

**APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)**

		3. DATE RECEIVED BY STATE	State Application Identifier
1. TYPE OF SUBMISSION*		4.a. Federal Identifier	
<input type="radio"/> Pre-application	<input checked="" type="radio"/> Application	<input type="radio"/> Changed/Corrected Application	b. Agency Routing Number
2. DATE SUBMITTED	Application Identifier	c. Previous Grants.gov Tracking Number	
5. APPLICANT INFORMATION			
Legal Name*: MAIPL THERAPEUTICS, INC.			
Department:			
Division:			
Street1*:	18 CIRCLE RD		
Street2:			
City*:	SCARSDALE		
County:			
State*:	NY: New York		
Province:			
Country*:	USA: UNITED STATES		
ZIP / Postal Code*:	105835322		
Person to be contacted on matters involving this application			
Prefix:	First Name*: Yong	Middle Name: G.	Last Name*: Yue
Position/Title:	Suffix:		
Street1*:	President & CEO		
Street2:	18 CIRCLE RD		
City*:	NEW YORK		
County:			
State*:	NY: New York		
Province:			
Country*:	USA: UNITED STATES		
ZIP / Postal Code*:	105835322		
Phone Number*:	000-000-0000	Fax Number:	Email: yong.yue@maipltx.com
6. EMPLOYER IDENTIFICATION NUMBER (EIN) or (TIN)* 00-000000			
7. TYPE OF APPLICANT* R: Small Business			
Other (Specify):			
Small Business Organization Type		<input type="radio"/> Women Owned	<input type="radio"/> Socially and Economically Disadvantaged
8. TYPE OF APPLICATION*		If Revision, mark appropriate box(es).	
<input checked="" type="radio"/> New	<input type="radio"/> Resubmission	<input type="radio"/> A. Increase Award	<input type="radio"/> B. Decrease Award
<input type="radio"/> Renewal	<input type="radio"/> Continuation	<input type="radio"/> C. Increase Duration	<input type="radio"/> D. Decrease Duration
	<input type="radio"/> Revision	<input type="radio"/> E. Other (specify):	
Is this application being submitted to other agencies?*		<input type="radio"/> Yes	<input checked="" type="radio"/> No
		What other Agencies?	
9. NAME OF FEDERAL AGENCY* National Institutes of Health		10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER TITLE:	
11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT* Prostaglandin F2a Receptor, FP Antagonism as a Therapeutic Option for Idiopathic Pulmonary Disease (IPF)			
12. PROPOSED PROJECT Start Date* 12/01/2024		13. CONGRESSIONAL DISTRICTS OF APPLICANT Ending Date* 11/30/2027	
NY-016			

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE**14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION**

Prefix: First Name*: Yong Middle Name: G. Last Name*: Yue Suffix:
 Position/Title: President & CEO
 Organization Name*: MAIPL THERAPEUTICS, INC.
 Department:
 Division:
 Street1*: 18 CIRCLE RD
 Street2:
 City*: NEW YORK
 County:
 State*: NY: New York
 Province:
 Country*: USA: UNITED STATES
 ZIP / Postal Code*: 105835322
 Phone Number*: 000-000-0000 Fax Number: Email*: yong.yue@maipltx.com

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	\$2,043,698.00
b. Total Non-Federal Funds*	\$0.00
c. Total Federal & Non-Federal Funds*	\$2,043,698.00
d. Estimated Program Income*	\$0.00

16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

- a. YES THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
 DATE:
- b. NO PROGRAM IS NOT COVERED BY E.O. 12372; OR
 PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

I agree*

* The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION

File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Yong Middle Name: G. Last Name*: Yue Suffix:
 Position/Title: President & CEO
 Organization Name*: MAIPL THERAPEUTICS, INC.
 Department:
 Division:
 Street1*: 18 CIRCLE RD
 Street2:
 City*: NEW YORK
 County:
 State*: NY: New York
 Province:
 Country*: USA: UNITED STATES
 ZIP / Postal Code*: 105835322
 Phone Number*: 000-000-0000 Fax Number: Email*: yong.yue@maipltx.com

