BRONCHIOLITIS

A MEDICAL DICTIONARY, BIBLIOGRAPHY,
AND ANNOTATED RESEARCH GUIDE TO
INTERNET REFERENCES

JAMES N. PARKER, M.D.
AND PHILIP M. PARKER, PH.D., EDITORS

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FORWARD

In March 2001, the National Institutes of Health issued the following warning: "The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading."[1] Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. Since only the smallest fraction of information dealing with bronchiolitis is indexed in search engines, such as **www.google.com** or others, a non-systematic approach to Internet research can be not only time consuming, but also incomplete. This book was created for medical professionals, students, and members of the general public who want to know as much as possible about bronchiolitis, using the most advanced research tools available and spending the least amount of time doing so.

In addition to offering a structured and comprehensive bibliography, the pages that follow will tell you where and how to find reliable information covering virtually all topics related to bronchiolitis, from the essentials to the most advanced areas of research. Public, academic, government, and peer-reviewed research studies are emphasized. Various abstracts are reproduced to give you some of the latest official information available to date on bronchiolitis. Abundant guidance is given on how to obtain free-of-charge primary research results via the Internet. **While this book focuses on the field of medicine, when some sources provide access to non-medical information relating to bronchiolitis, these are noted in the text.**

E-book and electronic versions of this book are fully interactive with each of the Internet sites mentioned (clicking on a hyperlink automatically opens your browser to the site indicated). If you are using the hard copy version of this book, you can access a cited Web site by typing the provided Web address directly into your Internet browser. You may find it useful to refer to synonyms or related terms when accessing these Internet databases. **NOTE:** At the time of publication, the Web addresses were functional. However, some links may fail due to URL address changes, which is a common occurrence on the Internet.

For readers unfamiliar with the Internet, detailed instructions are offered on how to access electronic resources. For readers unfamiliar with medical terminology, a comprehensive glossary is provided. For readers without access to Internet resources, a directory of medical libraries, that have or can locate references cited here, is given. We hope these resources will prove useful to the widest possible audience seeking information on bronchiolitis.

The Editors

[1] From the NIH, National Cancer Institute (NCI): **http://www.cancer.gov/cancerinfo/ten-things-to-know**.

CHAPTER 1. STUDIES ON BRONCHIOLITIS

Overview

In this chapter, we will show you how to locate peer-reviewed references and studies on bronchiolitis.

The Combined Health Information Database

The Combined Health Information Database summarizes studies across numerous federal agencies. To limit your investigation to research studies and bronchiolitis, you will need to use the advanced search options. First, go to **http://chid.nih.gov/index.html**. From there, select the "Detailed Search" option (or go directly to that page with the following hyperlink: **http://chid.nih.gov/detail/detail.html**). The trick in extracting studies is found in the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Journal Article." At the top of the search form, select the number of records you would like to see (we recommend 100) and check the box to display "whole records." We recommend that you type "bronchiolitis" (or synonyms) into the "For these words:" box. Consider using the option "anywhere in record" to make your search as broad as possible. If you want to limit the search to only a particular field, such as the title of the journal, then select this option in the "Search in these fields" drop box. The following is what you can expect from this type of search:

- **Recognizing the Extra-Articular Manifestations of RA**

  Source: Journal of Musculoskeletal Medicine. 19(8): 307-310,312,314-315. August 2002.

  Summary: This journal article discusses extra-articular manifestations of rheumatoid arthritis (ExRA). Predictors for ExRA include severe articular disease, a positive antinuclear antibody assay, the presence of IgA rheumatoid factor, increased levels of circulating immune complexes, and the early development of rheumatoid nodules. Rheumatoid nodules, atrophy, erythema nodosum, skin fragility, livedo reticularis, pyoderma gangrenosum, Sweet syndrome, and vasculitis are some cutaneous manifestations of rheumatoid arthritis (RA). The eyes are frequently involved in RA, with manifestations such as episcleritis, scleritis, limbic ulceration, keratoconjunctivitis sicca, and blepharitis. Pulmonary manifestations associated with RA consist of pleuritis, parenchymal lung disease, bronchiectasis, **bronchiolitis** obliterans with organizing

