

Cuban Research in Current International Journals

Abnormal corticospinal tract function and motor cortex excitability in non-ataxic SCA2 mutation carriers: A TMS study. Velázquez-Pérez L, Rodríguez-Labrada R, Torres-Vega R, Medrano Montero J, Vázquez-Mojena Y, Auburger G, et al. Clin Neurophysiol. 2016 Aug;127(8):2713–9.

Objective To evaluate if the corticospinal tract is affected in the prodromal stage of spinocerebellar ataxia type 2 (SCA2), prior to development of the cerebellar syndrome. **Methods** A cross-sectional study was conducted in 37 non-ataxic SCA2 mutation carriers and in age- and sex-matched healthy controls. All subjects underwent clinical assessment and transcranial magnetic stimulation to determine corticospinal tract integrity to the right abductor pollicis brevis and tibialis anterior muscles. **Results** Non-ataxic SCA2 mutation carriers showed significantly higher resting and active motor thresholds for both muscles, and prolonged cortical silent periods and central motor conduction times (CMCT), compared to controls. CMCT to the tibialis anterior correlated directly with CAG repeat size, and inversely with predicted time to ataxia onset. **Conclusion** Findings provide novel electrophysiological evidence for affection of the corticospinal tract and motor cortex in prodromal SCA2. Slowed conduction in the corticospinal tract to the lower limbs reflects polyglutamine neurotoxicity, and predicts time to ataxia onset. **Significance** Identification of corticospinal tract damage and decreases motor cortical excitability in the prodromal stage of SCA2 allows early disease monitoring. This will become important as soon as effective neuroprotective treatment will be available.

Active immunization with human interleukin-15 induces neutralizing antibodies in non-human primates. Rodríguez-Alvarez Y, Moreira-Díaz Y, Gerónimo-Pérez H, Castro-Velazco J, Martínez-Castillo R, Puente-Pérez P, et al. BMC Immunol. 2016 Sep 26;17(1):30.

Background Interleukin-15 is an immunostimulatory cytokine overexpressed in several autoimmune and inflammatory diseases such as Rheumatoid Arthritis, psoriasis and ulcerative colitis; thus, inhibition of IL-15-induced signaling could be clinically beneficial in these disorders. Our approach to neutralize IL-15 consisted in active immunization with structurally modified human IL-15 (mhIL-15) with the aim to induce neutralizing antibodies against native IL-15. In the present study, we characterized the antibody response in *Macaca fascicularis*, non-human primates that were immunized with a vaccine candidate containing mhIL-15 in Aluminum hydroxide (Alum), Montanide and Incomplete Freund's Adjuvant. **Results** Immunization with mhIL-15 elicited a specific antibodies response that neutralized native IL-15-dependent biologic activity in a CTLL-2 cell proliferation assay. The highest neutralizing response was obtained in macaques immunized with mhIL-15 adjuvanted in Alum. This response, which was shown to be transient, also inhibited the activity of simian IL-15 and did not affect the human IL-2-induced proliferation of CTLL-2 cells. Also, in a pool of synovial fluid cells from two Rheumatoid Arthritis patients, the immune sera slightly inhibited TNF- α secretion. Finally, it was observed that this vaccine candidate neither affect animal behavior, clinical status, blood biochemistry nor the percentage of IL-15-dependent cell populations, specifically CD56+ NK and CD8+ T cells. **Conclusion** Our results indicate that vaccination with mhIL-15 induced neutralizing antibodies to native IL-15 in non-human primates. Based on this fact, we propose that this vaccine candidate could be potentially beneficial for treatment of diseases where IL-15 overexpression is associated with their pathogenesis.

A Tetravalent Formulation Based on Recombinant Nucleocapsid-like Particles from Dengue Viruses Induces a Functional Immune Response in Mice and Monkeys. Gil L, Cobas K, Lazo L, Marcos E, Hernández L, Suzarte E, et al. J Immunol. 2016 Sep 28. pii : 1600927. [Epub ahead of print]

Despite the considerable effort that has been invested in elucidating the mechanisms of protection and immunopathogenesis associated with dengue virus infections, a reliable correlate of protection against the disease remains to be found. Neutralizing Abs, long considered the prime component of a protective response, can exacerbate disease severity when present at subprotective levels, and a growing body of data is challenging the notion that their titers are positively correlated with disease protection. Consequently, the protective role of cell-mediated immunity in the control of dengue infections has begun to be studied. Although earlier research implicated cellular immunity in dengue immunopathogenesis, a wealth of newer data demonstrated that multifunctional CD8+ T cell responses are instrumental for avoiding the more severe manifestations of dengue disease. In this article, we describe a new tetravalent vaccine candidate based on recombinant dengue virus capsid proteins, efficiently produced in *Escherichia coli* and purified using a single ion-exchange chromatography step. After aggregation to form nucleocapsid-like particles upon incubation with an oligodeoxynucleotide containing immunostimulatory CpG motifs, these Ags induce, in mice and monkeys, an IFN- γ -secreting cell response that significantly reduces viral load after challenge without the contribution of antiviral Abs. Therefore, this new vaccine candidate may not carry the risk for disease enhancement

associated with Ab-based formulations.

