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Foundation for the Study of PSC


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Mission

- Sponsor and facilitate both basic and clinical research to discover new treatments and ultimately a cure for primary sclerosing cholangitis.

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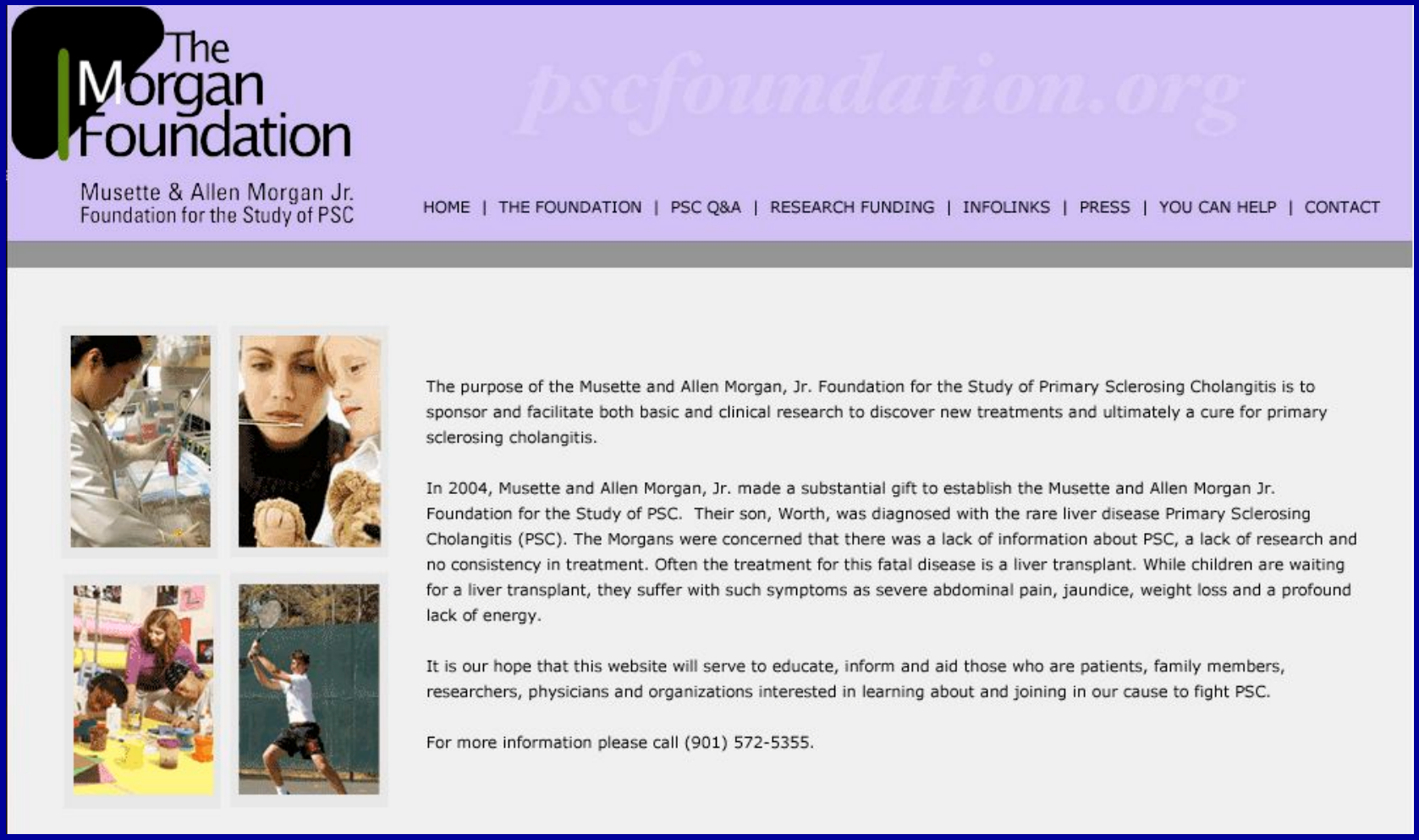
Web Site
www.pscfoundation.org



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NIH PSC Conference

- Sponsored by NIDDK, Office of Rare Diseases and Morgan Foundation
- September 19-20, 2005, Lister Hill Conference Center, Bethesda, MD
- Summary accepted for publication in *Hepatology*

Webcast at www.videocast.nih.gov/PastEvents.asp?c=1&s=21

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- Hypothesis-driven
- Adult and pediatric PSC patients
- PSC, AIH and overlap syndrome
- Database and serum, tissue and genetic repositories
- Contracted with EMMES Corporation
- Online target date July-August, 2006
- Web-based data entry and management
- Multicenter PSC research consortium