pneumonia, Caplan syndrome, pulmonary hypertension, and empyema. Cardiac manifestations include vasculitis, pericarditis, aortitis, myocarditis, and nodular valve disease. Vasculitic manifestations are common in patients with RA and include cutaneous arteriolitis, medium-sized arteritis, and small-vessel vasculitis. Chronic inflammation of the antlantoaxial joint, peripheral neuropathies, and CNS vasculitis are some of the neurologic manifestations of patients with RA. Kidney disease is a less common manifestation of RA. There is an increased incidence of both Hodgkin and non-Hodgkin lymphoma and leukenias in patients with RA. The most common hematologic manifestation of RA is hypergammaglobulinemia. Systemic disease may result from adverse effects of treatment with pharmacologic agents. Specific treatment depends on the organ system involved; the overall goal of therapy is control of the underlying rheumatoid process. 27 references, 4 figures, and 2 tables. (AAM).

Federally Funded Research on Bronchiolitis

The U.S. Government supports a variety of research studies relating to bronchiolitis. These studies are tracked by the Office of Extramural Research at the National Institutes of Health.[2] CRISP (Computerized Retrieval of Information on Scientific Projects) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other institutions.

Search the CRISP Web site at **http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen**. You will have the option to perform targeted searches by various criteria, including geography, date, and topics related to bronchiolitis.

For most of the studies, the agencies reporting into CRISP provide summaries or abstracts. As opposed to clinical trial research using patients, many federally funded studies use animals or simulated models to explore bronchiolitis. The following is typical of the type of information found when searching the CRISP database for bronchiolitis:

- **Project Title: 2-5A ANTISENSE INHIBITION OF RESPIRATORY SYNCTIAL VIRUS**

  Principal Investigator & Institution: Cramer, Hagen; Ridgeway Biosystems, Inc. 9500 Euclid Ave, Nd-50 Cleveland, Oh 44195

  Timing: Fiscal Year 2001; Project Start 01-AUG-2001; Project End 31-JUL-2004

  Summary: (Adapted from Applicant's Abstract): Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract disease in infants, young children and the elderly, particularly those that are institutionalized. It is the most common cause of viral **bronchiolitis** and pneumonia in children, and outbreaks frequently reach epidemic proportions during the winter months, accounting for roughly 90,000 hospitalizations and 4,500 deaths per year. Gemini Technologies, Inc. is developing novel antisense chimeras for use in the treatment of RSV infections. These chimeras are comprised of an antisense component to the targeted viral RNA genome, while the 2-5A portion of the chimera attracts and activates RNase L, an endoribonuclease that can cleave the associated genomic RNA strand. In the phase I studies, we succeeded in synthesizing and testing a second generation anti-RSV chimera that had potent antiviral activity in

[2] Healthcare projects are funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Healthcare Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).

cultured cells and in primates. Here we propose to carry this compound through more definitive animal studies, utilizing aerosol delivery to mimic the clinical application of this compound. In addition, we propose medicinal chemistry-based studies aimed at improving chimera synthesis, and preliminary toxicology studies. PROPOSED COMMERCIAL APPLICATION: NOT AVAILABLE

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: AGE-DEPENDENT INCREASES IN AIRWAY RESPONSIVENESS BY RSV**

  Principal Investigator & Institution: Gelfand, Erwin W.; National Jewish Medical & Res Ctr and Research Center Denver, Co 80206