Signature of Authorized Representative*

Completed on submission to Grants.gov

Date Signed*

03/26/2024

20. PRE-APPLICATION File Name:**21. COVER LETTER ATTACHMENT** File Name:

424 R&R and PHS-398 Specific

Table Of Contents

SF 424 R&R Cover Page.....	1
Table of Contents.....	3
Performance Sites.....	4
Research & Related Other Project Information.....	5
Project Summary/Abstract(Description).....	6
Project Narrative.....	7
Facilities & Other Resources.....	8
Equipment.....	11
Research & Related Senior/Key Person.....	13
Research & Related Budget Year - 1.....	32
Research & Related Budget Year - 2.....	35
Research & Related Budget Year - 3.....	38
Budget Justification.....	41
Research & Related Cumulative Budget.....	66
Research & Related Budget - Consortium Budget (Subaward 1).....	68
Total Direct Costs Less Consortium F&A.....	78
SBIR STTR Information.....	79
Commercialization Plan.....	81
PHS398 Cover Page Supplement.....	93
PHS 398 Research Plan.....	95
Specific Aims.....	96
Research Strategy.....	97
PHS Human Subjects and Clinical Trials Information.....	109
Vertebrate Animals.....	111
Bibliography & References Cited.....	113
Consortium/Contractual Arrangements.....	117
Letters of Support.....	119
Resource Sharing Plan(s).....	126
Other Plan(s).....	127
Authentication of Key Biological and/or Chemical Resources.....	128

Project/Performance Site Location(s)

Project/Performance Site Primary Location

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: MAIPL THERAPEUTICS, INC.

UEI: UKYVLM1WKBK7

Street1*: 18 CIRCLE RD

Street2:

City*: SCARSDALE

County:

State*: NY: New York

Province:

Country*: USA: UNITED STATES

Zip / Postal Code*: 105835322

Project/Performance Site Congressional District*: NY-016

Project/Performance Site Location 1

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Pennsylvania

UEI: GM1XX56LEP58

Street1*: 3451 Walnut Street

Street2: 5th Floor, Franklin Building

City*: Philadelphia

County:

State*: PA: Pennsylvania

Province:

Country*: USA: UNITED STATES

Zip / Postal Code*: 19104-6205

Project/Performance Site Congressional District*: PA-003

Additional Location(s)

File Name:

RESEARCH & RELATED Other Project Information**1. Are Human Subjects Involved?*** Yes No

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? Yes NoIf YES, check appropriate exemption number: 1 2 3 4 5 6 7 8If NO, is the IRB review Pending? Yes No

IRB Approval Date:

Human Subject Assurance Number

2. Are Vertebrate Animals Used?* Yes No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? Yes No

IACUC Approval Date:

Animal Welfare Assurance Number none

3. Is proprietary/privileged information included in the application?* Yes No**4.a. Does this project have an actual or potential impact - positive or negative - on the environment?*** Yes No

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an Yes No environmental assessment (EA) or environmental impact statement (EIS) been performed?

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* Yes No

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* Yes No

6.a. If yes, identify countries:

6.b. Optional Explanation:

Filename

7. Project Summary/Abstract* Summary-MaipI-V4.1.pdf**8. Project Narrative*** Narrative-MaipI-V4.1.pdf**9. Bibliography & References Cited** LitCitedRS-MaipI-V4.1.pdf**10. Facilities & Other Resources** Facilities_MaipI-2024.03.26.pdf**11. Equipment** Equipment_MaipI_2024.03.26.pdf