Chronic interstitial nephritis in agricultural communities: a worldwide epidemic with social, occupational and environmental determinants. Jayasumana C, Orantes C, Herrera R, Almaguer M, López L, Silva LC, et al. *Nephrol Dial Transplant*. 2016 Oct 13. pii: gfw346. [Epub ahead of print]

Increase in the prevalence of chronic kidney disease (CKD) is observed in Central America, Sri Lanka and other tropical countries. It is named chronic interstitial nephritis in agricultural communities (CINAC). CINAC is defined as a form of CKD that affects mainly young men, occasionally women. Its aetiology is not linked to diabetes, hypertension, glomerulopathies or other known causes. CINAC patients live and work in poor agricultural communities located in CINAC endemic areas with a hot tropical climate, and are exposed to toxic agrochemicals through work, by ingestion of contaminated food and water, or by inhalation. The disease is characterized by low or absent proteinuria, small kidneys with irregular contours in CKD stages 3-4 presenting tubulo-interstitial lesions and glomerulosclerosis at renal biopsy. Although the aetiology of CINAC is unclear, it appears to be multifactorial. Two hypotheses emphasizing different primary triggers have been proposed: one related to toxic exposures in the agricultural communities, the other related to heat stress with repeated episodes of dehydration heat stress and dehydration. Existing evidence supports occupational and environmental toxins as the primary trigger. The heat stress and dehydration hypothesis, however, cannot explain: why the incidence of CINAC went up along with increasing mechanization of paddy farming in the 1990s; the non-existence of CINAC in hotter northern Sri Lanka, Cuba and Myanmar where agrochemicals are sparsely used; the mosaic geographical pattern in CINAC endemic areas; the presence of CINAC among women, children and adolescents who are not exposed to the harsh working conditions; and the observed extra renal manifestations of CINAC. This indicates that heat stress and dehydration may be a contributory or even a necessary risk factor, but which is not able to cause CINAC by itself.

Continuous EEG monitoring at the emergency and intensive care unit: Presentation of a Cuban solution. Antelo Cordovez JM, Rodriguez Rodriguez V. *Clin Neurophysiol*. 2016 Sep;127(9) :e315.

Objective To present a monitor developed to solve continuous EEG monitoring in Cuban ICUs. Material and methods We review the state of the art and needs of the technology. Results Our monitor was developed on windows platform using the commercial 32 channel digital electroencephalographer Medicid-V – Neuronic SA. The monitor incorporates all requirement of the technology. Features include: video EEG acquisition, online data reviewing during acquisition, online quantitative processing of EEG/EKG/PO2 signals, online trends display of all computed parameters (ex: aEEG, DSA, AP, RP, frequency indexes, BSI, SI among others), easy annotation entry, easy access to raw data from trend displays, customizable screen display for edition/reviewing, visual alarms, artifact detection during acquisition, customized montages and protocols, standardized report of ICU EEG according to ACNS guidelines, configurable notification for remote users. Conclusions The development of an ICU EEG monitor will make possible to introduce and extent this technique in the Cuban health system with positive repercussion in the level of attention of critically ill patients.

Dengue infection. Guzmán MG, Gubler DJ, Izquierdo A, Martínez E, Halstead SB. *Nat Rev Dis Primers*. 2016 Aug 18;2:16055. DOI: 10.1038/nrdp.2016.55

Dengue is widespread throughout the tropics and local spatial variation in dengue virus transmission is strongly influenced by rainfall, temperature, urbanization and distribution of the principal mosquito vector *Aedes aegypti*. Currently, endemic dengue virus transmission is reported in the Eastern Mediterranean, American, South-East Asian, Western Pacific and African regions, whereas sporadic local transmission has been reported in Europe and the United States as the result of virus introduction to areas where *Ae. aegypti* and *Aedes albopictus*, a secondary vector, occur. The global burden of the disease is not well known, but its epidemiological patterns are alarming for both human health and the global economy. Dengue has been identified as a disease of the future owing to trends toward increased urbanization, scarce water supplies and, possibly, environmental change. According to the WHO, dengue control is technically feasible with coordinated international technical and financial support for national programmes. This Primer provides a general overview on dengue, covering epidemiology, control, disease mechanisms, diagnosis, treatment and research priorities.

