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## Preface

### Personal Recollection

I still remember these moments very vividly, as if they were today, when at the corner of my eye I saw a lovely young woman waiting patiently for her turn to talk to me. She later turned out to be Dr. Claudia Panuschka – Springer’s Editor of Biomedicine/Life Sciences, whom I learned to appreciate professionally, and enjoyed so much working with. Claudia looked as if of she simply wishes to ask me a small question, at the end of my invited lecture on “Glutamate Immunity and Autoimmunity”, in an international meeting in Vienna, on Thursday, August 6th 2009. In that talk, I used a novel term – “**Nerve-Driven Immunity**” that I coined a few years before, and like so much using ever since, in papers and lectures, when discussing the relatively new concept of “Neurotransmitters in the Immune System”.

When we were finally left alone, Claudia approached me gently, but not regarding a small matter as I thought. Rather, without any prior preparation or hesitation she threw to the air a huge idea that finally gave birth to this book: “As I enjoyed your talk and ideas so much, would you agree to write a book for Springer on ‘Nerve-Driven Immunity’?” she asked. This presumably simple question hit me by complete surprise, triggering a burst of fast inner thoughts: “Is she serious? . . . Can I do it? . . . Should I? . . . It could be a wonderful and unique opportunity to raise the awareness of people to this new important topic, which is to a large extent complementally unknown . . . a big challenge . . . a unique scientific and writing adventure . . . but . . . but at the same it would require endless amount of work . . . infinite time . . . huge commitment . . . heavy responsibility . . .”

While debating for a few seconds how should I in fact answer Claudia, I suddenly heard my own voice replying instead of me: “Thank you . . . that’s a huge complement . . . I would have to think about it . . . but I already know one thing for certain: if I finally accept your kind and flattering invitation, I wouldn’t like to write this book all by myself. It would have to be a team work, and for that I would need the full cooperation of very good people, each contributing a chapter on a different neurotransmitter and its role in the immune system”. When Claudia did not reject this idea on the spot I added more obstacles: “. . . It would be very difficult to find such rare people, since only relatively few people work on this topic, and even when I find them, I doubt they would agree to do a very sisyphic work and read, collect,

re-analyze carefully and summarize all the data published thus far in regards to the role of a given neurotransmitter in the immune system (rather than write only about their own work, which is usually the case) . . . and that they would also be willing to write the chapter along my own requested framework and subchapters, which I would probably ask to be similar to all the chapters”.

Well . . . since this conversation in 2009 in Vienna, so many things have happened . . . so many discussions between Claudia and me took place, and later so many emails were exchanged between all the great authors of the present book and myself, leading to our present exciting stand point, when we launch this book.

For me, the book exceeds all prior expectations, and I have no words to express how fortunate I feel to have been given this opportunity, and how deeply grateful I am to Springer, to Claudia, and of course to all the very good authors of the book chapters. Without all of you, this book would have never been born. Now, it is hoped that all of you share the enthusiasm and pride seeing this book come to life, and that the future readers of this book will enjoy it and learn from it many new things.

## **The Book, the Authors, the Vision . . .**

Hopefully, our book will become a rich and updated encyclopedia on the novel topic we cover: the major and active role played by many neurotransmitters and neuropeptides in the immune system. Indeed, the book can teach the readers what we know today on the “immune face” of 12 neurotransmitters and neuropeptides: Dopamine, Adrenaline, Noradrenaline, Acetylcholine, Glutamate, GABA, Somatostatin, Neuropeptide Y (NPY), *Vasoactive intestinal polypeptide (VIP)*, Calcitonin gene-related peptide (CGRP), Opioids and Cannabinoids. And it already seems to few of us that this book could easily become a text book for scientists, clinicians and students interested in Immunology, Neurobiology, NeuroImmunology or Pharmacology, and may even serve as the basis for a new Ph.D. or M.D. course on “Neurotransmitters in the Immune System”.

The authors of the book chapters are highly qualified scientists and/or clinicians, working in nine different countries: Doina Ganea, USA (VIP); Sabita Roy and Jana Ninković, USA (Opioids); Marco Cosentino and Franca Marino, Italy (Adrenaline and Noradrenaline); Talma Brenner and Eran Nizri, Israel (Acetylcholine); Bernhard Holzmann, Germany (CGRP); Bryndis Birnir, Zhe Jin, Suresh Kumar Mendu and Amol Bhandage, Sweden (GABA); Toomas Talme and Karl-Gösta Sundqvist, Sweden (Somatostatin); Cris Constantinescu and Radu Tanasescu, United Kingdom (Cannabinoids); Yonatan Ganor, France (Glutamate); Mario Delgado, Spain (VIP); Mirjana Dimitrijevic and Stanislava Stanojevic, Serbia and Montenegro (NPY), and myself – Mia Levite, Israel (Dopamine and Glutamate).

