Др сц. Игор Петрушић,
Факултет за физичку хемију,
Универзитет у Београду,
Студентски трг 12-16,
11000 Београд, РС

Декану Фамацеутског факултета Универзитета у Београду
Проф. др Слађани Шобајић

Члановима Изборног већа Фармацеутског факултета Универзитета у Београду

Предмет: Приговор на извештај комисије, број 1323/1 од дана 16.06.2022. године, за избор 1 доцента за ужу научну област Патофизиологија на одређено време од 5 година, за рад на Фармацеутском факултету Универзитета у Београду, због више неправилности у процени и вредновању кандидата, као и због повреде Правилника о стицању истраживачких и научних звања из 2020. године, Правилника о ближим условима избора у звање наставника на Фармацеутском факултету и Правилника о издавачкој делатности Фармацеутског факултета.

Поштовани,

Ценећи труд комисије у састављању извештаја потребно је указати на следеће неправилности:

1) Коришћен је Правилник о стицању истраживачких и научних звања из 2017. године, а не тренутно важећи правилник из 2020. године (у даљем тексту: Правилник).

2) У извештају се наводи да је кандидат др сц. Петар Поповић аутор 2 монографске студије/поглавља (М13) у књизи М11, 1 монографске студије/поглавља (М14) у књизи М12 и 1 монографске студије/поглавља (М44) у књизи М41. Према увиду у наведене 4 монографске студије/поглавља јасно се види да кандидат др сц. Петар Поповић **не испуњава услове да му се признају коауторства у монографским студијама/поглављима према Правилнику** (видети прилог Правилника - Разврставање и начин навођења научноистраживачких резултата). Кандидат др сц. Петар Поповић **ни у једној од наведених монографских студија/поглавља нема више од 16 ауторских страница текста** нити одговарајући број словних знакова (број страна је у распону од 12-14, а број коаутора од 3-8; дакле ауторских страница од 2 до 4 странице). Штавише, у тим монографијама у литератури кандидат **нема одговарајући број самоцитата**, нпр. у посебно истакнутом делу из извештаја (*Popovic PJ, Matta MM, Ochoa JB. Allergy and immunology. In: Gabrielli A, Layon AJ, Yu M, eds. Civetta, Taylor, & Kirby's critical care. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2009:749-760*), постоји само један самоцитат који није из категорије М20 тако да се ни тај самоцитат према Правилнику не може уважити, а потребно је минимум 10/3=3,33, тј. 3 самоцитата.

3) Претходно споменута публикација (*Popovic, Matta i Ochoa, 2009*) се у извештају наводи као поглавље у уџбенику и вреднује се са 20 поена, иако према правилницима Универзитета у Београду, Правилнику о ближим условима избора у звање наставника на Фармацеутском факултету и Правилнику о издавачкој делатности Фармацеутског факултета (члан 13) **не испуњава услове за овакву категоризацију**. Наиме, наведена публикација **није одобрена одлуком Наставно-научног већа као уџбеник за ужу научну област за коју се кандидат бира**, а и не испуњава услове за категорисање у монографску студију/поглавље. Посебно треба напоменути да у извештају стоји да је број страница 31, а

заправо има 12 страница (видети у Прилогу 1). Ова неправилност у извештају доводи до забуне да кандидат др сц. Петар Поповић има више поена у табели за вредновање наставног рада од мене, што је могло утицати на закључак комисије да кандидат др сц. Петар Поповић има значајније педагошке и научне резултате.

4) Код квантификације научноистраживачких резултата **није примењена корекција бодова** за оне радове где постоји више од седам аутора. Према Правилнику број поена за научно остварење одређује се по формули К/(1+0,2·(n-7)), n>7, ако је више од седам аутора. Кандидат др сц. Петар Поповић има 6 радова из категорије М20 који имају више од 7 аутора. Исправљањем ове неправилности знатно се смањује број поена у табели за квантификацију научноистраживачких резултата.

5) Кандидату др сц. Петру Поповићу је вреднован магистеријум (М72) који се по новом Правилнику не бодује, јер кандидати који завршавају интегрисане студије медицине аутоматски имају еквивалентни статус магистра/мастера (што је у мом случају занемарено у извештају и указује на различите критеријуме при вредновању).

6) Кандидату др сц. Петру Поповићу је вреднована награда на конкурсу (М102) која се не вреднује код области медицинскух наука, већ само у техничко-технолошким наукама.

7) У извештају у табели за квантификовање научноистраживачких резулта комисија је бодовала учешћа и руковођења у оквиру националних и међународних пројеката иако се ове активности не бодују према Правилнику, Правилнику о начину и поступку стицања звања и заснивања радног односа наставника Универзитета у Београду и Правилнику о ближим условима избора у звање наставника на Фармацеутском факултету.

8) У извештају се закључује да је кандидат др сц. Петар Поповић радио као доцент у САД, а заправо је био **ангажован као *Research assistant professor*, што представља еквивалент звања научног сарадника**, и огледа се превасходно у научном раду и менторству које кандидат нема. Такође, детаљном претрагом електронских медија се не може стећи увид у вид наставе коју је кандидат обављао током научног ангажовања у САД и на Медицинском факултету Војномедицинске академије Универзитета одбране у Београду, иако је комисија констатовала да кандидат др сц. Петар Поповић има вишегодишње педагошко искуство. Сматрам да би било од изузетне важности **приказати документацију** коју је кандидат др сц. Петар Поповић предао у вези свог **педагошког искуства** како би се транспарентно стекао увид у наводе из извештаја или да се **претконкурсна комисија изјасни** да ли је кандидат предао одлуку о избору у звање доцента и адекватне доказе за учествовање у настави који су бодовани у табели о прегледу вредновања наставог рада кандидата др сц. Петра Поповића.

9) Важно је напоменути и да се истовремено не препознаје моје педагошко искуство (поред вођења редовних вежби и семинара на предметима Патофизиологија, Патофизиологија 1 и Патофизиологија 2) у извештају, јер се **не спомиње моја улога у креирању предмета Патофизиологија 1 и Патофизиологија 2** (увођење и спровођење хибридне наставе, креирање садржаја на семинарима и форумима, креирање тестова на вежбама и *online* тестова, итд) и резултати приказани у оквиру унапређења наставничких компетиција наставника и сарадника Фармацеутског факултета где је присуствовало 39 наставника и сарадника Факултета, затим моје вишегодишње искуство као демонстратор на Медицинском факултету у Београду (10 семестара на предмету Хистологија са ембриологијом, 5 семестара на предмету Хумана генетика и 6 семестара на предмету Патологија) и искуство у вођењу вежби на мастер студијама (Прилог 2) и менторству (Прилог 3), као и учешће у настави и додељено менторство на докторским студијама на Факултету за физичку хемију (Прилог 2) и учешће у настави на докторским студијама при Универзитету у Београду (Прилог 4). Такође, важно је и напоменути да ме комисија

ниједном није контактирала у вези са недоумицама које су имали у вези са мојим педагошким искуством. **Последица ових неправилности у извештају је смањен број поена у табели за вредновање мог наставног рада.**

10) У извештају се потенцира искуство др сц. Петра Поповића у научноистраживачком раду и изучавању различитих патофизиолошких механизама и болести и закључује се да област истраживања кандидата др сц. Петра Поповића припада ужој области за коју се бира за разлику од мене. Заправо, научноистраживачки рад углавном припада **ужој области из имунологије** (М20 радови: 2, 4-6, 8-18 и докторска дисертација) што се јасно види из самих публикација и анализе публикованих радова у извештају. Анализом мојих публикованих радова (М20: 1, 5-7, 9, 10, 12, 14, 17-19), докторске дисертације и интернационалне сарадње на пројекту "Feel again" под руководством проф. др Станише Распоповића (Напомена: у извештају није споменута међународна сарадња са лабораторијом за неуроинжењеринг, на Одсеку за здравствене науке и технологију, на ETX Цириху, првопласираном Универзитету Континенталне Европе на свим међународним ранг листама) (Прилог 5), може се запазити да се изучавају патофизиолошке структурне и функционалне промене у централном нервном систему и цереброваскуларним судовима. Такође, занемарује се чињеница поводом процене искуства у научноистраживачком раду да имам велики број М20 радова које сам написао као **први аутор у** последњих 9 година (**15 радова у категорији М20**), **руковођење пројектним задатком** (напомена: није споменуто у извештају иако је потврда предата), **познавање различитих клиничких техника за истраживање патофизиолошких механизама** (Напомена: предмет патофизиологија се већински бави етиопатогенезом болести код хумане популације) **и познавање техника у базичним истраживањима** (Напомена: као дугогодишњи демонстратор из Хумане генетике савладао сам технике **PCR**, такође сам учествовао на научној размени где сам користио и усавршио PCR технику, затим радио студентске радове који су укључивали **рад са експерименталним животињама и културама ћелија** (предао потврду/препоруку комисији од проф. др Владимира Трајковића)). Такође, треба напоменути и да је моја дугогодишња међународна сарадња резултовала позивом да будем гостујући уредник у часописима *Frontiers in Neuroscience* (секција: *Brain Imaging Methods*), *Frontiers in Neurology* (секција: *Neurological Biomarkers*) и *Frontiers in Human Neuroscience* (секција: *Brain Health and Clinical Neuroscience*) заједно са водећим експертима и научницима у овој области (*Prof. Dr. Peter J Goadsby* (добитник *The Brain Prize* 2021), *Prof. Dr. Cristina Tassorelli* (актуелни председник *International Headache Society*) и *Prof. Dr. Gianluca Coppola*) (Прилог 6).

Када се сви ови пропусти узму у обзир долази се до тога да је комисија донела тендециозан закључак да кандидат др сц. Петар Поповић има боље научноистраживачке и педагошке резултате. Наиме, корекцијом претходно наведених пропуста у квантификацији резултата указују да имам **веће и научноистраживачке (142,2 наспрам 136,28 поена) и педагошке (25 поена наспрам 18?) резултате** (Напомена: занемарено је да сам учествовао у креирању наставе на Патофизиологији 1 и Патофизиологији 2 што је резултирало са 2 бода мање у вредновању наставног рада; учествовао у настави на предмету Патофизиологија што је резултирало са 1 бодом мање у вредновању наставног рада; као и моје учествовање у настави на предметима Напредна анализа неурорадиолошких снимака (1 поен), Магнетно-резонантни имиџинг (1) и Неуробиофизичке технике (1 поен)). С обзиром на све наведене пропусте у извештају предлажем да Изборно веће Фармацеутског факултета Универзитета у Београду пажљиво сагледа све пропусте у извештају и процени квалитете оба кандидата и у складу са тим донесе одлуку.

