

## 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).

### An Elevated Level of Physical Activity Is Associated With Normal Lipoprotein(a) Levels in Individuals From Maracaibo, Venezuela.

Bermúdez V, Aparicio D, Rojas E, Peñaranda L, Finol F, Acosta L, et al. *Am J Ther*. 2009 Dec 16;doi: 10.1097/MJT.0b013e3181c1236e

Coronary artery disease is the main cause of death worldwide. Lipoprotein(a) [Lp(a)], is an independent risk factor for coronary artery disease in which concentrations are genetically regulated. Contradictory results have been published about physical activity influence on Lp(a) concentration. This research aimed to determine associations between different physical activity levels and Lp(a) concentration. A descriptive and cross-sectional study was made in 1340 randomly selected subjects (males = 598; females = 712) to whom a complete clinical history, the International Physical Activity Questionnaire, and Lp(a) level determination were made. Statistical analysis was carried out to assess qualitative variables relationship by  $\chi^2$  and differences between means by one-way analysis of variance considering a P value < 0.05 as statistically significant. Results are shown as absolute frequencies, percentages, and mean  $\pm$  standard deviation according to case. Physical activity levels were ordinal classified as follows: low activity with 24.3% (n = 318), moderate activity with 35.0% (n = 458), and high physical activity with 40.8% (n = 534). Lp(a) concentration in the studied sample was 26.28  $\pm$  12.64 (IC: 25.59–26.96) mg/dL. Lp(a) concentration according to low, moderate, and high physical activity levels were 29.22  $\pm$  13.74, 26.27  $\pm$  12.91, and 24.53  $\pm$  11.35 mg/dL, respectively, observing statistically significant differences between low and moderate level (P = 0.004) and low and high level (P < 0.001). A strong association ( $\chi^2 = 9.771$ ; P = 0.002) was observed among a high physical activity level and a normal concentration of Lp(a) (less than 30 mg/dL). A lifestyle characterized by high physical activity is associated with normal Lp(a) levels.

### Attitudes Toward Living Kidney Donation in Transplant Hospitals: A Spanish, Mexican, and Cuban Multicenter Study.

Ríos A, López-Navas A, Ayala-García MA, Sebastián MJ, Abdo-Cuza A, Martínez-Alarcón L, et al. *Transplant Proc*. 2010 Jan–Feb;42(1):228–32.

**Introduction** Living donor kidney (LKD) transplantation provides better results than deceased donor donation, involving minimum risk for the donor. However, LKD donation rates are low in most countries. We analyzed attitudes toward LKD in transplant hospitals in Spain, Mexico, and Cuba. **Materials and Methods**

Data were obtained from five transplant hospitals through the International Collaborative Program "Proyecto Donante Vivo, Murcia" in three countries: Spain (n = 1168), Mexico (n = 903), and Cuba (n = 202). The random sample (2273 employees) was stratified according to job category. The instrument used to evaluate attitude was a validated questionnaire. Statistical analysis included Student t test, the  $\chi^2$  test, and multivariate analysis. **Results** Eighty-eight percent (n = 2002) of Spanish, Mexican, and Cuban transplant hospital personnel were in favor of related LKD and 24% nonrelated LKD (n = 555). Attitudes were more favorable among centers in Cuba 97% (n = 195), followed by Mexico 88% (n = 793) and by Spain 87% (n = 1014; P < .001). According to job category, 91% (n = 617) of physicians were in favor, 88% (n = 543) of nurses, 85% (n = 198) of health care assistants, and 85% (n = 198) of auxiliary personnel. Attitudes were related to variables of: attitude toward deceased donation (P < .001), discussion about organ donation and transplantation (P < .001), concern about body mutilation after donation (P = .001), a possible need for a transplant in the future (P < .001), and attitude toward living liver donation (P < .001). **Conclusions** Attitudes toward LKD in Hispanic/Latin Transplant Hospitals were favorable and could encourage an increase in LKD in the coming years assuming suitable sociopolitical and economic condition, as well as support from nephrologists.