Unfortunately, the planned and promised chapters on Serotonin, Substance P and GnRH (I and II) were finally not submitted on time, but may be included in the next updated edition of this book, if and once it will be published.

## ‘NeuroImmunoTransmitters’

As a whole, our ‘Nerve-Driven Immunity’ book shows beyond any doubt that neurotransmitters and neuropeptides have a huge impact on the immune system, not only on the nervous system. Based on the impressive wealth of data supporting this notion and covered by this book, I suggest that most if not all of the neurotransmitters deserve now a new title: ‘**NeuroImmunoTransmitters**’, replacing the “old” “classical” and what seems now to be a too narrow title: ‘Neurotransmitters’, which assigns to these molecules only or primarily effects in the nervous system. The new suggested criteria set herein for being named and considered a ‘NeuroImmunoTransmitter’ (rather than only a neurotransmitter) are listed below, and fulfilled by most, if not all the neurotransmitters and neuropeptides discussed in our book.

*Criteria 1 for being a ‘NeuroImmunoTransmitter’:* Most if not all types of immune cells ought to express receptors for the respective neurotransmitter/neuropeptide on their cell surface (not only on the mRNA level), and these receptors ought to be functional.

*Criteria 2 for being a ‘NeuroImmunoTransmitter’:* The neurotransmitter/neuropeptide by itself ought to induce direct and potent effects in at least some types of immune cells. The neurotransmitter-induced immune effects can be either an induction/elevation of a given immune function, or rather its suppression, depending on the context (whose parameters are discussed below).

The immune functions discussed throughout the book as those influenced by neurotransmitters/neuropeptides include, but are not limited to, the following: immune proliferation, cytokine secretion, adhesion, spontaneous migration, chemotactic migration (i.e. chemotaxis), cytotoxicity, T-helper polarization and differentiation, suppression of Effector T cells (Teffs) by Regulatory T cells (Tregs), phagocytosis by macrophages, antibody production by B cells, Nitric Oxide (NO) production, expression of various key receptors on the cell surface of the immune cells, inward  $\text{Ca}^{2+}$  ion currents, outward  $\text{K}^{+}$  ion currents, expression and activity of NF- $\kappa$ B and various others.

*Criteria 3 for being a ‘NeuroImmunoTransmitter’:* The selective agonists and antagonists of the native neurotransmitter/neuropeptide ought to exert various **direct** effects on the immune cells carrying the specific receptors for the native neurotransmitter/neuropeptide. While the agonists can be usually expected to mimic (at least partially) the effects of the physiological neurotransmitter, the antagonists would usually do the opposite and block the neurotransmitter-induced effects, but often also induce other effects on their own.

*Criteria 4 for being a ‘NeuroImmunoTransmitter’ (optional criteria):* Immune cells, at least some types, should produce the neurotransmitter, and under certain conditions ought to be able to release it to the extracellular milieu. The immune-derived neurotransmitter could then induce autocrine or paracrine effects.

*Criteria 5 for being a ‘NeuroImmunoTransmitter’ (optional criteria):* The neurotransmitter should be involved directly or indirectly in at least some immune diseases. These diseases can be any autoimmune disease, inflammatory disease,

immunodeficiency, immune malignancy – leukemia and/or lymphoma – or other. The neurotransmitter could also affect the host's immune resistance to infections.

It is suggested that if a currently entitled 'Neurotransmitter' or 'Neuropeptide' fulfills all these five criteria, or at least criteria 1–3, it should be considered as a 'NeuroImmunoTransmitter', or 'NeuroImmunoPeptide'.

## **'It's a Matter of Context'**

A paramount take home message of our book, is that neurotransmitter's effects on immune cells are highly dependent on the context, a phenomenon I call "It's a matter of context". The main factors that determine the context, and dictate the exact effect of a given neurotransmitter on a given immune cell are listed below.

