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(Day 2)

Lung-2015

Nancy Gupta et al., J Pulm Respir Med 2015, 5:3
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A novel mucosal lipopeptide based vaccine against mycobacteria

Nancy Gupta, Dennis Y Kunimoto, Babita Agrawal and **Rakesh Kumar**
University of Alberta, Canada

Tuberculosis (TB) is a major global health threat to humans, with 9.3 million new cases and 2 million deaths annually from *Mycobacterium tuberculosis* infection. BCG is the only available vaccine which is only 0-80% effective. Development of vaccine against mycobacteria is challenging and several experimental vaccine candidates did not demonstrate sufficient efficacy in clinical trials. Early secreted antigenic target 6-kDa (ESAT-6) has been suggested to be an important antigen for protective immunity and BCG lacks ESAT-6. In this study, we aimed to examine the immune responses generated upon immunization with lipopeptides of ESAT-6 and their protective efficacy in a mouse modal of *Mycobacterium tuberculosis* infection. Our results demonstrated that intranasal immunization with lipopeptides of ESAT-6 antigen is capable of stimulating potent and multifunctional antigen specific T-cell responses in spleen and lead to substantial infiltration of immune cells in the Bronchio Alveolar Lavage (BAL). Subcutaneous immunization also induced immune responses in spleen comparable to that obtained from intranasal route but failed to recruit immune cells in the BAL. Pre-immunization of mice with lipopeptides of ESAT-6intranasallyled to a significant reduction in *Mycobacterium tuberculosis* (H37Ra) loads in lungs, liver and spleen compared to subcutaneous vaccination. Our study revealed the potential of lipidated peptides of ESAT-6 antigen as a promising mucosal vaccine against tuberculosis.

Biography

Nancy Gupta completed her PhD and is working in Laboratory Medicine and Pathology under Dr. Rakesh Kumar, Dr. Dennis Kunimoto, University of Alberta Edmonton, Canada.

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Saurabh Garg et al., J Pulm Respir Med 2015, 5:3
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Investigation of novel alkynyl and alkynyloxy pyrimidine nucleoside analogs as antimycobacterial agents

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A rapid increase of the antibiotic resistance against microbial pathogens over the past several decades has become one of the most serious medical challenges to the world. Tuberculosis (TB) caused by *Mycobacterium tuberculosis* is the second leading cause of infectious deaths globally. In 2013, an estimated 9 million people developed tuberculosis and 1.4 million died from this disease. The resurgence of TB cases and the emergence of drug-resistant strains of mycobacteria necessitate the search for new antimycobacterial agents that are non toxic and distinct from the current drugs. We have designed, synthesized and evaluated novel pyrimidine nucleosides (1-20) for their antimycobacterial activities *in vitro*. The 3-N- and or 5-O-propynyl pyrimidine nucleosides (1-14) were synthesized by reacting 5-hydroxy and 5-hydroxymethyl pyrimidine nucleosides with propargyl bromide. 5-Acetylenic nucleosides (15-20) were prepared by coupling 5-iodo pyrimidine nucleosides with trimethylsilyl acetylene followed by de-protection with sodium methoxide. The antimycobacterial activity of compounds 1-20 alone and in combination with first line antituberculosis drug isoniazid was evaluated against *Mycobacterium tuberculosis* (*Mtb*), *Mycobacterium bovis* (*M. bovis*) and *Mycobacterium avium* (*M. avium*) using microplate alamar blue assay. Among alkynyl compounds 5-(2-propynyloxy) uridine (4) and N-3-propynylnucleoside analogs (5 and 12-14) exhibited modest activity against *Mtb* (H37Ra) and *M. bovis* with EC_{50}=160-180 μg/mL, however, they demonstrated strong synergistic interactions with isoniazid. C-5 Ethynyl substituted pyrimidine nucleosides analogs (15-20) were found to be inactive as antimycobacterial agents. Compounds 1-20 did not show cytotoxicity up to the highest concentration tested (CC50>200 μg/mL).

Biography

Saurabh Garg completed his PhD and is working at Laboratory Medicine and Pathology under Dr. Rakesh Kumar, Dr. Robert Rennie, University of Alberta Edmonton, Canada.

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Catheter-directed thrombolysis in patients with Acute pulmonary thromboembolism: A case series at The Brooklyn Hospital Center

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Pharmacomechanical catheter-directed thrombolysis in patients with acute pulmonary thromboembolism (PE) is a proven safe and effective method of preventing complications such as right ventricular collapse, cardiogenic shock and death. Three patients with massive or sub-massive pulmonary embolism presented to the Emergency Department at our institution with shortness of breath and were diagnosed with acute PE using computed tomography pulmonary angiogram (CTA). The patients were: A 57 year-old woman with a history of hypertension and previous thyroid cancer which was treated with thyroidectomy presented with a pulmonary arterial saddle embolus and right cardiac dysfunction; a 55 year-old woman on chemotherapy with a history of deep vein thrombosis (DVT), previous tumor-debulking and extended right hemicolectomy for metastatic leiomyosarcoma presented with a large central pulmonary embolus in the right main pulmonary artery without right ventricular strain; a 54 year-old man with a history of lower extremity DVT with a right main pulmonary artery embolus and right ventricular strain. Based on the clot location in each patient, an EKOS catheter was placed in the main pulmonary artery or its branches and alteplase was infused at a rate of 1mg per hour over 10-24 hours. Simultaneously, the patients were anticoagulated with heparin. The patient's hemodynamic status, coagulation profile and fibrinogen levels were continuously monitored for clinical improvement. The follow-up CTA showed 75% to 100% clot reduction in each patient. Complications included a right-sided groin hematoma at the catheter-insertion site in one patient which required temporary discontinuation of thrombolytic and anti-coagulation therapy. Our observations of these three patients show that this method of treatment is a safe and effective initial measure to restore pulmonary artery blood flow in patients diagnosed with acute PE. However, it is still associated with the risk of complications.