Effects of a combined therapy with D-002 (beeswax alcohols) plus D-003 (sugarcane wax acids) on osteoarthritis symptoms. Puente RA, Illnait J, Mas RM, Carbajal DM, Mendoza S, Ceballos A, et al. *Altern Ther Med*. 2016 Jun;22 Suppl 2:15–23.

Context Nonsteroidal, anti-inflammatory drugs effectively relieve osteoarthritis (OA) symptoms but also induce adverse effects (AEs) that limit their long-term use, which drives a search for safer treatments. D-002, a mixture of beeswax alcohols, and D-003, a mixture of sugarcane wax acids, have been effective in experimental and clinical studies for patients with OA. **Objective** The study intended to investigate the effects on OA symptoms of a combined therapy using D-002 and D-003 (D-002/D-003), which were administered for 6 wk. **Design** The study was a randomized, double-blind, placebo-controlled trial. **Setting** The study was conducted at the Surgical Medical Research Center in Havana, Cuba. **Participants** Participants were patients with mild-to-moderate OA. **Intervention** Participants were randomly assigned to 1 of 4 groups-(1) a control group, which received a placebo; (2) the D-002 group (intervention group), which received 50 mg/d of D-002; (3) the D-003 group (intervention group), which received 10 mg/d of D-003; or (4) the D-002/D-003 group (intervention group), which received a combined therapy of 50 mg/d of D-002 plus 10 mg/d of D-003. The control group received tablets that were indistinguishable in appearance from the D-002 and D-003 tablets and had a similar composition, except that the active ingredients were replaced by lactose. The groups took the medications once per day for 6 wk. **Outcome Measures** Symptoms were assessed using the Western Ontario and McMaster Individual Osteoarthritis Index (WOMAC) and a visual analogue scale (VAS). The primary outcome was the reduction in the total WOMAC score. The subscale scores on the WOMAC for pain, stiffness, and physical function, the VAS scores, and the use of rescue medications were secondary outcomes. **Results** Of the 120 enrolled participants, 116 completed the study. The treatments with D-002, D-003, and D-002/D-003 reduced the mean total WOMAC scores significantly from baseline to postintervention, by 75.1%, 72.8%, and 91.2%, respectively. Compared with the placebo, the treatments decreased the mean WOMAC scores for pain, joint stiffness, and physical function significantly. The VAS scores significantly decreased, showing a 71.4%, a 66.9%, and an 84.7% reduction for the D-002, D-003, and D-002/D-003 groups, respectively. All the reductions were significant from the first week and were enhanced during the trial. The D-002/D-003 treatment was more effective in improving all of the scores than either monotherapy. With respect to rescue medications, 3/30, 2/30, and 2/30 used the medications in the D-002, D-003, and D-002/D-003 groups, respectively, vs 17/30 in the control group. The treatments were well tolerated. **Conclusions** Administered for 6 wk, 50 mg/d of D-002 and 10 mg/d of D-003 ameliorated OA symptoms, but the combined therapy, D-002/D-003, was more effective than either monotherapy. All treatments were well tolerated.

Etiology of genital ulcer disease in male patients attending a sexually transmitted diseases clinic: first assessment in Cuba. Noda AA, Blanco O, Correa C, Pérez L, Kourí V, Rodríguez I. Sex Transm Dis. 2016 Aug;43(8):494–7.

Background Sexually transmitted diseases (STDs) and in particular genital ulcer disease (GUD) have a major impact on morbidity and mortality in developing countries. The World Health Organization recommends the use of syndromic guidelines for the treatment of sexually transmitted infections (STIs) in resource-constrained countries. Surveillance of autochthonous etiologies provides epidemiological information contributing to the prevention and treatment of STIs. We investigated the etiology and factors associated with GUD among male patients attending a STD clinic in Havana, Cuba. **Methods** Swabs from genital ulcers of 113 male patients, collected from May 2012 to June 2015, were analyzed using PCR for herpes simplex virus types 1 and 2, *Treponema pallidum*, *Haemophilus ducreyi*, and *Chlamydia trachomatis*. We also investigated the clinical and epidemiological characteristics associated with the presence of these pathogens in GUD. **Results** At least one of the pathogens was detected in 70% of patients. The occurrence of the pathogens was herpes simplex virus type 2 (HSV-2) (51.3%), *T. pallidum* (29.2%), and *C. trachomatis* (1.8%). Co-infections occurred as follows: *T. pallidum*-HSV-2 (10.6%), *C. trachomatis*-HSV-2 (0.9%) and *C. trachomatis*-*T. pallidum* (0.9%). Herpes simplex virus type 1 and *H. ducreyi* were not detected. Ages 15 to 40 years, HIV-positive serostatus, and no condom use were significant risk factors for the presence of HSV-2 in genital ulcers. **Conclusions** Our preliminary results highlight the predominance of HSV-2 and *T. pallidum* as the leading GUD etiologies in the study population and identified risk factors associated with HSV-2. This information should help to inform guidelines for better management of GUD in Havana, Cuba.

