Biotecnología Habana 2012 congress: Infectious Diseases symposium and satellite symposia on HIV and Dengue

REPORT

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ABSTRACT

The congress Biotecnología Habana 2012 was held at the Convention Center in Havana, Cuba, March 5-8. Organized by the Center for Genetic Engineering and Biotechnology (CIGB), this edition was dedicated to medical applications of biotechnology, with pre-Congress specialized satellite symposia and full conference sessions. Here we present information regarding the symposium on Infectious diseases (covering pertussis, adjuvants, hepatitis B and C treatment and vaccines) and also that related to two of the three pre-congress satellite symposia on dengue and the human immunodeficiency virus.

Keywords: Biotecnología Habana 2012, infectious diseases, pertussis, adjuvant, hepatitis B, hepatitis C, HIV, dengue

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RESUMEN

Congreso Biotecnología Habana 2012: Simposio de enfermedades infecciosas y simposios satélites sobre VIH y Dengue. El congreso Biotecnología Habana 2012 se celebró del 5 al 8 de marzo en La Habana, Cuba. Auspiciado por el Centro de Ingeniería Genética y Biotecnología (CIGB), esta edición se dedicó a las aplicaciones médicas de la biotecnología, con simposios satélites precongreso y conferencias plenarias. Este reporte expone información del simposio sobre enfermedades infecciosas (que incluyó temáticas relativas a pertusis, adyuvantes, vacunas y tratamiento de las hepatitis virales B y C), y dos de los simposios satélites precongreso referidos a dengue y virus de la inmunodeficiencia humana.

Palabras clave: Biotecnología Habana 2012, enfermedades infecciosas, pertusis, adyuvante, hepatitis B, hepatitis C, VIH, dengue

*I*ntroduction

The Infectious Diseases Symposium of the Biotecnología Habana 2012, held in Havana last 5-8 March and dedicated to medical applications of biotechnology, was comprised of three sessions: Pertussis and adjuvants, and hepatitis B and C. In addition, two satellite symposia about topics related to infectious diseases were celebrated: one devoted to the human immunodeficiency virus (HIV) and the other to dengue. Here we synthesize the lectures and debates in different sessions.

*P*ertussis and adjuvants

This session consisted of six lectures and short oral presentations during the morning of March 6, 2012. Prof. Camille Locht (France), one of the chairmen, delivered the lecture *Nasal vaccination with live attenuated* Bordetella pertussis *against pertussis and other respiratory illnesses*. He presented data about live attenuated *B. pertussis* vaccine strain, named BPZE1, that produces a genetically inactivated pertussis toxin. Pre-clinical studies have been carried out with this vaccine strain and Phase I clinical trial is currently ongoing. BPZE1 properties make it a promising and safe vaccine candidate to protect against pertussis and other respiratory infections by needle-free nasal administration. Dr. Verena Muzio (Cuba) delivered a talk entitled *Cuban pentavalent vaccines for the prevention of infectious diseases*. Results from clinical evaluation of the Cuban pentavalent vaccine and particularly, data on immune responses to *B. pertussis* were discussed. On the other hand, Dr. Gerardo Guillén (Cuba), the other chairperson, presented the speech *Virus-like particle-based adjuvants*. He showed results related to the use of VLPs for inducing immune response against the hepatitis B and C, dengue and human immunodeficiency viruses, and also, advantages of this approach were discussed. Particularly, VLPs were shown as very immunogenic and contributing to the immunogenicity of co-administered antigens.

Later on, the session was focused on adjuvants and delivery vehicles. Prof. Abdelwahab Omri (Canada) talked about *Liposomes drug delivery systems: Potentialities and limitations in infectious diseases applications*. Development of a modified dehydration/rehydration technique to produce small but stable vesicles with high yield drug entrapment was described. Encapsulation of aminoglycoside antibiotics into these liposomes significantly increased the antibacterial activity of these agents against strains of *Pseudomonas aeruginosa*. Liposome-entrapped antibiotics could overcome the drug resistance phenomenon associated with bacterial outer-membrane permeability. The lecture *Shooting to some immunological paradigms using potent adjuvants* was presented by Dr. Oliver Pérez (Cuba). Different elements regarding the adjuvants' potential mechanism of action were discussed. On the other hand, Dr. Fernando Goldbaum (Argentina) talked about *The BLS platform as a tool for the development of prophylactic and therapeutic vaccines*. He presented data about the use of the *Brucella* spp. lumazine synthase (BLS) platform

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as adjuvant, which could be potentially useful for enhancing the immune response against different vaccine candidates.