### Clonal distribution of disease-associated and healthy carrier isolates of *Neisseria meningitidis* between 1983 and 2005 in Cuba.

Climont Y, Yero D, Martínez I, Martín A, Jolley KA, Sotolongo F, et al. *J Clin Microbiol*. 2009 Dec 30. [Epub ahead of print]

In response to epidemic levels of serogroup B meningococcal disease in Cuba during the 1980s the VA-MENGOC-BC® vaccine was developed and introduced into the National Infant Immunization Program in 1991. Since then the incidence of meningococcal disease in Cuba has returned to the low levels recorded before the epidemic. A total of 420 *Neisseria meningitidis* strains isolated collected between 1983 and 2005 in Cuba were analyzed by multilocus sequence typing (MLST). The set of strains comprised 167 isolated from disease cases and 253 obtained from healthy carriers. By MLST analysis, 63 STs were identified, 32 of which were reported as a new ST. The Cuban isolates were associated with 12 clonal complexes and the most common were the ST-32 (246 isolates), ST-53 (86 isolates) and ST-41/44 (36 isolates).

This study also showed that the application of VA-MENGOC-BC®, the Cuban serogroups B and C vaccine, reduced the frequency and diversity of the hypervirulent clonal complexes ST-32 (vaccine serogroup B type-strain) and ST-41/44, and also impacted on other lineages. Lineages ST-8 and ST-11 were no longer found during the post-vaccination period. The vaccine also affected the genetic composition of the carrier-associated meningococcal isolates. The number of carrier isolates belonging to hypervirulent lineages decreased significantly after vaccination, and ST-53, a sequence type common in carriers, became the predominant ST.

### Coexistence of vasospasm and microembolism detected by transcranial Doppler ultrasonography in a patient with subarachnoid haemorrhage.

Scherle C, Pérez-Nellar J, Machado C. *BMJ Case Reports*. 2009 Dec 14; doi:10.1136/bcr.06.2009.2051.

Delayed cerebral ischaemia as a clinical expression of vasospasm is one of the main complications of subarachnoid haemorrhage. In some cases, ischaemic manifestations can be related to cerebral emboli, but the relationship between vasospasm, damaged endothelial lining, and embolism, remains to be proven. The case is presented of a 56-year-old female patient who, 5 days after the clipping of an aneurysm in the left middle cerebral artery (MCA), suffered transient ischaemic attacks (TIAs) of this arterial territory. Transcranial Doppler ultrasonography showed an increment of the left MCA mean flow velocity, and 12 microembolic signals were detected in 30 mins. The coexistence of microemboli signals with severe vasospasm in the same arterial segment might suggest a causal relationship between cerebral embolism, severity of vasospasm, and TIAs.

### Distinguishing Features of Cuban Children Referred for Professional Help Because of ADHD: Looking Beyond the Symptoms.

Schneider BH, Normand S, Soteras de Toro MD, González YS, Guilarte Téllez JA, Naranjo MC, et al. *J Atten Disord*. 2010 Jan 6. [Epub ahead of print]

**Objective** To distinguish Cuban children clinically referred because of ADHD from an at-risk community sample and a community control group in terms of symptoms, associated difficulties and impairment of family and peer relations. **Method** Parents and teachers of 1036 children (6–8 years old) completed an established ADHD rating scale and a behavioral screening measure, including peer functioning. We also

administered a structured clinical interview and measures of family impairment to the clinical sample and to an at-risk community-based subsample. **Results** Although both clinical and at-risk groups displayed more externalizing and internalizing symptoms than controls, referred children were not only characterized by higher levels of ADHD symptoms, but also by greater impairment of family and peer relations than at-risk community children or community controls. **Conclusion** The findings suggest that ADHD has major consequences on the family and peer functioning of Cuban children, which may lead to their referral for treatment.

