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Acknowledgements

The collective knowledge generated from academic and applied research summarized in various references has been critical in the creation of this book which is best viewed as a comprehensive compilation and collection of information prepared by various official agencies which produce publications on diaphragmatic hernia. Books in this series draw from various agencies and institutions associated with the United States Department of Health and Human Services, and in particular, the Office of the Secretary of Health and Human Services (OS), the Administration for Children and Families (ACF), the Administration on Aging (AOA), the Agency for Healthcare Research and Quality (AHRQ), the Agency for Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Healthcare Financing Administration (HCFA), the Health Resources and Services Administration (HRSA), the Indian Health Service (IHS), the institutions of the National Institutes of Health (NIH), the Program Support Center (PSC), and the Substance Abuse and Mental Health Services Administration (SAMHSA). In addition to these sources, information gathered from the National Library of Medicine, the United States Patent Office, the European Union, and their related organizations has been invaluable in the creation of this book. Some of the work represented was financially supported by the Research and Development Committee at INSEAD. This support is gratefully acknowledged. Finally, special thanks are owed to Tiffany Freeman for her excellent editorial support.
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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." 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 diaphragmatic hernia 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 diaphragmatic hernia, 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 diaphragmatic hernia, 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 diaphragmatic hernia. 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 diaphragmatic hernia, 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 diaphragmatic hernia.

The Editors

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1 From the NIH, National Cancer Institute (NCI): http://www.cancer.gov/cancerinfo/ten-things-to-know.
CHAPTER 1. STUDIES ON DIAPHRAGMATIC HERNIA

Overview

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

The Combined Health Information Database

The Combined Health Information Database summarizes studies across numerous federal agencies. To limit your investigation to research studies and diaphragmatic hernia, 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 “diaphragmatic hernia” (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:

- **Congenital Diaphragmatic Hernia: A Physiologic Approach to Management**


  Summary: Congenital diaphragmatic hernia (CDH) is an anatomically simple defect that is surgically correctable by removing the herniated viscera from the thorax and repairing the diaphragm. Although it is anatomically simple, the mortality associated with CDH is 50 to 80 percent, despite improvements in prenatal diagnosis, resuscitation, preoperative and postoperative stabilization, and ventilatory management. This article presents a physiologic approach to the management of CDH. The author discusses the anatomic and functional developmental abnormalities associated with CDH, prenatal and postnatal diagnosis, resuscitation, and preoperative stabilization of these infants. In addition, the methods of surgical correction, the primary care concerns in postoperative
management, and the long-term outcome for survivors of CDH repair are also addressed. 5 figures. 41 references. (AA-M).

- **Congenital Diaphragmatic Hernia: Implications for Nitrous Oxide Use in Dentistry**  

  Summary: This article describes the development of diaphragmatic hernias, their associated physical and diagnostic signs and symptoms, and the potential complications with nitrous oxide use and provides a case report. Depending upon the location and extent of the diaphragmatic defect, portions of the stomach, omentum, liver and/or intestine can occupy a portion of the thoracic cavity. Nitrous oxide's solubility properties allow for rapid expansion of the herniated bowel, resulting in compression of the thoracic organs or strangulation of the herniated abdominal viscera. The authors note that the presence of a **diaphragmatic hernia** may necessitate a change in sedation or anesthesia plans to eliminate the use of nitrous oxide during prolonged procedures. 3 figures. 13 references. (AA-M).

- **Prospective Study of the Outcome for Fetuses With Diaphragmatic Hernia**  

  Summary: This article reports on a study undertaken to investigate the natural history and outcome of isolated congenital **diaphragmatic hernia** (CDH) diagnosed before birth. The authors note that the mortality of CDH with currently available postnatal care, including extracorporeal membrane oxygenation (ECMO), reported in retrospective studies ranges from less than 25 percent to greater than 75 percent. The population consisted of 83 fetuses with isolated, potentially correctable CDH diagnosed prior to 24 weeks’ gestation referred to the University of California, San Francisco, Fetal Treatment Center between January 1989 and October 1993. In this study, the mortality for potentially correctable CDH diagnosed before 24 weeks’ gestation is 58 percent, despite optimal care presently available after birth. The authors mention that infants who die in utero and soon after birth constitute a substantial hidden mortality. 1 figure. 1 table. 21 references. (AA-M).