Поштујући каријеру кандидата др сц. Петра Поповића, на крају бих сумирао још једном моје предности у односу на другог кандитата у табели 1.

Табела 1. Компаративна анализа стручних, научних и педагошких резултата кандидата др сц. Игора Петрушића и кандидата др сц. Петра Поповића

	др сц. Игор Петрушић	др сц. Петар Поповић
1) Година дипломирања	2012. година	1992. година
2) Просечна оцена	9,37	8,46
3) Први аутор у M21a или M21	10	2
4) Први аутор у M20	15	3
5) **Искуство на предмету за које се кандидат бира**	3 семестра	0 семестара
6) Увођење, креирање и спровођење хибридне наставе, као и увођење студената демонстратора на предметима Патофизиологија 1 и 2 (Фармацеутски факултет, Универзитет у Београду)	2 семестра	0 семестара
7) Учешће у комисијама за одбрану докторске дисертације и мастер радова	3 (1 докторска дисертација и 2 матер рада)	/
8) Рецензирање радова у часописима са SCI листе	Frontiers in Neurology, Frontiers in Behavioral Neuroscience, Journal of clinical neuroscience, Journal of pain research, Neuroimage clinical, The Journal of Headache and Pain	/
9) **Број радова из категорије M21a, M21, M22 и M23 у последњих 10 година**	19	0
10) Актуелно научно звање	Научни сарадник	Нема
13) Оцена у студентској анкети	4,69	4,38
14) Гостујући уредник у часопису са SCI листе	Да (Прилог 6)	/

29.06.2022. године, Београд

Др сц. Игор Петрушић

Игор Петрушић

ПРИЛОГ 1

CHAPTER 50 ■ ALLERGY AND IMMUNOLOGY

PETAR J. POPOVIC ᵀ BENJAMIN M. MATTA ᵀ JUAN B. OCHOA

OVERVIEW

The modern word *immunity* is derived from the Latin word *immunis,* which referred to exemption from military services, tax payments, or other public services. Throughout the medical history literature, the term *immunity* referred to those who were disease free or protected from getting disease. Immunity as a medical term defines a state of having sufficient biologic defenses to avoid infectious disease or other unwanted biologic invasion. The collection of tissues, cells, and molecules responsible for immunity constitute the *immune system,* and their coordinated response to the potentially harmful (mostly foreign) substances is called the *immune response.*

The main physiologic function of the immune system—protection of the host from infection—for many years characterized the immune response in its ability to distinguish between "foreign" and "self"—the key issue being that foreign was to be attacked and eradicated, while self was not to be attacked. In recent years, however, from the wide range of diseases that are consequent to inappropriate immune functions, we have learned that the ability of the immune system to distinguish between harmful and harmless molecules or cells—rather than characterizing the dichotomy as foreign and self—is essential for mounting protective immune responses and preventing the induction of pathology (Table 50.1). For example, in addition to infectious diseases that develop when immune cells fail to recognize and quickly eradicate microorganisms (foreign and harmful), failure to recognize and eliminate transformed "self" cells (self, but harmful) might result in tumor growth and produce an even more serious clinical condition. On the other hand, the unwanted response to harmless self-proteins produces a variety of autoimmune (*auto* meaning directed at the self) diseases, some of which are severe and life threatening. Autoimmune diseases are classified as systemic or organ specific, although there is often a significant overlap between the two because some diseases that start as organ specific later affect other organs. Finally, immune response toward foreign but harmless substances produces a wide variety of clinical syndromes, defined as allergic diseases or *allergies.* The word *allergy* is derived from the Greek words *allos*, meaning different or changed, and *ergos,* meaning work or action, and roughly refers to an "altered or unusual reaction." Allergy-producing substances are called *allergens.* Examples of allergens include the dust mite, pollens, molds, and foods. It is estimated that more than 50 million North Americans are affected by allergic conditions, with a cost of more than $10 billion dollars yearly. Fortunately, in the majority of cases, allergic diseases are mild in onset and development, and annoying rather than serious medical conditions. However, sometimes serious and life-threatening clinical conditions that require immediate medical intervention develop as a result of allergic reactions. Some of those adverse allergic reactions, such as anaphylactic shock and severe asthma exacerbation, are elaborated in more detail in Chapters 60 and 142, respectively. Besides the previously mentioned, naturally occurring pathology associated with inappropriate immune response, additional problems arise with the development of transplantation medicine. Transplantation is the process of taking cells, tissues, or organs, termed *graft*, from one individual (graft donor) and placing them into a different individual (graft recipient). Although, from our point of view, transplantation is not only harmless but also beneficial and therapeutic, recipient immune cells recognize graft as foreign and potentially harmful. Unless suppressed, recipient immune cells respond to foreign molecules within the graft and induce graft rejection. In clinical practice, it is important to distinguish immune-mediated graft rejection from graft failure induced by other causes. On the other hand, transplanted cells sometimes contain a significant number of donor immune cells that can respond to recipient tissue and produce a serious and life-threatening condition, termed *graft-versus-host disease* (GVHD).

Immunology as a discipline is the study of immunity at the level of cellular and molecular events that control homeostasis and activation of the immune system. Immunology is helping us to better understand the complex processes involved in the immune reactions and to find a way to more appropriately modulate those processes once their malfunction (function) becomes harmful to the host.

CELLS AND TISSUES OF THE IMMUNE SYSTEM

There are two basic types of immune reactions: innate and adaptive (Table 50.2). Innate immunity (also called natural or native immunity) consists of cellular and biochemical defense mechanisms that are in place even before encounter with microbes, and are poised to respond rapidly to infection before the development of the adaptive immune response. The principal components of the innate immunity are (a) physical and chemical barriers, (b) phagocytes (neutrophils, macrophages) and NK (natural killer) cells, (c) the complement system and acute-phase proteins, and (d) cytokines. In contrast to innate immunity, the adaptive immune response needs to be stimulated by exposure to infectious agents or molecules, and it increases in magnitude and defensive capabilities with each successive exposure to a particular molecule. The defining characteristics of adaptive immunity are exquisite specificity for distinct molecules and an ability to "memorize" and respond more vigorously to repeated exposure. Because of its specificity for a particular antigen, adaptive immunity is also

TABLE 50.1

CHARACTERISTICS OF ANTIGEN AND IMMUNOPATHOLOGY

	Antigen	Pathology	Immune response	Treatment
Foreign	Harmful	Infections	Wanted	Stimulation
	Harmless	Allergies	Unwanted	Suppression
	Harmless	Graft rejection or GVHD	Unwanted	Suppression
Self	Harmful	Cancer	Wanted	Stimulation
	Harmless	Autoimmunity	Unwanted	Suppression

GVHD, graft versus host disease.

referred to as *specific immunity*. The main components of adaptive immunity are lymphocytes and their products. Substances and molecules that induce specific immune responses, or are the targets of such responses, are termed *antigens*. There are two types of adaptive response: *Humoral immunity* mediated by antibodies and B lymphocytes and *cell-mediated immunity*, which involves T lymphocytes. The cardinal features of adaptive immune responses, besides specificity and memory, are (a) diversity, the ability to respond to a large variety of antigens; (b) specialization, the optimal response for a particular antigen; (c) self-limitation, allows immune homeostasis; and (d) self-tolerance, nonreactivity to self. Both innate and adaptive immune responses can be divided into distinct phases: recognition of antigen, activation, and the effector phase of antigen elimination, followed by the return to homeostasis; and in the case of adaptive response, the maintenance of memory (1).

Lymphoid tissues are classified as generative or primary lymphoid organs and as peripheral or secondary lymphoid organs. Primary lymphoid organs are *bone marrow*, where all lymphocytes arise and also where B lymphocytes mature, and the *thymus*, where T lymphocytes mature and reach a stage of functional competence. The peripheral lymphoid organs and tissues include *lymph nodes, spleen,* and the *cutaneous and mucosal immune system*. Specialized microenvironments within primary immune organs support immune cell growth and maturation, while secondary lymphoid organs are sites in which optimal adaptive immune responses are initiated and developed. Lymph nodes are sites of immune response to lymph-borne antigens, and the spleen is the major site of immune response to bloodborne antigens. Similarly, cutaneous and mucosal immune systems are specialized for the best response to potential antigens coming through skin and mucosal surfaces, respectively. It is important to mention that, although some cells are permanently resident in one tissue, lymphocytes continuously move through the bloodstream and lymphatic system, from one peripheral (secondary) lymphoid tissue to another. Lymphocyte recirculation and migration to particular tissues are tightly regulated and mediated by adhesion molecules, chemokines, and their receptors, and depend on the cell maturation and activation stage. The main cells of the immune system involved in the adaptive immune response are antigen-specific lymphocytes, specialized antigen-presenting cells (APCs) that display antigens and activate lymphocytes, and effector cells that function to eliminate antigens (microbes). Lymphocytes are the only cells in the body capable of specifically recognizing and distinguishing different antigens. Lymphocytes consist of subsets that are different in their function, but are morphologically indistinguishable. Two main subpopulations of lymphocytes are designated as *B* and *T lymphocytes*, which refer to the organs in which those cells are found to mature, *bursa of Fabricius* in birds (equivalent to *bone marrow* in mammals) and *thymus*, respectively.

TABLE 50.2

TYPES OF IMMUNE RESPONSE

	Innate	Adaptive
Characteristics		
Specificity	Pathogen-associated molecular patterns	Antigenic determinants of protein, microbial and nonmicrobial
Diversity	Limited; germline encoded	Very large; somatic hypermutations of gene segments
Memory	None	Yes
Self-tolerance	Yes (innately)	Yes (acquired)
Components		
Physical barriers	Skin; mucosal epithelia	None
Chemical barriers	Antimicrobial substances	None
Blood proteins	Complement	Antibodies
Cells	Phagocytes (macrophages, neutrophils) and natural killer cells	Lymphocytes (B and T cells)

B lymphocytes are the only cells capable of producing antibodies. They recognize extracellular (soluble or cell surface) antigens and differentiate into antibody-secreting cells, thus functioning as the mediators of humoral immunity. T lymphocytes, the mediators of cellular immunity, consist of functionally distinct populations, the best defined of which are *helper* T cells, cytolytic or *cytotoxic* T cells (CTLs), and *regulatory* T cells. NK cells are the third population of lymphocytes with receptors different from those of B and T cells and with major function involving innate immunity (2).