Foxe1 Polymorphism Interacts with Dietary Iodine Intake in Differentiated Thyroid Cancer Risk in the Cuban Population. Ren Y, Lence-Anta JJ, Pereda C, Chappa M, Velasco M, Infante I, et al. Thyroid. 2016 Sep 9. [Epub ahead of print].

Background The incidence of differentiated thyroid cancer (DTC) is low in Cuba and the contribution of dietary factors to DTC in this population has not been investigated so far. Our aim was to evaluate the relationship between dietary iodine intake and DTC with regard to the interaction with environmental factors or some common single nucleotide polymorphisms (SNPs), based on a case-control study carried out in Cuba. **Methods** We interviewed 203 cases and 212 controls from the general population face to face by using

the dietary intake questionnaire and the photo booklet from the E3N cohort. A specific food composition table was elaborated for this study. For each parameter studied, the odds ratio (OR) was stratified on age group and sex, and further adjusted for dietary energy, smoking status, ethnic group, level of education, number of pregnancies and body surface area. **Results** The risk of DTC was significantly reduced with increasing consumption of fish (p-trend=0.04), but no association between total dietary iodine intake and DTC risk was evident (p-trend=0.7); this lack of significant association was true whatever the age, the smoking status, the dietary selenium intake and the ethnicity (all p-interactions > 0.05). DTC risk was positively and strongly associated with the number of copies in the minor allele (A) for SNP rs965513 near FOXE1 among people who consumed less iodine than the median (adjusted p-interaction=0.005). **Conclusion** Overall, the majority of the studied population had an optimal dietary iodine intake; DTC risk was inversely associated with high fish consumption. Furthermore, DTC risk was positively associated with the number of copies in the minor allele (A) of rs965513 among people who consumed less iodine than the median. Because these findings are based on post-diagnostic measures, studies with pre-diagnostic dietary iodine are needed for confirmation.

Fragments in cytologic smears from two intra-abdominal tumors (ovarian and hepatic) in female patients: A diagnostic pitfall with histologic correlation. Machado I, López-Soto MV, Pérez-López AS, Domínguez-Álvarez C, Llobart-Bosch A. *Diagn Cytopathol.* 2016 Jul 13. DOI: 10.1002/dc.23531. [Epub ahead of print]

Hyaline globules and papillary fragments in cytologic samples from two intra-abdominal tumors in young females are presented including the cytological features and the correlation with the histopathologic and immunohistochemical findings. In the first case a cytologic study from an ovarian mass showed papillary structures and isolated tumor cells with epithelioid morphology, irregular reniform-like nuclear contour, pale or vacuolated cytoplasm, abundant hyaline globules and occasional glomeruloid structures resembling Schiller-Duval bodies. Yolk sac tumor (YST) was the diagnosis on the histological slides. Tumor cells showed positivity for cytokeratin (AE1/AE3), epithelial membrane antigen (EMA), alpha-fetoprotein (AFP) and Sal-like protein 4 (SALL4). In case number two the cytologic study from a liver metastasis displayed papillary and rosette-like clusters composed of uniform and bland cells showing occasional long cytoplasmic tails, hyaline globules and nuclear grooves. A diagnosis of hepatic metastasis from solid pseudopapillary neoplasm of the pancreas (SPNP) was rendered from the histology. Tumor cells revealed immunoreactivity for cytokeratin (AE1/AE3), Vimentin, Galectin-1 (GAL-1), Neuron specific-enolase, CD10, progesterone and β -catenin (nuclear stain). Regarding differential diagnosis, in the patient with the ovarian mass an ovarian clear cell carcinoma was considered, as well as other germ cell tumors or metastatic carcinoma, while in the patient with a liver metastasis a neuroendocrine carcinoma was taken into account. YST and SPNP share some cytological findings, including hyaline globules, papillary structures, clear cells and intercellular eosinophilic basement membrane deposits. Thus, a detailed study and careful interpretation of the cytological, histological and immunohistochemical findings may be worthwhile to avoid a potential misdiagnosis, particularly in the cytologic specimens of the ovarian and/or intra-abdominal mass, when involving young females.