**Federally Funded Research on Diaphragmatic Hernia**

The U.S. Government supports a variety of research studies relating to diaphragmatic hernia. 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](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 diaphragmatic hernia.

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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).
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 diaphragmatic hernia. The following is typical of the type of information found when searching the CRISP database for diaphragmatic hernia:

- **Project Title: ADVANCING CLINICAL RESEARCH IN PEDIATRIC SURGERY**  
  Principal Investigator & Institution: Lally, Kevin P.; Surgery; University of Texas Hlth Sci Ctr Houston Box 20036 Houston, Tx 77225  
  Timing: Fiscal Year 2002; Project Start 01-JUN-2002; Project End 31-MAY-2007  
  Summary: Congenital disorders requiring major pediatric surgical intervention are infrequent and present complex management problems. Most pediatric surgical studies are methodologically weak, single-center studies, and improved outcomes are likely to require a series of multi-center studies of exemplary quality. The applicant, Dr. Kevin Lally, the A.G. McNeese Professor and Chief of Pediatric Surgery at UT Houston, is a leader in promoting such studies. He has participated in 19 diaphragmatic hernia (CDH). CDH occurs in 1 per 2-4,000 live births; 35% of infants die; survivors are ventilated a mean of 18 days; and 34% have chronic lung disease. K24 funding is requested to substantially increase Dr. Lally's time for 1) Clinical Research including: a) A Multi-center placebo-controlled, randomized trial of antenatal steroids for infants with prenatally diagnosed CDH to improve their oxygenation and reduce time to ventilator independence. Fifteen centers have committed to participate; 7 have IRB approval; and 8, including UT-Houston, have GCRCs. The UT-Houston GCRC provides substantial statistical and database support for this trial. Collaborators at UT Houston include Drs. Larry Gilstrap and Jon Tyson, both experienced in steroid trials, and well-funded investigators in steroid trials, and well-funded investigators in the NICHD Maternal-Fetal and Neonatal Research Networks; and b) Extensive analyses of the CDH registry to define improved predictors of outcome, assess geographic differences and temporal trends, and develop hypotheses and descriptive data needed to design trials to improve outcome. This database has strict quality control, data on 1650 infants and 48 institutions now participate. 2) Mentoring Dr. Lally is a talented mentor; 3 current mentees have recently received a K08 award, a K23 award, and a Young Investigator Award. To enhance his mentoring skills, promote the funding and productivity in his Division of Pediatric Surgery, and augment his methodologic skills in clinical research, Dr. Lally will complete the NIH funded Clinical Research Curriculum work and assist with mentoring teams for young investigators in the Curriculum. He will also conduct systematic reviews of the Cochrane Collaboration and complete the Master's Degree Program in Clinical Research at UT-Houston. K24 funding will help Dr. Lally with his research and mentoring to advance the quality of clinical research in pediatric surgery, develop an expanded international trials network, and improve the outcome of high-risk infants.  
  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: EFFECTS OF PHYSICAL STIMULI ON FETAL LUNG DEVELOPMENT**  
  Principal Investigator & Institution: Kitterman, Joseph A.; Professor of Pediatrics; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 941222747  
  Timing: Fiscal Year 2002; Project Start 08-JUL-2002; Project End 30-JUN-2003  
  Summary: During the previous grant period, we focused on (a) effects of lung distention on fetal lung growth and development and (b) apoptosis in the fetal lung. The current project extends our observation on fetal lung distention and relates them to the clinical
problem of congenital **diaphragmatic hernia** (CDH) and new methods of treating CDH prenatally. Congenital anomalies are a leading cause of neonatal death, with pulmonary hypoplasia the most common anomaly in infants dying the neonatal period. CDH, a major cause of pulmonary hypoplasia, occurs once in 2400 births and has a high mortality rate. Fetal lung growth depends primarily on physical, or mechanical factors, which influence lung growth by changes in lung distension, or stretch, a potent stimulus for diverse cellular effects. With CDH, pulmonary hypoplasia results from alteration of several of these factors. Occluding the fetal trachea distends the lung with fluid and stimulates lung growth, findings that have led to clinical efforts to treat CDH prenatally by tracheal occlusion. Although preliminary results have been encouraging, little is known about effects of tracheal conclusion on some aspect of lung development crucial to adequate pulmonary function, including quantitative lung morphology, the pulmonary vasculature, and lung water balance. Also, tracheal occlusion produces potentially adverse effects, such as decreases in surfactant and alveolar type II cells. Administration of the pesticide of the pesticide, nitrofen, to pregnant rats causes CDH and pulmonary hypoplasia in 60% of the fetuses; the condition resembles CDH in human infants. We propose to distend, by tracheal occlusion, the lungs in fetal rats with nitrofen-induced CDH and to study the effects on lung growth and maturation, on differentiation of the distal pulmonary epithelium, on quantitative pulmonary and vascular morphology, on lung water transport and on components of the cytoskeleton, which is involved in cellular transduction of mechanical stimuli. We will also examine effects on maternal (a) glucocorticoids, which accelerate lung maturation, but which may adversely affect septation and lung growth, and of (b) retinoic acid, which postnataally increases septation and reverses the decreased septation due to dexamethasone. We have shown that apoptosis is a normal process in fetal lung development. However, because changes in lung distension have little effect on apoptosis, further studies of that process are not included in the current project. Results of the proposed studies will increase our knowledge of fetal pulmonary biology and provide new information that may have direct bearing on the clinical problem of CDH.


