

# Immunopharmacology 2011: an updated report of clinical achievements and perspectives

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## Immunopharmacology 2011 Varadero, Cuba, 26–30 June 2011

On 26–30 June 2011 the Cuban Society of Pharmacology organized the Second International Congress on Immunopharmacology (Immunopharmacology 2011), held at the beautiful Convention Centre 'Plaza América' and the Meliá Varadero Hotel, in Varadero beach, Cuba. The main topics of the congress were immunopharmacology (including inflammation, cancer immunotherapy and immunomodulation), neuroimmunology, and the pharmacology of cytochrome P450 and transporters, among other relevant and updated related topics. Immunopharmacology 2011 offered an outstanding scientific program with the active contribution of 90 speakers from 23 foreign countries, as well as more than 170 Cuban researchers from the most important local institutions devoted to the development of immunology and pharmacology sciences.

**KEYWORDS:** clinical results • cytochrome P450 • immunomodulation • immunopharmacology • neuroimmunology • transporters

### Novel targets in immunopharmacology

Outstanding clinical data were shown by Crombet *et al.* in castration-refractory prostate cancer patients, where safety and clinical activity of nimotuzumab (a humanized monoclonal antibody [mAb]) and an anti-EGF cancer vaccine were demonstrated along with chemotherapy [1]. The authors showed that the same mAb inhibited the signal transduction and the growth of hormone-refractory prostate cancer, and suggested that the consequent tumor cell apoptosis could enhance the effect of an EGF vaccine, giving promising results in a separate trial [1].

García *et al.* showed the feasibility of a trivalent recombinant single-chain fraction variable antibody fragment, specific to carcinoembryonic antigen, as a tool for molecular radiotherapy in patients with colorectal carcinoma [2]. Previous preclinical studies with radiolabeled CIGB-M3 had demonstrated that the antibody fragment accumulates in human colon tumor xenografts growing in nude mice. No adverse events related to the injected product were recorded, and no immunological response was detected up to 6 months after the injection. The pharmacokinetic profile was better fixed

to a bicompartamental model, with  $\beta$  half-life values of 14.1 and 6.3 h for groups I and II, respectively. After 72 h following the administration of the product, 85% of the total injected dose was detected in urine in the form of free <sup>131</sup>I. The kidneys were identified as the organs that can limit the maximum tolerated dose. The biodistribution and pharmacokinetic data suggested that the product can be tested further for molecular radiotherapy of carcinoembryonic antigen-positive tumors [2].

Concerning the CIGB-300 novel anticancer peptide, Perera *et al.* and Farina *et al.* presented a substantial amount of experimental data demonstrating that such a peptide inhibits the C kinase 2 protein-mediated phosphorylation of B23 at the nucleolus in tumor cells and exhibits antiangiogenic properties in endothelial cells *in vitro* and *in vivo*, respectively [3,4]. According to Perera's research, CIGB-300 exerts a broad antiproliferative effect on tumors cells. Such an effect is mediated by B23 binding and phosphorylation impairment, followed by subsequent fast apoptosis induction [3]. On the other hand, the results from Farina and colleagues were focused on the demonstration that CIGB-300 was able

to inhibit adhesion, migration and tubular network formation induced by human umbilical vein endothelial cells [4]. CIGB-300 significantly decreased four genes strongly associated with tubulogenesis, growth and differentiation of endothelial cells, and the mechanism of action may be associated with partial inhibition of VEGF and Notch pathways.

Other targets identified were related with cytokines and its receptors. Kalet León and colleagues (Centro de Inmunología Molecular, Havana, Cuba) presented a panel of IL-2 mutants that fall into two classes. The first group has normal agonistic activity for effector T cells but reduced stimulation of Tregs, while the second group is antagonistic with preference for Tregs. The potential of these molecules for cancer therapy was demonstrated by the suppression of transplanted tumors. Several papers detailed the signaling pathways, mechanisms and therapeutic effects of mAbs against receptors of the EGF receptor (EGFR) family (HER-1 to -4), which are overexpressed and support the growth of several types of cancer. Meanwhile, Yosef Yarden (Weizmann Institute, Rehovot, Israel) gave an overview of signaling networks of the EGFR family, including breast and ovarian carcinomas. Against these receptors, mAbs exhibited synergistic effects in clinical trials when used in combination, even when directed against different epitopes of the same receptor – for example, trastuzumab combined with pertuzumab for immunotherapy of breast cancer patients.

### Immunomodulation in cancer

Agustín Lage (Centro de Inmunología Molecular) gave a very informative overview of the bottleneck between proof-of-concept and the development of mAbs and vaccines for cancer therapy. He discussed the problem of suppression of the immune response by the tumor and the difficulties in identifying appropriate mAbs for cancer therapy. Four critical questions for cancer therapy were identified:

- What are the relevant targets?
- How does one achieve long-term remission?
- How does one deal with the problem of variation in the response of individual patients to therapy?
- What are the rules for combinations of different therapies? For example, combining two mAbs against different epitopes on the same molecule or against different target antigens, or combining different vaccines.