Frequent co-expression of EGFR and NeuGcGM3 ganglioside in cancer: it's potential therapeutic implications. Palomo AG, Santana RB, Pérez XE, Santana DB, Gabri MR, Monzon KL, et al. *Clin Exp Metastasis.* 2016 Jul 23. [Epub ahead of print]

Interaction between epidermal growth factor receptor (EGFR) signaling with GM3 ganglioside expression has been previously described. However, little is known about EGFR and NeuGcGM3 co-expression in cancer patients and their therapeutic implications. In this paper, we evaluate the co-expression of EGFR and NeuGcGM3 ganglioside in tumors from 92 patients and in two spontaneous lung metastasis models of mice (Lewis lung carcinoma (3LL-D122) in C57BL/6 and mammary carcinoma (4T1) in BALB/c). As results, co-expression of EGFR and NeuGcGM3 ganglioside was frequently observed in 63 of 92 patients (68 %), independently of histological subtype. Moreover, EGFR is co-expressed with NeuGcGM3 ganglioside in the metastasis of 3LL-D122 and 4T1 murine models. Such dual expression appears to be therapeutically relevant, since combined therapy with mAbs against these two molecules synergistically increase the survival of mice treated. Overall, our results suggest that NeuGcGM3 and EGFR may coordinately contribute to the tumor cell biology and that therapeutic combinations against these two targets might be a valid strategy to explore.

Gradual reduction of testosterone using a gonadotropin-releasing hormone vaccination delays castration resistance in a prostate cancer model. Barranco JA, Millar RP, Fuentes F, Bover E, Pimentel E, Basulto R, et al. *Onco Lett.* 2016 Aug;12(2):963–70.

In a previous study aimed to design a novel prostate cancer vaccine, the authors of the present study demonstrated the advantage of combining the adjuvants Montanide ISA 51 with very small size proteoliposomes (VSSP) to promote a significant humoral immune response to gonadotropin-releasing hormone (GnRH) in healthy animals. The present study compared the efficacy of this vaccine formulation versus the standard treatment currently available in terms of preventing the development of tumors in DD/S mice injected with Shionogi carcinoma (SC) 115 cells. The results demonstrated that 5 non-vaccinated control mice exhibited a fast tumor growth, and succumbed to the disease within 19-31 days. Mice immunized with the GnRH/Montanide ISA 51/VSSP vaccine exhibited a moderate decline in testosterone levels that were associated with a decrease in anti-GnRH antibody titers, which lead to a sustained tumor growth inhibition. In total, 2 mice in the immunized group exhibited complete remission of the tumor for the duration of the present study. In addition, castrated mice, which were used as a control for standard hormonal therapy, exhibited an accelerated decrease in tumor size. However, tumor relapse was observed between days 50 and 54, and between days 65 and 85, following the injection of SC 155 cells. Therefore, these mice were sacrificed at day 90. The present study concludes that the slow and moderate reduction of testosterone levels observed using the GnRH-based vaccine may delay the appearance of castration resistance in a Shionogi prostate cancer model. These findings suggest that this vaccine may be used to delay castration resistance in patients with prostate cancer.

Impact of a focused antimicrobial stewardship program in adherence to antibiotic prophylaxis and antimicrobial consumption in appendectomies. Guanche Garcel H, Villanueva Arias A, Pancorbo Sandoval C, Valle Gamboa ME, Bode Sado A, Alfonso Serrano RN. J Infect Public Health. 2016 Jul 19. [Epub ahead of print].

Antibiotic use in appendectomy constitutes a fundamental practice to achieve the clinical outcomes and the prevention of surgical site infection. A prospective interventional study was performed in a community hospital from January 2013 to December 2015 with the aim of determining the effect of a focused antimicrobial stewardship program in the compliance with antibiotic prophylaxis and the antimicrobial consumption in appendectomies. The compliance with the antibiotic prophylaxis was monitored for the timing of administration, the selection and dose and the discontinuation. The monitoring of antimicrobial consumption was performed by a pharmacist using ATC/DDD methodology. The stewardship program includes the education of the staff and the monitoring of the quality of antibiotic prophylaxis and consumption, and feedback. Comparison of the variables over the years was performed using student's *t*-test or chi-square test as required. In 603 appendectomies performed the compliance with timely administration was achieved in 72.9%, 99.6% and 100% during 2013, 2014 and 2015 respectively and the compliance with the discontinuation had an increase from 86.4% (2013) to 96.7% in 2015. Consumption of antimicrobial was 355.1 DDD/100 procedures (DDD) in flemonous, 447.3 DDD in suppurative, 892.8 DDD in gangrenous and 1162.7 DDD in perforated appendectomies. Reduction in consumption for cefuroxime (26.2%), metronidazole (12.6%) and ceftriaxone (18.1%) was observed. The consumption of antimicrobials in flemonous and suppurated appendectomies achieved the lowest figure in 2015. The focused antimicrobial stewardship program was effective to improve the timely administration and the proper discontinuation of prophylactic antibiotic, with an important reduction of antimicrobial consumption.

