Editorial
Pharmacological Scenarios in Translational Research: A Current Multidisciplinary Overview and Possible Developments

Translational research is the process of applying knowledge from basic biology and clinical trials to techniques and tools to improve medical needs and outcomes. Basic scientific research, if translated into the current clinical surgical practice, allows for innovative therapies, medical procedures and diagnostics. Pharmacology makes full use of medicine and translational research, since, starting from animal models or from cell cultures, one can obtain a lot of useful data to produce drugs or medical devices that can then be used either in clinical-surgical practice or in meaningful health outcomes. Indeed, the translational research applies findings from basic science to enhance human health and well-being. Pharmacological translational research, from laboratory experiments to clinical studies to patient applications, uses the knowledge of basic sciences to produce new drugs, devices and treatment options for patients. The final point is the production of promising new treatments that can be used with practical applications, which can be used in medical practice. In this special issue, some aspects of pharmacological research to be translated into clinical practice are discussed.

Fibroids’ pharmacological treatments: innovative therapeutic options. In the uterine fibroid topic, research on fibroids has developed new drug therapies, including Vilaprisan and Ulipristal Acetate. Both molecules were very effective in controlling fibroid growth, limiting symptoms in women with uterine fibroma and allowing the patient to be operated on with blood chemistry parameters suitable for myomectomy. Vilaprisan (VPR) is a new orally available selective progesterone receptor modulator (SPRM), a class of progestin receptor (PR) ligands with clinical applications in many gynecological conditions, with anti-proliferative activity against uterine fibroids. The SPRMs have direct effects on the pituitary gland, the uterine fibroids, and the endometrium. Amenorrhea is induced by means of the direct effect on the pituitary gland, by inhibiting ovulation (in approximately 80% of patients) and simultaneously maintaining the estradiol level in the mid-follicular range. The SPRMs produce also a reduction in the uterine fibroids by inhibiting the cell proliferation and by inducing apoptosis, since progesteron plays a vital role in the regulation of uterine fibroid growth by modulating cell proliferation and apoptosis induction. VPR definitively causes suppression of ovulation and inhibition of proliferation of endometrial, myometrial and uterine fibroids’ cells. The review on VPR [1] summarized current knowledge on VPR from all studies, including clinical trials, conducted to date and to contextualize the potential role of VPR in future medical regimens for the treatment of uterine fibroids. VPR was shown to be effective in ameliorating uterine fibroids-related clinical symptoms, especially abnormal or excessive uterine bleeding and in shrinking uterine fibroids. The tolerability of VPR is roughly like that of ulipristal acetate (UPA) and it tends to be more favorable than that of GnRH-agonists. The other drug, the UPA, another SPRM, have demonstrated its clinical benefits by reducing tumor growth and extracellular matrix (ECM) deposition. The UPA modestly inhibits cell proliferation, induces a temporary phase of apoptosis and reduces ECM content. The review on UPA [2] summarized drug effects on signaling pathways frequently upregulated in uterine fibroids, exploring biological changes in the expression levels of proteins related to cell cycle regulation, cytoskeleton remodeling, and drug resistance after ex vivo on cultured myoma cells treated by UPA administration. This research showed that the UPA administration on fibroid reduced, ex vivo, colliin, Erk and Src phosphorylation, p27 and ezrin protein levels (all markers of tissue remodeling), but not Akt phosphorylation and cyclin D1 and β-catenin levels.