  Timing: Fiscal Year 2004; Project Start 01-SEP-1999; Project End 30-APR-2008

  Summary: (provided by applicant): Respiratory syncytial virus (RSV) is the leading cause of **bronchiolitis** and lower respiratory tract infection in infants. Acute RSV leads to wheezing, and re-infection, a common event, results in even more severe airway symptoms. The pathogenic basis for the association between RSV and reactive airway disease and the subsequent development of asthma is not clearly elucidated. Nonetheless, RSV **bronchiolitis** in infancy appears associated with an increased risk for later development of asthma, a risk that may persist for several years. We have demonstrated in a murine model that prior RSV infection enhances the airway response (airway inflammation and hyperresponsiveness) to subsequent allergen exposure. Our hypothesis is that the age at initial RSV infection not only plays an important role in response to the acute infection, but also dictates or shapes the response to subsequent re-infection with RSV or allergen exposure. Both the immune/inflammatory responses and neurogenic control of airway function are age-dependent. We now know that the younger the age at initial encounter with RSV, the more vigorous the inflammatory response and airway responsiveness are, both acutely and subsequently on re-infection or allergen-exposure. Using a model of RSV infection/re-infection/allergen exposure, we will further characterize the immune/inflammatory responses and airway function following RSV infection in < 1, 3 and 8 week old mice. In these responses, we will systematically define the role of RSV structural proteins, cytokine production, neuropeptide levels, the production of RSV-specific antibody, especially IgE, and identify, at the T cell level, how acute RSV at the different ages influences the differentiation of T helper cells. Based on this information, we will then define how these factors direct the subsequent response to re-infection or allergen. The approach proposed is supported by extensive preliminary data, the availability of all of the molecular and cellular techniques, reagents and mutant strains of mice, as well as the ability to monitor infection and lung function in mice less than 1 week of age. The information generated from these studies will delineate the important age-dependent influences on the immune/inflammatory response in the lung and reveal new options for therapeutic intervention to prevent the long-term sequelae of RSV infection in infancy.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: BASIS OF LONG-TERM VIRUS-INDUCED GOBLET CELL HYPERPLASIA**

  Principal Investigator & Institution: Holtzman, Michael J.; Professor; Internal Medicine; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 30-JUN-2007

Summary: (provided by applicant): The long-term goal of this proposal is to understand how respiratory viral infections lead to chronic hypersecretory airway diseases like asthma. The present proposal focuses on new findings related to the role of respiratory viruses in fine development of long-term goblet cell hyperplasia. This focus derives from our studies of mice and mouse tracheal epithelial cells successively defining that paramyxoviral infection produces not only acute **bronchiolitis** but also triggers a chronic response with airway hyperreactivity and goblet cell hyperplasia lasting at least a year after viral clearance. This chronic response proceeds despite protection from acute airway infammation and hyperreactivity, and in contrast to allergen challenge, the chronic response persists indefinitely and is uninfluenced by IFN-gamma deficiency. Similar to allergen, the chronic response is at least partially prevented by glucocorticoid treatment. The virus-induced chronic response also exhibits genetic susceptibility allowing for the identification of candidate target genes by a combined genetic/microarray strategy. Memory for the chronic response appears to be contained in the adaptive immune system allowing for adoptive transfer in vivo and in vitro. In addition, we find similar phenotypic responses in human subjects with asthma. Thus, we propose that paramyxoviruses cause both acute airway inflammation/hyperreactivity and chronic airway remodeling/hyperreactivity phenotypes (the latter by a hit-and-ran strategy since viral effects persist after clearance). Further, each of these phenols (acute inflammation/hyperreactivity, chronic hyperreactivity, and chronic goblet cell hyperplasia) may be genetically segregated and therefore depend on distinct controls that appear critical for the development of lifelong airway diseases. Accordingly, we have the following specific aims: I. Use a mouse model of **bronchiolitis** to define how specific candidate genes control longterm virus-induced goblet cell hyperplasia and how immune cells mediate this response. Here, we develop a plan to identify and characterize our first candidate gene, i.e. mouse calcium-activated chloride channel (mCLCA3) as well as a specific immune cell subset, i.e., virus-specific CD8+ memory T cells. II. Use isolated airway epithelial cells to define the molecular basis for how specific candidate genes and immune cells cause goblet cell hyperplasia in coordination with Aim I. III Use healthy and asthmatic subjects in a glucocorticoid treatment-withdrawal model to define the relationship between goblet cell hyperplasia and the status of candidates from Aims I and II.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CD40 AND TGFB IN HUMAN LUNG TRANSPLANT CHRONIC REJECTION**