In modern times, the use of monoclonal antibodies has allowed us to define unique surface proteins, which are present only in that particular cell population and have been used as their characteristic identification marker. The standard nomenclature for these proteins is the *CD* (cluster of differentiation) numerical designation that currently consists of 350 different molecules. The majority of characterized molecules, however, are present on more than one cell population, where their presence defines maturation stage or particular effector function. The classification of lymphocytes by CD antigen expression is now widely used in clinical medicine and experimental immunology. According to the CD classification, helper T cells are defined as $CD3^+$ and $CD4^+$; most CTLs are $CD3^+$ and $CD8^+$, while regulatory T cells are a subgroup of helper cells with an additional low expression of the CD25 activation marker—the α-chain of the surface receptor for interleukin-2 (IL-2Rα)—and are defined as $CD3^+$, $CD4^+$, and $CD25^+$. B cells are characterized with the expression of CD19, while NK cells express the CD56 molecule.

APCs are a cell population that are specialized to capture microbial and other antigens, display them to lymphocytes, and provide signals that stimulate the proliferation and differentiation of lymphocytes. The major type of APCs is the dendritic cell, which is found under epithelia and in most organs, where it is poised to capture antigens and transport them to peripheral lymphoid organs. There are two major subtypes of dendritic cells: myeloid and plasmacytoid. Dendritic cells are the most potent APCs capable of stimulating "naive" T cells as they encounter antigens for the first time. Mature mononuclear phagocytes, tissue macrophages, also function as APCs in a T cell–mediated, adaptive immune response. Macrophages that have ingested microbes may activate "naive" T cells, while, in turn, effector T cells may stimulate the macrophages to more efficiently kill ingested pathogens. Follicular dendritic cells (FDCs) are cells present in the lymphoid tissue that trap antigens in the complex with antibodies or complement products and display those antigens for recognition by B lymphocytes.

After being stimulated by APCs, lymphocytes differentiate into effector cells. Differentiated effector helper T cells secrete cytokines and interact with and activate macrophages and B lymphocytes. Effector CTLs develop granules containing proteins that kill virus-infected and transformed host (tumor) cells. B-cells differentiate into plasma cells that actively synthesize and secrete antibodies. Some antigen-stimulated B and T lymphocytes differentiate into memory cells whose function is to mediate rapid and enhanced responses to second and subsequent exposures to antigens (1,2).

Cytokines are proteins secreted by the cells of innate and adaptive immunity that mediate many of the functions of those cells. Cytokines are produced in response to microbes and other antigens, and different cytokines stimulate diverse responses of cells involved in immunity and inflammation. In the activation phase of the adaptive immune response, cytokines stimulate growth and differentiation of lymphocytes; in the effector phase, they activate different cells to eliminate microbes and other antigens. Based on their principal biologic action, cytokines might be classified into three main functional categories: those that mediate innate immunity (IL-1, IL-6, and tumor necrosis factor [TNF]-α), those that regulate adaptive immunity (IL-2, IL-4, IL-5, and interferon [IFN]-γ), and those that stimulate hematopoiesis (IL-3, IL-7, and some growth factors). Although different cells produce cytokines of innate and adaptive immunity, and those cytokines act on different target cells, this distinction is not absolute because cytokines produced during such reactions often have overlapping action (IL-10 and IL-12). Additionally, cytokine signals from multiple immune cells tightly regulate antigen-processing and clearance responses (3).

ANTIGEN RECOGNITION AND PROCESSING

Antigen recognition is the first phase of the adaptive immune response. Antibodies, major histocompatibility complex (MHC), and T-cell antigen receptors (TCRs) are the three classes of molecules used in adaptive immunity to recognize antigens. Antibodies produced in a membrane-attached form function as B-cell receptors for antigen recognition. The interaction of antigen with membrane antibodies initiates B-cell activation and, thus, constitutes the recognition phase of the humoral immune response. B-lymphocyte differentiation, upon activation, proceeds along two pathways: one that requires stimulation by helper T lymphocytes, the T cell–dependent pathway, or the T cell–independent pathway. The antigens recognized by B cells may be in their native, nondegraded form and not require prior processing of the antigen by other immune system cells. In order to get help from T cells, however, B cells need to internalize the membrane antibody–antigen complex, degrade protein, and display it back on the cell surface membrane in complex with the class II MHC molecule. As explained below, T cells can recognize antigens only if they are processed and presented on the membrane surface of APCs in complex with the MHC molecules. Antibodies are also produced in a secreted form by activated B cells. In the effector phase of the humoral immune response, secreted antibody binds to antigens and triggers several effector mechanisms that eliminate the antigens. Although of the same antigen specificity, membrane-bound antibodies are involved in antigen recognition and B-cell activation, while secreted antibodies are responsible for triggering the effector phase of the humoral immune response and antigen clearance. It is essential to know that specificity and effector functions of antibodies depend on their basic structure. An antibody molecule has a symmetric core structure composed of two identical light chains and two identical heavy chains. Both heavy chains and light chains consist of amino terminal variable (V) regions and carboxyl terminal constant (C) regions. While light- and heavy-chain amino terminal variable regions together participate in antigen recognition, only the constant regions of the heavy chains are involved in antibody effector functions (1,2).

In contrast to B cells and their secreted antibodies that can recognize soluble as well as cell-associated antigens in their

native form, T cells can only recognize antigens that are displayed on other cell surfaces and are degraded into fragments by the body's various APCs. The task of displaying cell-associated antigens for recognition by T cells is performed by specialized proteins that are encoded by genes in a locus called the *major histocompatibility complex*. MHC molecules are integral components of the ligands that most T cells recognize, because the antigen receptors of T cells are actually specific for the complex of (foreign) peptide antigens and (self) MHC molecules. MHC molecules are found on immune and nonimmune cells. There are two main types of MHC gene products: class I and class II MHC molecules, which sample different pools of protein antigens, cytosolic or intracellular antigens and extracellular antigens that have been endocytosed, respectively. MHC class I molecules are present on virtually all nucleated cells where they display antigens to be recognized by $CD8^+$ cytotoxic T lymphocytes. MHC class II molecules are found primarily on APCs and primarily activate $CD4^+$ helper T cells. Once an antigen enters an APC, it is degraded to its peptide fragments. These antigen fragments are then integrated with the MHC molecule and transported to the cell membrane, where they are exposed to neighboring cells within a complex that includes either class I or class II MHC molecules. T lymphocytes subsequently recognize the MHC–antigen (MHC–Ag) complex and initiate antigenic response (1,2).

All T lymphocytes recognize an antigen by specific T-cell receptor (TCR) molecules expressed on their cell membrane. These TCR molecules function similarly to a lock and key with the MHC–Ag complex. It is important to understand that only a few T lymphocytes constituting one T-cell clone are specific for one particular antigen. In addition to T-cell receptor binding to the MHC–Ag complex, multiple membrane receptors are used in APC–T-cell interaction. During the infection-free time, however, cells still express MHC–Ag complexes containing self-antigens that should not provoke an immune response under normal conditions because potentially harmful lymphocytes that might be activated by regular self-antigens are eliminated during their maturation process within the thymus or bone marrow. Unfortunately, not all self-antigens are presented during lymphocyte maturation, and some might be exposed later during their lifespan. Exposure of those "hidden" self-antigens could initiate an unwanted immune response toward self-molecules, resulting in the development of an autoimmune disease (1).

In contrast to appropriately processed antigens that stimulate a limited number of T cells (one clone) bearing the same TCR (approximately one in a million circulating T cells), some bacterial proteins and toxins are able to stimulate T cells without first undergoing endocytosis and degradation. Those molecules, characterized as *superantigens*, can simultaneously stimulate T cells with different antigen specificity, and subsequently induce *polyclonal activation* with the extensive systemic release of cytokines. The stimulatory effect of superantigens is a consequence of direct binding to the class II MHC on APCs and the non–antigen-specific part of TCR on T cells, thus being able to activate 2% to 20% of all T cells. The massive T-cell activation results in the release of large amounts of inflammatory cytokines that induce T-cell anergy or death (apoptosis), which severely disturbs the ability of the immune system to respond appropriately to infection. As a consequence of the systemic effects of released cytokines, infected patients may develop toxic shock syndrome. Systemic effects include fever, endothelial damage, profound hypertension, disseminated intravascular coagulation, and multiorgan failure (4).

ANTIGEN CLEARANCE AND INFLAMMATION: IMMUNE EFFECTOR FUNCTIONS

Once the immune system recognizes an antigen, inflammation and clearance processes are initiated. Activation and the effector phase of the adaptive immune response are intended to eliminate antigen in the most appropriate and efficient way. For example, one set of components of the immune system is activated in response to the extracellular antigen (antibodies and helper T cells), while others are more effective in the elimination of the intracellular antigen (CTLs and NK cells). Regardless of the type of antigen, processes involved in the activation and effector phase of immune response induce changes in the surrounding tissue, defined as *inflammation*. The antigen clearance process is enhanced within inflamed tissues by increased vascular flow, altered vascular permeability, and the recruitment of immune cells. Those changes also produce four cardinal clinical signs of inflammation or ongoing immune response: (a) warmness (*calor*), (b) redness (*rubor*), (c) swelling (*tumor*), and (d) pain (*dolor*), often accompanied by malfunction of the involved organ (*functio laesa*).

Several physiologic mechanisms are involved in circulating inflammatory cell adhesion to vascular endothelium and subsequent diapedesis. Multiple adhesion molecules are present on both circulating inflammatory cells (L-selectin, LFA-1, and MAC-1) and endothelial cells (P-selectin, E-selectin, ICAM-1, and ICAM-2 molecules) after stimulation. Expression and function of these molecules is modulated by "early response" cytokines (TNF-α and IL-1) secreted by activated tissue macrophages and other APCs. Additionally, IL-8 production by endothelial cells and tissue fibroblasts is a major component of the chemotactic gradient facilitating neutrophil migration across the endothelial surface. Neutrophils are capable of direct recognition and phagocytosis of circulating antigens. After neutrophil phagocytosis, enzyme-laden lysosomes fuse with the antigen-containing phagosome, digesting and destroying the antigen. Neutrophils possess receptors for the Fc portion of immunoglobulins as well as receptors for complement components. Thus, opsonization or coating of antigens by immunoglobulins and complement markedly enhances phagocytic capability and antigen elimination (5).