- **Project Title:** ENGINEERED VASCULAR TISSUE FOR CONGENITAL MALFORMATIONS

  Principal Investigator & Institution: Marler, Jennifer J.; Children's Hospital Med Ctr (Cincinnati) 3333 Burnet Ave Cincinnati, Oh 452293039

  Timing: Fiscal Year 2003; Project Start 26-SEP-2003; Project End 31-AUG-2008

  Summary: (provided by applicant): Congenital malformations, such as esophageal atresia, gastrochisis, congenital **diaphragmatic hernia**, and cutis aplasia remain a leading cause of neonatal morbidity and mortality. Traditional surgical reconstructive approaches have included the use of prosthetic materials, transfer of adjacent healthy tissues, and transplantation from donor individuals. These options are particularly limited in neonates, however, secondary to rapid growth, limited availability of healthy tissue for reconstruction, and lack of age and size-matched donor individuals. Tissue engineering is a multidisciplinary field that combines engineering and the life sciences to create structures, which restore, replace or augment tissues that have been lost secondary to congenital deficiency, disease, or trauma. The most common methodology combines bioresorbable polymer scaffolds and autologous cells that have been expanded in tissue culture to form new tissues. This approach holds particular promise for generating surgical replacement structures for reconstruction of several congenital malformations. There have been significant advances in engineering avascular tissues,
such as cartilage. There has also been some success in generating, "thin" tissues, such as cardiac leaflets and cultured skin substitutes. When tissues less than 2mm in thickness are transplanted, their metabolic requirements are supported initially through diffusion and later by the ingrowth of new blood vessels from adjacent structures. Thicker tissues, however, cannot rely initially on diffusion and are unable to survive the period required for vascular ingrowth. Thus, one strategy to engineer thicker tissues is to incorporate a blood supply de novo - assembling a microvasculature in tissue culture prior to implantation, allowing other cell types to grow around it, and then connecting this with existing vessels using microsurgical techniques. The principal objective of this project is to create a three-dimensional, branching, functional microvascular network in vitro which will provide a structural and metabolic framework to permit the engineering of thicker vascularized tissues for surgical reconstruction.


- **Project Title:** FETAL MRI & ULTRASOUND FOR CONGENITAL DIAPHRAGMATIC HERNIA IN FETUSES
  
  Principal Investigator & Institution: Harrison, Michael R.; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 941222747
  
  Timing: Fiscal Year 2002; Project Start 01-DEC-2000; Project End 31-MAR-2002
  
  Summary: This abstract is not available.
  