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- Harvard
  - Steven Freedman
  - Harpreet Pall
- U of Tennessee
  - Dennis Black
  - Claudio Tombozzi
  - Gene Whitington
- Virginia Commonwealth
  - Veldimir Luketic
- Mt. Sinai
  - Joseph Odin
  - Benjamin Shneider
- Toronto
  - Peter Durie
- UCSF
  - Philip Rosenthal
- Mayo
  - Deborah Freese
  - Konstantinos Lazaridis
  - Keith Lindor
  - Jayant Talwalkar
- Denver
  - Ronald Sokol
- Cincinnati
  - William Balistreri
- Northwestern
  - Estella Alonso
- Tufts
  - Marshall Kaplan

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STOPSC Objectives

- To identify risk factors, including genetic and environmental factors, for development of PSC and understand the mechanisms involved in pathogenesis of PSC.
- To identify the role of genetic factors in the predilection for disease, disease severity and response to treatment (HLA haplotypes, cftr, mdr3, nod2, as well as inflammatory mediator gene polymorphisms, and liver disease modifier genes).
- To help develop diagnostic tests/approaches that can diagnose the disease in its early stages, as well as surrogate markers for the severity, progression and response to treatment of the disease.

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STOPSC Objectives

- To collect information that will help characterize the disease and clarify the relationship between childhood and adult forms of PSC.
- To study the natural history and clinical course of the disease in children and adults.
- To better understand the relationship of PSC with associated diseases, such as autoimmune hepatitis and inflammatory bowel disease.

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STOPSC Objectives

- To identify risk factors and biomarkers for the development of cholangiocarcinoma.
- To develop and test models which predict patient outcomes (cirrhosis, portal hypertension, cholangiocarcinoma, death, transplantation, etc.).
- To characterize and follow trends in therapies of PSC.
- To characterize the side effects associated with various therapies of PSC.
- To evaluate and compare the efficacy and safety of various treatments of PSC in multicenter controlled clinical trials.

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Definitions

- Disease definitions
  - PSC (large and small duct disease)
  - AIH
  - Overlap syndrome
  - Adults and children
- Criteria
  - Clinical
  - Biochemical
  - Serologic
  - Imaging
    - ERCP
    - MRCP
  - Liver histology

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Inclusion

- Children
  - PSC
  - AIH
  - Overlap syndrome
- Adults
  - PSC
  - Overlap syndrome

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Hypotheses

- Incidence
  - The incidence of PSC in children with IBD is underestimated
    - Inclusion of IBD registry
    - Imposition of more strict and comprehensive diagnostic criteria through PSC registry

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Hypotheses

- Genetics
  - Specific gene mutations/SNPs/HLA profiles are associated with development of PSC and are predictive of:
    - Predilection to develop PSC
    - Disease severity
    - Response to therapy

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Hypotheses

- Specific genes
  - HLA profile
    - Class II haplotypes
  - Transporters
    - CFTR
    - MDR3
  - Fibrosis
    - MMP (stromelysin)
    - TIMP

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Hypotheses

- Specific genes
  - Inflammation
    - Cytokine promoter/gene polymorphisms
      - TNF-alpha
      - IL-1, IL-10
      - CTLA-4
    - PPAR-alpha
  - Intestinal epithelial barrier function
    - NOD2
    - Claudin
  - Liver disease modifiers
    - Alpha-1-antitrypsin

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Hypotheses

- Pathogenesis
  - Specific T-lymphocyte populations are present in liver portal areas in PSC
    - Intestinal mucosal lymphocytes (‘primed” T-cells)
    - Restricted T-cell receptor repertoire
  - Autoantibodies to cholangiocyte surface Ag in PSC patients increase biliary CD44 expression and IL-6 expression

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Hypotheses

- Pathogenesis
  - Bacterial products (LPS, CpG DNA) from the intestine activate Kupffer cells and cholangiocytes to initiate and propagate biliary tract injury in PSC
  - Patients with PSC have increased intestinal permeability, even in the absence of active IBD

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Hypotheses

- Pathogenesis
  - Large-scale gene-expression analyses will uncover a unique transcriptional profile in livers/biliary tracts of patients with PSC vs AIH
    - Requires RNA from liver tissue
    - Expensive

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Hypotheses

- Treatment
  - Specific treatment will alter the course of PSC
    - Probiotics in patients with predisposition (IBD) or early stage disease
    - Anti-TNF-alpha antibodies or other immunomodulatory therapy
    - Antibiotics (oral vancomycin)
    - DHA in patients with CFTR mutations