The predominant mechanism for adequate reaction to, and rapid clearance of, extracellular antigen involves antibodies or immunoglobulins. Antibodies possess unique antigen specificity, thereby narrowing the inflammatory response to the specific antigenic target. Antibodies circulating in the bloodstream or interstitial fluid promptly recognize, and bind to, an antigen; but because antibodies do not directly perform any effector function, the elimination of antigen requires interaction of antibody with the components of innate immunity such as complement proteins or phagocytes and eosinophils. Antibody-mediated effector functions include neutralization of microbes or toxic microbial products, activation of the complement system, opsonization (coating) of antigens for enhanced phagocytosis, antibody-dependent cell-mediated cytotoxicity

(ADCC), and immediate hypersensitivity in which antibodies trigger mast cell activation.

Antibody molecules or immunoglobulins (Ig) can be divided into distinct classes and subclasses on the basis of differences in the structure (heavy chain), tissue and biologic fluid distribution, and functional capability. In order from the highest to the lowest serum concentration, those classes of antibody molecules (also referred to as isotypes) are designated as IgG, IgA, IgM, IgD, and IgE. It is important to note that different classes of antibodies perform different effector functions. Among the most notable functions of immunoglobulins are opsonization and the capacity to activate complement. IgG, IgM, and IgA are crucial to normal opsonization functions. Opsonization by IgG and IgM expedites the clearance of circulating antigens, whereas the secretion of IgA onto mucosal surfaces facilitates the clearance of invaders by mucosal surface macrophages and neutrophils. Because of its larger size, the function of IgM is confined primarily to the intravascular clearance of antigens, whereas IgG readily diffuses into the extravascular space. After being coupled with an antigen, antigen–antibody complexes—also termed immune complexes—are normally cleared by phagocytic and red blood cells. The clearance of immune complexes from the circulation is dependent on effective opsonization, binding of the immune complex–bound C3b fragment to CR1 on erythrocytes, and subsequent transport to the liver and spleen (6). IgD is primarily found on the surface of naive B cells where it functions as the receptor for antigen recognition. Although a little amount of IgD is also secreted, it is believed that IgD does not perform any physiologic immune function. In contrast to other immunoglobulin classes, once secreted, IgE is present free in the serum for a very short time, since it binds rapidly to the specific receptor on basophils, eosinophils, and mast cells. Antigen activation of cell-bound IgE results in the immediate release of various mediators, including histamine, serotonin, and leukotrienes. Although IgE is commonly connected to the allergic reactions, the physiologic function of IgE seems to be an immediate response to antigen and the induction of vascular dilation, increased vascular permeability, and the recruitment of immune cells. An important immune function of IgE is also to protect the host against parasites.

The complement system is capable of generating a broad series of inflammatory actions associated with antigen clearance. These actions include lysis of cells bearing antigen–antibody complexes, opsonization of antigens, chemotaxis of inflammatory cells, and generation of anaphylactic reactions. Complement activation may be accomplished by either the classic pathway, initiated by antigen–antibody complexes, or the alternate route initiated by antigenic protein aggregates, endotoxin, or insoluble compounds with certain surface characteristics. With sequential proteolysis of complement substrates, various complement fragments with neutrophil and eosinophil chemotactic properties, as well as vasodilatory effects, are generated that produce the previously mentioned cardinal signs of inflammation (7).

The major cells involved in antigen clearance include APCs and lymphocytes, neutrophils, and various organ-specific structural cells or tissue macrophages. Although many antigens may be destroyed within mononuclear phagocytic cells by intracellular enzymes, some antigens may become sheltered within the cells. Elimination of these antigens requires additional activation from helper T cells, which predominates in the case of bacterial infection. In general, the helper population of T lymphocytes ($CD4^+$) supports the function of mononuclear phagocytic cells and enhances antibody production by the B-lymphocyte population, thus supporting the clearance of extracellular antigens. Activated T cells increase the secretion of cytokines that are crucial for regulation of the immune response. On the basis of the pattern of cytokines secreted, $CD4^+$ lymphocytes are subdivided into two major classes: Th1 or Th2. The Th2 group of $CD4^+$ cells secretes cytokines, such as IL-4 and IL-10, that stimulate secretion of antibodies but partially suppress the cellular immune response and initiate the healing process. The cytokines secreted by the Th1 group of $CD4^+$ cells, including IL-2 and IFN-γ, are potent stimulants of the cell-mediated immune response. The systemic predominance of $CD4^+$ cell stimulation with either the Th1 or Th2 cytokine pattern has been associated with altered resistance to certain infections (8).

The $CD8^+$ population of T lymphocytes (CTLs) functions to destroy cells sheltering an antigen presented within a class I MHC complex, and is involved in the clearance of intracellular antigens. Lysis of the infected cell by CTLs, however, dominates during viral infections. Besides the important role of the T lymphocyte in clearing microbial pathogens, those cells are crucial for the recognition and elimination of self-transformed tumor cells. As a part of tumor cell growth, new antigens arise, which are presented on the cell surface in the complex with class I MHC molecules. As those antigens are new or changed self-antigens, CTLs cells might recognize them and induce tumor cell lysis. The CTL response refers primarily to cell killing by cytotoxic $CD8^+$ lymphocytes. After exposure to processed antigen, and under the influence of the lymphokines IL-2 and IFN-γ, activated $CD8^+$ cells proliferate, synthesize, and secrete membrane attack molecules, which results in lysis of the antigen-bearing cell. Similar to the cell lysis by CTLs, natural killer cells lyse neighboring cells by secreting membrane attack molecules (perforin and granzymes). Unlike the CTL response, the natural killer cell lysis of antigen-bearing cells does not seem to be antigen specific. Killer lymphocytes, the third major cytolytic cell population, are coated with surface receptors for antibodies. Killer lymphocytes may localize to antigen–antibody-coated cells, where they release their cytotoxic granules. Antibody recognition is crucial to this system, and killer lymphocyte function seems to be a component of antibody-dependent cytotoxicity. Natural killer cells and killer lymphocytes can be activated and made to proliferate in vitro under the influence of cytokines. These lymphokine-activated killer (LAK) cells may be reinfused into the body and have been investigated as cancer immunotherapy (8,9).

In addition to the primary immune APCs or professional APCs, structural cells, such as those of the endothelium, epithelium, and connective tissue, are also important to an effective immune response. Not only are these cells capable of secreting cytokines and inflammatory mediators, but after stimulation, they also express class II MHC molecules and may function in antigen presentation to T lymphocytes. Those cells are termed *nonprofessional APCs*, and their activation by particular cytokines (IFN-γ) may underlie the organ dysfunction associated with chronic immune stimulation and inflammation (1).

The release of multiple inflammatory mediators from migrating leukocytes—proteases, oxygen radicals, leukotrienes, platelet-activating factor—expands the local inflammatory process. Conversely, several cytokines and soluble cytokine receptors are normally present to down-regulate or limit the

inflammatory response. Among these "anti-inflammatory" factors are IL-4, IL-10, IL-13, transforming growth factor (TGF)-β, and IL-1 receptor antagonist. Cytokines released into the systemic circulation as a consequence of either localized or systemic inflammation have been directly implicated in the pathophysiologic mechanisms of the organ dysfunction associated with major trauma, sepsis, and burns. If high plasma concentrations are achieved, IL-1, TNF-α, and IL-6 have been shown to have profound effects on body metabolism and are capable of inducing hypotension, fever, and cachexia. Their functions have been implicated in the manifestations of septic shock, and their concentration correlates with mortality. In response to TNF-α, nitric oxide is produced by endothelial cells and, along with the other mediators, promotes smooth muscle relaxation and vasodilation. Whether these cytokines and mediators are the primary pathogenetic mediators for the shock syndrome or are markers for systemic inflammation is unclear (10).

Adequate response to the antigen, and successful and fast antigen elimination, results in the development of signs and symptoms defined as *acute* inflammation. In contrast, failure of immune cells to appropriately respond and eliminate antigen might result in the long-term stimulation of immune reaction and the development of *chronic* inflammation. Chronic inflammation is characteristic of most autoimmune diseases in which unwanted, rather than inappropriate, response toward self-antigens induces pathology.

HYPERSENSITIVITY REACTIONS

Adaptive immunity serves the important function of host defense against microbial infections, but immune responses are also capable of causing tissue injury and disease. Disorders caused by immune responses are termed *hypersensitivity diseases* (Table 50.3). This term arose from the clinical definition of immunity as "sensitivity," which is based on observations that an individual who has been exposed to an antigen exhibits a detectable reaction or is "sensitive" to subsequent encounters with the antigen. A common cause of hypersensitivity diseases is failure of self-tolerance, which, under physiologic conditions, ensures that the individual's immune system does not respond to his or her own antigens. Hypersensitivity diseases also result from uncontrolled or excessive responses against foreign antigens, such as microbes and noninfectious environmental antigens (11).

Hypersensitivity diseases represent a clinically heterogeneous group of disorders. The two principal factors that determine the clinical and pathologic manifestations of such diseases are the type of immune response that causes tissue injury, and the nature and location of antigen that is the target of this response. According to the nature of the immune response and the effector mechanisms responsible for cell and tissue injury, hypersensitivity diseases are commonly classified into four main types.

Type I

Type I hypersensitivity reaction, also called *immediate* hypersensitivity, is the most prevalent type of hypersensitivity diseases. IgE antibodies that are bound to mast cells, basophils, and eosinophils cause immediate hypersensitivity. When cell-associated IgE antibodies are cross-linked by the antigen, the cells are activated to rapidly release a variety of mediators. These mediators collectively cause increased vascular permeability, vasodilation, bronchial and visceral smooth muscle contraction, and local inflammation. Under normal conditions, this type of response is first triggered by antigen, but is short lived and beneficial for antigen clearance. In clinical medicine, these reactions are commonly referred to as allergy or atopy, and are the most common disorders of immunity that affect 20% of all individuals in the United States. The most common forms of atopic disease are allergic rhinitis (hay fever), bronchial asthma, atopic dermatitis (eczema), and food allergies. Immediate systemic hypersensitivity, characterized by edema in many tissues and fall in blood pressure secondary to vasodilation, is termed *anaphylaxis*, and may be fatal.