  Principal Investigator & Institution: Mckee, Charlotte M.; Brigham and Women's Hospital 75 Francis Street Boston, Ma 02115

  Timing: Fiscal Year 2002; Project Start 16-JUL-2001; Project End 01-AUG-2002

  Summary: Chronic rejection is the most important clinical problem in human lung transplantation. The underlying causes of this process (which is manifest as obliterative **bronchiolitis** (OB) in lung transplants) are not completely understood, but host anti-donor cellular immunity has been shown to be a key factor. The CD40 costimulatory pathway is critical for optimal cellular immune responses, and evidence suggests that CD40 activity plays a major role in chronic rejection. However, the mechanism(s) by which CD40 facilitates chronic rejection are not known. CD40 signaling can induce the production of TGFbeta, a pro-fibrotic cytokine whose role in chronic rejection and organ fibrosis is well-established, in human B cells. We postulate that CD40-mediated induction of TGFbeta1 by alveolar macrophages (AM), which are important sources of this cytokine in pulmonary fibrosis, represents a mechanistic link between CD40 activity

and chronic rejection. We therefore propose to study 1) indices of CD40 activity in tissues from lung transplant patients with OB and from patients with acute rejection (who are at increased risk of developing OB) and 2) the ability of CD40 signaling to induce TGFbeta1 in AM from lung transplant patients. The Principal Investigator has an extensive background in basic immunology and clinical lung transplantation. The research project outlined here will train her to integrate these elements of her background and to approach clinical problems such as chronic rejection with the combined tools of basic science and clinical research. This award will provide her with the training, resources and protected time she needs to establish a successful career as an independent investigator in lung transplant immunology.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CELLULAR NECROSIS INDUCED BY MYCOBACTERIUM TUBERCULOSIS**

  Principal Investigator & Institution: King, C Harold.; Medicine; Emory University 1784 North Decatur Road Atlanta, Ga 30322

  Timing: Fiscal Year 2002; Project Start 15-SEP-2002; Project End 31-DEC-2003

  Summary: (provided by applicant): A key step in the pathogenesis of M tuberculosis is its ability to cause caseating necrosis, parenchymal lung destruction, and cavity formation, which develop into the characteristic necrotizing bronchointerstitial pneumonia and **bronchiolitis** of tuberculosis. M tuberculosis is cytotoxic to epithelial cells in vitro, and we have shown that this cytotoxicity is associated with cell membrane permeation to lactose dehydrogenase and is mediated by necrosis of lung epithelial cells after infection with virulent mycobacteria (Dobos, K. M., Quinn, F. D. and King, C. H. 2000, Infect. Immun. 68:6300-6310). Interestingly, the attenuated M bovis BCG does not induce necrosis in this epithelial cell model suggesting that necrosis is related to the virulence of mycobacteria. Our working hypothesis is that M tuberculosis possesses factors that cause necrosis. We intend to identify the genes that encode or synthesize such factors and determine their functions. Towards this goal, we have been successful in isolating two such (necrosis-deficient) mutants with insertions into genes that have no known function by screening a transposon library of the Erdman strain of M tuberculosis (TN5370) for mutants that have lost their ability to cause cell membrane permeation and necrosis. Both nec mutants possess extremely interesting phenotypes when grown in mice. The first mutant (necA) appears to be highly attenuated for growth and virulence in SCID mice. This is an important result as it suggests that we have identified a gene whose product either directly causes necrosis or induces necrosis and thus should enhance our understanding of tuberculosis pathogenesis. Interestingly, the second mutant (necB) appears to kill SCID mice more rapidly than the parental strain. We intend to characterize these mutants, characterize the functions of the gene products, and extend this mutant isolation strategy to identify a large battery of mutants defective for necrosis of host cells.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CHEMOKINE BIOLOGY IN BRONCHIOLITIS OBLITERANS SYNDROME**

  Principal Investigator & Institution: Belperio, John A.; Medicine; University of California Los Angeles 10920 Wilshire Blvd., Suite 1200 Los Angeles, Ca 90024