1. *The neurotransmitter concentration.* A different concentration of the very same neurotransmitter often causes a different, and even opposite effect. Thus, whenever studying the effect of a given neurotransmitter/neuropeptide on a specific immune function of a given immune cell, it is very important and highly recommended to test several concentrations of that neurotransmitter/neuropeptide and draw a wide range dose–response curve, or at least test three concentration ranges: low  $\sim 0.1$  nM, medium  $\sim 1$   $\mu$ M, or high  $\sim 0.1$ – $1$  mM. As described in this book, for many neurotransmitters the low  $\sim 0.1$  nM concentration is the most effective one for the specific induction/elevation or rather suppression of various immune functions, while the very high  $\sim 0.1$ – $1$  mM concentration is usually non specific and even toxic to the immune cells.
2. *The neurotransmitter receptor subtype/s being activated.* Most if not all neurotransmitters and neuropeptides have more than one receptor, and many of them have a broad family of receptors, which are coded by different genes, and coupled to different downstream elements. Usually, activation of different neurotransmitter receptor subtypes results in very different effects. Also, different immune cells have been shown to express a different composition of neurotransmitter-receptor subtypes. It is thus crucial to identify in each case which specific neurotransmitter receptor subtype/s are expressed on the immune cells being studied, and which one/s mediate the immune effect induced by the physiological neurotransmitter or by its agonist or antagonist.
3. *The activation state of the immune cell being exposed to the neurotransmitter.* One characteristic feature of immune cells is their existence in two very distinct states: a resting/naïve state and an activated state, and their frequent shift between these two states. It turns out, as described in the book, that it makes a huge difference if the very same neurotransmitter binds a resting/naïve immune cell or rather a cell that has already been activated, by either an antigen, mitogen, CD3/CD28 antibodies, cytokine or any other stimuli, or even an immune cell that is simultaneously activated on the one hand by a neurotransmitter, and on the other hand by any other stimuli. As discussed in this book, at least for some neurotransmitters/neuropeptides, there is also a big difference between the neurotransmitter-receptor subtypes being expressed in a resting/naïve immune cell vis-à-vis its activated

counterpart, and activation of an immune cell often causes a downregulation or upregulation of certain neurotransmitter-receptor subtypes. It is thus very important, whenever possible, to study the effects of neurotransmitters on both naïve/resting and activated immune cells. And it is also important to remember that what one observes in resting immune cells is not necessarily valid to activated cells, and *visa versa*.

4. *The specific immune cell subtype being exposed to the neurotransmitter.* There are many different types and subtypes of immune cells, each having its own characteristics and functions. As reported in this book, different immune cell types and subtypes often express a different composition of receptors for the same neurotransmitter/neuropeptides, and therefore respond differently to the very same neurotransmitter/neuropeptide. For example, it has been shown that dopamine at the very same concentration, induces very different effects in CD4<sup>+</sup> vis-à-vis CD8<sup>+</sup> T cells; in naïve CD45RA<sup>+</sup> vis-à-vis CD45RO<sup>+</sup> memory T cells, in Teffs vis-à-vis Tregs, and in resting/naïve vis-a-vis activated T cells.

All these parameters determine the exact effect of a given neurotransmitter on a specific immune function of a specific immune cell, and whether it will activate or rather suppress it. Without looking at these details, confusion, misinterpretation, and even contradictory data can be created, and no predication can be made as to how will a given neurotransmitter affect given immune responses of given immune cells.

## **Few Intriguing Broad Questions Raised by the Book and ‘Pleading’ to Be Studied, as Their Answers May Be Translated to Improved Understanding and Therapy of Various Human Diseases**

*Question 1:* It is true that immune cells and neuronal cells – which have so many different characteristics, missions and functions – also share much much more in common than we ever realized, especially in terms of the signaling molecules and transmitters they produce, secrete and use for “talking” to cells of other systems, and in the molecules they respond to via cell their surface receptors? The solid evidences covered by our book show we ought to add neurotransmitters and neuropeptides to the list of common molecules shared by neuronal cells and immune cells, and used by both cells for multi-level and multi-system communication. Another type of ‘communication molecules’ known already to be produced, secreted and used by both immune cells and neuronal cells are various types of cytokines.

*Question 2:* Can the neurotransmitters that are produced and secreted by immune cells (as shown in this book for most neurotransmitters), i.e. the immune-derived neurotransmitters, bind and affect neuronal cells, and by doing so contribute to the ongoing neuro-immuno cross talks taking place in physiological conditions and needed for maintaining health?

Can in fact the very same neurotransmitter serve for conveying information between four different sets of cellular counterparts: (1) from one neuronal cell to

another (or to the same neuronal cell that secreted it); (2) from a neuronal cell to an immune cell; (3) from an immune cell to a neuronal cell; (4) from one immune cell to another (or to the same immune cell that secreted it)?

The data discussed in the book suggest all these four communication paths might exist for at least some of the neurotransmitters/neuropeptides, but much more evidence is needed, especially for the use of neurotransmitters by certain immune to 'talk' to neuronal cells, as well as to other immune cells.

