with T2D may be determined by the ratio of metformin and insulin effects. Metformin activates the AMPK and inhibits mTORC1 activity, but improves insulin signaling. Insulin activates the signaling cascade of PI3K/Akt/mTORC1 and inhibits the activation of AMPK by metformin [12]. The final result of the interaction of these drugs and the signaling mechanisms induced is the state of Akt activity.

The PBMC include monocytes/macrophages and lymphocytes (T cells, B cells and NK) involved in the processes of cellular and humoral immunity as well as in pathogenesis of diabetes and its complications. PI3K/Akt/mTOR is a signaling cascade that largely determines the functioning of these blood cells in diabetes and malignant neoplasm [7-9, 13].

The level of insulin in the blood of patients with breast and endometrial cancer was significantly (more than 2 times) higher compared to control, whereas it did not differ from control in the blood of patients with colorectal and pancreatic cancer (Table). The highest level of insulin was observed in the blood of patients with type 2 diabetes solely. Almost the same pattern was observed concerning IGF-1 blood concentration, which was highest in diabetic patients with breast and endometrial cancer.

Akt1/2/3 S473 phosphorylation (and activation) by mTORC2, normalized with respect to the total amount of Akt in the cells, was higher

Table. IGF/insulin content in the blood and Akt/mTORC1/ p70S6K1 activation in the PMBC of oncological patients with type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>Insulin</th>
<th>IGF-1</th>
<th>p/t-Akt</th>
<th>p-AKT1S1</th>
<th>p/t- p70S6K</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Contr.</td>
<td>7.56</td>
<td>141.57</td>
<td>0.0602</td>
<td>1.168</td>
<td>0.0063</td>
</tr>
<tr>
<td>SD</td>
<td>0.81</td>
<td>10.12</td>
<td>0.0066</td>
<td>0.052</td>
<td>0.0009</td>
</tr>
<tr>
<td>2. Breast cancer</td>
<td>15.27*</td>
<td>191.17*</td>
<td>0.0748*</td>
<td>0.647*</td>
<td>0.0047*</td>
</tr>
<tr>
<td>+ T2D</td>
<td>0.54</td>
<td>12.71</td>
<td>0.0047</td>
<td>0.072</td>
<td>0.0003</td>
</tr>
<tr>
<td>SD</td>
<td>2.76</td>
<td>15.55</td>
<td>0.0036</td>
<td>0.16</td>
<td>0.0007</td>
</tr>
<tr>
<td>3. Endometrial</td>
<td>17.59*</td>
<td>189.96*</td>
<td>0.0731*</td>
<td>0.901*</td>
<td>0.0047*</td>
</tr>
<tr>
<td>cancer + T2D</td>
<td>2.76</td>
<td>15.55</td>
<td>0.0036</td>
<td>0.16</td>
<td>0.0007</td>
</tr>
<tr>
<td>SD</td>
<td>0.17</td>
<td>27.80</td>
<td>0.0196</td>
<td>0.04</td>
<td>0.0002</td>
</tr>
<tr>
<td>4. Colorectal</td>
<td>7.35+</td>
<td>172.75</td>
<td>0.0427**</td>
<td>0.423**</td>
<td>0.0045*</td>
</tr>
<tr>
<td>cancer + T2D</td>
<td>0.17</td>
<td>27.80</td>
<td>0.0196</td>
<td>0.04</td>
<td>0.0002</td>
</tr>
<tr>
<td>SD</td>
<td>1.64</td>
<td>10.84</td>
<td>0.0234</td>
<td>0.041</td>
<td>0.0002</td>
</tr>
<tr>
<td>5. Pancreatic</td>
<td>8.60+</td>
<td>158.16*</td>
<td>0.0291**</td>
<td>0.322**</td>
<td>0.0029**</td>
</tr>
<tr>
<td>cancer + T2D</td>
<td>1.64</td>
<td>10.84</td>
<td>0.0234</td>
<td>0.041</td>
<td>0.0002</td>
</tr>
<tr>
<td>SD</td>
<td>2.43+</td>
<td>175.54*</td>
<td>0.0665</td>
<td>1.7142*</td>
<td>0.0092*</td>
</tr>
<tr>
<td>6. T2D solely</td>
<td>4.94</td>
<td>5.46</td>
<td>0.0075</td>
<td>0.07</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