Biography

Jomo Osborne earned his medical degree in his native country Guyana and later completed a Masters of Health Science degree in Cuernavaca, Mexico. He has presented at many international conferences and co-authored several peer review articles and conference abstracts. He is currently a surgical resident at The Brooklyn Hospital Centre. His research interest includes sub-massive pulmonary embolism, minimally invasive surgery and surgical quality improvement.

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Impact of patient education on health related quality of life of COPD patients-A randomized controlled study

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Background: Chronic Obstructive Pulmonary Disease (COPD) comprises a group of diseases associated with airflow obstruction and breathing-related problems. COPD cannot be cured but adherence to the therapy can improve management of symptoms and delay disease progression. Patients' knowledge and awareness about the disease are important in improving quality of life.

Aim: Our study was aimed to assess the impact of patient education on Health Related Quality of Life (HRQoL) of COPD patients.

Method: An open label randomized controlled study was conducted among 206 COPD patients who were admitted in the university hospital after obtaining the ethical clearance. HRQoL of the patients in the control and intervention group at baseline and follow-up visits were measured using St. George Respiratory Questionnaire. Patients were followed up at 6 months during a scheduled visit. Statistical analyses were performed using SPSS® version 20.

Result: Mean age of the study population (n=206) was 58.42±9.72. 93.5% were males. There is no significant difference in overall HRQoL between control (45.2%) and intervention group (44.8%) at baseline. After intervention, overall HRQoL was improved in intervention group ($P<0.05$) compared to control group ($P>0.05$) at follow-up. Study population in the intervention group (at follow-up) has reported better HRQoL compared to the intervention group (at baseline), control group (at baseline) and control group (at follow-up).

Conclusion: The results of the study suggest that the clinical pharmacist can play a major role in improving patient knowledge and thereby improve medication adherence and health related quality of life.

Biography

Suhaj A is an Assistant Professor-Senior Scale in the Department of Pharmacy Practice at MCOPS. He has an expertise and research interest in Drug Safety and Pharmaco-economics, Clinical Pharmacy and Pharmaco therapeutics, Pharmaceutical Care in COPD patients. He is also serving as the member of ISPOR.

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Exobronchial pulmonary eye: Ultrasound guided transbronchial lung biopsy in pulmonary shadows with negative endobronchial findings

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Background: Transbronchial lung biopsy (TBLB) is one of the most imperative applications of flexible bronchoscopy. A diagnostic TBLB may preclude the need for an open lung biopsy.

Purpose: The aim of this study is to clarify the diagnostic acquiesce of ultrasound guided TBLB in pulmonary shadows with negative endobronchial findings in variant parenchymal pulmonary lesions.

Patients & Methods: One hundred and seventeen patients with radiological pulmonary shadows were submitted for fiberoptic bronchscopy and underwent TBLB supported by computed tomography (CT) chest for segmental localization and in place ultrasonographic assessment with ultrasound unit by convex two dimensional probes.

Results: TBLB succeeded in the diagnosis of 79 cases out of 117 cases (67.52%) from first session and failed in 38 cases. Follow up of these cases was considered for two weeks; 18 cases proved to be inflammatory consolidation and improved with nonspecific antimicrobial and 12 cases underwent CT guided true cut biopsy and proved to be:2 cases of pulmonary tuberculosis (TB), 6 cases of squamous cell carcinoma and 4 cases of pulmonary Hodgkin lymphoma. Six cases diagnosed to be adenocarcinoma and 2 cases of sarciodosis by a second TBLB.

Conclusion: The ultrasound guided TBLB specimen can provide valuable information for clinical management in the setting of unifocal localized pulmonary disease without obvious endobronchial finding lending a hand with transthoracic ultrasound for selecting appropriate patients to undergo biopsy and in limiting the differential diagnosis.

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IOS for differential diagnosis of asthma and COPD: An Indian experience

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Introduction: Managing severe persistent asthma with airway remodeling and severe or very severe COPD is a daily challenge for the respiratory practitioner. Impulse Oscillometry (IOS) is simple technique with potential to measure frequency dependent resistive, elastic and inertial properties of the lung during tidal breathing. Understanding the differences in lung functions measured by IOS between asthma and COPD, compared to healthy subjects should help in differential diagnosis and choice of therapy.

Aim: To compare lung physiology by IOS in patients of COPD, Asthma versus Healthy subjects.

Methods: 100 stable-asthma, 101 stable-COPD and 55 healthy subjects underwent pre-post bronchodilator IOS measurement according to ERS/ ATS criteria. Age-corrected Post-bronchodilator measurements were used for comparison analysis using log transformation and ANCOVA.