Uterine fibroids morcellation: analysis of critical biological issues and drawbacks from a medical-legal prospective. In November 2014, the Food and Drug Administration (FDA) discouraged the power morcellation during laparoscopy in all pre-menopausal and post-menopausal women with leiomyomas, for the risk of cancerous cell dissemination in undiagnosed uterine leiomyosarcomas (ULMs). This banning has thus created a series of major medical, administrative, insurance and legal problems, with the sudden decrease in laparoscopic procedures and increase in laparotomies, with the abandonment of the use of power morcellation and with the sudden emergence of containing devices, in which to morcellate or crush myomas. The most important step in the surgical choice, in open or in minimally invasive surgery, is to balance the risks (complications) and benefits of different interventions. Obviously, all this chaos has generated many doubts about the real opportunity of this sudden change in the American scientific community and especially in countries that are not influenced by FDA recommendations, since there are no unique data on the real incidence of ULMs in women (they are quite rare) and there are no reliable data on the effectiveness of these containing devices. Another unsolved question is whether the power morcellation should worsen the prognosis and the overall survival of patients with an occult ULM. The review on uterine fibroid morcellation [3] has highlighted all the problems related to the choices of many doctors and some scientific societies, that criticized fibroids morcellation after myomectomy by power morcellation, potentially disseminating occult tumor cells. In fact, the unsolved biological issues have raised concerns about FDA banning, as the "myometrial spillage" during myoma enucleation (which may result in upstaged ULM), the fast-growing fibroid (which is often not an ULM at all), the lack of accurate preoperative diagnostics and adequate markers, the problem of the spread by contact and by CO2 of the hypochthonic cancer (after its removal from uterus), and so on. New techniques to overcome the issue of uterine tissue spreading, as the in-bag morcellation, is proving to be a promising, safe and feasible technique, even if it may prolong the operative times. Presently the available data are still preliminary and not enough to provide strong evidence to recommend the in-bag morcellation as a general tool in laparoscopic surgery. From a medical-legal prospective, the FDA statement and the above-mentioned concerns raise several considerations and raise many drawbacks, all discussed and analyzed in this review.

The problem of HPV infection in the world: analysis of epidemiological spreading and vaccination. The HPV nowadays represent the most common worldwide sexually transmitted diseases, with an estimated prevalence of approximately 12%, in a population of over one million asymptomatic women [4] and around 90% of infected individuals are asymptomatic and clear the infection within two years [5]. Carcinogenesis due to HPV is responsible for around 4.5% (630,000 cases) of all new cases (8.6% in females, 0.9% in males) and around 29.5% of all HPV-related cancers. In particular, HPV 16 and 18 cause 70% of the cervical cancers, and a relevant proportion of vaginal (78%) and anal (88%), as well as some vulvar (25%) and penile (50%) cancers and, together with HPV types 31/33/45/52/58, are responsible for about 90% of HPV-related cancers worldwide [6]. Cervical cancer remains the fourth most common female cancer globally, with an estimated 570,000 cases and 311,000 deaths yearly [7]. Despite these enormous problems that also involve the oncological sphere, recognized effective and safe preventive strategies, knowledge, attitudes and awareness on HPV are considerably low. Health education programs aimed at increasing knowledge, attitudes and awareness on HPV are needed to implement the outcomes of HPV immunization programs, especially if supported by the physicians involved in counselling and vaccination processes. Bahmagambetova et al. [8] in their review discussed a current point of view regarding the HPV as a causative factor in tumorigenesis, highlighting the role of the most problematic property of these virus’s fam-
ily, its ability to continuous evolution. Present trends in HPV infection diagnostics throughout the human fluids and tissues are also reported, including the latest novelties in this field, such as HPV assay/self-sample device combinations. Concerned actual issues of current cervical cancer prevention are summarized in this review. Icardi et al. [9] analyzed the evolution of preventive tools, the complexity of the vaccine choice process, and the challenges posed by HPV vaccine hesitancy and refusal among pre-adolescents and their parents and assessed knowledge, practices and attitudes toward HPV infection and vaccination in a sample of Italian pre-adolescents and their parents. They highlighted a significant increase in HPV vaccination awareness was observed among pre-adolescents after the educational sessions. Thus, the inclusion of parents in the evaluation of knowledge gaps and attitudes about HPV should be encouraged in order to obtain an exhaustive list of the factors that influence the decision-making process. Moreover, the role of physicians in providing counselling and recommendations for HPV vaccine target populations plays a crucial role together with school-based vaccination programs and social media in the case of pre-adolescents. Guido et al. [10] reviewed the utility of HPV vaccination, that has globally leading to a significant reduction of vaccine-targeted HPV infections, cross-protective genotypes, precancerous lesions and anal-genital warts. They realized a review of the most recent literature to evaluate the effects after vaccine introduction on effectiveness of vaccine-targeted and cross-protected HPV genotypes. Moreover, they evaluated the progress of HPV infection in southeast Italian region, as an ideal territorial study model, by an epidemiological investigation on the vaccination impact on genotype and on the prevalence and distribution of HPV during last 12 years (2006-2017) in the Local Health Unit.