  Timing: Fiscal Year 2002; Project Start 15-MAR-2001; Project End 28-FEB-2006

Summary: (Adapted from applicant's abstract) Chronic lung allograft rejection, **Bronchiolitis** Obliterans Syndrome (BOS) is a chronic process that demonstrates features of dysregulated and aberrant repair of airways. This process of fibroproliferation and deposition of extracellular matrix that ultimately leads to fibro-obliteration of airways, and impaired lung function. In this proposal, the investigators hypothesize that the persistent expression of monocyte chemoattractant protein-1 (MCP-1) during an allogeneic response and recruitment and activation of mononuclear phagocytes expression CC chemokine receptor 2 (CCR2) is a pivotal event that promotes the continuum of acute to chronic lung allograft rejection. Specifically, MCP-1 production, and the recruitment and activation of CCR2 expressing mononuclear phagocytes occurs during acute rejection. Moreover, the persistent presence of MCP-1 in the allograft maintains recruitment and activation of specific populations of mononuclear phagocytes expressing CCR2. These cells have a unique pro- fibrogenic phenotype that promotes fibrogenesis of chronic allograft rejection, BOS. Understanding the interaction between MCP-1 and CCR2 during the continuum of acute to chronic lung allograft rejection, will lead to novel therapies in the treatment and prevention of BOS. This proposal ,will test this hypothesis by performing the following experiments: I) determine the time-course, magnitude of expression, and cellular sources of MCP-1, as correlated to the recruitment of monocular cells expression CCR2 in an orthotopic rat model of acute lung allograft rejection. II) determine the specific contribution of MCP-1 to the pathogenesis of acute lung allograft rejection by a strategy of depletion of MCP-1. III) determine the time-course of MCP-1 expression, as correlated to the recruitment of mononuclear cells expression CCR2 in a murine model of BOS. B) determine the specific contribution of MCP-1/CCR2 biology to the pathogenesis of BOS by using genetic approaches for deletion of the bioactivity of MCP-1 and/or CCR2. IV) determine if CCR2 expression mononuclear phagocytes are phenotypically profibrogenic (i.e., produce higher levels of TGF-beta and PDGF) and promote fibrogenesis during the pathogenesis of BOS. By successfully completing these objectives, the applicants hope to have gained significant insight into the persistence of MCP-1/CCR2 biology that impacts on the continuum and transition of acute lung allograft rejection to BOS. The understanding of this pathobiology will lead to novel therapies in the treatment and prevention of chronic lung allograft rejection, BOS.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CHEMOKINES IN LUNG TRANSPLANTATION**

  Principal Investigator & Institution: Medoff, Benjamin D.; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114

  Timing: Fiscal Year 2003; Project Start 04-AUG-2003; Project End 31-JUL-2008

  Summary: (provided by applicant): With the proposed Mentored Clinical Scientist Development Award the applicant will continue his investigations into basic mechanisms of lung inflammation. After two productive years in this laboratory the applicant remains firmly committed to a career in academic pulmonary medicine. The proposed research will allow the applicant to master a broad range of laboratory techniques in immunology, cell, and molecular biology. The research experience will be supplemented by a program of study of immunology and medical science. The project focuses on the development of inflammation and fibrosis following lung transplantation and the role of chemokines in these processes. After a lung is transplanted there may be several types of injury to the graft, including ischemia-reperfusion injury, acute rejection, and chronic rejection. These immune mediated injuries contribute to the development of scarring of the airways, so called **bronchiolitis** obliterans (BO). Over

50% of all lung transplants will develop BO after transplantation, and this remains the major cause of morbidity and mortality after lung transplantation. Neutrophils have been shown to be a prominent component of ischemia-reperfusion injury while T lymphocytes are the primary mediators of both acute and chronic rejection. The proposed project will determine which chemokines are produced after transplantation and their contribution to the development of graft injury and subsequent BO. Further experiments will manipulate chemokine or chemokine receptor expression in animal models of lung transplantation to investigate their role in the development of graft injury and BO. The applicant specifically proposes to: (1) investigate the expression of chemokines and chemokine receptors in the lung following transplantation in patients with and without acute rejection and BO; (2) investigate the role of chemokines in the development of ischemia-reperfusion injury in the airways using the murine tracheal heterotopic model of lung transplantation; (3) investigate the role of chemokines in the development of acute airway rejection and the development of BO in the murine tracheal heterotopic model of lung transplantation; (4) develop a novel murine model of airway rejection and BO.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: COMPLEMENT MEDIATED INJURY IN ALLOGRAFT REJECTION**