- **Project Title:** GENE MUTATIONS AND RESCUE IN HUMAN DIAPHRAGMATIC HERNIA
  
  Principal Investigator & Institution: Donahoe, Patricia K.; Marshall K. Bartlett Professor of Surger; Massachusetts General Hospital 55 Fruit St Boston, MA 02114
  
  Timing: Fiscal Year 2003; Project Start 05-JUL-2001; Project End 31-MAR-2006
  
  Summary: (provided by applicant): This is a competitive supplemental request for grant # PO1 HD39942-02 "Comparative Genomics to Correct Human Lung Hopoplasia" which expands at least four-fold the patient base for mutational analysis in project IV "Gene Mutation and Rescue in Human Diaphragmatic Hernia". In this supplemental grant, we will be able to capture a large percentage of all the cases of congenital diaphragmatic hernia (CDH) born in the Boston and New England region. The reviewers of the grant anticipated that the number of cases accrued at the MGH would be too small for meaningful interpretation. However, initiating Projects I, II, III, and establishing a database for Project IV, has convinced us of the value of this Program Project and its likelihood of success. Completion of the database has demonstrated that the number of patients is even smaller then anticipated. Thus, we will add the impressive professional experience and patient numbers of the Children's Hospital Medical Center (CHMC) to the proposal, as suggested by the original reviewers of the Program Project and fortunately, agreed to by Dr. Jay Wilson and his team at the CHMC. The advantage of adding Dr. Wilson's program to that of the MGH is his unique multidisciplinary follow-up clinic where we can interact directly with a large number of CDH patients and families in one locale. A database will be established for all CDH patients and their families who come to the Boston CHMC for prospective care, as well as for all of those patients cared for by the CHMC Pediatric Surgical Service since 1990 (Aim I) and cared for by the multidisciplinary CDH clinic. These will be added to those generated at MGH. These patients and families giving consent will provide blood and tissue from which cell lines will be immortalized for chromosomal and genetic analysis. As with the
original study, we will use the same previously collected and prospective CDH and normal fetal lungs to study the expression of genes known to be associated with human CDH, gene knockouts which have strong CDH phenotypes, and candidates that arise from Drosophila, chick, or rodent screens. Replaced genes which show complementation which corrects phenotypes of CDH in these models (Aim II) will satisfy the final and most stringent selection criteria necessary but not absolutely essential to be carried forward for extensive mutational analysis. We will clone or obtain human homologs and design PCR probes from the coding regions of the most promising candidates for mutational scanning of the anticipated much larger number of CDH patients and their families (Aim HI). Loss of homozygosity scanning will be done for 15q22-ter, 12q, and 8q regions (Aim IV) and candidate genes revealed by the scans will be tested for expression in the discarded fetal normal and CDH lungs and for complementation of CDH phenotype in the animal models. Genes which are abnormal in CDH lungs can be complemented in the various small animal models, and show abnormalities on mutational analyses of the patients, will be used to design treatment strategies for humans with CDH after appropriate testing in larger animal models.

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

- **Project Title: GENETIC APPROACHES TO DISCOVER NEW TREATMENTS FOR CDH**
  Principal Investigator & Institution: Kawaguchi, Akemi L.; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114
  Timing: Fiscal Year 2003; Project Start 01-APR-2003; Project End 31-MAR-2005
  Summary: (provided by applicant): Congenital **diaphragmatic hernia** (CDH) remains a difficult clinical problem with a mortality rate of nearly fifty percent. In CDH, the abdominal contents may herniate into the thoracic cavity, resulting in poor pulmonary development with resulting pulmonary hypoplasia. Even when the compression is reduced early in gestation, the lungs remain hypoplastic, suggesting a genetic component of the defect. Early lung development is remarkably conserved between humans and avian species. Therefore, a chick model was chosen for series of experiments designed to describe the function of four candidate factors- FT68, FT137, FT347, and FT399. These factors were described in our laboratory, and have been shown to be expressed in normal chick lung development. We will first study the temporal and spatial expression of these factors using in situ hybridization. Next, we will perform targeted lung infection with avian-specific retrovirus constructed with full-length, wild type candidate cDNA for overexpression and misexpression studies. The lungs will be analyzed at various developmental stages for gross morphology, histology, cytodifferentiation, and expression of known factors important in pulmonary development. If these factors are found to play a significant role in chick pulmonary development, the expression of human orthologs will be studied further with a library of archived normal and abnormal fetal and neonatal human lung samples. We hope that by better understanding the molecular events of normal and abnormal lung development, we will better understand pulmonary hypoplasia and to develop novel pharmacologic therapies for CDH.
  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: LUNG DEVELOPMENT IN CONGENITAL DIAPHRAGMATIC HERNIA**
  Principal Investigator & Institution: Larson, Janet E.; Ochsner Clinic Foundation New Orleans, La 70121
Studies 9

Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 30-JUN-2005

Summary: (provided by applicant): Congenital **diaphragmatic hernia** (CDH) is associated with the structural abnormality of pulmonary hypoplasia. These changes are mimicked in the rodent model of nitrofen-induced CDH. Nitrofen (2,4-dichlorophenyl-p-nitrophenyl ether) is an herbicide that when fed to a pregnant rodent at day 9 or 10 creates **diaphragmatic hernia** and/or lung hypoplasia in the fetuses. When treated with nitrofen the fetuses demonstrate epithelial cell immaturity as well as hypoplasia. In contrast, the investigators have found that in utero gene therapy with CFTR (the gene responsible for Cystic Fibrosis) results in epithelial cell hyperplasia and accelerated epithelial cell differentiation. The investigators hypothesize that in utero gene therapy with cftr will reduce the pulmonary hypoplasia and epithelial cell immaturity associated with CDH. This hypothesis can be tested in the fetal rat by treatment with nitrofen at 9-10 days gestation followed by in utero gene therapy at 16-17 days gestation.


- **Project Title: MOLECULAR CONTROL OF PATTERN FORMATION IN THE CHICK LUNG**

Principal Investigator & Institution: Roberts, Drucilla J.; Massachusetts General Hospital
55 Fruit St Boston, Ma 02114

Timing: Fiscal Year 2002

Summary: Pulmonary malformations are common human congenital anomalies that carry a high morbidity and mortality rate. Pulmonary hypoplasia (PHP), a lung growth and patterning anomaly, accounts for the majority of neonatal mortality in otherwise salvageable cases of congenital **diaphragmatic hernia**. There is very little known about the molecular aspects of PHP. In this program project we exploit the fact that molecules responsible for normal lung development are conserved across animal species from fly to man and hypothesize that alterations in their function or express pattern cause PHP. Our goal is to identify which pattern the lung and may be mutated, absent or misexpressed in human PHP to find novel treatments, prevention or early diagnosis. We propose to identify and characterize these factors in three different model systems: Drosophila, chick, and rodent- and translate our findings to humans using or archives of normal and abnormal human fetal lungs and families with an affected PHP member. In Project I (herein), the avian retroviral expression system will be used to identify factors necessary for normal lung development by analysis of candidate factors in their developmental expression patterns and function by mis-, over-, and mutated expression in the chick embryonic lung in ovo. Project I has three specific aims: (1) Analyze the expression pattern of candidate factors in normal lung development in the chick. Candidate factors include those from the published literature implicated as candidates by their expression pattern in the developing lung or by mutations resulting in a pulmonary phenotype: secreted factors (Shh, Bmp4, Fgf10), transcription factors (Hoxa5, Hoxb5, Sox2, Nkx2.1, Gli2, Gli3), and receptors (Fgf42I1b). In preliminary data we present new factors identified in a chick lung bud screen (1 novel factor, 2 transmembrane receptors, 1 transcription factor) we will test for developmental pulmonary expression. Additionally, we factors to be identified in the Drosophila screen (Project II) will be cloned in the chick and studied for pulmonary developmental expression. Only those candidates with spatial and/or temporally restricted expression in the developing lung will be studied in Specific Aim 2. (2) Analyze the function of candidates in chick pulmonary development. Avian specific retroviral constructs made from wild-type full-length candidate cDNAs as well as directed mutated forms will be used to mis- and/or over-express these factors in the developing avian lung in ovo.
Only those factors which can phenocopy PHP in these experiments will be studied in Specific Aim 3. (3) Identify which factors are expressed in human lungs and if they are altered in expression in hypoplastic lungs. Fetal and pediatric normal and abnormal lungs are available from an archived tissue bank and will be collected prospectively. Human homologs will be obtained or cloned to analyze their expression in these tissues. Those candidates that are deemed strong will be analyzed for expression (as well as function and rescue) in rodent models of pulmonary hypoplasia (Project III) and a genetic analysis of PHP families in Project IV. We expect to identify factors which when mutated or aberrantly expressed result in PHP. This information may provide novel treatment regimes and early diagnosis making early intervention possible. We hope to increase the survival rates of infants with isolated congenital diaphragmatic hernia and PHP.