Insights into the biological features of the antigenic determinants recognized by four monoclonal antibodies in redia and adult stages of the liver fluke *Fasciola hepatica*. Alba A, Sánchez J, Hernández H, Mosqueda M, Rodríguez SY, Capó V, et al. Wxp Parasitol. 2016 Sep;168 :39–44.

Fasciola hepatica is a digenean trematode which infects a wide variety of domestic animals and also humans. Previous studies have demonstrated that four monoclonal antibodies (Mabs) against the total extract of *F. hepatica* redia (named as 1E4, 6G11, 4E5 and 4G11) also recognized the excretion - secretion antigens (ES Ag) of adult parasites, which is a biologically-relevant mixture of molecules with functional roles during infection and immune evasion on definitive hosts. In the present report we describe the partial characterization of the epitopes recognized by these Mabs by heat treatment, mercaptoethanol reduction, pronase proteolysis and sodium peryodate oxidation, which suggested their predominant protein and conformational nature. Also, a comparative study using immunodetection assays on crude extracts and on histological sections of both rediae and adults of *F. hepatica* were performed to explore the expression pattern of the antigenic determinants in these developmental stages. From these experiments it was found that the Mabs reacted most likely with the same proteins of approximately 64 and 105 kDa present on both rediae and adult's extracts. However, the 1E4, 6G11 and 4E5 Mabs also recognized other molecules of the total extract of *F. hepatica* adults, a fact that constitutes an evidence of the antigenic variation between both stages and points at a certain biological relevance of the recognized antigenic determinants. Immuno localization studies on histological sections revealed that all Mabs reacted with the tegument of *F. hepatica* in both rediae and adults stages, while the

epitopes recognized by 1E4, 6G11 and 4E5 antibodies were also preferentially localized in the intestinal caeca and in different organs of the reproductive system of adult specimens. The immunogenicity of these antigenic determinants, their conserved status among different stages of the life cycle of *F. hepatica* and their presence in both tegument and ES Ag of adult parasites, are suitable features that suggest their potential use for developing an epitope-based vaccine for fasciolosis control.

Medical ozone increases methotrexate clinical response and improves cellular redox balance in patients with rheumatoid arthritis. León Fernández OS, Viebahn-Haensler R, Cabreja GL, Espinosa IS, Matos YH, Roche LD, et al. Eur J Pharmacol. 2016 Jul 20. pii: S0014-2999(16)30471-X. doi: 10.1016/j.ejphar.2016.07.031. [Epub ahead of print]

Medical ozone reduced inflammation, IL-1 β , TNF- α mRNA levels and oxidative stress in PG/PS-induced arthritis in rats. The aim of this study was to investigate the medical ozone effects in patients with rheumatoid arthritis treated with methotrexate and methotrexate+ozone, and to compare between them. A randomized clinical study with 60 patients was performed, who were divided into two groups: one (n = 30) treated with methotrexate (MTX), folic acid and Ibuprofen (MTX group) and the second group (n = 30) received the same as the MTX group + medical ozone by rectal insufflation of the gas (MTX+ozone group). The clinical response of the patients was evaluated by comparing Disease Activity Score 28 (DAS28), Health Assessment Questionnaire Disability Index (HAQ-DI), Anti-Cyclic Citrullinated (Anti-CCP) levels, reactants of acute phase and biochemical markers of oxidative stress before and after 20 days of treatment. MTX+ozone reduced the activity of the disease while MTX merely showed a tendency to decrease the variables. Reactants of acute phase displayed a similar picture. MTX+ozone reduced Anti-CCP levels as well as increased antioxidant system, and decreased oxidative damage whereas MTX did not change. Glutathione correlated with all clinical variables just after MTX+Ozone. MTX + Ozone increased the MTX clinical response in patients with rheumatoid arthritis. No side effects were observed. These results suggest that ozone can increase the efficacy of MTX probably because both share common therapeutic targets. Medical ozone treatment is capable of being a complementary therapy in the treatment of rheumatoid arthritis.