Results: Compared with healthy subjects, both asthmatic and COPD-subjects had higher resistance (R5Hz, R20Hz), impedance at 5Hz (Z5Hz), reactance at 5Hz (X5Hz), area-of-reactance (Ax) and resonance-frequency (Rf). The differences between asthma and COPD were not appreciable with pre-bronchodilator IOS parameters. However, compared to asthmatics, COPD subjects had higher post bronchodilator frequency dependency R5Hz-R20Hz [0.15 (0.07,0.30) vs. 0.30 (0.21,0.41) P=0.016], X5Hz [kPa/(L/s)] [(median (IQR): -0.20 (-0.37, -0.13) vs. -0.51 (-0.84, -0.29) p<0.0001)], Ax [kPa/L] [median (IQR): (1.293 (0.673, 3.725) vs. 4.702 (2.741, 7.796), p<0.0001)] and Rf [median (IQR) 22.34 (16.40, 28.38) 30.73 (25.60, 35.92), p<0.0001].

Conclusion: IOS can differentiate severe asthma and COPD. The differences are appreciable with post-bronchodilator elastance components (higher in COPD patients e.g. frequency dependency, X, Fers and AX values) but not resistive components, at tidal breathing maneuvers.

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The wheezing child- Is it always asthma?

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Wheezing in infancy and childhood is a common condition; however it is not a single disorder and can be due to causes other than asthma. Not all wheezing is asthma. Wheezing-associated respiratory illnesses in children are often described as asthma, however while most children with asthma show symptoms of wheezing, not all wheezing is related to asthma. Wheezing, coughing and breathlessness are common in young children, and can all be symptoms of conditions other than asthma. Even with all these wheezy children, we still do not know the answers to a number of basic questions. What is the cause and type of the wheezing illness in an individual child? What does it portend for the future of this child? Bronchiolitis refers to a first episode of wheezing, with respiratory distress triggered by a viral infection. Episodic wheezing refers to discrete episodes of wheezing without intermittent symptoms. Unremitting wheezing refers to distinct episodes of wheezing with intermittent symptoms, such as coughing or wheezing at night or in response to exercise, crying, laughter, mist, or cold air. Wheezing Phenotype during the first 6 years of life 1. Never wheezers 51.5% 2. Transient early wheezers 19.8% 3. Late wheezers 19.84%. Persistent wheezers 13.7%. Environmental conditions that increase the rate of bacterial and viral infections are risk factors for transient wheezing, but its relationship to asthma remains unclear. Children with frequent simple colds and other common childhood infections in infancy are less likely to develop persistent wheezing in later childhood. Many preschool children with viral induced wheezing will outgrow these symptoms, and do not have asthma. Generally, asthma is identified by the presence of cough, wheeze and breathing difficulty, together with features of atopy (or a family history of atopy or asthma) and impaired lung function evidenced by spirometry. It is important to explain to parents/carers that wheezing in an infant or preschooler does not mean the child will have asthma or allergies by primary school age. In preschool-aged children with recurrent wheeze (e.g. four or more episodes per year), consider using the Asthma Predictive Index, to estimate whether children are likely to have asthma during primary school years. Asthma Prediction Index has some major criteria and minor criteria. Major criteria are diagnosis of asthma in one or both parent, Diagnosis of atopic dermatitis during the first 3 yr of life, Sensitization against >1 allergen, Minor criteria- Milk, egg, or peanut sensitization. Associated with respiratory infections, Eosinophilia >4%. In the first 3 years of life if anyone who have 1 major criteria or 2 minor criteria is present in one episode, the possibility of asthma in 6-13 years is 59% but 2 episodes possibility is 77%. Investigation -Chest X-Ray, spirometry, CT scan of Chest and Fiber-optic Bronchoscope. It is usually not necessary if history of "classic" asthma or, patient response to salbutamol and or steroid; then only spirometry should be done. But need other investigation when Chronic cough (>1 month), recurrent pneumonia, persistent signs or symptoms are seen despite therapy.

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MicroRNAs in lung cancer development and drug resistance

Bing-Hua Jiang
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Our recent study demonstrates that a number of microRNAs (miRNAs) are downregulated in human lung cancer and those levels of miRNA suppression correlate with advanced cancer stages and drug resistance. The miRNA suppression is involved in inducing tumor growth and angiogenesis through the induction of their direct target genes. To understand the suppression mechanism, we found that some miRNAs are inhibited by the DNA methylation while some miRNAs are inhibited by higher levels of reactive oxygen species (ROS) production in cancer cells. MiRNA suppression is important for autophagy response and drug resistance.

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Lumps, bumps, spots and shadows: The unnerving world of the solitary pulmonary nodule

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The pulmonary nodule is a single, spherical, well circumscribed, radiographic opacity that measures, 3 cm in diameter and is completely surrounded by aerated lung. There is no associated atelectasis, hilar enlargement, or pleural effusion. Approximately 150,000 such nodules are identified each year according to dated estimates. The incidence is likely much higher than this because of the increasing use of chest CT scan for the evaluation of a myriad of pulmonary symptoms and disorders. The National Lung Screening Trial has shown screening patients with low-dose CT (LDCT) scanning led to a relative risk reduction in death from lung cancer by 20%. Over the 3-year screening period, however, 39.1% of the participants in the LDCT scanning group had a nodule discovered, of which (96.4%) were benign. Currently, 7 million Americans meet the National Lung Screening Trial screening criteria. Even if only one-fourth of those eligible are screened, a possible 680,000 new nodules could be discovered over 3 years. Should a national policy for screening for lung cancer with LDCT imaging be broadly implemented in the United States, the incidence of pulmonary nodules has the potential to rise dramatically. During the evaluation of a pulmonary nodule, clinicians usually decide on one of three management strategies: Serial imaging, biopsy, or surgery. This decision is based on their initial assessment of the probability that the nodule is malignant and should take into account the patient's comorbidities and preferences. The focus of this talk is to highlight the challenges with each of the management options and future directions in pulmonary nodule management.