  Principal Investigator & Institution: Baldwin, William M.; Associate Professor; Pathology; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2003; Project Start 01-AUG-1994; Project End 31-MAR-2008

  Summary: (provided by applicant): This continuation application is based on our novel finding that a deficiency of C6, which prevents assembly of the membrane attack complex (MAC), can delay acute allograft rejection from 7-10 days to greater than 6 weeks. This finding is of potential importance for 4 reasons. First, it demonstrates that complement (C), which is not suppressed adequately by conventional immunosuppressive agents used clinically, can play a significant role in acute allograft rejection. Second, this does not appear to be a strain-specific or anecdotal effect, because acute rejection is inhibited in all of the high responder strains into which we have now bred the C6 deficiency. Third, the effects C6 deficiency are not limited to one type of vascularized allografts, but affects transplants of both heart and lung. Fourth, C6 deficiency delays both acute rejection and chronic graft vasculopathy. Preliminary data indicate that donor and recipient sources of C6 can contribute to graft injury and rejection. Our hypothesis is that C from donor and recipient sources contribute to early tissue injury initiated by physiological stress as well as antibody deposition. The specific aims are to test mechanisms that control C6 production and activation in allografts. We will use an interrelated series of in vivo experiments that take advantage of congenic C6 deficient rat strains that we have bred to determine: 1) the source of C6 in acute injury cardiac and lung transplants, 2) the source of C6 in chronic vasculopathy and obliterative **bronchiolitis,** and 3) the role of altered expression of membrane-associated C regulators. The experimental approach will utilize the novel C6 deficient strains of rats that we developed in the first funding period of this project for both in vivo cardiac transplant studies and as sources of C6 deficient cells for in vitro studies. Most importantly, we will use our extensive clinical material to verify the relevance of our experimental findings to humans.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DENDRITIC CELLS, RSV AND INFLUENZA INFECTION IN CHILDREN**

  Principal Investigator & Institution: Ramilo, Octavio; Associate Professor; Pediatrics; University of Texas Sw Med Ctr/Dallas Dallas, Tx 753909105

  Timing: Fiscal Year 2004; Project Start 15-APR-2004; Project End 31-MAR-2006

  Summary: (provided by applicant): Respiratory syncytial virus (RSV) is the principal etiologic agent of **bronchiolitis** and viral pneumonia in infants and young children worldwide. Influenza viruses also contribute to significant number of hospitalizations among children. While the clinical manifestations are similar, there are remarkable differences in terms of their immune responses. In a simplified comparison, RSV does not induce protective immunity, there is no available vaccine, and it is associated with recurrent wheezing. In contrast, influenza does induce a more effective protective immune response, vaccines are quite effective, and it is not associated with long-term wheezing. This provides an ideal setting for a comparative analysis of the immune responses of children with these two viral infections. Dendritic cells (DCs) constitute a complex system of cells with a unique ability to induce primary immune responses. In addition, emerging evidence indicates that DCs control cytokine production by T cells and regulate the Th1/Th2 balance of the immune responses. Numerous studies have demonstrated the importance of the interaction between viruses and different DCs subsets and how that initial interaction influences the development of the subsequent immune responses. Although to date, not much is known about the interaction between DCs and RSV, our preliminary results suggest a direct participation of DCs in the immune response to RSV infection in children. Our hypothesis is that RSV and influenza virus target DC differentially leading to different immune responses, mostly deleterious in case of RSV and protective in case of influenza. We will begin to address this hypothesis in the following specific aims: 1. To determine how RSV and influenza infection affect human DC subsets in vivo, and 2. To determine how RSV and influenza infection affect human DC subsets in vitro, These studies will permit us to define the nature of the DC subset(s) that constitute the target of RSV and influenza infection in children, and begin to identify the mechanisms implicated in the interaction between these respiratory viruses and DCs.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DETERMINANTS OF EPITHELIAL SURVIVAL IN AIRWAY ALLOGRAFTS**