**The problem of infections in pregnancy: rational, safety and effectiveness of pertussis immunization.** Pertussis remains a serious public health problem, as the coverage is not optimal, due to increasing vaccine hesitancy. The pertussis is a highly contagious respiratory tract infection, commonly known as whooping cough, caused by a type of bacteria called * Bordetella pertussis*. This Gram-negative bacterium. *B. pertussis* adheres to the cilia of the epithelium of the upper respiratory tract, damaging it through the production of toxins [11]. Generally, pertussis affects patients by a severe hacking cough followed by a high-pitched intake of breath, that sounds like "whoop" [12]. The highest risk in terms of cases, severity and mortality is greater in the neonatal period and in the first months of life, when children have not yet started vaccination cycles [11]. Before the vaccine was developed, whooping cough was considered a childhood disease. Maternal immunization in pregnancy allows for the transplacental passage of maternal antibodies to the fetus, guaranteeing its protection already at birth [13]. Gabuttiet al. [14] reviewed the rational, safety and effectiveness of pertussis immunization in pregnancy, starting from the 2012, when the Advisory Committee on Immunization Practices (ACIP) recommended a dTap dose for each pregnancy, especially between the 27th and 36th gestational week. Several observational studies supported maternal vaccination, as it is effective in protecting newborns in their first months of life and pertussis vaccine in pregnancy has proven to be safe, effective and well tolerated. This vaccination approach has demonstrated the safety, immunogenicity and efficacy in preventing pertussis in new-borns, resulting in substantial reduction in pertussis incidence and mortality. Maternal immunization, therefore, offers the best opportunity to prevent pertussis-related incidence and deaths in newborns/infants and is therefore an important and undeniable priority.

**Reproduction in advanced age. uterine innervation and premature ovarian failure.** Nowadays, the number of aged patients and in peri/post-menopause wishing pregnancy is increasing, and it increases obstetrical and neonatal related problems. This is because the physiology of reproduction changes with advancing age, with ovarian and myometrial changes that cause many problems. Normally, the human uterus is richly innervated and modified especially during pregnancy and labor, and it is endowed with different sensory, parasympathetic, sympathetic and peptidergic neurofibers. They are differently distributed in uterine fundus, body and cervix, and they are mainly observed in the stroma and around arterial vessel walls in the myometrial and endometrial layers [15]. Many neurotransmitters playing important roles in reproductive physiology are released after stimulation by adrenergic or cholinergic nerve fibers (the so called parasympathetic/parasympathetic co-transmission). Adrenergic and cholinergic effects of the autonomous nervous system are the most implicated in the uterine functionality [16]. Kosmas et al. [17] evaluated, in aged women, the Adrenergic and AChE neurofibers distribution in the fundus, body and cervix is progressively reduced by increasing age. Adrenergic and AChE neurotransmitters were closely associated with the uterine arteries and myometrial smooth muscles, and they reduced markedly by ageing, with a dramatic and negative impact on uterine physiology, as for conception and uterine growth, with the increase risk of spontaneous abortion and prematurity. To this problem is added another problem in older women, the premature ovarian failure (POF), with the loss of ovarian functionality around 40 years. When this happens, your ovaries don't produce normal amounts of the hormone estrogen or release eggs regularly, and this condition often leads to infertility and several negative effects on overall health [18]. Kosmas et al. [19] reviewed the pathways involved in POF by a systematic review to understand the impact of various pathways on the follicular growth. They analyzed experimental studies on the stage-specific function of PTEN/PI3K-AKT-mTOR signaling, the VeGF gene and one of its receptors, the KDR, the expression of TGFβ, FOXL2 and FOXO3A proteins, autoimmune disease, the Xp18 gene and chemotherapy for cancer. Most of the analyzed studies were experimental, using mostly mice and rats, but there were also various case reports studying women suffering from POF or having an autoimmune disease. Certain experimental studies combined both * in vivo* and * in vitro* experiments. A wide spectrum of techniques has been performed in the above studies, including histological analysis, microarray analysis, Western Blotting, histological analysis as well as statistical analysis.