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Regulatory dendritic cell approaches for asthma immunotherapy

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Asthma affects some 300 million people globally and kills ≈250,000 annually. While we can manage most asthmatics pharmacologically these therapies are life-long symptom-based approaches and do not address the underlying Th2 immunologic basis of the disease. What we need are therapies that will reverse these Th2 responses such that the treated individual responds to their allergens in the same way as healthy subjects by mounting regulatory T cell (Treg) responses. Tolerogenic dendritic cells (DC) are found in many body compartments but can also be generated in vitro from bone marrow or monocyte precursors by DC differentiation in the presence of mediators like IL-10, dexamethasone or retinoic acid (RA; reviewed in Front Imm 5:7, 2014). For example, treatment of severely asthmatic mice with allergen-presenting IL-10-induced DC (DC10) abrogates airway hyper responsiveness (AHR) within 3 week of treatment in an IL-10-dependent fashion and progressively diminishes all other asthma traits to background for at least 8 mo. DC10 induce Th2 effector T cells to trans-differentiate into CD25+Foxp3+Treg. Human monocyte-derived DC10 similarly suppress autologous Th2 cells converting these into CD25+LAG3+Foxp3+Treg. However, given that some inflammatory environments can suppress Foxp3 expression by such Treg and thereby convert the Treg into highly pathogenic Th17 cells, we have also developed protocols to generate RA-induced DC (DC-RA) which in turn can induce Th2 cells to differentiate into CD25+LAG3+CD49b-Foxp3-Treg in an IL-27-dependent fashion. Thus, we have the option of inducing distinct kinds to Treg to suit different pathologies.

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Innovating pulmonary rehabilitation for Chronic Obstructive Pulmonary Disease

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Studies have shown that pulmonary rehabilitation and Tai Chi are beneficial to patients with chronic obstructive pulmonary disease (COPD), which is a major public health problem. Long term effectiveness of exercise interventions at completion of formal pulmonary rehabilitation requires exercise adherence. Tai Chi has also been shown to have proven benefits in improving exercise capacity, physiological status, quality of life health related status, self-efficacy and associated with higher compliance to exercise in COPD patients. The author hypothesized that innovating pulmonary rehabilitation by incorporating Tai Chi elements in the exercise component could have complementary benefits. A single-blind randomized controlled study was conducted from March 2011 to May 2012 with a total of 192 COPD patients recruited from four primary care clinics in Hong Kong. They satisfied the eligibility criteria and consented to randomization to either pulmonary rehabilitation program group (PRP) or the group with Tai Chi elements added to PRP (TC). Both groups received rehabilitation consisting of 2 sessions per week for 6 weeks with totally identical content except that Tai Chi exercises were added to TC group. Data collection was performed at baseline, 2 and 6-month post-intervention. Intention-to-treat analysis was performed for 192 subjects. Both groups did not differ in demographics and baseline variables except for COPD staging, mean FEV1, FEV1%-Pred, Saint George Respiratory Questionnaire SGRQ activity score and COPD-CSES self-efficacy score. Statistical improvements were seen in exercise capacity, health status and self-efficacy within both groups at 6-month post-intervention. Although more favorable improvements in physiological outcomes and health status were demonstrated in Tai Chi group, only the functional exercise capacity showed statistical improvement between groups at 6 months post-intervention (β=12.786 meters ; 95% CI=3.794, 21.777; p=0.006). The adjuvant effect of incorporating Tai Chi in pulmonary rehabilitation showed a modest complementary benefit in exercise capacity.

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Pulmonary arterial hypertension, is it a vascular neoplasm?

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Pulmonary arterial hypertension (PAH) is a disease of the small pulmonary arteries characterized by vascular obstruction leading to progressive elevations in pulmonary vascular resistance and pulmonary artery pressures and ultimately right heart failure. In PAH, a distinct vascular lesion known as the plexiform lesion is considered the histological hallmark of this disease. Although plexiform lesions involve the three components: Smooth muscle layer, adventitia and the endothelium, most studies have focused on the smooth muscle component and the role of vasodilators although less than 10% of PAH patients respond fully to simple vasodilators therapy. Thus, the development of new theories has become necessary. Subsequently, augmented endothelial cell proliferation leading to complicated capillary-like channels (angio-proliferation) as the main component of the plexiform lesion has been reported. Furthermore, the discovery of endothelial monoclonality in plexiform lesions of idiopathic PAH further support the "neoplastic hypothesis" of the disease. Several mutations have been linked to both angio-proliferation and inhibition of apoptosis in endothelial cells from plexiform lesions, the whole mark of tumor formation. For instance, alterations in transforming growth factor-β (TGF-β) receptor II may turn endothelial cell insensitive to the cell growth-controlling effects of TGF- β5. Moreover, expression of anti-apoptotic protein survivin has been reported in PAH plexiform lesions. Furthermore, a shift from oxidative phosphorylation to aerobic glycolysis (the Warburg effect) which is originally described in tumor cells has been also described in PAH. Although the recently published IMPRES study using Imatinib, a tyrosine kinase inhibitor in treating severe pulmonary hypertension was considered negative because of the drug toxicity, it has nevertheless confirmed the significant efficacy of these agents in improving the exercise tolerance, symptoms and hemodynamics and further supports the neoplastic features of the disease. This should certainly open the door to develop new diagnostic techniques and targeted therapies against the vascular remodeling component.