Summary: Idiopathic pulmonary fibrosis (IPF) is an irreversible, chronic, progressive, degenerative age-related interstitial lung disease. At an average life expectancy of only 2–5 years following diagnosis, IPF affects ~140,000 Americans with up to 50,000 new cases each year. The standard of care (SoC) therapeutics, nintedanib and pirfenidone, available for IPF have severe side effects, are expensive, and some IPF patients are non-responsive. Given the complexity of the IPF pathogenic process, and the heterogeneous patient population, there is a substantial unmet need for drugs targeting various pathways. Most drugs currently in development target a TGF β -dependent pathway that is known to be associated with systematic toxicity. Additional TGF β -independent pathways play a key role in fibrogenesis, but there are few drugs targeting these fibrotic pathways. Maipl Therapeutics is targeting the prostaglandin F2 α (PGF2 α) pathway by inhibiting its receptor (FP), which has been implicated as a TGF β -independent signaling hub. We have identified a highly selective, potent FP antagonist with preclinical studies indicating promising characteristics for oral administration. The objective of this Direct to Phase II SBIR proposal is to evaluate the *in vivo* efficacy specifically in IPF disease models, determine the mechanism of action (MoA) of PGF2 α /FP in IPF disease pathophysiology, and assess *in vivo* (non-GLP) safety of our lead candidates, MA-4586 and MA-4604. **Aim 1. Determine the anti-fibrosis efficacy of lead candidates in two IPF disease models.** In preparation for IND-enabling studies, two well-established preclinical IPF disease models will be used to determine the efficacy of MA-4586 and MA-4604 (compared to nintedanib) - the bleomycin (intra-tracheal)-induced pulmonary fibrosis mouse (C57BL/6) model and a tamoxifem-induced spontaneous lung fibrosis genetic mouse model, I^{ER}-Sftpc^{I^{73T}}. **Aim 2. Determine changes in alveolar niche crosstalk and fibrotic signaling following FP inhibition.** This aim will determine which cellular targets our candidates (MA-4586 and MA-4604) hit, what process gets altered, and how this ultimately impacts the effect size of these drugs. The transcriptional signatures of lung cell populations will be distinguished, and fibrotic, alveolar, and regenerative niche dynamics defined after FP antagonist and nintedanib interventions. These studies will define the MoA of MA-4586 and MA-4604 in IPF disease pathophysiology in support of an IND submission. **Aim 3. Establish non-GLP preclinical safety in two species.** Following exploratory pharmacokinetics (PK) and formulation optimization, dose range finding and repeated dose toxicology studies will be conducted in rodent (rat) and non-rodent (dog) species in preparation for IND-enabling GLP studies. **Future Work:** The proposed studies lay the framework for Chemistry, Manufacturing, and Controls (CMC), IND-enabling (GLP) studies, IND filing, and a phase I clinical trial for this novel IPF treatment.

Narrative: Idiopathic pulmonary fibrosis (IPF) prevalence is similar to that of many types of cancers, with worse survival prognosis than all cancers except lung and pancreas, and increasing in incidence worldwide. Apart from lung transplantation, currently there are no curative treatments and existing pharmaceutical therapies suffer from severe side effects, expense, and lack of response in some patients. Maipl Therapeutics is developing first-in-class medications to treat IPF by taking advantage of the potent antagonist against a novel target, the PGF2 α receptor.

FACILITIES AND OTHER RESOURCES

Maipl Therapeutics (Maipl)

Office: We have very recently received notice of acceptance to JLABS in New York, NY. The facility is located at 101 6th Ave 3rd floor, New York, NY 10013 and we will be touring and selecting a space in late March 2024, near the time of submission.

JLABS, established as Janssen Research & Development in La Jolla, CA in 2012, provides innovative companies with an efficient way to discover and develop solutions to today's healthcare challenges. This no-strings attached, turnkey facility gives companies access to individual units for wet laboratory research and fully furnished office spaces, along with shared facilities containing over 90 pieces of equipment. These shared facilities include core biology and chemistry facilities, tissue culture rooms, medical device prototype rooms, conference/meeting rooms and a business center.



Laboratory: The individual lab units at JLABS have modern amenities for research and come equipped with features such as central RODI water and vacuum lines, fume hoods, emergency showers/eye wash stations, HazMat storage cabinets, 110V and 220V power supplies for instruments, and emergency power outlets.

Clinical/Animal: N/A (provided by partner CROs and CDMOs as well as our UPenn consortium)

Computer: The office space is equipped with several computers, monitors, and a printer/scanner. Tenants of the space also have access to Wi-Fi service.

Environment: JLABS invites emerging companies to join based on the following criteria: compelling and credible science and/or technology; potential to meet an area of significant medical or market need; and the quality of the team. We will therefore be surrounded by talented entrepreneurs and resources.

