# **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