TABLE 50.3

TYPES OF PATHOLOGIC IMMUNE REACTIONS

Type	Effectors	Mechanism injury	Diseases
Type I, immediate hypersensitivity	IgE antibodies, Mast cells	Cell degranulation and mediator release	Hay fever, asthma, anaphylaxis
Type II, antibody mediated	Antibodies to single cell's antigens	Complement-dependent lysis and phagocytosis of cells	Anemia, thrombocytopenia, agranulocytosis
	Antibodies to tissue antigens	Enzyme release from activated leukocytes	Goodpasture disease, blistering skin diseases
	Antibodies to hormones or receptors	Function inhibition or activation	Diabetes, hyperthyroidism, myasthenia gravis
Type III, immune complex mediated	Antibody–antigen complexes	Immune complex–mediated leukocyte activation	Glomerulonephritis, vasculitis, SLE, serum sickness
Type IV, T-cell mediated	$CD4^+$ helper T cells	Macrophage activation and inflammation	Diabetes, multiple sclerosis, RA
	$CD8^+$ cytotoxic T cells	Target cell lysis	Acute hepatitis, graft rejection

SLE, systemic lupus erythematosus; RA, rheumatoid arthritis.

Type II

Antibodies other than IgE can cause tissue injury by recruiting and activating inflammatory cells. Diseases induced by such antibodies are identified as type II *hypersensitivity reactions*. Those antibodies are specific for antigens of particular cells or the extracellular matrix, and are found attached to these cells or tissue. Antibodies against tissue antigens cause disease by three main mechanisms:

1. First, antibodies against antigens on circulating cells promote complement activation and cell lysis or phagocytosis. Those antibodies might promote development of anemia, thrombocytopenia, and/or agranulocytosis.
2. Second, antibodies deposited in the tissue recruit neutrophils and macrophages. As phagocytosis is not possible, those cells release their products and induce tissue injury. This is the case with blistering skin diseases, vasculitis, and some forms of glomerulonephritis.
3. Third, some antibodies to a hormone, hormone receptors, blood-clotting factors, growth factors, an enzyme, or a drug might cause disease or treatment failure by inactivating or activating vital biologic function of these molecules without inducing any inflammation and tissue damage. Diseases mediated by this mechanism are myasthenia gravis, hyperthyroidism (Graves disease), diabetes, and myeloblastic anemia.

Type III

Immune complex disease or type III hypersensitivity is caused by antibody–antigen complexes formed in tissues. In certain disease states, immune complexes may freely circulate or be deposited within tissues, stimulating inflammatory reactions throughout the body. Immune complexes easily activate and complement neutrophils that cause tissue injury. In contrast to the type II diseases, type III hypersensitivity diseases are often systemic, such as serum sickness and systemic lupus erythematosus (SLE).

Type IV

Finally, tissue injury may be due to T lymphocytes that activate the effector mechanisms of delayed-type hypersensitivity (DTH) or directly kill target cells. Such conditions are type IV hypersensitivity *disorders*. In those diseases, tissue injury results from the products of activated macrophages, such as hydrolytic enzymes, reactive oxygen species, nitric oxide, and proinflammatory cytokines. Many organ-specific autoimmune diseases are caused by hypersensitivity reactions induced by T cells, such as insulin-dependent diabetes mellitus, multiple sclerosis, rheumatoid arthritis, contact sensitivity, and inflammatory bowel diseases (IBDs) (11).

IMMUNE DEFECTS AND CRITICAL ILLNESS

In contrast to the hypersensitivity reactions, many life-threatening diseases represent the consequences of immune system defects or deficiencies. Recurrent or unusual infections, increased susceptibility to tumors, and delayed healing characterize patients with immune system disorders. Although many immune system diseases overlap in immunopathogenesis, most may be classified on the basis of the predominant immune defect, be that defect congenital or acquired (Tables 50.4A and B). Additionally, many other chronic illnesses might be associated with subtle immunologic abnormalities, potentially contributing to clinical disease. Immune system disorders may be grouped into disorders of humoral immunity (Table 50.4A), cell-mediated immunity (Table 50.4B), and phagocytic cell function.

TABLE 50.4A

IMMUNODEFICIENCY SYNDROMES: ANTIBODY AND COMPLEMENT

Defect	Etiology	Consequence
IgG deficiency	Acquired, common variable hypogammaglobulinemia; congenital, X-linked or associated with ataxia telangiectasia	Recurrent infections, especially with *Streptococcus pneumoniae* and *Haemophilus* sp.
IgA deficiency	Thought to occur primarily as a congenital abnormality	Recurrent sinopulmonary infections, especially with *S. pneumoniae*
Early complement component (C2–C4) deficiencies	Congenital	Predisposition to autoimmune disease (e.g., SLE), increased risk for infections
Late complement component (C5–C8) deficiencies	Congenital	Increased risk for infections, especially with *Neisseria*
C1 inhibitor deficiency	Primarily congenital, rarely acquired	Angioedema, abdominal distress, upper airway obstruction
Complement receptor deficiency	Congenital or acquired	Predisposition to autoimmune disease
Alternate complement pathway defects	Associated with sickle cell disease	Increased risk for infections, especially with *S. pneumoniae*

SLE, systemic lupus erythematosus

TABLE 50.4B

IMMUNODEFICIENCY SYNDROMES: CELL MEDIATED

Defect	Etiology	Consequence
T-lymphocyte defects	AIDS, lymphoma, iatrogenic (especially glucocorticoid therapy and immunosuppressants used in solid organ transplantation)	Infection with opportunistic pathogens, *Pneumocystis jirovecii,* CMV, herpes simplex, *Cryptococcus neoformans,* and *Legionella*
Chronic granulomatous disease	Abnormal neutrophil oxidative metabolism, ineffective microbicidal activity, congenital	Recurrent bacterial and fungal infections; pyogenic infection of the skin, lymph nodes, liver, and lungs
Neutropenia	Most commonly iatrogenic (cytotoxic chemotherapy)	Bacterial and fungal infections
Leukocyte adhesion deficiency	Congenital absence of leukocyte adhesion molecules (LFA, MAC-1, selectins)	Recurrent skin, soft tissue, and lung infections; persistently elevated peripheral leukocyte counts
Chediak-Higashi syndrome	Congenitally abnormal neutrophil chemotaxis and degranulation, decreased microbicidal capacity	Associated with albinism and photophobia; recurrent infections
Job syndrome	Congenitally abnormal neutrophil chemotaxis, delayed catabolism of IgE	Elevated serum IgE; sinusitis; otitis media; eczema; recurrent skin and soft tissue infections, with *Staphylococcus aureus*

AIDS, acquired immunodeficiency syndrome; CMV, cytomegalovirus.

Defects of the complement system include deficiencies of individual complement component proteins, regulatory proteins, or complement receptors. Complement component deficiencies may be broadly grouped into early (C1–C4) or late component (C5–C8) deficiencies. A predisposition to *Streptococcus pneumoniae* and *Haemophilus influenzae* infections has been observed in patients deficient in early complement components. *Neisseria meningitidis* infections have been recognized as sequelae of late-component deficiencies. In contrast to patients with late-component deficiencies, patients with early-component deficiencies possess a uniquely higher incidence of autoimmune disease, especially SLE. In these patients, it has been suggested that the complement deficiency impairs effective clearance of circulating immune complexes, predisposing to autoimmune diseases. The consumption of complement in sepsis and septic shock has been clearly demonstrated. Whether complement activation is pathogenic or physiologic in septic shock remains unclear. Both the alternate and classic pathways of complement activation have been shown to be activated in septic shock, potentially related to a sepsis-induced inactivation of C1 inhibitors (12).

The most clinically significant complement regulatory protein deficiency is loss of C1 inhibitor activity. This nonspecific esterase inhibitor is strategic in controlling the classic complement cascade and inhibiting the action of several clotting factors. Although acquired forms of C1 inhibitor deficiency have been described, the autosomally dominant genetic defect is the most common. In patients with hereditary angioedema, trauma or stress may precipitate uncontrolled activation of the complement system, culminating in a systemic angioedema–nonpruritic limb edema, gastrointestinal disturbances, and upper airway obstruction. Unlike the angioedema associated with anaphylaxis, the angioedema associated with C1 inhibitor deficiency is much less responsive to epinephrine and glucocorticoids. In addition to subcutaneous or inhaled epinephrine, the management of acute angioedema may include the use of fresh frozen plasma or, when available, purified C1 inhibitor replacement. As maintenance therapy, androgens such as danazol or stanozolol offer effective therapy and are usually effective in increasing the levels of serum C1 inhibitor. C1 inhibitor deficiency is characterized by deficient C1 functional activity in serum, along with low levels of C2 and C4, especially during acute episodes. Notably, the serum level of C3 or total hemolytic complement activity is commonly normal. Few patients deficient in complement receptors have been described. The lack of cell surface complement receptors results in poor clearance of immune complexes. The elevated level of circulating immune complexes is thought to underlie the high prevalence of SLE in these patients (12).

Abnormalities of immunoglobulin production manifest most commonly as deficiencies, although the excessive production of immunoglobulins occasionally results in severe sequelae, as may occur in Waldenstrom macroglobulinemia. Infectious consequences of immunoglobulin deficiency result from most forms of immunoglobulin deficiency. The most common adult type of primary immunoglobulin deficiency is a selective deficiency of IgA. Although IgA deficiency has been associated with recurrent sinopulmonary infections and with *Giardia* intestinal infections, many of these patients remain asymptomatic. The clinical consequences of hypogammaglobulinemia are more frequent in patients with the heterogeneous disorders that compose common variable hypogammaglobulinemia. Common variable hypogammaglobulinemia includes a group of disorders characterized by low or absent serum immunoglobulin levels and an enhanced risk for bacterial infections, especially sinopulmonary infections. Because the infections are usually recurrent and generally responsive to treatment, these patients may present in adulthood with bronchiectasis and lung destruction. Infections with encapsulated bacteria, such as *Haemophilus* and *Streptococcus,* are especially prevalent. The most frequently diagnosed immunoglobulin deficiency pattern in these patients is a decrease

in all classes of immunoglobulins. Prophylactic therapy with γ-globulin has proven to be effective in preventing infections (7,13).

Among the many disorders associated with elevated serum concentrations of immunoglobulins, diseases associated with excessive IgM production are especially notable for acute clinical sequelae. Because of their size and structure, IgM globulins possess unique properties, including cold insolubility (cryoglobulins) and the potential to greatly increase blood viscosity. Excessive IgM production may result from a clearly benign response to mycoplasma and viral infections, or a neoplastic-like B-lymphocyte response (Waldenstrom macroglobulinemia). The cold agglutinin response to infections rarely results in more than a mild hemolytic anemia, but the IgM levels associated with Waldenstrom macroglobulinemia may produce life-threatening consequences. Viscosity-related sequelae include confusion, coma, visual impairment, and congestive heart failure. Plasmapheresis to lower the serum IgM level is effective therapy for these acute complications (7,13).