**The epithelial mesenchymal transition program and alterations of large proteome-based networks.** Several physiological and pathological processes in human beings are characterized by proteome modifications including alterations of protein abundance, subcellular protein localization, and alterations of protein-protein interactions (PPIs) networks. These networks are involved in several processes including cancer, tissue regeneration, and differentiation. The epithelial to mesenchymal transition (EMT) is a multistep process that transforms an epithelial cell with well-characterized morphological features into a mesenchymal model [20]. Several studies profiled this transition at the mRNA, protein, and metabolomic level in order to obtain a system-level understanding of the process [20]. Molecular changes associated with the initiation of the EMT program involve alterations of large proteome-based networks, but the role of protein products mapping to non-coding genetic regions is still unexplored. Monica et al. [24] studied the identification of an alternative protein signature in breast cancer cellular models with a distinct expression of EMT markers. They profiled MCF-7 and MDA-MB-231 cells using liquid-chromatography mass/spectrometry (LC-MS/MS) and interrogated the OpenProt database to identify novel predicted isoforms and novel predicted proteins from alternative open reading frames (AltProt). The analysis revealed an AltProt and isoform protein signature capable of classifying the two breast cancer cell lines. Among the most highly expressed alternative proteins, authors observed proteins potentially associated with inflammation, metabolism and EMT. The data support the presence of a specific alternative protein signature associated with the epithelial and mesenchymal features of the breast cancer models.

**Aptamers use in the lab and clinical research: a translation to diagnosis and therapy.** Aptamers, small fragments of ssDNA or RNA, artificially assembled to achieve high binding affinity to their targets, as proteins to simple ions, are relevant for diagnosis in macular degeneration, cancer, thrombosis and many inflammatory diseases, and promising in drug discovery and development [22]. Their low dimension,
short half-time, low immunogenicity and production cost, coupled with their high affinity and specificity, make them formidable competitors to antibodies in both diagnosis and therapy [23]. Many aptamers have reached therapeutic clinical trials, diagnostic markets, or that have immediate translational potential for therapeutics and diagnostics applications [23]. Vergara et al. [21] briefly review the literature, discussing if and how general network parameters in the framework of Proteotronics and graph theory (such as electrical features, link number, free energy change, and assortativity), are important in characterizing the complexes, anticipating some features of the biomolecules. Authors described a case study to better explain this complex topic. The study constituted by a set of anti-angiopoietin (Ang2) aptamers, whose performances are known from the experiments, and for which two different types of conformers were predicted. A topological indicator was proposed, named Möbius (M), which combined local and global information, and seemed able to discriminate between the two possible types of conformers, so that it can be considered as a useful complement to the in vitro screening for pharmaceutical aims.

The calcium-activated potassium channel KCa3.1: new features and possible use in the structuring of new drugs. The human intermediate conductance calcium activated potassium channel, Kca3.1, is involved in several pathophysiological conditions playing a critical role in cell secretory machinery and calcium signalling. The recent cryo-EM analysis opens new insights in the understanding of the modulation led by both endogenous and pharmacological agents. A typical feature of this channel is the low open probability in saturating calcium concentrations and its modulation by potassium channel openers (KCOs, such as benzoimidazolone 1-EBIO) without changing calcium-dependent activation. The calcium-activated potassium channel KCa3.1 regulates membrane potential and calcium signaling in erythrocytes, activated T and B cells, macrophages, microglia, vascular endothelium, epithelia, and proliferating vascular smooth muscle cells and fibroblasts [25]. Besides its role in cell volume regulation, the KCa3.1 channel modulates other cellular processes such as cell proliferation and endothelium-dependent. KCa3.1 has therefore been suggested as a potential therapeutic target for diseases such as sickle cell anemia, asthma, coronary restenosis after angioplasty, atherosclerosis, kidney fibrosis and autoimmunity, where activation and excessive proliferation of one or more of these cell types is involved in the pathology [26]. The review "New insights on KCa3.1 channel modulation" [27] present an accurate and wide review about the human intermediate conductance calcium activated potassium channel KCa3.1 that is widely expressed by many types of cells in normal and even cancer conditions (e.g. glioblastoma). The importance of this potassium channel, in influencing the ion exchanges regulating the cell membrane potential and under the functional modulation by Ca++ levels and variations, is well documented and described. Particularly intriguing the part discussing the modulators of the channel opening/blocking and how a same chemical class, like benzimidazolone molecules, can furnish possible opposite derivatives. The hypothesis proposed are also a useful point for critical discussion about the importance of KCa3.1 channel in the cell physiology, behavior and cytopathology, opening perspectives for new approaches also in anticancer treatments.

