

## Cuban Research in Current International Journals

The following selection—alphabetical by title—reflects Cuban medical publishing in international journals over the last quarter on an array of topics. Links to these journal articles may be found at [www.medicc.org/mediccreview](http://www.medicc.org/mediccreview).

**Anti-HIV-1 and Anti-HBV Immune Responses in Mice After Parenteral and Nasal Co-Administration of a Multiantigenic Formulation.** Iglesias E, García D, Carrazana Y, Aguilar JC, Sánchez A, Gorobaya L, et al. *Current HIV Research*. 2008 Sept;6(5):452-460.

The cell-mediated immune response to HIV-1 is an essential element of the mechanisms for viral replication control. Currently, most of the vaccine candidates in clinical trials were developed to stimulate HIV-1-specific CD8+ cytotoxic (CTL) and CD4+ T helper (Th) lymphocytes. We have been working on a novel approach to develop a vaccine formulation for HIV-1 using a recombinant multiepitopic protein (named CR3), which comprises CTL and Th epitope-rich regions of HIV-1 from several subtype B isolates, co-inoculated with the hepatitis B virus surface (HBsAg) and core (HBcAg) antigens of the hepatitis B virus (HBV) as adjuvant. According to our studies in mice, the nasal-subcutaneous co-administration of this multiantigenic formulation induces a strong Th1-biased specific response against CR3, CD8+ T cells in mice spleen and IFN- $\gamma$ -secreting cells in mesenteric lymph nodes. Cross-reactive p24-specific IFN- $\gamma$ -secreting cells in spleen were also detected. Moreover, Nef-specific antibodies were elicited in mice sera which might avoid the toxic effects of this antigen. However, a marginal anti-CR3 antibody response was elicited in vaginal mucosa. Additionally, we observed anti-HBsAg and anti-HBcAg cellular and humoral responses. In this regard, our multiantigenic formulation might provide immunity against HBV as an additional benefit considering the high HIV-1-HBV co-infection rate reported worldwide.

**Can We Reduce the Number of Low-Birth-Weight Babies? The Cuban Experience.** López NB, Choonara I. *Neonatology*. 2008 Sep 18;95(3):193-197.

Low-birth-weight (LBW) infants have a significantly greater mortality than other babies, not only within the neonatal period but also in infancy and early childhood. Babies are LBW either because they are preterm or they have experienced intrauterine growth retardation. Reducing the prevalence of LBW babies is important in reducing child and infant mortality. Risk factors for prematurity and intrauterine growth retardation are well established. Socioeconomic conditions and nutrition during pregnancy are two key factors. Interventions to reduce the prevalence of LBW infants in developed countries have usually been unsuccessful. A few studies in developing countries have, however, achieved

positive results. Cuba has managed to reduce the prevalence of LBW infants and their model of healthcare in relation to achieving this is described. Key features of the Cuban healthcare system are that it is both free and universal, and additionally there is a strong emphasis on primary healthcare. It is likely that a similar approach in both developing countries and disadvantaged communities in developed countries would reduce the prevalence of LBW babies. This would have a major impact in relation to reducing infant mortality rates.

**Diagnostic validity of an expert tuberculosis commission that assists the diagnosis of bacteriologically negative suspected TB cases in Havana, Cuba.** Matthys F, Peralta Pérez M, Valdés Díaz S, García Silvera E, Crespo Díaz T, Armas Pérez L, et al. *Trans R Soc Trop Med Hyg*. 2008. Epub ahead of print.

The Provincial Tuberculosis Commission of Havana, Cuba, a multi-specialty committee, assists clinicians in diagnosing bacteriologically negative tuberculosis (TB). At its weekly meetings, clinicians present the files of suspected TB cases for discussion, diagnosis and recommendations. This prospective study assessed the validity of the diagnoses made by the Commission by comparing the diagnoses made with diagnoses ascertained after one year of follow-up. Between October 2002 and December 2003, 126 patients suspected to have TB but who were bacteriologically negative completed diagnostic work at the Commission. Fifty-three (42%) were diagnosed as TB cases. The definite diagnosis of 116 patients (92%) was ascertained after one year of follow-up. Six patients diagnosed by the Commission as TB cases were suffering from other diseases, while one patient diagnosed with pneumonia had a definite diagnosis of pulmonary TB. The diagnostic sensitivity and specificity of the Commission were 98% (95% CI 93-100) and 92% (95% CI 85-98), respectively. The Provincial Tuberculosis Commission of Havana can be considered a valuable tool for the diagnosis of TB in patients suspected of TB but who are bacteriologically negative. A comparable approach, adapted to the local conditions, could prove useful in other epidemiological and healthcare settings.