A normal antibody immune response to foreign material may occasionally result in dramatic clinical symptomatology. Especially notable examples are serum sickness and leukoagglutinin reactions. Serum sickness is characterized by the formation of circulating antigen–antibody complexes 7 to 10 days after injection of an antigenic protein into the body. With systemic deposition of the immune complexes, complement is activated and edema, rash, arthralgia, and fever result. The most common cases of serum sickness follow treatment with antithymocyte globulin (equine or rabbit origin) or snake antivenom (equine origin). Glucocorticoid therapy is usually indicated for severe serum sickness symptoms. The leukoagglutinin reaction results from the incidental transfusion of antibodies with red blood cells or plasma. Leukoagglutinin reactions result from the interaction of transfused antibodies with recipient neutrophils, prompting neutrophil sequestration in the lungs. Cough, dyspnea, and respiratory failure may follow the transfusion. Treatment is supportive, as there is no specific therapy for the reactions (14).

Acquired defects in lymphocyte- and macrophage-regulated immunity are the most common immunodeficiencies encountered in adults. Three major groups of disorders account for most of these disorders: the acquired immunodeficiency syndrome (AIDS), various lymphohematologic malignancies, and iatrogenic immunosuppression. These diseases are associated with enhanced susceptibility to infections with common pathogens, as well as a unique predisposition to infections with opportunistic microorganisms. The pathogenesis of one of the most devastating immune disorders, AIDS, involves selective depletion of the $CD4^+$ subset of T lymphocytes by retroviral infection. In these patients, lymphocyte depletion, combined with abnormal macrophage function and certain B-lymphocyte malfunctions, culminates in a plethora of potentially life-threatening infections. As with other patients with profound defects in lymphocyte-regulated immunity, patients with AIDS may commonly present with acute and severe respiratory failure in association with diffuse pulmonary infiltrates. Notable opportunistic respiratory pathogens in patients with defects in lymphocyte-regulated immunity include *Pneumocystis jirovecii, Listeria monocytogenes, Nocardia* sp., *Mycobacteria* sp., *Cryptococcus neoformans,* and cytomegalovirus. Before the AIDS epidemic, most cases of *Pneumocystis* pneumonia in adults occurred among iatrogenically immunosuppressed patients or patients with lymphoma, especially Hodgkin lymphoma. Immunosuppressants primarily affecting lymphocyte function include those used in organ transplantation: glucocorticoids, antithymocyte globulin, OKT3 antilymphocyte globulin, azathioprine, and cyclosporine.

The most common abnormalities of phagocytic function are related to either an abnormal number or function of circulating neutrophils. The consequence of almost all neutrophil defects is infection, primarily bacterial and fungal, and, less commonly, viral. The incidence of infection among neutropenic patients correlates with the depression of the circulating neutrophil count and the duration of neutropenia. Neutropenia is graded based on absolute neutrophil count as mild (1,000 to 1,500 cells/μL), moderate (500 to 1,000 cells/μL), or severe (less than 500 cells/μL) (15). The risk of infection increases proportionally as the circulating neutrophil count falls and is greater when the neutropenia persists over several days. Universally, patients with an absolute neutrophil count below 1,000 cells/μL have a substantially increased risk of infection over time, while serious infections are uncommon until more severe neutropenia develops with counts less than 500 cells/μL. With neutrophil counts below 100 cells/μL, the incidence of severe infection increases dramatically (15, 16). This risk forms the basis for empiric antimicrobial therapy in neutropenic patients before pathogen identification. The pathogenesis of neutrophil functional abnormalities has been most extensively studied among patients with congenital neutrophil defects. A history of recurrent lymphocutaneous or pulmonary infections with staphylococci or Gram-negative bacilli, especially *Pseudomonas* sp. or *Serratia* sp., provides a clue to a potential underlying neutrophil function disorder. Notably, infections with obligate anaerobic bacilli are exceedingly rare among patients with neutrophil defects. Multiple congenital functional defects of neutrophils have been identified and are outlined in Table 50.4B. Specific therapy exists for only one of these congenital disorders. Among certain patients with chronic granulomatous disease, the administration of IFN-γ has been shown to partially correct the neutrophil abnormality and dramatically lessen the incidence of infections (17).

IMMUNOTHERAPY

A broad spectrum of immunotherapies has evolved over the last several years (Table 50.5A). Immunotherapies may be broadly classified as either immune system stimulants or suppressants, but there is much mechanistic overlap. For example, the therapeutic effect of intravenous immune globulin (IVIG) administration in the treatment of idiopathic thrombocytopenia purpura has been partially attributed to the immunosuppressive properties of the transfused immunoglobulin complexes. Likewise, the actions of most immunosuppressive drugs are relatively global, with alterations in both cell-mediated immunity and humoral immunity (18).

Immunotherapies and Critical Illness

Although the complications of immunosuppression commonly result in serious illnesses, only a few specific immunotherapies are used in caring for critically ill patients. These immunotherapies include the use of certain antibodies, antibody fragments,

TABLE 50.5A

IMMUNOTHERAPY

Agents	Indications	Major side effects
Immunosuppressive drugs		
Corticosteroids	Multiple diseases associated with inflammation, graft rejection	Adrenal suppression, infection, altered glucose metabolism, cataracts, osteoporosis
Cytotoxic chemotherapies	Cancer therapy	Neutropenia, infection, mucosal ulceration
Methotrexate	Multiple diseases associated with inflammation, cancer therapy	Pneumonitis, hepatitis, neutropenia, infection
Cyclosporine	Graft rejection	Nephrotoxicity, hypertension
Azathioprine	Graft rejection, rheumatoid arthritis	Leukopenia, thrombocytopenia, infection
Immunomodulatory drugs		
Levamisole	Cancer therapy	Diarrhea, nausea, stomatitis, neurotoxicity, leukopenia, rash

and plasmapheresis (Table 50.5B). Multiple other forms of immunotherapy for critically ill patients have been used less consistently or with no success. The use of immunosuppressives and antibodies in the management of septic shock has failed to demonstrate any clinical benefit. The administration of antibodies, either as pooled γ-globulin fractions or antigen-specific immunoglobulins, has demonstrable efficacy in many chronic medical illnesses. Certain antibodies and antibody fragments occupy a novel therapeutic role in the management of the critically ill patient (19).

A unique detoxifying mechanism for digoxin intoxication involves the use of the Fab fragment of an anti-digoxin antibody. These fragments, produced in sheep, facilitate digoxin clearance with minimal side effects. Within minutes of infusion, serum-free digoxin levels are usually undetectable, whereas immunoreactive digoxin levels (detecting the inactive digoxin–Fab complexes) are usually elevated. Digoxin–Fab complexes are excreted by the kidneys without the latent release of digoxin. In general, anti-digoxin Fab therapy is indicated for digoxin-intoxicated patients presenting with life-threatening arrhythmias or digoxin intoxication accompanied by hyperkalemia. In addition to correcting the cardiac toxicity, the occasional hyperkalemia induced by digoxin poisoning commonly resolves with the Fab therapy. The commercially available anti-digoxin Fab product contains 40 mg of the Fab fragment, which is capable of binding 0.6 mg digoxin. The amount of Fab to be administered may be calculated either from knowledge of the amount ingested or by the formula (assuming that the drug has reached equilibrium levels):

$$\text{Body burden of digoxin (mg)} = [\text{Serum digoxin level (ng/mL)} \times 5.6(\text{L/kg, distribution volume}) \times \text{Weight (kg)}]/1{,}000$$

The body burden of digoxin should be calculated and the appropriate number of anti-digoxin Fab vials administered. Clinical experience suggests that it is better to deliver the correct number or a slight excess of Fab vials rather than underdose the patient. Side effects, even in the presence of moderate renal

TABLE 50.5B

IMMUNOTHERAPY: ANTIBODIES

Agents	Indications	Major side effects
Immunoglobulin (pooled human)	Ig deficiency diseases, ITP, myasthenia gravis, Guillain-Barré syndrome, CMV pneumonia in immunosuppressed patients	Myalgia, arthralgia, fever, aseptic meningitis, reactions in IgA-deficient patients, rarely anaphylaxis
Hyperimmune human Ig (hepatitis B, rabies, tetanus, Rho globulin, hepatitis A, measles)	Passive prophylaxis for specific diseases	Myalgia and injection site inflammation when administered intramuscularly
Hyperimmune sera	Antidotes for envenomization	Anaphylaxis, serum sickness
Antithymocyte globulin	Graft rejection, aplastic anemia	Fever, chills, thrombocytopenia, serum sickness, anaphylaxis
OKT3 (monoclonal antibody to T cells)	Graft rejection	Cytokine syndrome (especially with first injection, infection)
Anti-digoxin Fab fragment	Digoxin intoxication with arrhythmias	Hypokalemia, heart failure
Antiplatelet integrin receptor (ReoPro)	Prevention of acute reocclusion after coronary angioplasty	Hemorrhage

ITP, idiopathic thrombocytic purpura; CMV, cytomegalovirus.

TABLE 50.5C

IMMUNOTHERAPY: CYTOKINES AND GROWTH FACTORS

Agents	Indications	Major side effects
Interleukin-2 (IL-2)	Cancer therapy	Capillary leak syndrome, hypotension, pulmonary edema
Interferon-α (IFN-α)	Cancer therapy, certain forms of hepatitis	Flu-like syndrome: fever, headache, chills, myalgia
Interferon-γ (IFN-γ)	Chronic granulomatous disease with recurrent infections	Flu-like syndrome
Interferon-β (IFN-β)	Multiple sclerosis	Flu-like syndrome: injection site inflammation
Granulocyte colony stimulating factor (GCSF)	Prevention of infections and episodes of febrile neutropenia after chemotherapy	Bone pain
Granulocyte–macrophage colony stimulating factor (GM-CSF)	Myeloid reconstitution after bone marrow transplantation	Capillary leak syndrome; pulmonary edema; pericardial effusion; flulike syndrome

insufficiency, have been mild. Rarely is there a need to readminister a Fab dose. After the Fab administration, serum potassium levels should be monitored because the most common side effect is hypokalemia, and cautious potassium supplementation may be necessary. Once the anti-digoxin Fab has been administered, serum digoxin levels are uninterpretable. With normal renal function, the digoxin–Fab complex is excreted with a half-life of 10 to 20 hours (20).

