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
    - Biomarkers of early lung or liver disease or of disease exacerbations
    - 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
    - Microbiome as a potential disease modifier
    - 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
    - Development of recombinant therapy approaches
    - Development of aerosolized AAT therapy
    - Determining the utility of AAT therapy in deficient lung transplant recipients
    - Therapeutic dose analysis
- Improving outcomes in lung and liver transplant recipients
    - 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
    - Gene replacement therapy
    - 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
    - Psychosocial impact on families
    - State policy and budget implications of expanded testing/screening
    - Determining access to “second-tier” screening, including carrier testing
- Ethical issues with targeted detection (preserving confidentiality, stigmatization)
    - Familial communications issues
- Social dimensions of living with A1ATD
    - Employment discrimination and accommodations
    - Is disease risk an environmental health problem or a disability?
- Equitable access to, and distribution of, medical therapies
    - Conflicts of interests in lay/commercial entanglements
    - 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
    - The ethics of “nudging” for public health gains
- Impact of alpha-1 on families
    - Risk behavior within A1 families
    - Familial communication issues
    - 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