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The epidemiological situation of Pulmonary tuberculosis in the penitentiary system

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Relying on the data from World Health Organization and Center for Disease Prevention and Control, we can say that TB is a global epidemic and is among the world's leading deadliest diseases. TB has caused more deaths in youth and adults than any other infectious disease, such that 1 person dies every 10 seconds. The first Guidelines for the Control of Tuberculosis in Prisons were developed and published by the World Health Organization (WHO) and the International Committee of the Red Cross (ICRC) in 1998. TB registered cases in all age group tallies to about 2.8% of the world's population and of this 2.8%, 26% of the cases could have been avoided. This is in the case of developing countries. Since 1990, the society has achieved significant success in the fight against TB as TB cases and related deaths has declined. TB deaths are expected to decrease by 50% globally by 2015. TB is a serious problem in the prison system. TB is 10 times more common in prisoners than in civilians. Approximately, there are about 10 million prisoners in the world. Most of them are men, ages varying between 15 to 45 years. Many of them are either carriers or infected with hepatitis B, C and HIV/AIDS. Infection risk is higher in closed spaces. TB control program in prison consists of three types of screening which includes: Entry screening, re-screening (in a massive scale) and contacts screening. It is important to reduce the risk of transmission of TB in the prison facilities with adequate infection control measures.

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Video-assisted intubation: A case of best evidence practice

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Introduction: Emergency intubation outside the operating room (O.R.) is often performed by non- anesthesia providers and is associated with a higher rate of complications. In our institution we recently introduced the Glidescope Cobalt (Verathon, Bothell, WA) for use in emergency intubations outside the O.R. but it was unclear what impact this introduction would have on intubation outcomes when they were performed by non-anesthesia providers. Therefore the purpose of this study was to evaluate the efficacy of the Glidescope for emergency intubations performed by non- anesthesia personnel.

Methods: After IRB approval a total of 92 subjects (70 Glidescope (GS); 22 Conventional Laryngoscopy (CL)) requiring emergency intubation by non-anesthesia providers (Respiratory Therapists (RT), attending ER and ICU physicians and resident physicians) outside the O.R. were enrolled in this prospective, descriptive study. RT's were required to use the GS exclusively, whereas attending or resident physicians could choose between GS or CL to facilitate the intubation. All personnel were trained on proper use of the GS prior to implementation of the study.

Results: No difference in demographic patient variables, reasons for, or place of intubations was noted between groups. Intubations were primarily performed by attending ER and ICU physicians (44%), medical and surgical residents (31%), and respiratory therapists (RT) (25%). Time to place ETT was 202±297 seconds in the GS group as compared to 560 ± 544 seconds in the CL group ($p<0.001$). ETT placement was more successful in one attempt in the GS group (79%) as compared to the CL group (50%) ($p=0.009$).

Discussion: This study suggests that GS enables a wide range of providers to perform emergency intubations with a higher ratio of success on first attempt. Avoidance of multiple intubation attempts promotes favorable patient outcomes. GS may therefore be useful for emergency airway management in facilities lacking 24 hour anesthesia coverage.

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Genetic diversity of *Mycobacterium tuberculosis* circulating in Indonesia and its geographical distribution and transmission

Mochammad Hatta
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Our recent study demonstrates that a number of microRNAs (miRNAs) are downregulated in human lung cancer and Tuberculosis is still mostly occurring health problem in Indonesia particularly on isolated areas and remote islands. The implementation of National Tuberculosis Programme (NTP) remains low (i.e., other infectious diseases programme) in 29 islands in Flores sea including Liukang Tangaya sub district, Pangkep District, South Celebes Province and also other islands at Kalmas sub district, Indonesia. The purpose of this operational research is to review the exiting TB programme planning and implementation on dispersed remote islands; also to understand the genotyping of M. tuberculosis circulation and its distribution and transmission of tuberculosis. Active survey and structured questionnaires were administered to patients suspect TB and providers' in-charge of TB clinics from isolated islands and search the genotyping all M. tuberculosis samples. The outcome measure was NTP parameters validated using PCR and compared with clinical finding. All data were analyzed by using EPI-Info version 6.02 and clustering effect by GIS. Our results from this research are: Implementation of TB program on Liukang Tangaya island is not working, not as expected; the TB prevalence rate in Liukang Tangaya island is still higher (endemic); the rate of failed TB treatment patients is still high due to transportation obstacles, economic problems and lack of TB medicine supplies; the sensitivity of the Acid fast staining method is lower than culture and PCR assay, measurement of TB infection rate in the corresponding island populations is impossible to be performed because no measurement on its population serologic prevalence; there is a big gap on TB knowledge between community and Health worker; It is not possible to measure the sensitivity of microscopic assay done by Primary health centre (PUSKESMAS) worker because there is no special health worker for TB in the islands and Distribution of cluster TB suspect in the island can be showed by GIS. It is recommended that a new formulation in strategy and application of TB program should be established.