Multiple immunomodulatory agents, including cytokines (Table 50.5C), antibodies to cytokines, and soluble cytokine receptors, are under active investigation in the management of critical illnesses and their complications. Whereas initial clinical trials suggested some efficacy of certain anti-endotoxin antibodies, studies in larger patient populations clearly demonstrated no benefit and perhaps a harmful effect. Considering the complexity of the immune system regulatory mechanisms in critical illnesses, the interpretation of preliminary immunomodulatory studies should be done with caution (21).

Plasmapheresis, the removal of plasma from blood with the reinfusion of cells and replacement fluids, has been used in many illnesses with variable success. Plasmapheresis has been shown to be effective in several illnesses that commonly require management in the intensive care unit, including idiopathic thrombocytopenia purpura (ITP), Guillain-Barré syndrome, myasthenia gravis, Waldenstrom macroglobulinemia, and Goodpasture syndrome. In general, plasmapheresis requires placement of either large-bore peripheral venous catheters or a temporary hemodialysis catheter. Most of the severe complications associated with plasmapheresis have been related to placement and maintenance of the venous access catheter. Hemorrhagic and septic complications are major concerns with respect to the choice of vascular access because of catheter manipulation during the pheresis sessions, the predisposition to hemorrhage associated with plasma extraction, and underlying renal and hemostatic derangements. Peripheral venous catheters or femoral catheters are probably preferable to subclavian or internal jugular sites for patients with hemostatic derangements. Similarly, the appropriate replacement fluid varies with the clinical condition and disease. In general, fresh frozen plasma is the most appropriate replacement fluid in treating ITP, whereas 5% albumin with isotonic saline is usually used for most neurologic indications. The volume of replacement fluid is estimated by approximating the amount of plasma removed. Considering that one plasma volume is commonly removed with each session, the replacement volume can be estimated from the following equation:

$$\text{Blood volume} = \text{Weight (kg)} \times 70\ \text{mL}$$

$$\text{Replacement volume} = \text{Blood volume} \times (1 - \text{hematocrit, as a decimal})$$

Hence, for a 70-kg adult with a hematocrit of 40%, the replacement volume would be 2,940 mL. The plasma volume to be removed, replacement volume, and type of replacement fluid must be individualized based on the patient's clinical condition. Almost 50% of patients undergoing plasmapheresis experience some complication. Most of the complications, such as muscle cramps, are mild and have been related to the citrate used in the circuit. Less commonly, hypofibrinogenemia, electrolyte deficiencies, and total protein deficiencies may develop. Patients undergoing frequent sessions should be monitored regularly for electrolyte levels, blood counts, and fibrinogen levels. Fibrinogen depletion, especially in patients with clinical conditions predisposing to hemorrhage, may be treated with cryoprecipitate (22).

Complications of Immunotherapy

The side effects of many immunotherapies include several severe illnesses. Infectious complications of immunosuppressive therapy account for the most common severe consequences of immunotherapies. However, several other severe, noninfectious clinical syndromes have been attributed to certain immunotherapies. These systemic reactions have been described most commonly with certain immunoglobulin or cytokine therapies. The infusion of γ-globulin (IVIG) may result in myalgia, low-grade fever, and back pain. These relatively minor symptoms have been partially attributed to complement activation by immunoglobulin complexes, and are usually effectively managed by slowing the rate of infusion or prophylaxis with antihistamines (23). Occasionally, IVIG infusions may result in systemic hypotension or anaphylaxis. These severe reactions, although rare, have been described most commonly among patients with IgA deficiencies who have pre-existing antibodies to IgA. The IgA in the IVIG infusate is thought to initiate the subsequent antigen–antibody reaction. Immunoglobulins

produced in animals, such as antithymocyte globulin and the antivenins, are among the most common causes of anaphylaxis or serum sickness. The immunosuppressive monoclonal antibody OKT3 is occasionally associated with a "cytokine release syndrome" shortly after infusion. OKT3 is a murine monoclonal antibody that selectively depletes T lymphocytes and has proven useful in solid organ transplantation. The cytokine release syndrome manifests as fever, myalgia, dyspnea, and hypotension. This reaction is most common after the initial OKT3 infusion and has been attributed to the systemic release of IFN-γ and TNF-α. This syndrome may be prevented by prophylaxis with corticosteroids. Another cytokine-mediated syndrome is the capillary leak syndrome associated with IL-2 administration and used in certain cancer therapies and multiple other investigational studies. The capillary leak syndrome, although apparently dose related, is common, and in certain patient populations, the incidence rate approaches 50%. The sepsis-like syndrome consists of hypotension, extravascular fluid sequestration, and, occasionally, pulmonary edema. Treatment includes vasopressor cardiovascular support and corticosteroids. Development of the syndrome may require a decrease in the interleukin dose or cessation of therapy (24).

SUMMARY

It is important to keep in mind that all aspects of immunity are tightly integrated, such that cell-mediated immune responses and humoral responses do not function as independently of each other as was once thought. Similarly, almost all nonimmune cellular and organ functions, such as those responsible for hemodynamic stability and body metabolism, have been shown to be partially modulated by networking cytokine messages from the multiple immune system cells. Appropriate immunologic responses are crucial to recovery from most critical illnesses. The complex intercommunication among immune and non-immune system cells manifests itself as many of the systemic symptoms commonly associated with acute illness, such as fever, hypotension, and protein depletion. Perturbation of the immune defense systems, whether on a congenital or acquired basis, complicates the recovery process and commonly prolongs otherwise curable illnesses. The expanding use of immunotherapies has been accompanied by the recognition of several severe systemic side effects and infectious consequences that, in themselves, result in serious illnesses.

References

1. Sakaguchi S. Regulation of immune response. In: Rich RR, ed. *Clinical Immunology: Principles and Practice.* 2nd ed. St. Louis: Mosby-Year Book; 1995:15.1.
2. Nossal GJ. The basic components of the immune system. *N Engl J Med.* 1987;316:1320.
3. Romagnani S. Lymphokine production by human T cells in disease states. *Annu Rev Immunol.* 1994;12:227.
4. Marrack P. The staphylococcal enterotoxins and their relatives. *Science.* 1990;248:705.
5. Abbas KA, Lichtman HA. Innate immunity. In: Abbas KA, Lichtman HA, eds. *Cellular and Molecular Immunology.* 5th ed. Philadelphia: Saunders; 2003:275.
6. Schifferli JA, Ng YC, Peters DK. The role of complement and its receptor in the elimination of immune complexes. *N Engl J Med.* 1986;315:488.
7. Popovic P, Dubois D, Rabin SB, et al. Immunoglobulin titers and immunoglobulin subtypes. In: Lotze MT, Thomson AW. *Measuring Immunity.* San Diego, CA: Elsevier Academic Press; 2005:159.
8. Abbas AK, Lichtman AH. Effector mechanisms of cell-mediated immunity. In: Abbas AK, Lichtman AH, eds. *Cellular and Molecular Immunology.* 5th ed. Philadelphia: Saunders; 2003:298.
9. Rosenberg SA. Adoptive immunotherapy for cancer. *Sci Am.* 1990;262:62.
10. Casey LC, Balk RA, Bone RC. Plasma cytokine and endotoxin levels correlate with survival in patients with the sepsis syndrome. *Ann Intern Med.* 1993;119:771.
11. Sell S. Immunopathology. In: Rich RR, Fleisher TA, eds. *Clinical Immunology: Principles and Practice.* St. Louis: Mosby-Year Book; 1995:449.
12. Frank MM. Complement in the pathophysiology of human disease. *N Engl J Med.* 1987;316:1525.
13. Rosen FS, Cooper MD, Wedgwood RJP. The primary immunodeficiencies. *N Engl J Med.* 1984;311:300.
14. Welborn JL, Hersch J. Blood transfusion reactions. *Postgrad Med.* 1991;90:125.
15. Schwartzberg LS. Neutropenia: etiology and pathogenesis. *Clin Cornerstone.* 2006;8(Suppl 5):S5.
16. Bodey G, Buckley M, Sathe Y, et al. Quantitative relationships between circulating leukocytes and infection in patients with leukemia. *Ann Intern Med.* 1966;64:328.
17. Ezekowitz RAB, Dinauer MC, Jaffe HS, et al. Partial correction of the phagocytic defect in patients with X-linked chronic granulomatous disease by subcutaneous interferon gamma. *N Engl J Med.* 1988;319:146.
18. Abe Y, Horiuchi A, Miyake M, et al. Anti-cytokine nature of natural human immunoglobulin: one possible mechanism of the clinical effect of intravenous immunoglobulin therapy. *Immunol Rev.* 1994;139:5.
19. Suffredini AF. Current prospects for the treatment of clinical sepsis. *Clin Exp Immunol.* 1994;22:(Suppl):12.
20. Taboulet P, Baud FJ, Bismuth C. Clinical features and management of digitalis poisoning: rationale for immunotherapy. *Clin Toxicol.* 1993;31:247.
21. Luce JM. Introduction of new technology into critical care practice: a history of HA-1A human monoclonal antibody against endotoxin. *Crit Care Med.* 1993;21:1233.
22. Strauss RG, Ciavarella D, Gilcher RO, et al. An overview of current management. *J Clin Apheresis.* 1993;8:189.
23. Duhem C, Dicato MA, Ries F. Side-effects of intravenous immune globulins. *Clin Exp Immunol.* 1994;97(Suppl 1):79.
24. Rieves DR, Levine SJ, Shelhamer SH. Allergy and immunology. In: Civetta MJ, Taylor RW, Kirby RR, eds. *Critical Care.* 3rd ed. Philadelphia: Lippincott-Raven; 1997:303.

ПРИЛОГ 2

Универзитет у Београду
ФАКУЛТЕТ ЗА ФИЗИЧКУ ХЕМИЈУ
www.ffh.bg.ac.rs
Студентски трг 12-16, п. пр. 47, 11158 Београд 118, ПАК 105305 // тел +381 11 2635-545, тел/факс +381 11 2187-133, ffh@ffh.bg.ac.rs

ПОТВРДА

Овим се потврђује да је др Игор Петрушић, доктор медицинских наука и научни сарадник, од 04.10.2021. - 14.01.2022. у својству наставника држао наставу на предмету „Напредна анализа радиолошких снимака“ на докторским студијама Факултета за физичку хемију. У периоду од 23.02.2022. - 3.06.2022. на мастер студијама био је ангажован у својству сарадника за вежбе на предмету „Магнетно-резонантни имиџинг“.