Hepatitis C

This session took place on March 7th, 2012 and the program included eight lectures. Prof. Jean Dubuisson (France) and Dr. Santiago Dueñas-Carrera (Cuba) acted as chairmen. Precisely, Prof. Jean Dubuisson talked about *Targeting hepatitis C virus entry for the development of new antiviral molecules*. He described that epidermal growth factor receptor and ephrin receptor A2 act as host cofactors for hepatitis C virus (HCV) entry by regulating Claudin1-CD81 co-receptor association. Some data regarding the characterization of Griffithsin, a lectin from a red alga, which specifically binds N-linked high mannose oligosaccharides that are present on the viral envelope, as well as epigallocatechin-3-gallate, a flavonoid present in green tea extract, which belongs to the subclass of catechins, was presented. These two molecules affect HCV by targeting an early step in the entry process. On the other hand, Dr. Daniel Lamarre (Canada) presented the speech *Novel classes of HCV-specific inhibitors targeting membrane protein-protein interactions*. Particularly, he showed the development of a drug discovery platform based on membrane protein-protein interactions in live cell assays. Later on, Dr. Naglaa Shoukry (Canada) delivered the lecture *Innate and Adaptive Immune responses during Acute HCV Infection*. She discussed recent findings examining the role of natural killer cells and the cross-talk between innate and adaptive immunity during acute HCV infection. In addition, data on how the quality of HCV-specific T cells measured by the number of functions expressed (polyfunctionality) could be predictive of the outcome of HCV infection and enhanced response to therapy, was analyzed. She also presented some new unpublished results about the role of CD4+ T cell help and the pattern of cytokines they produce to preserve and rescue virus-specific CD8+ T cells and how helper cytokines could be used to modulate the outcome of HCV infection. Afterwards, Dr. Arwind Patel (United Kingdom) talked about *Virus-host interactions in hepatitis C virus infection*. He showed that HCV core sequesters DDX3, the DEAD box helicase 3, to the virus assembly site around lipid droplet, although this interaction seems to be dispensable for viral replication. Multiple roles of DDX3 in HCV life cycle were discussed.

Moreover, during this session Dr. Marlen Castellanos (Cuba) presented the characterization of a Cuban HCV-infected patient population with respect to epidemiological, virological and histological aspects. In addition, Dr. Santiago Dueñas-Carrera presented the lecture *Therapeutic vaccination against HCV: important or irrelevant in the antiviral era?* Several questions around the opportunities and challenges of therapeutic vaccination against HCV infection were discussed. Recent results on the clinical evaluation of CIGB-230 vaccine candidate in a Phase II clinical trial were analyzed and evidenced immunogenicity and contribution to treatment outcome in early concomitant administration of CIGB-230 with IFN plus Ribavirin. Furthermore, Dr. Gillian Martínez-Donato (Cuba) delivered a talk entitled *A vaccine candidate containing HCV structural proteins and NS3 induces neutralizing antibodies and multi-specific cellular immune response in animal models*. She presented data on the immunogenicity of a preparation based on Core, E1, E2 and NS3 in mice and monkeys. This preparation induced both humoral and cellular immune responses against the targeted HCV antigens. Finally, Dr. Maria Isaguliants (Sweden) presented the lecture *In vivo monitoring of immune response in preclinical trials of genetic vaccines*. She described an *in vivo* imaging technique that records the expression of gene-encoded immunogens based on co-localizing by the administration methods used their expression vectors together with plasmids coding for bioluminescent reporters genes. She showed data on immune clearance of expressing cells after immunization with DNA vaccines encoding wild-type and drug resistant enzymes of HIV-1 and the nucleocapsid protein of HCV.