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MicroRNAs in lung cancer development and drug resistance

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Our recent study demonstrates that a number of microRNAs (miRNAs) are downregulated in human lung cancer and those levels of miRNA suppression correlate with advanced cancer stages and drug resistance. The miRNA suppression is involved in inducing tumor growth and angiogenesis through the induction of their direct target genes. To understand the suppression mechanism, we found that some miRNAs are inhibited by the DNA methylation while some miRNAs are inhibited by higher levels of reactive oxygen species (ROS) production in cancer cells. MiRNA suppression is important for autophagy response and drug resistance.

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A dual hit of HIV-1 plus IVDU on Pulmonary vascular remodeling

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Intravenous Drug Use (IVDU) has been found to be one of the major risk factors for HIV-infection in the HIV Related Pulmonary Arterial Hypertension (HRPAH) patients. Our previous findings showing enhanced pulmonary vascular remodeling in HIV-infected lung tissues from IV heroin and/or cocaine abusers indicates that IVDU and HIV-1 potentially act in concert to cause pulmonary arteriopathy. Our study of lung tissues from simian immunodeficiency virus (SIV)-infected morphine treated macaques (VM) demonstrated significant pulmonary vascular remodeling when compared with either the SIV-infected or un-infected morphine treated groups. Furthermore, the endothelial cells (ECs) lining the vessels showing medial hypertrophy or initial stage intimal lesions in lung sections from VM macaques demonstrated an increase in positivity for both TUNEL and Ki67. This observation was supported by cell culture studies demonstrating enhanced apoptosis followed by enhanced proliferation of apoptotic resistant endothelial cells upon simultaneous treatment with HIV-Tat and morphine compared to either treatment alone. However, what causes the polarization of endothelial cells from apoptosis to apoptosis resistant hyper-proliferative state is not clear. In light of the emerging realization of cross talk between autophagy and apoptosis is controlling the cell death and cell-survival, we examined autophagy in ECs exposed to Tat and morphine. Our findings indicate that morphine in combination with viral protein(s) results in the synergistic induction of autophagy of pulmonary ECs that may be involved in switching of apoptotic cells to apoptosis resistant proliferative ECs. This may have led to the increase in the severity of angio-proliferative remodeling of the pulmonary vasculature that was observed on SIV/HIV-infection in the presence of opioids.

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Sensitivity of direct smear microscopy for the diagnosis of TB in high HIV prevalent population Nnewi, Nigeria

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Background: Diagnosis of tuberculosis (TB) amongst HIV patients is a great challenge due to the low density of Acid Fast bacilli (AFB) in their sputum.

Objective: The study was conducted to determine the sensitivity of direct smear microscopy (DSM) for TB diagnosis in HIV endemic setting using culture as a gold standard.

Method: Sputum specimen of 550 TB suspects were screened microscopically for AFB using Ziehl-Nielsen method at NAUTH Nnewi and positive samples subjected to culture on Lowenstein-Jensen medium with each patient also screened for HIV status.

Result: They comprised of 238 (43%) DSM TB positive cases and 312 (57%) DSM TB negative cases. Out of 238 DSM TB positive cases, 180(33%) were culture positive cases with 12(2.1%) culture negative cases, 13 (2.4%) contaminated specimen, 3 (0.5%) NTM and 30(5.5%) lost specimen resulting in 58 (10.5%) specimen which were excluded from analysis respectively. Among the 180 culture positive TB cases 34 (19%) were HIV-positive patients while 146 (81%) were HIV Negative culture positive TB cases, 109 (61%) males as compared to 71 (39%) females within 21-40 years age group mostly affected. Findings from this study showed that the difference in the detection of PTB between these two methods was statistically significant (p=0.0001), identifying high sensitivity case detection rate of DSM as compared to specificity by culture detection more especially in HIV positive persons.

Conclusion: To improve TB case detection for effective treatment, we recommend the use of culture as back up to enhance the specificity and accuracy of DSM especially in HIV positive persons.

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Mesothelioma mimics

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The histological diagnosis of pleural mesothelioma can be very challenging to the histopathologist. Separation of benign from malignant pleural disease is one the most difficult areas in pleural pathology and this topic will be considered. In 22% of 217 cases coming to the US and Canadian Mesothelioma Panel, there was disagreement between one or more panelists as to whether a case was mesothelioma or benign. Mesothelioma has three subtypes such as epithelioid, sarcomatoid (including desmoplastic) and biphasic. The differential diagnosis will therefore be considered in these three categories with demonstration of how to separate the entities. The diagnosis of mesothelioma requires full clinico-radiological-pathological correlation, the availability of adequate samples for the histopathologist, including the parietal pleura, which can provide helpful pointers and the use of special stains, including immunocytochemistry. However special stains have their limitations, as will be shown.

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Pulmonary Tumour Thrombotic Microangiopathy (PTTM)

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Pulmonary tumour thrombotic microangiography (PTTM) is a rare cause of pulmonary hypertension (PH) and is usually discovered at post-mortem. It is associated with gastric and rarely with other carcinomas. We describe the pulmonary vascular pathology and propose a role for transforming growth factor β1 (TGFβ1) in the causation of the vascular occlusion.