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**Duplicated middle cerebral artery.** Pérez J, Machado C, Scherle C, Hierro D. *BMJ Case Reports*. 2009 Dec 3; doi:10.1136/bcr.06.2009.2035.

Duplicated middle cerebral artery (DMCA) is an anomalous vessel arising from the internal carotid artery. The incidence DMCA is relatively low, and an association between this anomaly and cerebral aneurysms has been documented. There is a controversy whether DMCA may have perforating arteries. This is an important fact to consider in aneurysm surgery. We report the case of a 34-year-old black woman who suffered a subarachnoid hemorrhage and the angiography a left DMCA, and an aneurysm in an inferior branch of the main MCA. The DMCA and the MCA had perforating arteries. The aneurysm was clipped without complications. The observation of perforating arteries in our patient confirms that the DMCA may have perforating arteries. This is very important to be considered in cerebral aneurysms surgery. Moreover, the DMCA may potentially serve as a collateral blood supply to the MCA territory in cases of MCA occlusion.

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**False discovery rate and permutation test: an evaluation in ERP data analysis.** Lage-Castellanos A, Martínez-Montes E, Hernández-Cabrera JA, Galán L. *Stat Med*. 2010 Jan 15;29(1):63–74.

Current analysis of event-related potentials (ERP) data is usually based on the a priori selection of channels and time windows of interest for studying the differences between experimental conditions in the spatio-temporal domain. In this work we put forward a new strategy designed for situations when there is not a priori information about 'when' and 'where' these differences appear in the spatio-temporal domain, simultaneously testing numerous hypotheses, which increase the risk of false positives. This issue is known as the problem of multiple comparisons and has been managed with methods that control the false discovery rate (FDR), such as permutation test and FDR methods. Although the former has been previously applied, to our knowledge, the FDR methods have not been introduced in the ERP data analysis. Here we compare the performance (on simulated and real data) of permutation test and two FDR methods (Benjamini

and Hochberg (BH) and local-fdr, by Efron). All these methods have been shown to be valid for dealing with the problem of multiple comparisons in the ERP analysis, avoiding the ad hoc selection of channels and/or time windows. FDR methods are a good alternative to the common and computationally more expensive permutation test. The BH method for independent tests gave the best overall performance regarding the balance between type I and type II errors. The local-fdr method is preferable for high dimensional (multichannel) problems where most of the tests conform to the empirical null hypothesis. Differences among the methods according to assumptions, null distributions and dimensionality of the problem are also discussed.

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**Identification of a novel antitumor peptide based on the screening of an Ala-library derived from the LALF<sub>(32-51)</sub> region.** Vallespi MG, Fernández JR, Torrens I, García I, Garay H, Mendoza O, et al. *J Pept Sci*. 2010 Jan;16(1):40–7.

Novel therapeutic peptides are increasingly making their way into clinical application. The cationic and amphipathic properties of certain peptides allow them to cross biological membranes in a non-disruptive way without apparent toxicity increasing drug bioavailability. By modifying the primary structure of the *Limulus*-derived LALF<sub>(32-51)</sub> peptide we designed a novel peptide, L-2, with antineoplastic effect and cell-penetrating capacity. Interestingly, L-2 induced cellular cytotoxicity in a variety of tumor cell lines and systemic injection into immunocompetent and nude mice bearing established solid tumor, resulted in substantial regression of the tumor mass and apoptosis. To isolate the gene transcripts specifically regulated by L-2 in tumor cells, we conducted suppressive subtractive hybridization (SSH) analysis and identified a set of genes involved in biological processes relevant to cancer biology. Our findings describe a novel peptide that modifies the gene expression of the tumor cells and exhibits antitumor effect *in vivo*, indicating that peptide L-2 is a potential candidate for anticancer therapy.