Biohazards: All work involving biological agents/materials will be carried out in compliance with NIH Guidelines and the CDC/NIH Biosafety in Microbiological and Biomedical Laboratories (BMBL) practices. Maipl is responsible for the safe practices of biohazard handling and waste disposal as defined in our policies and procedures. All appropriate personnel are required to maintain strict adherence to safety practices. Personal protective equipment requirements are implemented, where necessary.

Intellectual Property: Maipl Therapeutics has in-licensed a series of FP antagonist compounds from Ferring Pharmaceuticals. Of the five compounds in-licensed from Ferring, Maipl is developing two of these for a separate indication, endometriosis-associated menstrual pain, while two other compounds, MA-4586 and MA-4604, are being developed for IPF.

University of Pennsylvania School of Medicine (Beers Lab)

Laboratory: Dr. Beers has exclusive use of new laboratory space consisting of 1500 sq feet of wet bench space located in the PENN-CHOP Lung Biology Institute (PCLBI) at the Perelman School of Medicine at the University of Pennsylvania (Opened Fall 2016). The LBI is an interdisciplinary center that combines basic, clinical and translational research being conducted by Pulmonary faculty, both here at Penn (adult patients) and at CHOP (neonatal and pediatric patients). The LBI is housed in a completely renovated, state of the art research space in Stemmler Hall with more than 12,000 square feet of newly designed open concept BSL-2 lab spaces, offices, and support areas. There are dedicated areas for histochemistry and microscopy, PCR and molecular techniques, cell culture, animal surgery and preparative and analytical biochemistry as well as walk-in cold rooms, tissue culture suites, and core equipment rooms housing centrifuges and freezer storage.

The PCLBI together with the UPENN Division made an investment of over \$1,000,000 of capital equipment including a Quant7 384 well Q PCR machine, a Lynx Superspeed centrifuge, a Licor Chemidoc Imaging System, a Nanodrop spectrophotometer, a Miltenyi Biotec MACS Tissue dissociator, a FlexiVent rodent pulmonary function machine, a Zeiss microscope station, and an 18-color BD Fortessa FACS machine. In addition to the research lab space, the LBI houses the Human Lung Pipeline Tissue Bank which provides support in the design and implementation of experiments involving the use of human lung samples and has independently developed and optimized protocols for the isolation and generation of high quality, reproducible human primary cell 3D organoids. The LBI houses six core research labs that encompass a myriad of scientific interests including: developmental biology, epithelial biology, oncology, immunology and inflammation research through basic science, clinical and translational research approaches. This new major investment of resources facilitates a rich interdisciplinary environment and markedly benefit this grant proposal.

In addition, PCLBI maintains a dry bench laboratory with a dedicated on-site bioinformatics staff person and the availability of high throughput computing and data storage hosted in the PENN Cardiovascular Research Institute located on the PSOM campus in close proximity to Dr. Beers' lab.

Clinical: N/A

Animal: A fully equipped animal barrier facility is located in the Clinical Research Building, directly connected to the Stemmler Hall research spaces. Laminar airflow racks equipped with HEPA filters as well as quarantine cubicles are available for the husbandry and experimentation of mice. The University of Pennsylvania, under the supervision of the School of Veterinary Medicine, provides daily observation and necessary medical care. Vivarium facilities are serviced and maintained by University Laboratory Animal Research (ULAR) organization according to NIH guidelines. Animal ordering, delivery and pre-surgical care are provided by the University Laboratory Animal Resources. Fully equipped sterile and non-sterile facilities are available for terminal and survival animal surgeries as needed.

Computer: The Beers laboratory maintains a fully networked PC based computer system (10 workstations) with direct T1 internet access. Peripheral hardware includes digital cameras, writeable USB hard drives for data storage and data back-up, scanners, video, and microscopes. Software package are available for word processing, spreadsheet calculations, statistical analysis, image processing and DNA analysis. Data backup and storage is also available through Penn Medicine Academic Computer Services.

Office: Dr. Beers' office is directly adjacent to the laboratory research space. Joint administrative support for PCLBI faculty is in the administrative cubicles outside of faculty offices. Video and phone conferencing is available for use in a shared conference room located at the rear of the laboratory spaces.