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Non-smoking causes of primary lung cancer

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Up to 25% of lung cancer cases worldwide can arise in never smokers. As fewer people smoke in the West, it is now important to consider the non-smoking causes of primary lung carcinoma, as steps will be needed to identify susceptible individuals early, so prevention and/or early diagnosis can be made. We will consider if there is a predisposition for individual (histological) types of carcinoma, polymorphisms may account for differences in response to exposure and if there is a familial predisposition to develop lung cancer. Second-hand smoke alone is not thought to induce cancer, without other factors. Different polymorphisms are described for smokers and recently in never smokers. Epigenetic factors have also been discovered. Occupational factors are considered, such as asbestos and if there needs to be fibrosis for the carcinoma to develop. Nickel, Chromium, Beryllium, Radon and chlorinated solvents will be mentioned. Lifestyle effects, such as cooking (fumes in poorly-ventilated areas from oils), and coal fume exposure, which is possibly due to a polymorphism of glutathione S-transferase. Lifestyle effects such as obesity, dietary factors, including the intake of vegetables with antioxidant properties (carrots, greens), smoking marijuana, bidis and the effect of social class will be discussed, as well as cancers arising post chemotherapy, single nucleotide polymorphisms can affect response to chemotherapy and post radiotherapy.

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A phenotype-based approach to validate biomarkers and identify molecular targets in cancer

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Current methods to predict anti-cancer drug efficacy in humans is often inaccurate in clinical trials. Our novel "disease in a dish" approach overcomes challenges associated with identifying key, disease-relevant targets, in order to rationally develop (combinations of) targeted therapeutics. The ineffectiveness of treatment is in large part attributable to both inter- and intra tumor heterogeneity. Our approach uncovers the molecular basis of aggressive tumor cell phenotypes, directly from individual clinical bio specimens. We segregate tumor cell subsets that are more competent than others for mediating aggressive behavioral properties (form tumors, metastasize, and/or resist therapy). Collectively, these properties have been attributed to "cancer stem cells" or CSC. We have developed novel processes and methods to extract CSC from clinical bio specimens in primarily cultures, and have been able to validate that CSC subsets exhibit distinctive behavioral properties, which can then be directly associated with molecular differences in the same bio specimen.

1. Personalized targeted therapy is important for the effective treatment of cancers; however, it requires the identification and validation of relevant molecular drivers.
2. Our approach introduces phenotypic bioassays for both driver discovery and target validation.
3. Advanced stage disease does not prohibit (and may be advantageous) for associating specific biomarkers with functional phenotypes.
4. Biological discovery that emphasizes the design of appropriate functional bioassays to characterize aggressive cancer cell phenotypes and molecular biology may enable us to rationally halt tumor progression.

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Micro-RNA involvement in Progressive interstitial lung disease associated to systemic sclerosis

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Objective: Systemic sclerosis associated interstitial lung disease (SSc-ILD) is still one of the leading causes of mortality in SSc patients. We analyzed the micro-RNA (miRNA) gene expression of lung tissue and serum in prospective cohorts of patients with SSc-ILD and compared to controls.

Methods: RNA was isolated from lung tissue obtained by open lung biopsy in 12 SSc-ILD patients and from 5 control lungs. High-resolution computed tomography (HRCT) was performed at baseline and 2-3 years after treatment. miRNA and mRNA were analyzed by microarray and the resulting data analyzed by MirConnX network software. miRNA expression was correlated with mRNA expression and changes in the HRCT score (FibMax). Quantitative polymerase chain reaction (qPCR) was performed to confirm differential levels of miRNA.

Results: Lung miRNA microarray data distinguished patients with SSc-ILD from healthy controls with 185 miRNA differentially expressed ($p<0.05$, $q<0.25$). The MirConnX analysis in the lungs revealed 4 relevant upregulated miRNA in the complex mRNA-miRNA network: mir-182, mir-141, mir-155, and mir-195. Mir-21 was also found highly expressed in SSc-ILD lungs. mir-155 and mir-21 correlated strongly with altered lung mRNA expression such as CXCL13, SPP1, collagens and others. Several miRNAs were confirmed to be upregulated in the lungs of SSc-ILD by qPCR. Most importantly, both mir-155 and mir-21 correlated strongly with an image score of lung fibrosis (delta FibMax) with higher expression related to worsening disease.

Conclusions: miRNAs are dysregulated in lungs of SSc-ILD patients with mir-155 and mir-21 associated with progressive lung fibrosis. miRNAs show great potential as biomarkers for progressive SSc-ILD.

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Targeting Nrf2 and AP-1 stress signaling in acute lung injury and repair

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Oxidative stress has been implicated in acute lung injury (ALI) and its severe form, acute respiratory distress syndrome (ARDS) both of which are clinical disorders with significant morbidity and mortality. Cellular stress related to oxygen supplementation (or hyperoxia) which is used as a therapy to maintain adequate tissue oxygenation in pre-term babies has been linked to the development of bronchopulmonary disease (BPD), a chronic lung disease with significant morbidity and mortality. Dr Reddy's lab research is focused primarily on understanding the exact mechanisms underlying defective lung tissue repair and persistent inflammation that are known to enhance susceptibility to bacterial/viral infection in ALI/ARDS patients leading to morbidity and often death in adults and neonates. We found that disruption of the Nrf2 transcription factor which is crucial for antioxidant gene expression impairs the resolution of oxidant (hyperoxia)-induced acute lung injury leading to defective lung tissue repair and persistent inflammation in both neonatal and adult mice. Importantly, our findings revealed that Nrf2 deficiency promotes susceptibility to bacterial infection after hyperoxic exposure ultimately leading to death of the host.We are using both genetic and pharmacologic approaches to elucidate the exact mechanisms by which Nrf2 and AP-1 signaling balance mediate the resolution of lung injury as a means of gaining insight into the development and perpetuation of ALI leading to infectious complications in neonates and adults. We are exploring how to pharmacologically amplify Nrf2-regulated signaling as a novel means to intervene and improve the outcomes of ALI and BPD using preclinical models and ex vivo samples.