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**Immunization with a DNA vaccine candidate in chronic hepatitis C patients is safe, well tolerated and does not impair immune response induction after anti-hepatitis B vaccination.** Castellanos M, Cinza Z, Dorta Z, Veliz G, Vega H, Lorenzo I, et al. *J Gene Med*. 2010 Jan;12(1):107–16.

**Background** In the present study, we evaluated the safety of CIGB-230, a novel vaccine candidate based on the mixture of a plasmid for DNA immunization, expressing hepatitis C virus (HCV) structural antigens, with a recombinant HCV Core protein. **Methods** Fifteen HCV chronically-infected volunteers with detectable levels of HCV RNA genotype 1b, who were non-responders to previous treatment with interferon plus ribavirin, were intramuscularly injected with

CIGB-230 on weeks 0, 4, 8, 12, 16 and 20. Individuals were also immunized at weeks 28, 32 and 36 with a recombinant vaccine against hepatitis B. Adverse events were recorded and analyzed. Blood samples were taken every 4 weeks up to month 12 for hematological, biochemical, virological and immunological analysis. **Results** All patients completed the treatment with CIGB-230. Adverse events were only slight (83.6%) or moderate (16.4%). No significant differences in hematological and biochemical parameters, including serum aminotransferases, were detected between the baseline and post-treatment state. Induction of a CD4+ T lymphocyte response against a particular region in HCV E1, spanning amino acids 230-312 in HCV polyprotein, was detected in 42.8% of patients during treatment with CIGB-230. The ability of T cells to proliferate in response to mitogenic stimulation was not weakened. Most individuals (78.6%) were seroprotected after anti-hepatitis B vaccination and 42.8% were hyper-responders (antibody titers > 100 UI/ml). No anti-mitochondrial, anti-nuclear and anti-extractable nuclear antigen antibodies were generated during immunization with CIGB-230. **Conclusions** Vaccination with CIGB-230 in HCV chronically-infected individuals was safe, well tolerated and did not impair the ability to respond to non-HCV antigens.

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**Intra-lesional injections of recombinant human epidermal growth factor promote granulation and healing in advanced diabetic foot ulcers: multicenter, randomised, placebo-controlled, double-blind study.** Fernández-Montequín JI, Valenzuela-Silva CM, Díaz OG, Savigne W, Sancho-Soutelo N, Rivero-Fernández F, et al. *Int Wound J*. 2009 Dec;6(6):432–3.

A multicenter, double-blind, placebo-controlled trial was carried out to evaluate the intra-lesional infiltration of recombinant epidermal growth factor (EGF) in Wagner's grade 3 or 4 diabetic foot ulcers (DFUs). Subjects (149) were randomised to receive EGF (75 or 25 µg) or placebo, three times per week for 8 weeks and standard good wound care. The main endpoint was granulation tissue covering ≥ 50% of the ulcer at 2 weeks. It was achieved by 19/48 controls versus 44/53 in the 75 µg group [odds ratio (OR): 7.5; 95% confidence interval (CI): 2.9–18.9] and 34/48 in the 25 µg group (OR: 3.7; 1.6–8.7). Secondary outcome variables such as end-of-treatment complete granulation response (28/48 controls, 46/53 with 75 µg and 34/48 with 25 µg EGF), time-to-complete response (controls: 5 weeks; both EGF dose groups: 3 weeks), and wound closure after follow-up (25/48 controls, 40/53 with 75 µg and 25/48 with 25 µg EGF) were also treatment dependent. Multivariate analyses yielded that they were significantly enhanced by 75 µg EGF treatment and neuropathic versus ischemic ulcers. Most adverse events were mild and no drug-related severe adverse reactions were reported. It was concluded that recombinant human EGF (rhEGF) local injections offer a favourable risk-benefit balance in patients with advanced DFU.

**Level of Acceptance of a Clinical Solid Organ Xenotransplantation Program Among Personnel in Organ Transplant-Related Services in Spanish, Mexican, and Cuban Hospital Centers.** Ríos A, Martínez-Alarcón L, Ayala-García MA, Sebastián MJ, Abdo-Cuza A, López-Navas A, et al. *Transplant Proc.* 2010 Jan–Feb;42(1):222–7.