Hepatitis B

This session was carried out during the morning of March 8th, 2012. Prof. Marie-Louise Michel (France) and Eduardo Pentón (Cuba) were the chairpersons. First, Prof. Marie-Louise Mitchel made the introductory remarks of the session, on the main challenges and most relevant aspects in the field, some of which were later discussed in the five lectures delivered. Prof. Christian Trepo (France) presented the talk *Relevance of occult HBV infection (OBI)*. The occult hepatitis B virus (HBV) infection is characterized by the absence of hepatitis B surface antigen in the serum and the presence of detectable levels of viral DNA in the liver and the circulation, and has risk for the patient and importance from an epidemiological point of view. The presence of antibodies against hepatitis B core antigen could be used as a surrogate marker of OBI since it is observed in 80% of cases. The patients with OBI develop severe complications like cirrhosis and hepatocellular carcinoma with higher probability. High prevalence of OBI is detected in HBV-HCV co-infected patients, which is related to a reduced response to treatment in this group. Nowadays, the causes making HBV infection to evolve into OBI remain unknown. Dr. Trepo considered the eradication of HBV infection as a very difficult task.

Among the most expected lectures was the one delivered by Dr. Gerardo Guillén (Cuba), replacing Dr. Mamum Al-Mahtab (Bangladesh) who could not attend the meeting but send the presentation *Clinical experience with NASVAC in bangladeshi patients*. In this work, results from a Phase I/II (concluded) and Phase III (ongoing) clinical trials, both in Bangladesh, were presented. Results of the Phase I/II clinical trial indicated that the NASVAC nasal vaccine candidate is safe and induces an effective response in HBV chronic patients, evidenced by the reduction of viral DNA load, non-detectable in 50% of patients for up to a one-year follow-up after vaccination. Moreover, normalization of liver enzymes was observed in all the patients treated. These results are really encouraging, the same as those preliminary described for the Phase III clinical trial vaccination with NASVAC, which is comparable to administering pegylated-interferon. The Phase III study is in the follow-up period. The

presentation of this work provided great interest and several inquiries from experts who asked for results related to aspects of the immune response elicited by the vaccine, some of which are under evaluation and samples being processed.

Dr. Ruksana Raihan (Bangladesh) shared data on detection of the hepatitis B core antigen in liver cells of HBV chronic patients in Bangladesh and Prof. Vittorio Colizzi (Italy) presented the results about the development of a combined HBV-BCG vaccine and their use in African children. This work has being carried out with support from the Center for Genetic Engineering and Biotechnology (Cuba), the institution producing the vaccine HBsAg component. Finally, Dr. Yasmin Thanavala (USA) stated the results of the HBsAg expression in potato plants, as a strategy to develop an oral vaccine. Modest results have been obtained with this approach, already evaluated in a Phase I clinical trial in the USA, employing this formulation as booster in previously vaccinated individuals. Currently, a second clinical trial is under revision for approval. Dr. Thanavala stated that in USA, despite the availability of prophylactic vaccines, the prevalence of HBV infection has not decreased.

HIV satellite symposium

Six lectures were presented in this symposium. Dr. Surita Roux (South Africa) showed the design of the STEP study, commented the reasons for stopping this trial and speculated on the probable causes of failure although she clarified that nothing was confirmed yet. She also explained the design of the Phambili study, that being an extension STEP study was also stopped, in this case at the recruitment stage. She also discussed, as a future possibility, the adaptive design for clinical trials in order to accelerate the efficacy results. However, she made clear that South Africa does not accept this type of study yet. On the other hand, Dr. Enrique Iglesias (Cuba) presented the main results obtained in mice supporting the development of the Teravac vaccine candidate against HIV-1, based on a multiantigenic formulation. It was shown that the simultaneous nasal-subcutaneous inoculation of Teravac induced Th1 cellular immune responses in both the systemic and gastrointestinal tract compartments. In addition, antibodies against viral proteins such as the envelope and Nef were generated in serum, which could have certain relevance to interfere the toxic effects of both viral antigens. Moreover, humoral immune response in vagina was verified. Also in this session, Dr. Luis E Fernández (Cuba) reported partial results of a Phase II clinical trial of an adjuvant therapy in HIV patients, still in course in Argentina. This study is based on the use of the very small size proteoliposomes combined with the GM3 ganglioside (VSSP-GM3) as adjuvant therapy. VSSP-GM3 has been previously developed as a vaccine against cancer and stimulates mainly the CD4+ T cell population. Experiments in a transgenic mouse model also suggested the possible effect of VSSP-GM3 for restoration of the antigen-presenting cells population. It was notorious that these two last strategies are trying to circumvent the deficiency of antigen presenting cells in HIV infection either by recruiting non-professional antigen-presenting cells (B cells in the case of Teravac) or, otherwise, by rescuing conventional antigen-presenting cells from the deleterious fate caused by the virus.