  Principal Investigator & Institution: Neuringer, Isabel P.; Medicine; University of North Carolina Chapel Hill Aob 104 Airport Drive Cb#1350 Chapel Hill, Nc 27599

  Timing: Fiscal Year 2002; Project Start 07-MAY-2001; Project End 30-APR-2006

  Summary: (provided by applicant) Lung transplantation has become a viable option for the treatment of end-stage lung disease, as surgical techniques and immunosuppressive therapies have improved. The major cause of late mortality and morbidity post-transplant is obliterative **bronchiolitis** (0B), characterized by a progressive decline in lung function and small airway fibroobliteration. Recurrent acute rejection predisposes to 0B, but HLA mismatch, ischernic injury, and infection may contribute, resulting in irreversible injury to the airway epithelium. A mouse model of heterotopic airway transplantation reproduces the histopathological lesion of 0B, and has been employed to investigate the pathogenesis of this disorder. In this model, allograft epithelium regenerates and proliferates vigorously, yet undergoes rapid, irreversible injury, through augmented apoptotic pathways, leading to airway denudation and

fibroobliteration. We hypothesize that the survival of the airway epithelium is critical to preventing the ingrowth of fibroproliferative matrix, and that pro-apoptotic mediators present in the alloirnmune environment alter the normal kinetics of airway epithelial cell cycle-regulated proliferation and repair. The overall objective of this proposal is to determine dominant pathways of airway epithelial death in OB as mediated through cell cycle regulators p2l and p53, and assess the role of TGFB-1, a potent inhibitor of airway epithelial cell growth, in modulating the expression of these proteins. Specifically, we will quantitatively assess epithelial cell proliferation and cell cycle regulatory proteins in heterotopic mouse airway grafts, test the role of TGFB-1 in promoting airway epithelial cell death using in-vitro cell culture and in-vivo animal models, and lastly evaluate the kinetics of airway epithelial cell growth and death in clinical specimens with active OB lesions. This project will involve intensive training in tissue culture of rodent and human airway epithelium, protein chemistry, immunology, molecular biology techniques, and pulmonary pathophysiology and pathology, in a unique environment that will facilitate the development of independent investigation in pulmonary diseases.

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- **Project Title: EFFECT OF DENERVATION ON THE FUNCTION OF THE AIRWAYS**

  Principal Investigator & Institution: Perez Fontan, J Julio.; Aluni Endowed Professor; Pediatrics; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2002; Project Start 01-APR-1997; Project End 31-MAR-2005

  Summary: The nervous system modulates the responses of the airways to inflammatory stimuli. The studies described here continue ongoing research into the role of substance P and other preprotachykinin (PPT)-A gene-encoded tachykinins in this modulation. The proposed work applies genetically altered murine systems to: 1. define the topographical organization and hierarchical connectivity of the airway's peptidergic sensory-motor network, 2. identify the cellular origin of the PPT-A tachykinins released in response to inflammatory stimuli and elucidate the contribution of three candidate cell types (sensory neurons, intrinsic ganglia, or hemopoietic cells) to the ensuing injury, and 3. establish whether over-expression of the PPT-A gene can in itself produce an inflammatory injury or requires a separate inflammatory stimulus. Aim 1 will be accomplished by examining the expression of a fluorescent protein (ECFP) placed under the transcriptional control of the PPT-A 5' regulatory region in conjunction with tracking studies using pseudorabies virus as a retrograde trans-synaptic marker. Aim 2 will be approached by a combination of selective chemical ablation of C-fibers by capsaicin and bone marrow reconstitution experiments in wild type mice and mice homozygous for targeted disruptions of the PPT-A and NK-1 receptor genes. The effects of these manipulations will then be compared in intact, inflamed (immune complex, Sendai virus, and stretch-induced), and denervated airways (selective C-fiber ablation and heterotopic tracheal transplantation). Aim 3 will be achieved by analyzing the effects of transgenic manipulations of the PPT-A gene resulting either in ectopic constitutive overexpression of PPT-A in airway epithelial cells or in isotopic inducible over-expression of PPT-A in intact and inflamed airways (see above). Completion of these aims will improve our understanding of airway neurogenic injury and may help to develop therapeutic strategies to minimize tachykinin amplification of immune-mediated inflammation of the lungs and airways in disease processes such as **bronchiolitis** obliterans after lung transplantation or hyperoxic/stretch injury after mechanical ventilation.