**Introduction** Xenotransplantation is far from becoming a clinical reality. However, in vital organs it could be used as a bridge until a human organ becomes available, in an emergency situation. We analyzed the attitude toward xenotransplantation among personnel in transplant-related services in several hospitals in Spain and Latin America. **Methods** A random sample stratified by type of service and job category ( $n = 738$ ), in transplant-related services (procurement units, transplant units, and transplant patient follow-up units) was examined in eight hospital centers from three different countries: Spain ( $n = 349$ ), Mexico ( $n = 269$ ), and Cuba ( $n = 120$ ). A self-administered validated questionnaire was completed anonymously. **Results** Based on the assumption that all the results of xenotransplantation were similar to those achieved with human donors, most respondents [66% ( $n = 484$ )] would be in favor. The employees from Cuban centers had the most favorable attitudes (72% in favor), followed by the Spanish (64%) and the Mexicans (61%;  $P = .013$ ). However, the differences were mainly determined by job category: Physicians showed the most favorable attitudes and auxiliary staff the least (67% vs 40%;  $P = .010$ ). Attitudes were significantly related to beliefs about different types of human donation [deceased ( $P < .001$ ) and living ( $P < .001$ )], the possibility of needing a transplant for oneself ( $P < .001$ ), and a favorable attitude toward donating the organs of a deceased family member ( $P = .004$ ). **Conclusions** Currently, a third of health care employees working in transplant-related services are not in favor of xenotransplantation. More information should be provided about the subject, especially in centers with preclinical xenotransplantation programs.

**Prevalence and diagnostic aspects of sputum smear positive tuberculosis cases at a tertiary care institution in Rwanda.** Muvunyi CM, Masaisa F, Bayingana C, Musemakweri A, Mutesa L, Carbonell Hernández T. *Afr J Microbiol Res.* 2010 Jan;4(1):88–91.

Approximately one third of the world's population is infected with *Mycobacterium tuberculosis* and 9.27 million new cases of TB occurred in 2007. Developing countries disproportionately shoulder the global burden of disease with the highest estimated rates in the world, with an estimated 55% of global cases in Asia and 31% in the African region. The incidence of new sputum smear positive in Rwanda through recent national survey was an estimated 162 per 100 000 population. The aim of our study

was to evaluate the prevalence of smear positive pulmonary TB among patients at the University of Butare Teaching Hospital, a tertiary health facility in South province, Rwanda. In addition, some aspects of the performance of the pulmonary TB diagnosis are discussed. The overall prevalence of sputum smear positive cases were 17.3% (63 of 364) and most of the positive patients were within the age range 15–44 years. The highest percentage of TB was seen in the age group of 15–24 years compared with the lowest percentages in the age group below 14 years and above 45 years. A total of 63 (17.3%) suspects were found to have at least one positive. Of these, 56 (88.9% of those with one or more positive smears and 92% of those who fulfilled the case definition) were detected from the first specimen and 7 (11.1%) were positive on the second specimen but not the first. The third specimen did not have any additional diagnostic value for the detection of AFB. The prevalence of sputum smear positive cases of 17.3% increases with age up to the age 44 years. Our result show that examining two sputa smears was sufficient for the detection of AFB in our laboratory. Further research involving different laboratories from all of the regions of Rwanda is needed to reassess these findings.

**Progression markers of Spinocerebellar Ataxia 2. A twenty years neurophysiological follow up study.** Velázquez-Pérez L, Rodríguez-Labrada R, Canales-Ochoa N, Sánchez-Cruz G, Fernández-Ruiz J, Montero JM, et al. *J Neurol Sci.* 2010 Mar 15;290(1–2):22–6. Epub 2010 Jan 12.