These are all serious problems yet to be solved [5].

Along the same lines, Fernandez and colleagues presented data describing two novel therapeutic anticancer antibodies specific to *N*-glycosylated ganglioside [6]. By mutational approach they demonstrated the role of the affinity for the cytotoxicity induced by anti-GM3 (Neu5Gc) antibodies and described a humanized antibody that is produced in mammalian cells and will soon be used for the treatment of cancer patients [6]. David I Stott (University of Strathclyde, Glasgow, UK) presented work on the intratumor, ectopic germinal center response in human breast cancer and studies on the vaccination of a transgenic mouse

model of breast cancer using an ErbB-2–tetanus toxin peptide fusion protein vaccine, causing complete abrogation of spontaneous tumor development. In a novel approach to cancer therapy, Luca Vangelista (San Raffaele Scientific Institute, Milan, Italy) attempted to fool the immune system into regarding a tumor as an invading parasite by coupling a mAb directed against a tumor-associated antigen to IgE. This triggered basophiles to degranulate and induced strong protection in a mouse tumor model. A recombinant vaccinia virus vaccine, incorporating truncated human IgE (Cε3 + Cε4), avoided the risk of anaphylactic shock. Meanwhile, Angus Dalglish (St George's Hospital, London, UK) addressed the question of why so many Phase III clinical trials were inconclusive after passing Phase II, giving examples from his own experiences with vaccines against melanoma, prostate and lung cancer. He ascribed the problem to poor adherence to design in large, multicenter trials and the inclusion of inappropriate patients. He also gave examples demonstrating that vaccines can enhance the effects of chemo- and radio-therapy.

### Advances in neuroimmunology

Hugo Besedovsky (Institute of Physiology and Pathophysiology, Marburg, Germany) spoke on the role of cytokines in the brain involved in interactions between the nervous and immune systems. He proposed that activation of the immune system against innocuous antigens can trigger a neuroendocrine response, which is normally controlled but can be unbalanced by infection. Animal experiments demonstrated that peripheral cytokines produced during an immune response induce secondary production of cytokines by astrocytes in the brain and a corticosteroid response, leading to strain-dependent, potentially fatal, TNF secretion. Similar effects were observed in several human autoimmune diseases, bacterial and viral infections, including pulmonary tuberculosis and Chagas disease. A network of interactions is involved, including the effects of cytokines on the hypothalamus, pituitary, adrenals, gonads and thymus.

Jack Antel (Department of Neurology and Neurosurgery, McGill University, Canada) reviewed the mechanisms of tissue injury and repair in multiple sclerosis. From his presentation, we learnt that multiple sclerosis follows a course of recurrent relapses, variable recovery and evolution into a more progressive phase. Therapeutic advances will require defining the biologic substrate underlying each of these. Hence, his presentation described the potential immune mechanisms activated within the inflamed CNS microenvironment that underlie initial tissue injury, considered the potential mechanisms that account for the recovery of function, and discussed the combined contributions of continued injury and failure of repair to disease progression [7–10].

Jose A Cabrera (Centro Internacional de Restauración Neurológica, Havana, Cuba) presented epidemiological data on neuromyelitis optica (NMO) in multiethnic populations. Seropositivity to NMO-IgG antibody demonstrated a lower rate in the Caribbean (33.3%), where more general attacks, more spinal attacks and a higher Expanded Disability Status Scale than NMO-IgG-negative cases were displayed, while brain and

spinal cord lesions were more frequent during remission, suggesting the influence of ethnic factors in conferring a worse course, greater disability and MRI lesions in this population [11]. Similarly, the contributions of Goncalvez *et al.* and Robinson *et al.* were focused on the extracellular S100 $\beta$ , a calcium-binding protein that is predominantly expressed and secreted by astrocytes in brain tissue, as a signal of astrocyte activation. They presented an overview on the current knowledge of S100B secretion, its putative role as a neurotrophic cytokine, inflammatory cytokine or alarmin, as well as the differential regulation of IgG-NMO anti-aquaporin 4 autoantibodies on this marker and the disability, at least in relapsing NMO patients [12,13].

### Pharmacology of cytochrome P450 & transporters

At the end of the congress, the role of biotransformation and excretion systems in herb–drug interaction systems and its relevance of the clinical practice were analyzed. The inhibition of the cytochrome P450 as an antimutagenesis mechanism, the metabolism studies using human hepatocytes in primary culture as novel methodologies, and data about modulations of P450 systems and transporters by natural products were presented. The

current evidence suggests that healthcare professionals and consumers should be aware of the potential for adverse interactions with the herbs. The patients must be asked about the use of herbs, especially those whose disease is not responding to treatments as expected [14,15].

In addition, pharmacogenetic data about CYP2D6 and its clinical implication for antidepressant treatment and suicide in Latin–American populations were presented. The potential use of pharmacogenetic data in cardiovascular diseases was also analyzed. Pharmacogenomics helps identify interindividual variability in drug response, considering both toxicity and efficacy. This information will make it possible to individualize therapy with the purpose of maximizing effectiveness and minimizing risk [16].

### Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents.*

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