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Massive pulmonary embolism: Diagnosis and treatment

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Acute pulmonary emboli can be further classified as massive or sub massive. Massive PE is a catastrophic entity that frequently results in acute right ventricular failure and death. Urgent diagnosis and treatment is vital since death is often within one to two hours of the event. Specific symptoms and signs are not helpful diagnostically because their frequency is similar among patients with and without PE. Thus, additional testing is needed to confirm or exclude the diagnosis of PE. The major diagnostic tests employed in the evaluation of a patient with suspected PE include computed tomography pulmonary angiography (CT-PA), ventilation-perfusion (V/Q) scanning, D-dimer testing, ultrasonography, and conventional pulmonary angiography. Thrombolysis is the mainstay of therapy for massive PE. Other treatment strategies include anicoagulation, vena caval filters, and embolectomy, either catheter directed or surgical.

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Treatment and prevention of asthma through yoga

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According to WHO estimates, 235 million people suffer from asthma. Asthma is the most common chronic disease among children and older people. Asthma is not just a public health problem for high income countries: it occurs in all countries regardless of level of development. Over 80% of asthma deaths occur in low and lower-middle income countries. Asthma is under-diagnosed and under-treated, creating a substantial burden to individuals and families and possibly restricting individuals' activities for a lifetime. Asthma is a universal chronic airway inflammatory disease of the air passage characterized by recurring symptoms, excessive air sensitiveness and airflow obstruction. Asthma can be managed, controlled and cured by alternative medicine like yoga. Some of the yoga exercises like pranayam and meditation have been found very useful for the prevention and treatment of asthma and can be practiced easily by common people. In populous countries including India, yoga practice can be a very cost effective alternative medicine for the prevention and treatment of asthma.

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Lipid nanocarriers: Potential for pulmonary delivery

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Lipid nanoparticles are extensively explored colloidal systems as a potential vehicle for site specific delivery of drugs to different organs or systems such as lung, brain, skin and lymphatic etc. Lipid nanoparticles such as solid lipid nanoparticles, nanostructured lipid carriers, liposomes etc. can help in improving efficacy while lowering toxicities of actives. Cellular uptake of drugs can also be enhanced by using lipid nanocarriers. Pulmonary route of delivery is an alternative non-invasive approach for both local and systemic delivery of therapeutic agents. Formulation of drug into inhalable form with sufficient stability and aerodynamic properties are the key challenges associated with the development of pulmonary drug delivery system. In course of our last few years endeavor to deliver drug loaded lipid nanocarriers for the treatment of local lung disorders, we have come up with efficient systems such as proliposomal dry powder for inhalation and nanostructured lipid carrier dry powder for inhalation. We have explored different approaches for the development of the lipid nanocarrier's inhalation system. In one approach, we have developed proliposomes using single step spray drying method and in other we employed lyophilization technique for the successful development of powders for inhalation with desirable aerodynamic properties. Our studies demonstrate encapsulation of drugs such as rifapentine, montelukast, rosuvastatin etc. in lipid nanocarriers modifies the physicochemical as well as in-vivo pharmacokinetic properties. Pulmokinetic parameters such as Cmax, Tmax, AUC0-24, KE, MRT and t1/2 were improved as compared to pure drug. An interesting finding was increased IC50 value of the encapsulated drug, thus reduced in-vitro cytotoxicity in pulmonary cells as compared to the conventional system. Our focus is on application of Quality by Design (QbD) principles for the development of inhalation delivery systems so as to comply with the current regulatory demand. Thus, our group is the first to report the successful application of QbD principles with design of experiment for the efficient development of proliposomal system for inhalation. The talk will highlight the findings of our research.

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The progress of our understanding of pulmonary vascular disease and treatment options

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Pulmonary vascular disease (PVD) is a progressive and potentially fatal disease. Our understanding of PVD has significantly improved over the last 2 decades. This understanding of the different pathophysiologic pathways that lead to PVD has led to the successful development of multiple effective therapeutic interventions. Although this is in general an incurable disease, these therapies are able to control the disease, improve quality of life, and potentially prolong survival. Not all pulmonary vascular diseases are the same. The above mentioned therapies are effective for only one sub-group of pulmonary hypertension (PH): The one classified by the World Health Organization as WHO group 1 PH. This WHO classification of PH is not perfect and there is a lot of overlap in the clinical and pathophysiologic features of the different groups, however it is this classification that facilitated research trials enrollment that lead to effective therapeutics. Better phenotyping of PVD is much needed. The 3 successfully targeted pathways in pulmonary vascular disease in WHO group 1 PH are the Nitric Oxide, Endothelin-1, and prostanoid pathways. The primary effect of the approved drugs targeting these different pathways is vasodilation, although many of them have supplementary but secondary potential effects, such as anti-platelets and/or anti-inflammatory effects. Drugs targeting the primary pathologic processes in WHO group 1 PH are still lacking, and that's a major reason why a cure has not been identified yet. In summary, although progress has been made, we still have ways to go to better understand and treat pulmonary vascular disease.

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