**Effect of dolomite oral exposure in Wistar rats during organogenesis period of pregnancy.** Lagarto A, Bellma A, Tillán J, Gabilondo T, Guerra I, Ocanto Z, et al. *Exp Toxicol Pathol*. 2008 Oct;60(6):499-504.

The potential of oral exposure to dolomite, a natural product that contains calcium and magnesium, to initiate teratogenesis was analyzed in Wistar rats. Animals received dolomite oral dosages of 500 and 1500mg/kg during the period of gestation from day 6-15 post conceptionem (p.c.). Maternal, embryo and fetal toxicity were evaluated. Dolomite exposure did not produce maternal toxicity assessed by clinical observations, body weight gain, hematology parameters and relative organs weight. Signs of embryo-fetal toxicity were not observed. Skeletal malformations and visceral variations were similar in control and dolomite-treated groups. On the other hand, slight increase was observed in fetal body weight in the dolomite-treated group. Treatment with dolomite resulted in significantly decreased incidences of unossified xiphisternum, incomplete ossification of xiphisternum and sternbrae. These effects could be caused by a beneficial influence of calcium and magnesium salts present in dolomite on ossification process. In conclusion, in this study we found that the oral exposure to rats of up to 1500mg/kg of dolomite during organogenesis did not induce significant maternal and embryo-fetal toxicity.

**Effect of Yoga and Traditional Physical Exercise on Hormones and Percentage Insulin Binding Receptor in Patients with Type 2 Diabetes.** Gordon L, York Morrison E, McGrowder D, Fraser Y, Martorell E, Garwood D, et al. *Am J Biochem & Biotech*. 2008;4(1):35-42.

The objective of the study was to investigate the short-term impact of a brief lifestyle intervention of yoga and traditional Physical Training (PT) exercise regimens on: serum insulin percentage insulin binding receptor, internalization of insulin-receptor complex, T3, T4, TSH and cortisol at baseline, 3 months and 6 months in patients with type 2 diabetes mellitus. A total of 231 patients completed this prospective randomized study with 77 type 2 diabetic patients in the yoga group (62 females and 15 males) that were matched with the same number of patients in the traditional Physical Training (PT) exercise and control groups. Biochemical parameters such as fasting Blood Glucose (FBG), serum insulin, percentage insulin binding receptor and internalization of insulin-receptor complex were determined at the beginning (baseline) and two consecutive three monthly intervals. The effect of the lifestyle interventions on hormones such as cortisol, TSH, T4 and T3 were also investigated. The FBG concentration in the yoga and the traditional PT exercise groups were markedly decreased compared with control ( $P < 0.05$ ). The percentage of insulin

binding receptor increased in the yoga and traditional PT exercise groups at the sixth month when compared to baseline and this parameter in the traditional PT exercise group differs significantly from that of the control group at the six month ( $P = 0.024$ ). There was no significant difference in the percentage of internalization of the insulin receptor complex amongst the three groups ( $P = 0.465$ ). There was no significant change in T3, T4, TSH or cortisol in any of the three groups over the six month period ( $P > 0.05$ ). The findings indicates the beneficial effects of yoga and traditional PT exercise regimens in improving glycaemic control by increasing percentage insulin binding receptor in type 2 diabetic patients with no significant change in cortisol and thyroid hormones.

**Factors associated with impaired quality of life in younger and older adults with epilepsy.** Canuet L, Iwase M, Ikezawa K, Kurimoto R, Azechi M, Takahashi H, et al. *Epilepsy Res.* 2008 Oct 29. Epub ahead of print.

The purpose of this study is to weigh psychological state, patients' demographics, seizure-related factors, and medical comorbidity in older adults with epilepsy against the same parameters in younger adults in an attempt to identify best quality of life (QoL) predictors. The Quality of Life in Epilepsy Inventory for Adults (QOLIE-31) and the Beck Depression Inventory-II (BDI-II) were completed by 146 patients with localization-related epilepsy. There was no statistical difference in the QOLIE-31 total score between younger and older adults. Best QoL predictors were BDI-II and seizure frequency, with BDI-II providing more than 3 times the impact of seizure frequency. BDI-II also substantively predicted most QOLIE-31 domains. Additionally, epilepsy duration positively correlated with overall QoL only among older adults. In summary, in younger as well as older adult epilepsy patients, depressive symptoms emerge as the strongest predictor of QoL. However, older adults appear to adapt better to their chronic health problem.

**First report on fatal myocarditis associated with adenovirus infection in Cuba.** Valdés O, Acosta B, Piñón A, Savón C, Goyenechea A, González G, et al. *J Med Virol.* 2008 Oct;80(10):1756-61.