У Београду

28. 06. 2022.

др Мирослав Кузмановић, редовни професор
декан Факултета за физичку хемију

ПРИЛОГ 3

Датум: 10.06.2022.
Број: 819

На основу члана 33. Статута Универзитет у Београду – Факултета за физичку хемију, Наставно-научно веће Факултета, на IX редовној седници одржаној 10.06.2022. године, доноси следећу

О Д Л У К У

1.- За ментора за израду мастер рада студента **дипл. физ.-хем. Миле Опачић** одређује се др Игор Петрушић, научни сарадник Факултета за физичку хемију.

2.- Прихвата се образложење теме за израду мастер рада студента, под називом **„Испитивање разлика у активацији елоквентних зона у кори великог мозга код пацијената са класичном и мигреном праћеном вишим кортикалним поремећајима помоћу функционалног МРИ“.**

3. Именује се Комисија за одбрану мастер рада студента у саставу:

1) др Игор Петрушић, научни сарадник, Факултет за физичку хемију,
2) др Марко Даковић, ванредни професор, Факултет за физичку хемију,
3) др Милош Мојовић, редовни професор, Факултет за физичку хемију.

Одлуку доставити:
- студенту,
- члановима Комисије,
- Служби за студентске послове,
- архиви Факултета.

Универзитет у Београду - Факултет за физичку хемију

проф. др Мирослав Кузмановић, декан

ПРИЛОГ 4

УНИВЕРЗИТЕТ У БЕОГРАДУ

Адреса: Студентски трг 1, 11000 Београд, Република Србија
Тел.: 011 3207400; Факс: 011 2638818; E-mail: kabinet@rect.bg.ac.rs

Београд, 28. јун 2022. год
06 Број: 612-21133/98-22
МР

На основу члана 29 Закона о општем управном поступку ("Службени гласник РС", бр. 18/2016), а на захтев Игора Д. Петрушића, издаје се се следећа

П О Т В Р Д А

да је др Игор Д. Петрушић, научни сарадник са Института за медицинска истраживања у Београду, ангажован као наставник – сарадник на докторским академским студијама Биофизика 180 ЕСПБ који је акредитован као студијски програм на студијама при Универзитету у Београду. Др Игор Д. Петрушић ангажован је од 2021. године на изборном предмету Неуробиофизичке технике.

Потврда се издаје на лични захтев.

П Р О Р Е К Т О Р

Проф. др Дејан Филиповић

ПРИЛОГ 5

Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Prof. Dr. Stanisa Raspopovic
Neuroengineering LAB
Institut für Robotik und Intelligente Systeme IRIS
Departement Gesundheitswissenschaften u. Technologie
ETH Zürich, TAN E2
Tannenstrasse 1, CH-8092 Zürich
stanisa.raspopovic@hest.ethz.ch
https://neuroeng.ethz.ch/

Cirih, 5. Maj 2022.

Pismo preporuke za Dr. Igora Petrušića

Poštovani,

Pišem ovo pismo da bih odobrio i snažno podržao prijavu dr sci med. Igora Petrušića za mesto docenta na Katedri za patobiologiju Farmaceutskog fakulteta Univerziteta u Beogradu. On je veoma talentovan i pripremljen kandidat, svrstava se u prvih 5% istraživača sa kojima sam radio.

Radi konteksta, ja sam profesor i šef laboratorije za neuroinženjering, na Odseku za zdravstvene nauke i tehnologiju, na ETH Cirihu, prvoplasiranom Univerzitetu Kontinentalne Evrope na svim medjunarodnim rang listama. Moja laboratorija se fokusira na upotrebu neuronske stimulacije za obnavljanje senzorne i motoričke funkcije nakon amputacije, moždanog udara ili povrede kičmene moždine, kao i neurodegenerativnih poremećaja. Ja posedujem značajno međunarodno iskustvo u istraživanju nervnog sistema i inženjeringa koje je kulminiralo dodelom ERC Starting granta 2018., Science i PINS Grand Prize nagrade za neuromodulaciju 2021., kao i ETH Latsis Prize 2021. Objavljivao sam u najprestižnijim naučnim časopisima kao što su Science, Nature Materials, Nature Medicine i Science Translation Medicine i osvajao švajcarske grantove kao i sredstva neprofitnih organizacija. Moja laboratorija kombinuje rad na kompjuterskim modelima i klinička ispitivanja na ljudima

Dr sci med. Igor Petrušić je izuzetno doprineo realizaciji studije o praćenju fiziološkog i patofiziološkog neuroplasticiteta kod osoba kod kojih je implantirana bionička noga posle natkolene amputacije u okviru projekta: "FeelAgain". Ova multidisciplinarna i internacionalna saradnja dovela je do publikacije: "Plastic changes in the brain after a neuro-prosthetic leg use" u časopisu Clinical Neurophysiology. Takođe, prihvaćen je sažetak rada na FENS forumu 2022. godine pod nazivom: "A neuroimaging study of the brain changes due to peripheral nerve stimulation". Bitno je naglasiti da su rezultati ove studije prvi u oblasti istraživanja funkcionalnih promena u mozgu prikazanih funkcionalnom magnetnom rezonancijom posle korišćenja bioničke noge i kao takva predstavljaju osnovu za dalja istraživanja i buduće internacionalne saradnje

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Prof. Dr. Stanisa Raspopovic
Neuroengineering LAB
Institut für Robotik und Intelligente Systeme IRIS
Departement Gesundheitswissenschaften u. Technologie
ETH Zürich, TAN E2
Tannenstrasse 1, CH-8092 Zürich
stanisa.raspopovic@hest.ethz.ch
https://neuroeng.ethz.ch/

koje sa dr sci med. Igorem Petrušićem planiramo. Iz naše saradnje sam uvideo da dr sci med. Igor Petrušić ima konstruktivan i nesebičan pristup u saradnji sa svim članovima istraživačkog tima i da bi njegovo znanje i kvalitete trebalo iskoristiti i u nastavi na Univerzitetu u Beogradu.

Iskreno sam začuđen da dr sci med. Igor Petrušić već nije u nastavnom zvanju pored ogromnog naučnog i pedagoškog doprinosa koje je ostvario na Univerzitetu u Beogradu. To je od specijalnog znacaja danas vise nego ikada, jer se nazalost dogadja egzodus talenata ka inostranstvu.

Ovu poziciju smatram velikom profesionalnom i ličnom šansom za njega. Verujem da će mu to pomoći u njegovom kontinuiranom težnji ka izvrsnosti, a sa druge strane, obogatiće zajednicu Univerziteta u Beogradu sa veoma talentovanim i strastvenim istraživačem.

Zbog svega iznad navedenog, veliko mi je zadovoljstvo da preporučim dr sci med. Igora Petrušića za mesto docenta na Katedri za patobiologiju Farmaceutskog fakulteta Univerziteta u Beogradu.

Ostajem na raspolagnju za svaku dodatnu konsultaciju ili pitanje,

Srdačni pozdrav,

Prof. Dr. Stanisa Raspopovic,
Head of Neuroengineering Lab *at ETH Zurich*

Прилог 6

Research Topic

Subtypes of Typical Migraine with Aura: Exploring Markers for Subtype Classification and Treatment Response

About this Research Topic

Typical migraine with aura is a complex primary headache with highly variable clinical manifestation, including visual, somatosensory and dysphasic symptoms. Visual auras are ranging from simple visual phenomena, such as flashes of bright light or zig-zag lines, to more complex disturbances of visual perception. Similar to visual phenomena, somatosensory symptoms can be ranging from simple tingling sensations on one hand to more complex manifestations such as dyspraxia. Also, various manifestations of dysphasia and disturbances of memory are present in the aura phase of the attack. Some patients have only simple auras during migraine attacks, while some patients have combinations of attacks with only simple symptoms and attacks with simple and complex symptoms and in a minority of cases some patients

Topic Editors

Igor Petrusic
Faculty of Physical Chemistry, University of Belgrade Belgrade, Serbia

19 publications

Peter Goadsby Follow

Currently, there is no difference in the treatment of patients who suffer from only visual disturbances during the aura phase and those who report additional somatosensory symptoms or even higher cortical dysfunctions. This is due to a lack of understanding of pathophysiological mechanisms that allow migraineurs' brains to develop heterogeneous phenotypes. However, recent neuroimaging and electrophysiological studies have highlighted that people suffering from complex migraine with aura differ from people who only report visual auras that precede the headache phase. Moreover, a recently developed migraine aura complexity score (MACS) shows that people with more complex aura tend to have thicker cerebral cortex in various sites which may be affected by cortical spreading depolarization/depression. Thus, potential genetic, biochemical, electrophysiological and neuroimaging markers for subtype classification could significantly advance individualized treatment and enable new therapeutic strategies. Also, the relationship between the complexity of migraine aura and other migraine phases could reveal a new piece of the puzzle in the complex pathophysiology of migraine.

The aim of this Research Topic is to explore potential markers for subtype characterization of typical migraine with aura and to further investigate the differences between clinical subtypes and the relevance of the aura complexity on the treatment outcome. We welcome submissions of Original Research and Review papers, as well as interesting Case Reports that investigate the pathophysiology of typical migraine with aura by using multimodal techniques.

Keywords: Typical migraine with aura, complex aura, clinical characterization, neuroimaging, electrophysiological studies, genetic and biochemical biomarkers.

London
London,
United
Kingdom

3 publications

Follow

Cristina Tassorelli

Department of Brain and Behavioral Sciences, University of Pavia
Pavia, Italy

251 publications

Follow

Gianluca Coppola

Department of Medical-Surgical Sciences and Biotechnologies, Faculty of Pharmacy and Medicine, Sapienza University of Rome

journal to which they are submitted, as defined in their mission statements. Frontiers reserves the right to guide an out-of-scope manuscript to a more suitable section or journal at any stage of peer review.

About Frontiers Research Topics

With their unique mixes of varied contributions from Original Research to Review Articles, Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author.

More info › Publishing fees ›

223 publications

Submission Deadlines

25 July 2022 Abstract

23 September 2022 Manuscript

Author guidelines ›

Participating Journals

Manuscripts can be submitted to this Research Topic via the following journals:

Frontiers in
Human Neuroscience
Brain Health and Clinical Neuroscience

Frontiers in
Neurology
Neurological Biomarkers

Frontiers in
Neuroscience
Brain Imaging Methods

Neuroimaging

Brain Imaging Methods