Note: * — differences from control are significant, P≤0.05; 
+ — differences from groups 2 and 3 are significant, P≤0.05; 
^ — differences from other types of cancer are significant, P≤0.05.
than control values in PBMC of breast and endometrial cancer patients that corresponds to increased insulin and IGF-1 concentrations in the blood (Table). The level of Akt phosphorylation in PBMC of patients with colorectal and pancreatic cancer was substantially lower than in control cells and especially in the PBMC of patients with breast and endometrial cancer. There was no activation of Akt by mTORC2 in PBMC of diabetic patients compared with control, which indicates an absence of association between the level of insulin/IGF-1 in the blood and the activation of kinase in the blood cells.

The Akt1-1 substrate (AKT1S1), also known as the proline-rich Akt substrate 40kDa (PRAS40), is a component of the mTORC1/p70S6K signaling mechanism, which binds raptor and interferes with the interaction of mTOR1 kinase with its substrates [14, 15]. AKT1S1 is both a substrate and a negative regulator of mTORC1 and is phosphorylated by Akt (T246) and mTORC1 (S183/S212/S221). Phosphorylation causes binding of AKT1S1 to the protein 14-3-3-ζ, the dissociation of AKT1S1 and raptor and, respectively, the activation of mTORC1 [13, 14]. It is interesting that over-expression of AKT1S1 enhances insulin sensitivity in skeletal muscle [15].

We observed high level of AKT1S1 phosphorylation in PBMC of control samples and lower quantity of p-AKT1S1 in PMBC of diabetic patients with all types of cancer, especially in the PBMC of patients with colorectal and pancreatic cancer (Table) that may indicate the absence of mTORC1 activation in the blood cells of these patients. In contrast, the level of AKT1S1 phosphorylation in PBMC of patients with type 2 diabetes was 1.5 times higher than the control.

Phosphorylation and activation of the mTORC1 substrate — p70S6K1 in PBMC of diabetic patients with all types of cancer coincides with the corresponding phosphorylation of AKT1S1 (Table).

Thus, based on the pattern of phosphorylation of AKT1S1 and the substrate of mTORC1 — p70S6K1, we can conclude that there is no activation of mTORC1 in PBMC of patients with cancer and diabetes but there is its significant activation in the cells of patients with T2D only. It is also likely that Akt activation by mTORC2 is not associated with activation of mTORC1 in the cells of patients with T2D.

It should be noted that Akt is phosphorylated by the mTORC2 on S473 in a partially IRS-independent manner, which indicates a weak connection of such phosphorylation with IRS/PI3K signaling [16, 17]. Therefore, it was interesting to check also the activation of mTORC1 in these conditions. It is known that mTORC1 is regulated by the availability of nutrients, energy and growth factor signals, while mTORC2 is activated by growth factor signals [18, 19]. Thus, studying of Akt phosphorylation by the mTORC2 we can try at least partially to separate the effect of nutrients from the effects of growth factors, and metabolic effects from mitogenic.

Phosphorylation of AKT1S1 causes its sequestration from the mTOR1 complex and, thus, activation of the latter. Activated mTORC1 phosphorylates the hydrophobic motif of p70S6K1 to initiate translation [20, 21]. We observed significant increase of p70S6K1 phosphorylation in PBMC of patients with diabetes (Table). Together, this indicates the activation of the last kinases of the insulin cascade.