Myocarditis is caused frequently by viral infections of the myocardium. In the past, enteroviruses (EV) were considered the most common cause of myocarditis in all age groups. Other viruses that cause myocarditis are adenovirus and influenza viruses. Parvovirus B19 infection is associated sometimes with myocarditis. Members of the Herpesviridae family, cytomegalovirus (CMV), and human herpesvirus 6 (HHV-6) have been associated occasionally with myocarditis. During an atypical outbreak of acute febrile syndrome, eight children, with ages from 5 months to 15 years, died in cardio-

genic shock due to myocarditis in July-August 2005, in the city of Havana, Cuba. Nested polymerase chain reaction (nPCR) and nested reverse transcription-PCR (nRT-PCR) were carried out on fresh heart muscle and lung tissue to analyze the genomic sequences of adenovirus, CMV, HHV-6, herpes simplex virus, Epstein-Barr virus (EBV), varizella zoster virus, influenza virus A, B, C, respiratory syncytial virus (RSV) A and B, parainfluenza viruses, rhinoviruses, coronavirus, flaviruses and enteroviruses. Evidence was for the presence of the adenovirus genome in 6 (75%) of the children. Phylogenetic analyses of a conserved hexon gene fragment in four cases showed serotype 5 as the causal agent. No others viruses were detected. Histological examination was undertaken to detect myocardial inflammation. After exclusion of other possible causes of death, the results indicated that viral myocarditis was the cause of death in patients with adenovirus infection.

**Immunization with a recombinant fowlpox virus expressing a hepatitis C virus core-E1 polyprotein variant, protects mice and African green monkeys (*Chlorocebus aethiops sabaues*) against challenge with a surrogate vaccinia virus.** Álvarez-Lajonchere L, Amador-Cañizares Y, Frías R, Milian Y, Musacchio A, Guerra I, et al. *Biotechnol Appl Biochem.* 2008 Oct;51(Pt 2):97-105.

HCV (hepatitis C virus) is a worldwide health problem nowadays. No preventive vaccine is available against this pathogen, and therapeutic treatments currently in use have important drawbacks, including limited efficacy. In the present work a recombinant fowlpox virus, FPCoE1, expressing a truncated HCV core-E1 polyprotein, was generated. FPCoE1 virus generally failed to elicit a humoral immune response against HCV antigens in BALB/c mice. By contrast, mice inoculated with FPCoE1 elicited a positive interferon-gamma secretion response against HCV core in ex-vivo ELISPOT (enzyme-linked immunospot) assays. Remarkably, mice inoculated with FPCoE1 significantly controlled viraemia in a surrogate challenge model with vvRE, a recombinant vaccinia virus expressing HCV structural antigens. In fact, 40% of the mice had no detectable levels of vvRE in their ovaries. Administration of FPCoE1 in vervet monkeys [*Chlorocebus* (formerly *Cercopithecus*) *aethiops sabaues*] induced lymphoproliferative response against HCV core and E1 proteins in 50% of immunized animals. Monkeys immunized with FPCoE1 had no detectable levels of vvRE in their blood, whereas monkeys inoculated with FP9, the negative control virus, had detectable levels of vvRE in blood up to 7 days after challenge. In conclusion, recombinant fowlpox virus FPCoE1 is able to induce an anti-HCV immune response in mice and monkeys. This ability could be rationally employed to develop effective strategies against HCV infection by using FPCoE1 in combination with other vaccine candidates or antiviral treatments.

**Multidimensional Problems Among Advanced Cancer Patients in Cuba: Awareness of Diagnosis Is Associated with Better Patient Status.** Roll IJ, Simms V, Harding R, Dip SW. *J Pain Symptom Manage.* 2008 Oct;36(4):335-450.

Cancer is one of the major causes of death in Cuba, and in current practice, patients are not usually informed of their diagnosis. Palliative care is an emerging discipline in this country. Cuban cancer patients with advanced disease completed the Palliative Outcome Scale (POS), and the researcher elicited patient knowledge of their condition and prognosis. The POS consists of 12 items that address the clinical, psychosocial, spiritual, family, and service delivery elements considered relevant to patients with advanced disease. Ten items are scored 0 (no problem) to 4 (worst problem), with one open-response question about the main problems experienced and one question about whether the questionnaire was completed with help or alone. Mann-Whitney tests were used to compare POS item scores by patient awareness. Of the 91 patients who participated in the study, 41% knew they had cancer and 9% were believed to be aware that they were dying. The most burdensome problems recorded on the POS were wasted time on appointments (70% of patients scored 3 or 4), pain (42%), patient anxiety (39%), and family anxiety (37%). Those patients who were aware of their diagnosis had statistically significantly better scores with respect to symptoms, patient anxiety, receiving information, and receiving support from family and friends. This study adds to knowledge about characteristics of terminal cancer patients in Cuba and the factors contributing to patient burden. It is the first study to explore the palliative care needs of Cuban patients with advanced cancer. An association has been demonstrated between patient knowledge and quality of life in Cuba, a setting where disclosure is contrary to current clinical practice.

