# **Research Agenda of the Alpha-1 Foundation**

# **(Scientific version)**

# **Revised by MASAC 08/19/2020**

**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
* 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 the 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 the 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