Thus, despite the absence of Akt activation, the final kinases of the Akt/mTORC1/p70S6K1 cascade activation in PBMC of patients with diabetes were observed. Obviously, the Akt and the downstream kinases are activated by Akt phosphorylation on Thr308 by PDK1. It is possible also that the MAPK signaling pathway mediating the effects of IGF may be involved in the activation of the insulin cascade.

There is increasing evidence that selective mTORC1 inhibition can elicit increased Akt Ser473 phosphorylation and attenuates the signal effects on tumor cell proliferation [22, 23]. It is possible that there is a reciprocal relation between Akt and the two mTOR complexes, between the two activating phosphorylation sites, Thr308 and Ser473, of Akt. The energy charge, the ATP/AMP concentration ratio, may represent a switch between the active and inactive state of Akt and sites of phosphorylation as well. High ATP/AMP ratio activates mTORC1 and the energy consuming synthetic processes. Under nutrient deprived conditions, active FoxO transcribes rictor promoting participation of mTORC2 [24].

Given the decrease in phosphorylation of AKT1S1, we can conclude that activation of mTORC1 in cancer + T2D samples (especially colorectal and pancreatic cancer) was essentially...
lower than in control PBMC. This is confirmed by phosphorylation of p70S6K1. The lowest quantity of p-p70S6K1 was observed in PBMC of patients with pancreatic cancer. At the same time, in PBMC of patients with T2D, we observed a significant stimulation of mTORC1/p70S6K1 activity. Thus, diabetes-related PI3K/Akt signaling in PBMC is likely to interfere with cancer-related signaling mechanisms. A certain universality of the latter should be noted, since a decrease in mTORC1 activity, although to a different degree, occurred in the cells of patients with all studied types of cancer.

We can note the coincidence of the Akt phosphorylation pattern in PBMC and the levels of insulin and IGF-1 in the blood of patients with T2D and cancer. In contrast, the activation of mTORC1 and p70S6K1 did not correspond to hormones levels. Therefore, it can be concluded that Akt phosphorylation by mTORC2 in this context is not associated with the activation of mTORC1.

High levels of IGF-1 and insulin in the microenvironment provide a potential mechanism for carcinogenesis and early tumor growth through antiapoptotic signaling and metabolic reprogramming mediated by PI3K/Akt/ mTOR. It is known that patients with obesity are characterized by higher levels of IGF-1 in the blood, compared with people with normal BMI [25]. This is consistent with the conclusion that diabetes and obesity increase the risk of developing types of cancer with the Warburg phenotype [26, 27].

The differences between breast and endometrial cancer on the one hand, and pancreatic and colorectal cancer on the other hand, are apparently explained by the specific hormonal background that accompanies the first types of cancers.

Early studies have shown that IGFs and estrogens are strong mitogens for breast cancer cells and that high circulating IGF-1 and estrogens are risk factors of breast cancer. Data indicated that these hormones act synergistically on the pathogenesis of breast cancer. Estrogens increase the effect of IGF-1 on breast cancer cells by stimulating the expression of IGF-1 and IGF-1 receptor [28].

The insulin/IGF system and estrogens act synergistically as potent mitogens in normal breast as well as in breast tumor cells. The evidences were obtained that the insulin/IGF and estrogen-mediated signaling pathways are closely connected [29]. Estradiol upregulates the expression of several IGF family members including IGF-1/2, IGFBP2 (IGF-binding protein), IGF-1R, and insulin receptor substrate 1 (IRS-1) [6]. It was shown that IRS-1 is associated with breast cancer progression [30].

The insulin/IGF system is frequently dysregulated in cancer, contributing to cancer progression, metastases, and resistance to cancer therapies [6, 31]. Common alterations include overexpression of IR and IGF-1R by the malignant cells, increased IR/IGF-1R hybrid formation, deregulated autocrine secretion of IGFs, and increased IGFs secretion by the tumor stroma. IGFBPs production in the tumor microenvironment may also be dysregulated [31].