Neuroprotective effect of epidermal growth factor plus growth hormone-releasing peptide-6 resembles hypothermia in experimental stroke. Subirós N, Pérez-Saad H, Aldana L, Gibson CL, Borgnakke WS, Garcia-Del-Barco D. Neurol Res. 2016 Sep 26:1–9.

Background Combined therapy with epidermal growth factor (EGF) and growth hormone-releasing peptide 6 (GHRP-6) in stroke models has accumulated evidence of neuroprotective effects from several studies, but needs further support before clinical translation. Comparing EGF + GHRP-6 to hypothermia, a gold neuroprotection standard, may contribute to this purpose. **Objectives** The aims of this study were to compare the neuroprotective effects of a combined therapy based on EGF + GHRP-6 with hypothermia in animal models of (a) global ischemia representing myocardial infarction and (b) focal brain ischemia representing ischemic stroke. **Methods** (a) Global ischemia was induced in Mongolian gerbils by a 15-min occlusion of both carotid arteries, followed by reperfusion. (b) Focal brain ischemia was achieved by intracerebral injection of endothelin 1 in Wistar rats. In each experiment, three ischemic treatment groups - vehicle, EGF + GHRP-6, and hypothermia - were compared to each other and to a sham-operated control group. End points were survival, neurological scores, and infarct volume. **Results** (a) In global ischemia, neurological score at 48-72 h, infarct volume, and neuronal density of hippocampal CA1 zone in gerbils treated with EGF + GHRP-6 were similar to the hypothermia-treated group. (b) In focal ischemia, the neurologic score and infarct volume of rats receiving EGF + GHRP-6 were also similar to animals in the hypothermia group. **Discussion** With hypothermia being a good standard neuroprotectant reference, these results provide additional proof of principle for EGF and GHRP-6 co-administration as a potentially neuroprotective stroke therapy.

Prevalence of Pneumococcal Nasopharyngeal Carriage Among Children 2-18 Months of Age: Baseline Study Pre-Introduction of Pneumococcal Vaccination in Cuba. Toledo ME, Casanova MF, Linares-Pérez N, García-Rivera D, Peraza GT, Pina IB, et al. Pediatr Infect Dis J. 2016 Sep 19. [Epub ahead of print].

Background A new vaccine candidate against pneumococcus is being developed in Cuba, and it is a priority of the national health system. There is limited information on nasopharyngeal colonization burden, though it is essential for monitoring the impact of the vaccine. The study aims to estimate the prevalence of nasopharyngeal colonization in 2-18 month old toddlers, identify circulating serotypes, antimicrobial resistance, and its association with selected risk factors. **Methods** A cross-sectional study was conducted between October and December 2013 in Cienfuegos municipality. Inclusion criteria were evaluated and informed consent was obtained from the parents. Clinical and epidemiologic data were collected through a semi-

structured questionnaire. Nasopharyngeal swabs according to established protocols were taken. Data analysis included frequency distributions and comparison of proportions. The association between colonization and selected risk factors was assessed by multivariate analysis. **Results** 984 children (87.2% living in urban areas) were included. The overall prevalence of colonization was 21.6%. The most frequent serotypes isolated were: 6A (23.1%), 23F (10.8%), 6B (10.3%), 19F (8.5%) and 14 (3.3%). We found no resistance to beta-lactamases in circulating serotypes. Living with sibling younger than 5 years, previous respiratory infections, previous hospitalization, and day-care attendance were determinants of NP carriage. **Conclusions** The findings suggest that the burden of pneumococcal disease and colonization in Cuba could be significantly impacted after vaccine introduction.

Seroprotection against Vaccine-Preventable Diseases amongst Health Care Workers in a Community Hospital, Qatar. Guanche Garcell H, Villanueva Arias A, Guillarte García E, Alfonso Serrano RN. Int J Occup Environ Med. 2016 Oct;7(4):234–40.

