Research Agenda of the Alpha-1 Foundation  
(Scientific version)  
Revised by MASAC 10/14/2016

**BASIC RESEARCH: IDENTIFYING TARGETS & DEVELOPING THERAPEUTIC APPROACHES**

- Molecular biology of alpha-1 antitrypsin (AAT) expression
  - Mechanisms of AAT synthesis, folding and secretion
  - Molecular pathology of Z AAT gene expression
  - Evaluation of novel mutations on AAT function
- Animal Model Development
  - Development of an AAT deficient animal model for lung
  - Development of an AAT deficient animal model for liver
- Lung-Focused Research
  - Determinants of lung growth, turnover, maintenance and regeneration
  - Mechanisms of tissue destruction, response to injury, and inflammation
  - Role of inflammation in the pathogenesis of AAT lung disease
- Liver-Focused Research
  - Determinants of liver growth, maintenance, turnover and regeneration
  - Mechanisms of hepatocellular toxicity and liver damage
- Technology Development
  - Hepatocyte transplantation
  - Gene therapy: enhancement, replacement, editing, extinction and repair
  - Epigenomics of Alpha-1 gene regulation
  - Small molecule anti-proteases
  - Small molecule, high through-put library screening
- Stem Cell Research and Regenerative Medicine
  - In vitro disease modeling, drug screening, and precision medicine
  - Stem cell-based therapies
  - Lung and liver tissue development and engineering artificial organs
  - Induced pluripotent stem cell therapies for AAT deficiency

**CLINICAL RESEARCH: IDENTIFYING ALPHAS & DEFINING THE EPIDEMIOLOGY & NATURAL HISTORY OF AAT DEFICIENCY**

- Epidemiology and Natural History of AAT deficiency
  - Impact of primary care and allied health care providers in detecting alpha-1
  - Prevalence studies of AAT deficiency
  - Prenatal and newborn screening pilot studies
  - Predicting course and outcomes
  - Defining the risk of clinical manifestations in heterozygote carriers
    - Longitudinal study of PI*MZ individuals
  - Natural history following lung transplantation
  - Natural history of lung disease following liver transplantation
- Genetics of AAT in the lung and liver
  - Precision Medicine approach to analyze genotype/phenotype correlations in lung and liver disease
  - Modifier Genes affecting lung and liver in AAT deficient individuals.
  - Epigenomic of A-1 Gene Regulation
  - Transcriptomic correlates of lung disease progression or stability
• New diagnostic technologies
• Establishment of effective clinical outcomes measures in AAT deficiency
  o Biomarkers of early lung or liver disease or of disease exacerbations
  o MRI, Quantitative CT scanning, fibroscan or other new modalities to assess lung or liver disease progression and response to therapy
• Quality of life, patient reported outcomes, healthcare utilization, and symptom management
• Environmental modifiers of lung and liver disease in AAT deficient individuals
  o Microbiome as a potential disease modifier
  o Gene-environment interactions
• Clinical manifestations of AAT deficiency other than in the lungs and liver
• Evaluation and treatment of comorbidities in AAT deficiency

**EVALUATING NOVEL THERAPEUTIC APPROACHES**
• Alpha-1 antitrypsin augmentation therapy
  o Development of recombinant therapy approaches
  o Development of aerosolized AAT therapy
  o Determining the utility of AAT therapy in deficient lung transplant recipients
  o Therapeutic dose analysis
• Improving outcomes in lung and liver transplant recipients
  o Use in post-transplant rejection
• Treatment of pathophysiological manifestations (e.g., hyperinflation, cirrhosis, cholestasis) of AAT deficiency in lung and liver
• Anti-inflammatory therapy
• Small molecule antiprotease and other strategies to prevent destruction of or restore matrix integrity
• Cell-based therapies
• Gene therapies
  o Gene replacement therapy
  o Enhancing, silencing, or gene editing of AAT expression
• Chemical chaperone therapy
• Biomarkers as an index of therapy in lung and liver

**ETHICAL, SOCIAL & LEGAL ISSUES RESEARCH: ELIMINATING BARRIERS FOR ALPHAS**
• Newborn testing/screening
  o Psychosocial impact on families
  o State policy and budget implications of expanded testing/screening
  o Determining access to “second-tier” screening, including carrier testing
• Ethical issues with targeted detection (preserving confidentiality, stigmatization)
  o Familial communications issues
• Social dimensions of living with A1ATD
  o Employment discrimination and accommodations
  o Is disease risk an environmental health problem or a disability?
• Equitable access to, and distribution of, medical therapies
  o Conflicts of interests in lay/commercial entanglements
  o Competition vs. cooperation in A1F funded research
• Impact of genomic information on alpha-1 patients and their families
• Impact of interventions on patient adherence and emotional well-being
  o The ethics of “nudging” for public health gains
• Impact of alpha-1 on families
  o Risk behavior within A1 families
  o Familial communication issues
  o Impact of social media and family networking on A1 families
• Impact of big data on Alpha-1 cohort of patients and their care
• Social scientific research to characterize and address caregivers needs
• Communicating risk to diagnosed individuals and their families within a context of uncertainty
• Ethical issues related to individualized return of results
• Affecting behavioral change to reduce risks of disease
• Gaining a better understanding of factors that influence key health behaviors among Alphas
• Ethical and policy issues related to community engaged research

DEVELOPING AND RENEWING THE ALPHA-1 RESEARCH WORKFORCE
• Clinical research training in AAT deficiency
• Basic research training in AAT deficiency
• Alpha-1 career development