In estrogen-induced endometrial carcinogenesis, IGF-1 plays an important role. Estrogens increase the expression of IGF-1 in tissues, and IGF-1 is required to mediate their mitogenic effects on the endometrium. In addition, estrogens modulate IGF-1 signaling by regulating the expression in other members of the IGF family, including the IRS-1 and IGFBPs [32].

Estrogen and insulin play a synergistic role in type 1 endometrial carcinogenesis and progression. Epidemiologic studies have found that estrogens, insulin, and IGFs are higher in patients with type 1 endometrial cancer than in healthy individuals. Steroid hormones, such as estrogen, and growth factors, such as IGF/insulin, can be major drivers of this type of cancer. Besides, insulin also promotes the development of type 1 endometrial cancer in other ways. It was shown that insulin resistance and compensatory hyperinsulinemia provoke androgen synthesis [33]. Increased free androgens supply more substrate for peripheral estrogen conversion. Also, insulin has been reported to inhibit the synthesis of sex hormone binding globulin (SHBG), which tightly binds and regulates the activity of sex hormones. Thus, when insulin levels increase due to insulin resistance, this inhibition results in an increase in free sex hormone levels (of both estrogens and androgens) and further stimulates type 1 endometrial tumorigenesis [34].

It is also important that tissue macrophage infiltration, which make up a substantial part of PBMC, correlated positively with endometrial cancer development [35].
**Conclusion**

Thus, chronic diseases such as type 2 diabetes and cancer may have a systemic effect on signaling mechanisms in different tissues of the body, including blood cells.

There are the differences in oncological patients with type 2 diabetes between breast/endometrial cancers, and pancreatic/bowel cancers considering IGF/insulin content in the blood and Akt activation in the PBMC, that could be associated with the hormonal background of the first types of cancers.

The state of Akt phosphorylation by mTORC2 in PBMC apparently is not associated with IGF/insulin levels and obviously reflects their mitogenic effect more than metabolic. Thus, mTORC2 has little or no involvement in enhancing Akt/mTORC1/S6K activation in diabetes that confirms hypothesis of reciprocal Akt phosphorylation by the PDK1 and mTORC2 complexes on Thr308 and Ser473, respectively.

**References**

Резюме
Сигнальний путь Akt/mTOR/p70S6K1 відіграє важливу роль в патогенезі раку та діабету. Макрофаги та лімфоцити беруть участь у патогенезі діабету, діабетичного атеросклерозу, формуванні резистентності до інсуліну, а також імунного відповіді на рак та підтриманні опухолів.

Висновок.
Вивчення взаємовідносин між системами активної гликогенезу, метаболічних шляхів інсулінового сензитизації, а також імунної системи визнає небезпеку відчуттю активної активності мікроядр ознакам патогенезу резистентності до інсуліну. Якщо активність мікроядер активна, то резистентність до інсуліну є досить розповсюдженою у пацієнтів з діабетом і раком.

Ключові слова: Akt, mTORC1/2, p70S6K1, макрофаги, лімфоцити, імунна система, інсулінова сензитизація.
Львівський Медичний Форум
07-09 квітня
Палац мистецтв
(вул. Коперника, 17)
Медична виставка "ГалМЕДи"

ТЕМАТИЧНІ РОЗДІЛИ ВИСТАВКИ:
- Лікувальне, діагностичне та реабілітаційне обладнання;
- Медичні прилади та інструменти;
- Лабораторна медицина;
- Засоби реабілітації та товари для людей з обмеженими можливостями;
- Офтальмологічне обладнання та оптика;
- Організації та оснащення медичних закладів;
- Фармацевтичні препарати;
- Сучасна клініка та послуги;
- Медичний одяг, засоби санітарії та дезінфекції;
- Страхова медицина

В рамках виставки:
- V спеціалізовані експозиції «Медичний туризм»
- V спеціалізовані експозиції «Реабілітація»