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- **Project Title: EFFECTS OF MAJOR BASIC PROTEIN ON HUMAN AIRWAY CELLS**

  Principal Investigator & Institution: Wylam, Mark E.; Mayo Clinic Coll of Medicine, Rochester 200 1St St Sw Rochester, Mn 55905

  Timing: Fiscal Year 2002

  Description (provided by applicant): Eosinophils are central to the pathogenesis of asthma. Activated eosinophils release several polycationic protein substances, which are associated with an increase in airway smooth muscle (ASM) contractile response. The long-term goal of the proposed studies is to understand the mechanism(s) by which eosinophil-derived proteins alter ASM contractile responses. Deposits of polycationic proteins released from activated eosinophils, including MBP, are found within both airway epithelial and smooth muscle layers of airways of patients dying from status asthmaticus. Recent studies by others indicate that MBP increases force in airways indirectly through an effect on airway epithelium or by inhibiting airway muscarinic M2 receptors. In addition, recent work in our laboratory indicates that MBP and other model polycationic proteins directly elevate intracellular calcium concentration ([Ca2+]i) in cultured ASM cells in a concentration-dependent manner and increase basal force generation in an epithelium-independent manner in ASM strips. It is possible that alteration in both epithelial and myocyte [Ca2+]i mobilization induced by eosinophil-derived polycationic proteins may indirectly and/or directly influence clinical disease states of altered airway force, such as asthma and viral **bronchiolitis.** The overall hypothesis of the proposed studies is that MBP causes an increase in airway cell [Ca2+]i that in airway epithelium elicits epithelial broncho-constrictor release and in ASM elicits smooth muscle contraction. In the proposed studies, human airway epithelium and human airway smooth muscle strips and freshly dissociated human airway myocytes will be used to examine the effects of MBP on epithelial broncho-constrictor release and ASM force generation, [Ca2+]i regulation and Ca2+ sensitivity. Critique: The comments below represent essentially unedited comments from the reviewers of this application. They are included to indicate the range of comments made during the discussion and may not reflect the final thinking of the committee.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: EPITHELIAL MMPS IN AIRWAY REPAIR**

  Principal Investigator & Institution: Parks, William C.; Professor of Pediatrics, Medicine and Ce; Pediatrics; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2004; Project Start 01-JUL-2004; Project End 30-JUN-2009

  Summary: (provided by applicant): The accumulative, progressive remodeling of airways seen in many conditions, such as **bronchiolitis** obliterans, asthma, cystic fibrosis, and more, indicates that normal repair processes have gone awry. To understand the pathogenic mechanisms of destructive diseases, the mechanisms of normal airway repair need to be better understood. Injury sets off a programmed series of interdependent yet separate responses, such as re-epithelialization, inflammation, scarring, and eventually resolution. During each stage in this process, a number of extracellular proteinases are released by all cells. Acting on specific substrates, these enzymes serve numerous and diverse functions, including regulating cell-cell and cell-matrix signaling by both gain and loss-of-function mechanisms. In particular, members of the matrix metalloproteinase (MMP) family can activate the latent forms of a number of proteins involved in cellular communication, among several other functions. The goal of this project is to identify actual, physiologic protein substrates of specific MMPs, to understand the biological consequence of proteolytically processing a given protein, and