In the afternoon session, Dr. Luis Menéndez-Arias (Spain) reviewed current knowledge about mutations conferring resistance to reverse-transcriptase inhibitors. Dr. Vivian Kourí (Cuba) spoke about the evolution of the Cuban HIV epidemic with respect to the distribution of HIV isolates belonging to different viral subtypes and recombinant forms. The subtype B was and still is the predominant subtype in the Cuban HIV epidemic, and an increase in recombinant forms is observed and continuously growing. During the time, Dr. Kourí also showed retrospective studies on resistance to antiviral compounds among Cuban HIV patients. The data evidenced a tendency to an increase in mutations conferring resistance to antiretrovirals in use. Finally, Dr. Jorge Pérez (Cuba), Director of the Institute of Tropical Medicine Pedro Kourí, made an update in the number of cases and deaths by AIDS in Cuba. He explained that all Cuban patients requiring anti-retroviral therapy receive treatment with generic antiretroviral compounds produced in our country free of charge.

Dengue satellite symposium

The Dengue satellite symposium took place on the morning of March 5, 2012. Three speakers and ten delegates from different countries attended the symposium together with Cuban delegates. Dr. Mabel Carabali (Colombia) and Dr. Lisset Hermida (Cuba) acted as chairpersons. In the first part of the symposium Dr. Glay Chinea (Cuba) and Dr. Vivian Huerta (Cuba) exposed basic research about structural aspects of the dengue virus. Specifically the two presentations were focused on the DomIII region of the envelope protein of the virus and its potential role in the interaction with receptors. The second important topic dealt with the epidemiological data on dengue in Cuba in the last 25 years. Prof. Guadalupe Guzmán (Cuba) explained in detail the most important findings based on the clinical data and the immune pathogenesis research. Basically, she pointed out the secondary infection as the main risk factor to develop the most severe form of the disease.

The second part of the symposium was directed towards Dengue vaccine research. Firstly, Dr. Mabel Carabali (Colombia) presented the main objectives of the Dengue vaccine initiative and its role to improve the vaccine introduction in developing countries. In the following, Dr. Gerardo Guillén reviewed the state of the art on dengue subunit vaccines, emphasizing the most significant advantages of this approach. On the other hand, Dr Laura Lazo explained one of the strategies of the Cuban dengue vaccine program based on the recombinant P64k-dengue proteins. Particularly, she described the successful results obtained in monkeys with serotypes 1 and 2 as well as preclinical data upon mice immunization with a tetravalent formulation. Later on Dr. Samantha Brandler (France), from the Pasteur Institute, Paris, discussed their results in mice with the attenuated vaccine candidate Measles-dengue and its potential use in heterologous prime/boost regimes combining it with the P64k-dengue proteins developed at CIGB. The combination of both types of candidates, as tetravalent

formulations, notably improved the neutralizing antibody response against the four serotypes. Finally, to end the vaccine topic, Dr. Lisset Hermida (Cuba) discussed the other strategy of the Cuban program: a subunit vaccine containing dengue capsid-based proteins. Particularly, she discussed preclinical data from mice and monkeys vaccinated with the serotype 2 candidate, showing evidences about both, the protective capacity of the DomIII-capsid protein (serotype 2) in mice and the boost effect, measured by neutralization test, in monkeys previously infected with the dengue-2 virus.

The third part of the symposium was directed to animal models for dengue vaccine testing. In this sense, Dr. Lazaro Gil (Cuba) presented all the work performed by the Cuban group to establish vervets and baboons monkeys as suitable models for testing dengue vaccines. At the end, Dr. Roger Le Grand (France), from the French Atomic Alternative Energies and Atomic Energy Commission, Paris, also discussed their results on the *Macaca* specie to test a vaccine candidate against Chikungunya virus.

Conclusions

The Infectious disease symposium and the satellite symposia on HIV and Dengue created high expectations among delegates and the press attending the meeting. High level lectures motivated scientific discussions on several hot topics, relevant for the future treatment of diseases caused by the pathogens under scrutiny. Different actions are expected to be derived from this fruitful scientific debate.