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

- **Project Title: PHOSPHOCREATINE RECOVERY IN WOMEN W/ CHRONIC FATIGUE SYNDROME**
  Principal Investigator & Institution: McCully, Kevin; University of Pennsylvania 3451 Walnut Street Philadelphia, Pa 19104
  Timing: Fiscal Year 2002
  Summary: In Utero surgical techniques for the reversal of anatomical malformations are developed in small mammalian models. The design of new techniques suffers from lack of non-invasive pre- and post-surgical fetal monitoring. We have applied high resolution MRI to in-vivo, in-utero imaging of a rat model for Congenital Diaphragmatic Hernia (CDH). CDH is a developmental anomaly which involves incomplete closure of the diaphragm, herniation of the liver and abdominal viscera into the thoracic cavity, and lung hypoplasia. Eight dams were imaged on days 19-22 of gestation (once a day) to diagnose the presence or absence of CDH and monitor the effects of surgery. Those who were shown to be CDH+ on day 19 underwent immediate surgical tracheal ligation to reverse pulmonary hypoplasia and force the abdominal contents from the thoracic cavity. 39 rat fetuses were imaged using a multislice, T2 weighted, fast spin echo sequence on a 4T whole body imaging system (GE, Signa). Pathology and results of surgery were confirmed post-mortem by high resolution imaging (9.4T) and subsequent microscopic dissection. This information will help in the use and development of in utero intervention for treatment of congenital abnormalities.
  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: REGULATORS OF FETAL RODENT PULMONARY HYPOPLASIA**
  Principal Investigator & Institution: Schnitzer, Jay J.; Associate Visiting Surgeon; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114
  Timing: Fiscal Year 2002
  Summary: Infants with congenital diaphragmatic hernia (CDH) die from inadequate lung function, which is a combination of 1) pulmonary hypertension of the newborn. The pulmonary hypoplasia is characterized by immature, small lungs. We have demonstrated the efficacy of prenatal glucocorticoid therapy in accelerating pulmonary maturation in CDH lung in fetal rats and sheep. We have further shown that prenatally administered antioxidants, particularly vitamin E, accelerate prenatal growth of CDH-associated hypoplastic lungs in vitro and in vivo. We have demonstrated significant differences in the levels of mitogen- activated protein (MAP) kinase phosphorylation (extracellular signal regulated protein kinases, ERK-1 and -2) between CDH and normal
Studies

fetal lungs, and have shown increased phosphorylation towards that observed normally, in CDH lungs after treatment with vitamin E in vivo. We hypothesize that important regulators and pathways of normal and hypoplastic fetal lung growth converge on the mitogen-activated protein (MAP) kinase pathways. We further hypothesize that antioxidants stimulate hypoplastic fetal lung growth via the MAP kinase cascade, and, in particular, via up-regulation of the MAP kinase kinases (MEK +) and Raf-1. We propose to define the molecular mechanism(s) in the rodent responsible for the salutary effects of the anti-oxidants and define the modulators of signal transduction pathways responsible for CDH-associated pulmonary hypoplasia. We will reestablish that the observed stimulation of embryonic lung growth by antioxidants occurs via a reductant mechanism and determine where antioxidants impact the MAP kinase pathways. We will establish the role of other candidate genes and pathways in fetal lung hypoplasia, define whether differences exist in gene expression patterns in the various rodent CDH models, and study in the rodent model worthy candidate genes identified in Projects I, II, and IV. We hope that these studies will provide new insights into the mechanisms of prenatal lung growth control. These, in turn, can provide a platform for the future development of prenatal targeted therapies.