Background Health care workers (HCW) are at high risk of contracting various infectious diseases and play a dual role in the transmission of infections in health care facilities. **Objective** To determine the seroprotection against hepatitis B, measles, rubella, and varicella among HCWs in a community hospital in Qatar. **Methods** This is a cross-sectional survey conducted in a 75-bed community hospital in Dukhan, Qatar. From August 2012 to December 2015, 705 HCWs were tested for the presence of IgG antibodies for measles, rubella, and varicella, and also for hepatitis B surface antigen (HBsAg). They were also asked about previous history of hepatitis B vaccination. **Results** 595 (84.4%) HCWs received a full hepatitis B vaccination schedule; 110 (15.6%) received a single dose. The full schedule was reported with higher frequency by nurses (90.2%) compared to physicians (74.1%) or technicians (79.7%). Those aged ≥ 30 years (90.4%) and < 20 years of work experience had received a full vaccination schedule more frequently than younger and less experienced HCWs. Female HCWs (87.8%) received full schedule more frequently than males (78.8%). 73.4% of the staff had seroprotection against hepatitis B, with the lowest anti-HBsAg titers observed in physicians (58.8%) compared with other categories; males (64.9%) were less protected than females. The seropositivity was 85.6% (95% CI 82.4% to 88.4%) for measles, 94.7% (95% CI 92.2% to 97.3%) for rubella, and 92.2% (95% CI 89.7% to 94.7%) for varicella. **Conclusion** HCWs, particularly physicians, are not enough protected against hepatitis B. The seroprotection against measles, rubella, and varicella.

SUMA technology and newborn screening tests for inherited metabolic disease in Cuba : an overview of the first 30 years. González-Reyes EC, Castells EM, Frómata A, Arteaga AL, Del Río L, Tejeda Y, et al. J Inborn Errors Metabol Screening. 2016 Sep 22.
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The ultramicroanalytic system (SUMA), created in the 1980s, is a complete system of reagents and instrumentation to perform ultramicroassays combining the sensitivity of the micro-enzyme-linked immunosorbent assay (ELISA) tests with the use of ultramicrovolumes. This technology permitted establishing large-scale newborn screening programs (NSPs) for metabolic and endocrine disorders in Cuba. This article summarizes the main results of the implementation during the 30 years of SUMA technology in NSP for 5 inherited metabolic diseases, using ultramicroassays developed at the Department of Newborn Screening at the Immunoassay Center. Since 1986, SUMA technology has been used in the Cuban NSP for congenital hypothyroidism, initially studying thyroid hormone in cord serum samples. In 2000, a decentralized program for the detection of hyperphenylalaninemias using heel dried blood samples was initiated. These successful experiences permitted including protocols for screening congenital adrenal hyperplasia, galactosemia, and biotinidase deficiency in 2005. A program for the newborn screening of CH using the thyroid-stimulating hormone Neonatal ultramicro-ELISA was fully implemented in 2010. Nowadays, the NSP is supported by a network of 175 SUMA laboratories. After 30 years, more than 3.8 million Cuban newborns have been screened, and 1002 affected children have been detected. Moreover, SUMA technology has been presented in Latin America for over 2 decades and has contributed to screen around 17 million newborns. These results prove that developing countries can develop appropriate diagnostic technologies for making health care accessible to all.

The Cuban Institute of Oncology and Radiobiology experience on the beliefs and opinions about digital rectal exam in urological patients. García Figueredo I, Pereda-Meira CM, Morejón Morales A, Correoso Braña K, Candia MN, Zarut Portillo P, et al. Medwave. 2016 Jul 22;16(6):e6501. DOI: 10.5867/medwave.2016.06.6501.

Objective To describe the beliefs, knowledge and opinions that influence the practice of digital rectal examination in a group of urological patients. **Methodology** A descriptive study was conducted using convenience sampling and an anonymous questionnaire with 15 questions. The questionnaire was divided in three blocks: socio-demographic variables; delay in going to the urology clinic and taking the rectal examination; evaluation of patients' perception of pain and discomfort during digital rectal examination and the impact of discomfort on potential future screening compliance. Percentages were used for the descriptive analysis. **Results** Eighty-five surveys were conducted at the Institute of Oncology and Radiobiology of Cuba. The results showed that 70.24% of participants to some extent had information about prostate cancer and 64.29% about prostate specific antigen. Only 27% thought that the digital rectal examination would be helpful, while 66.66% delayed their visit to the urologist in order to avoid the digital rectal examination and 79.76%, to elude the biopsy. It was observed that 52.39% and 36.90% of men complained of moderate and severe pain, respectively. Digital rectal examination was deemed traumatic by 61.9% of the surveyed men. A high number of patients responded they would repeat prostate exam the following year (88.09%) and 94.05% would encourage a friend to have the prostate exam. **Conclusions** More than half of the sample claimed to know about prostate cancer and prostate specific antigen; however, they did not consider helpful to undergo digital rectal examination. The main reasons for not assisting to the urologist was to avoid biopsy and the digital rectal examination. Nonetheless, in most patients traumatic digital rectal examination was performed and responders said they would repeat it in the future.