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Hypotheses

- Outcome
  - Clinical outcome of PSC is better in children than adults
    - Children have higher levels of IgG and AST than adults due to a higher prevalence of AIH that confers a better response to therapy

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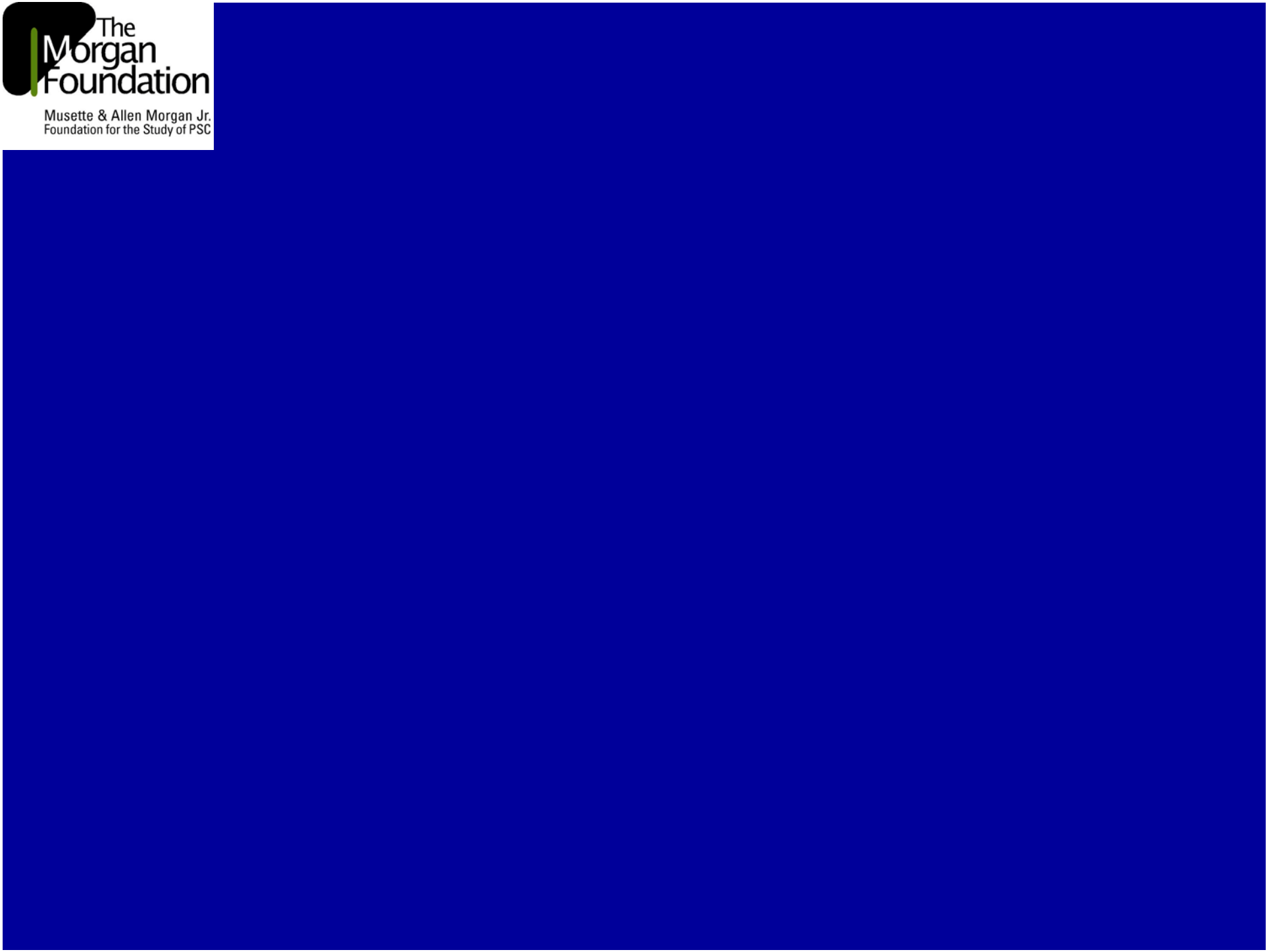
Research Support

- Investigator-initiated grants
- Investigators supported by the Foundation will develop research projects that will ultimately be competitive for extramural funding from the NIH and other sources.
- Clinical and basic
- Letter of intent
- Web-based application process
- Funding levels
  - Senior investigators $30,000/year for P & F grants
  - Junior investigators $60,000/year for Young Investigator grants
  - Funding up to 3 years
- Peer Review
  - Scientific Advisory Board
  - *Ad hoc* reviewers when appropriate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