ОСНОВНІ ЗАХОДИ ФОРУМУ:
07 квітня Міжнародна науково-практична конференція "Неврологічна патологія - нові тенденції в діагності та лікуванні з позиції міждисциплінарного підходу"
08 квітня Всукраїнська науково-практична конференція "Репродуктивні аспекти гінекологічної патології"
08 квітня Міжнародна науково-практична конференція "Сучасні аспекти фізичної та реабілітаційної медицини"
09 квітня Науково-практична конференція "Дитяча Алергологія Вчора, Сьогодні І Завтра"
09 квітня Практичний майстер-клас по новітнім технологіям в галузі реабілітації

ШАНОВНІ КОЛЕГИ!!!

ПЛАН РЕЄСТРОВИХ КОНФЕРЕНЦІЙ НА 2020 РІК

26 березня
м. Київ
Науково-практична конференція з міжнародною участю
«ІНФЕКЦІЙНІ ЗАХВОРОЮВАННЯ У ДІТЕЙ. СУЧАСНИЙ ПОГЛЯД НА ДІАГНОСТИКУ, ЛІКУВАННЯ ТА ПРОФІЛАКТИКУ»
Нціональний медичний університет імені О.О. Богомольця МОЗ України

14-15 травня
м. Київ
Науково-практична конференція
«АКТУАЛЬНІ ПИТАННЯ ДИТАЧОЇ ГЕПАТОЛОГІЇ»
ДУ інститут педіатрії, акушерства та гінекології імені академіка О.М. Лук’янової НАМН України

4-5 вересня
м. Кам’янець-Подільський
Науково-практична конференція з міжнародною участю
«ПОДІЛЬСЬКІ ДІНИ ОНКОЛОГІЇ. Сучасні акценти діагностики та лікування злоякісних новоутворень грудної залози, легень, шкіри»
Хмельницька обласна державна адміністрація Департамент охорони здоров’я Хмельницької ОДА
КНП «Хмельницький обласний противузлуватий центр» ХОР Українське науково-медичне товариство онкологів Нціональний інститут раку ГО «Асоціація онкологів Хмельницького»

02 жовтня
м. Київ
Науково-практична конференція з міжнародною участю
«СУЧАСНІ ПІДХОДИ ДО ДИАГНОСТИКИ ТА ЛІКУВАННЯ ЗАХВОРОЮВАНЬ НЕРВОВОЇ СИСТЕМИ»
Нціональний медичний університет імені О.О. Богомольця МОЗ України

28 жовтня
м. Київ
Науково-практична конференція з міжнародною участю
«АКТУАЛЬНІ ПИТАННЯ ДІАГНОСТИКИ, ЛІКУВАННЯ ТА ПРОФІЛАКТИКИ ІНФЕКЦІЙНИХ ТА ПАРАЗИТАРНИХ ХВОРОБ В УКРАЇНІ»
До ювілею кафедри інфекційних хвороб НМУ імені О. О. Богомольця Нціональний медичний університет імені О.О. Богомольця МОЗ України

5-7 листопада
м. Київ
Науковий конгрес з міжнародною участю
«ПСИХОСОМАТИЧНА МЕДИЦИНА ХХІ СТОЛІТТЯ: РЕАЛІЇ ТА ПЕРСПЕКТИВИ»
Нціональний медичний університет імені О.О. Богомольця МОЗ України

Докладніше про програму науково-практичних конференцій, місце проведення та реєстрацію відвідувачів — на офіційному сайті співорганізатора конференцій ТОВ «МЕДІАМЕД»

Media.med

ВІДВІДУВАННЯ КОНФЕРЕНЦІЙ БЕЗКОШТОВНЕ
Попередня реєстрація можлива на сайті mediamed.com.ua
Витрати на проїзд та проживання здійснюються за кошти учасників

+38 098 080-72-66  E-mail: info@mediamed.com.ua
www.mediamed.com.ua  @mediamedconferences