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

• Project Title: REGULATORS OF TRACHEAL MORPHOGENESIS IN DROSOPHILA
Principal Investigator & Institution: Perkins, Lizabeth A.; Associate Professor of Surgery/Genetics; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114
Timing: Fiscal Year 2002
Summary: All multi-cellular animals must transport fluids and gases to and from all cells of the body. In many instances this process is achieved by branching tubular organs with lumen by epithelial cells. In vertebrates, organs composed of branching tubes include the vasculature system, lungs, pancreas, and kidney. In vertebrates, the tracheal system of Drosophila is a branching tubular organ conserved at the molecular level; e.g., both require the reiterative use of an FGF receptor tyrosine kinase (RTK) signaling pathway. A unique environment within the Massachusetts General Hospital is providing an opportunity to elucidate pulmonary development from flies to humans. The identification of genetic analyses of conserved molecules that function during normal tracheal development in flies will guide the analyses of these same molecules during mammalian lung development. These integrated, comparative studies, therapies and/or therapeutics that will positively impact the treatment of the pulmonary hypoplasia associated with the common and tragic malformation Congenital Diaphragmatic Hernia. Project 2. Regulators of Tracheal Morphogenesis to Drosophila
Using Drosophila as a model system, a genome wide screen has identified regions encoding genes that modify the function of Csw, a tyrosine phosphatase that transduces RTK signals, including those required for tracheal morphogenesis. Six regions that enhance and 14 that suppress Csw function encode genes not presently identified as components of RTK signaling. The goal of Aim 1 is to identify which regions alter tracheal development, and then to isolate and characterize selected modifiers of tracheal development. Building upon findings from chick and mouse animal models (Project 1 and 4), as well as genomic and chromosomal analyses derived from the study of patients with CDH (Project 4) the goal of Aim 2 is to analyze conserved genes functioning during tracheal morphogenesis. We will determine if Drosophila homologues of genes expressed during lung morphogenesis are conserved in flies. If so, we will genetically characterize selected Drosophila homologues to elucidate their functions during tracheal
Diaphragmatic Hernia development. The goal of Aim 3 is to establish Drosophila as a model genetic system to search for new, or analyze existing pulmonary therapeutics. As in vertebrates, tracheal morphogenesis in flies is modified by the molecular environment. Drosophila will be used to screen existing “lung maturing” therapeutics, antioxidants, and selected drugs (Project 3) for their effects on the developing tracheal system. As the first step toward an ultimate goal to develop new lung maturing therapies, we will modify the environment with these compounds to create a “sensitized background” from which to screen for genes whose functions are modified by the compound.

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- **Project Title:** VEGF REGULATION OF PULMONARY VASCULAR DEVELOPMENT  
  Principal Investigator & Institution: Akeson, Ann L.; Children's Hospital Med Ctr (Cincinnati) 3333 Burnet Ave Cincinnati, Oh 452293039  
  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 30-JUN-2007  
  Summary: (provided by applicant): VEGF is a critical component of the highly integrated, multidirectional signaling that orchestrates lung development. Disruption of this coordinated development is reflected in neonatal lung disease with aberrant VEGF expression including congenital diaphragmatic hernia and bronchopulmonary dysplasia. VEGF activity is regulated by generation of multiple isoforms, each with unique biological properties. The temporal and spatial expression patterns suggest that each VEGF-A isoform provides distinct positional and differentiation cues required for lung vascular development. In this proposal, we will test the hypothesis that each VEGF-A isoform regulates distinct endothelial functions required for progressive pulmonary vascular specification through differential accessibility and binding to VEGF receptors, VEGFR1 and VEGFR2. We propose that early in lung development the diffusible isoforms VEGF-A120 and VEGF-A164 induce different signal pathways that activate distinct angioblast and endothelial responses. Further, midway through lung development, the heparin-bound isoform, VEGF-A188, expressed by distal epithelial cells generates a morphogenic gradient that induces endothelial migration and alveolar-capillary alignment. Finally, we propose that during the saccular and alveolar stages, VEGF-A164 and VEGF-A188 drive endothelial specification required for microvascular development, distal airway development and formation of the air blood barrier. We will use in vitro model systems to analyze the mechanisms of cellular activation by examining isoform-specific receptor activation and associated kinase signaling pathways. Newly developed transgenic models with conditional, lung-specific expression of VEGF-A and dominant-negative soluble receptor will be used to determine the requirements for VEGF-A at each stage of development. Completion of this project will increase understanding of the mechanism of VEGF action and expand knowledge of pulmonary vascular development.

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3 Adapted from the National Library of Medicine: [http://www.pubmedcentral.nih.gov/about/intro.html](http://www.pubmedcentral.nih.gov/about/intro.html).