**Neutralizing antibody response variation against dengue 3 strains.** Álvarez M, Pavón OA, Rodríguez-Roche R, Bernardo L, Morier L, Sánchez L, et al. *J Med Virol.* 2008 Oct;80(10):1783-9.

To evaluate the neutralizing antibody activity of a human sera panel against seven strains of the homotypic virus. Sera were collected from DENV-3 immune individuals. Two DENV-3 genotypes and strains isolated at different time-points during the 2000 and 2001-2002 Havana epidemics were included. A panel of 20 late convalescent sera collected 16-18 months after acute illness from DF and DHF patients are studied. These individuals were infected during the 2001-2002 Havana DENV-3 epidemic. All but four sera collected from DF cases had a secondary DENV-1/DENV-3 infection. Sera neutralizing antibody titer against the seven DENV-3 strains were determined by plaque

reduction neutralization technique. Sera samples were tested simultaneously. Studied sera showed higher levels of neutralizing antibodies to DENV-3 strains of genotype III compared to genotype V. Interesting, higher levels of neutralizing antibodies were detected to DENV-3 strain isolated at the end of the epidemic 2001-2002. An increased tendency of GMT of neutralizing antibodies according to epidemic evolution was observed for the 2001-2002 outbreak. In general, antibody levels in sera collected from DF cases were higher. Differences in the neutralization capacity of immune DENV-3 sera tested against two homologous genotypes including strains of the same genotype are demonstrated. Observed results suggest that virus changed in the course of the epidemic. The implications of this finding in terms of dengue pathogenesis and vaccine development need to be considered.


**New Flavonoids from *Boldoa purpurascens* Cav.** Mosquera DM, Kilonda A, Toppet S, Compernelle F, Dehaen W, François IE, et al. *Planta Med.* 2008 Oct;74(12):1468-73. Epub 2008 Aug 14.

Phytochemical analysis of the leaves of *BOLD-OA PURPURASCENS* Cav. led to isolation of four flavone glycosides, three of which are

new compounds. Their structures have been determined by mass spectrometry and by 1D and 2D NMR analysis, i. e., 4',5-dihydroxy-6,7-methylenedioxyflavonol 3-O-alpha-L-rhamnopyranosyl-(1-->2)-beta-D-xylopyranoside (1), 4',5-dihydroxy-6,7-methylenedioxyflavonol 3-O-beta-D-xylopyranoside (2), and 4',5-dihydroxy-6,7-methylenedioxyflavonol 3-O-alpha-L-rhamnopyranosyl-(1-->2)-beta-D-glucopyranoside (3). The known compound was 4',5-dihydroxy-6,7-methylenedioxyflavonol 3-O-beta-D-glucopyranoside (4). The aglycone 4',5-dihydroxy-7-methylenedioxyflavonol is known as gomprenol. Compounds 1 and 2 failed to show antifungal activity when tested against three different strains of fungi, i.e., *FUSARIUM CULMORUM*, *BOTRYTIS CINEREA*, and *ASPERGILLUS FLAVUS*.

**The Prevalence, Correlates and Impact of Dementia in Cuba. A 10/66 Group Population-Based Survey.** Llibre Rodríguez J, Valhuerdi A, Sánchez II, Reyna C, Guerra MA, Copeland JR, et al. *Neuroepidemiology.* 2008 Oct 20;31(4):243-251.

**Background** We aimed to estimate the prevalence, correlates and impact of dementia in Ha-

vana and Matanzas, Cuba. **Methods** A 1-phase catchment area survey of all over 65-year-old residents of 7 catchment areas in Havana and 1 in Matanzas was conducted. Dementia diagnosis was established according to DSM-IV and our own, pre-validated 10/66 criteria. The impact of dementia was assessed through associations with needs for care, cutting back on work to care and caregiver psychological morbidity. **Results** We interviewed 2,944 older people, a response proportion of 96.4%. The prevalence of DSM-IV dementia was 6.4% and that of 10/66 dementia 10.8%. Both dementia outcomes were associated with older age, less education, a family history of dementia, shorter leg length and smaller skull circumference. Dementia, rather than physical health problems or depression, was the main contributor to needs for care (population-attributable prevalence fraction = 64.6%) and caregiver cutting back on work (population-attributable prevalence fraction = 57.3%). **Conclusion** The prevalence of dementia in Cuba is similar to Europe. Among health conditions, dementia is the major contributor to dependency and caregiver economic and psychological strain. More attention needs to be given to it and other chronic diseases associated more with disability than premature mortality. 

## Erratum

Neusy, AJ, Palsdottir, B. A Roundtable of Innovative Leaders in Medical Education. *MEDICC Review.* 2008;10(4):20-24.

The correct website for the Ateneo de Zamboanga University School of Medicine in the Philippines is: <http://som.adzu.edu.ph>