*Question 3:* Are there cases in which there is a defect (genetic or acquired) in the ability of immune cells to produce and secrete certain neurotransmitters? If so, is the abnormal secretion of neurotransmitters by immune cells 'felt' by neuronal cells, since they are normally dependent on, and beneficially-affected by, the immune-derived neurotransmitters?

And if this is true, can an abnormal secretion of immune-derived neurotransmitters contribute to impaired neurological function and thereby to various neurological/neuropsychiatric diseases?

*Question 4:* Can an abnormal secretion of neurotransmitters by neuronal cells lead to an abnormal immune function, since immune cells are normally dependent and beneficially-affected by such nerve-driven neurotransmitters? And if this is true, can an abnormal secretion of neurotransmitters by neuronal cells contribute to impaired immunological function and various immune/autoimmune/inflammatory/immunodeficiency diseases and/or immune malignancies: leukemia and lymphomas?

## **The Goals of the Book, the Hopes, the Fascinating Journey . . .**

The first main goal of this book is to increase the awareness of the scientific and medical communities to the key role played by neurotransmitters, neuropeptides and their receptors in the immune system, both in maintaining health, and in various immunological or neurological diseases. Currently, the receptors, effects and secretion of neurotransmitters in the immune system is to a large extent still unknown to the vast majority of immunologists, neurologists and other scientists and clinicians. It is our aim to stimulate further research and validating studies on this topic (which are so much needed), and to encourage collaborative multidisciplinary work on the various issues discussed in this book.

The second goal and hope is that the novel knowledge covered by the book would lead to the development of new therapies of various human diseases. Some specific pathways and recommendations how to reach such neurotransmitter-based therapies are discussed in several chapters of the book.

The third goal of the book stems from the fact that various neurotransmitters and/or their analogues are in medical use and commonly given to patients with various diseases. It is therefore our aim to draw the attention of clinicians that prescribe such

neurotransmitters analogues to the fact that such drugs most certainly influence immune cells too.

Thus, one may easily envision that once introduced into the body, the neurotransmitters-based drugs could bind immune cells migrating at all times in large numbers in the circulation and present in most body organs (including the brain) and affect them. If so, one can expect immune side effects which could be either positive or negative. It is therefore recommended that whenever a neurotransmitter-based drug is used, its immune effects will be studied and documented as much as possible. Doing so may even lead to modulation of the treatment, either to avoid negative immune side effects or to augment positive ones. And on top of all that, the immune side effects of the neurotransmitters-based drugs, be them as they may, should also be registered in the data sheets of the respective drugs, so that the patients taking such drugs would be fully aware of them.

The forth aim of the book is to hopefully solve what seem to be few inconsistencies and different conclusions reached in different publications regarding the effects of a given neurotransmitter/neuropeptide on a given immune cell population, or on the immune system in general. Also, sometimes, a neurotransmitter or neuropeptide is wrongly called “inhibitory” or “stimulatory”, but can in fact induce both opposing effects in different setups and context. The way to solve these discrepancies is once again to pay careful attention in each publication to the small details and to the factors that dictate the context, as specified above under ‘It’s a matter of context’. Often “the devil is in the details”...

## **Sailing Towards New Horizons . . .**

If allowed to end this introduction in a personal viewpoint (like I started it), and by using a metaphor, I would say that reading through our book may be looked at as a fascinating nautical sailing boat journey, in the ocean of science and medicine.

We sail along shores rich in stimulating phenomenon, and between mysterious islands yet to be discovered. On board of the boat are the skilled authors of the book, aside curious readers. The readers may include both scientists that share common interest and knowledge with the authors and contributed to the findings and concepts described in the book, and ‘outsiders’ in the field that may nevertheless become the followers, collaborators and even navigators of the future cruises.

During our sailing adventure in the sea of life science, more and more secrets are being revealed, new connections and associations are being made, old data is suddenly re-analyzed, some enigmatic issues are being shed with a new light, and many attractive treasures are unveiled from a distance on remote islands, and flagged as ones we wish to return to and explore.

All these trigger our curiosity, imagination and creativity. So Yes . . . even after we end the current journey, let’s continue sailing towards these new horizons . . . and let’s devote careful attention and quality time for carrying basic research expeditions

on the one hand, and pharmacological-clinical-therapeutic expeditions on the other hand . . . I foresee that our future cruises will be very interesting and rewarding . . . and I bet there is much more valuable knowledge hidden in these treasure-islands than currently meets our eyes . . .

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