The anticancer property of resveratrol: the possible use in cerebral cancer. Natural product compounds have recently attracted significant attention from the scientific community for their potent effects against inflammation-driven diseases, including cancer. Resveratrol (3,4′,5-trihydroxy-trans-stilbene) is a dietary polyphenol derived from grapes, berries, peanuts, and other plant sources. Resveratrol is a phytoestrogen, a natural stilbene and a non-flavonoid polyphenol, that possesses anti-oxidant, anti-inflammatory, cardioprotective, and anti-cancer properties [28]. It has been reported that resveratrol can reverse multidrug resistance in cancer cells, and, when used in combination with clinically used drugs, it can sensitize cancer cells to standard chemotherapeutic agents [29]. Resveratrol affects all three discrete stages of carcinogenesis (initiation, promotion, and progression) by modulating signal transduction pathways that control cell division and growth, apoptosis, inflammation, angiogenesis, and metastasis. The anticancer property of resveratrol has been supported by its ability to inhibit proliferation of a wide variety of human tumor cells in vitro. These in vitro data have led to numerous preclinical animal studies to evaluate the potential of this drug for cancer chemoprevention and chemotherapy [30]. Authors reviewed these resveratrol anti-tumor effects and evaluated them on glioblastoma (GBM) [31], the most frequent and malignant form of glioma cancer, with a general high chemo and radio-resistance and patients’ very poor prognosis, with a median overall survival of about of 14.6 months. They evaluated data especially from preclinical studies conducted with resveratrol as a possible adjuvant during standard protocol of GBM. Resveratrol can reach brain parenchyma at submicromolar concentrations when administered through convention routes. In this context, resveratrol reduces cell invasion and increases the efficacy of radiotherapy (radio sensitizers effects) and of temozolamide. The molecular mechanism of the adjuvant action of resveratrol may depend upon the reduction of PI3K/AKT/NF-Kb axis and downstream targets O-6-methylguanine-DNA methyltransferase (MGMT) and metalloproteinase-2 (MMP-2). The involvement of redox status is also discussed as regulator of the autophagy process. Resveratrol administration through intra carotid external (ECA) or lumbar puncture (LP) can reach brain parenchyma growth. Curr Pharm Des 2020; 26(3): 310-17.

Anticoagulant therapy and bleeding problems: a computational systems biology models analysis. Anticoagulant therapy is often refrained from due to the fear of hemorrhagic complications. The problem of correct antithrombotic targeting is critical for this system because, although several anticoagulants is currently available, all of them are associated with bleeding risks. The most frequent type of major bleeding is gastrointestinal but intracranial hemorrhage has the worst prognosis. In addition, for life-threatening or massive hemorrhages reversal of the anticoagulant effect is also crucial [32]. Moreover, situations that ordinarily necessitate consideration of anticoagulation, such as arterial and venous thrombotic events and prevention of stroke in atrial fibrillation, become challenging in patients with inherited bleeding disorders such as hemophilia A, hemophilia B, and von Willebrand disease. There are no evidence-based guidelines to direct therapy in these patients, and management strategies that incorporate anticoagulation must weigh a treatment that carries a risk of hemorrhage in a patient who is already at heightened risk against the potential consequences of not treating the thrombotic event [33]. Panteleev et al. [34] have faced this problem, reviewing and discussing the application of the computational systems biology models to address this problem using the blood coagulation cascade as an example. The advantages and the drawbacks of different sensitivity analysis strategies are considered, focusing on the approaches that emphasize: 1) the functional modularity and the multi-tasking nature of this biological network; 2) the need to normalize hemostasis during the anticoagulation therapy rather than completely suppress it. To illustrate this effect, Panteleev et al showed the possibility of the differential regulation of lag time and endogenous thrombin potential in the thrombin generation. These methods allowed to identify of the elements in the blood coagulation cascade, that may serve as the targets for the differential regulation of this system.

REFERENCES


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