Nerve conduction is profoundly affected in Spinocerebellar ataxia 2 (SCA2) even before the onset of the disease, but there is no information regarding its progression to the final stage of SCA2. In order to study the progression patterns of nerve conduction abnormalities in SCA2 we performed a prospective follow up evaluation of sensory and motor conduction in 21 SCA2 mutation carriers—initially presymptomatics—and 19 non-SCA2 mutation carriers during 20 years. The earliest electrophysiological alterations were the reduction of sensory amplitudes in median and sural nerves, which could be found 8 to 5 years prior disease onset and in the last 4 years of the preclinical stage respectively. These abnormalities were followed by the increase of sensory latencies and decrease of conduction velocities. Sensory amplitudes progressively decreased during the follow-up clinical stage, rendering almost all patients with abnormal amplitudes and lack of sensory potentials, with faster progression rates in patients with larger CAG repeat lengths. Peripheral motor nerves showed the later involvement. These findings were used to define three distinct stages that describe the progression of the peripheral neuropathy. We suggest that sensory amplitudes could be useful biomarkers to assess the progression of peripheral

nerve involvement and therefore to evaluate future clinical trials of therapeutic agents.

**Secondary heterologous dengue infection risk: Disequilibrium between immune regulation and inflammation?** Sierra B, Pérez AB, Vogt K, García G, Schmolke K, Aguirre E, et al. *Cell Immunol.* 2010 Feb 10. [Epub ahead of print]

Increased serum levels of cytokines released by cells of the immune response have been detected in patients suffering from dengue disease. Likewise, secondary infections by a different dengue virus serotype result in a highest risk of development of the severe dengue disease. Both findings suggest that the memory immune response is one of the key players in the pathogenesis of this disease. Here we take advantage of the particular Cuban epidemiological situation in dengue to analyze a broad spectrum of cell-mediated immune response mediators at mRNA and protein level. Evidences for a regulatory immune pattern in homologous (TGF- $\beta$ , IL-10) vs. pro-inflammatory pattern (IFN- $\gamma$ , TNF- $\alpha$ ) in heterologous dengue virus re-challenge were found, suggesting a possible association with the higher incidence of severe dengue cases in the latter case.

**Spanish and Latin American Nursing Personnel and Deceased Organ Donation: A Study of Attitude.** Ríos A, Martínez-Alarcón L, Ayala MA, Sebastián MJ, Abdo-Cuza A, Alán J, et al. *Transplant Proc.* 2010 Jan–Feb;42(1):216–21.

**Objective** To analyze the attitude of nursing personnel about organ donation and transplantation in hospitals in Spain and Latin America, and factors that affect this attitude. **Methods** Data were selected from 12 hospitals and 32 primary care centers participating in an international study (Proyecto Donante, Murcia) in 4 countries including Spain ( $n = 650$ ), Mexico ( $n = 428$ ), Cuba ( $n = 89$ ), and Costa Rica ( $n = 27$ ). The sample was random and stratified by type of service among nursing personnel ( $n = 1194$ ). Attitude was evaluated using a psychosocial questionnaire. **Results** Of nursing personnel surveyed, 77% ( $n = 922$ ) were in favor of organ donation. No differences were found according to whether they were directly involved in transplantation-related services ( $P < .05$ ). Attitude in favor of organ donation varied between countries: 92% in Cuba, 85% in Costa Rica, 80% in Mexico, and 73% in Spain ( $P < .001$ ). This attitude was also related to donation of a family member's organs ( $P < .001$ ), having discussed organ donation and transplantation within the family ( $P < .001$ ), the concept of brain death ( $P < .001$ ), fear of body mutilation ( $P < .001$ ), and manipulation of the body after death ( $P = .001$ ). **Conclusion** Attitude toward deceased organ donation among nurses varies between countries. There is a discrepancy between those in favor vs actual donation rates in countries and work centers. These fears may become worse when donation is seen as common in daily clinical practice.