Other:

PENN CORE Facilities Relevant To The Proposal:

Histology: The Penn Cardiovascular Institute Histology and Gene Expression Core (PCHC) was established 20 years ago. The PCHC is staffed with 5 personnel and provides expert professional services for more than 30 research Labs of the Penn CVI and affiliated members, departments, centers, and institutes. The PCHC offers all histology services including tissue processing, embedding, sectioning, staining, immunocytochemistry and in situ hybridization. The PCHC uses advanced IHC and in situ hybridization (ISH) methods including RNAscope to meet all basic histology needs of the community. PCHC manually processes more than 6,000 samples and provides 25,000 to 40,000 slides to researchers each year. The PCHC is equipped with multiple microtomes, embedding stations, cryostats, and other histological equipment.

Flow Cytometry: A 18-Color BD Fortessa is housed in the Stemmler research space; all laboratory members have full access to this device. In addition, 5 other flow cytometers and two cell sorters in addition to training courses are available under the auspices of the Penn Flow Cytometry Core and are deployed throughout the campus. Dedicated FACS cell sorting with technical guidance is also managed by the core

Next-Generation Sequencing Core: The proposed genomic sequencing experiments will be conducted on an Illumina NextSeq500 sequencing machine housed in the Next-Generation Sequencing Core (NGSC), which serves the high-throughput sequencing needs of the School of Medicine. The services of the facility include consultation on experimental design, sample preparation and quality control, analysis and interpretation of

results for and next-generation sequencing experiments. The NGSC's staff has been performing Illumina sequencing since 2008. The facility occupies over 700 sq. ft. in Dr. Kaestner's laboratory, located in the Smilow Research Building. Through the core, lab members have access to other important pieces of equipment for NGS experiments, including: Agilent BioAnalyzer 2100, Agilent TapeStation, LifeTechnologies Qubit fluorimeter, a Biomek FP robot for sample handling, Illumina HiSeq2500, NextSeq500 and hiSeq 2000 machines and a 10X Genomics system for performing single cell analytical experiments.

HD Biosciences

HD Biosciences is a biology-focused preclinical R&D services provider located in San Diego, CA and Cranbury, NJ. They have ~50,000 SF of well-equipped state-of-the-art facilities with an HTS/SAR screening center, BSL2/2+ labs, and onsite vivaria. Their ~150 employees are composed of ~50% PhDs/MDs and they have served ~400 pharma and biotech customers each year. They provide an extensive range of services including discovery biology, cancer cell screening, comprehensive cell line generation, CRISPR/Cas9 platform, iPSC capabilities, iPS cell differentiation, assays and screening, comprehensive assay formats and technologies, extensive HDB/WuXi compound library collection, HTS & SAR workflow operation process, compound management, ASMS, SPR capabilities, LC-MS capabilities, phenotypic functional assay platform, high content screening platform, comprehensive immunology assay platform, antiviral platform, *in vivo* pharmacology, PK/BD, biodistribution and non-GLP toxicology, oncology models, CNS models, fibrosis (lung and kidney) models, ex vivo capabilities, and histology services.



Labcorp

LabCorp is a global preclinical service provider with extensive worldwide facilities. Pharmaceutical development is focused in a 1M+ sq. ft. facility located in Madison, WI. This facility houses more than 330 animal rooms, 60+ PhDs, and more than 1500 total employees. The AAALAC-accredited facility offers many capabilities including bioanalysis, DART, drug metabolism, general toxicology, immunotoxicology, infusion toxicology, *in vivo* PK screening, ocular toxicology, pathology, cell and gene therapy (ABSL2), preclinical pharmacology, specialty pathology, and vaccine testing



TCG GreenChem

TCG GreenChem provides extensive CDMO facilities for CMC development services including process research & development and delivery of cGMP APIs in discovery, development, and commercialization domains. End to end services include medicinal chemistry, biology & bioanalytics, analytical chemistry, rapid scale-up, process R&D and CMC support, and manufacturing. TCG operates a 3000 sq. ft. lab/office space in Richmond Virginia Biotechnology Research Park and a 54,000 sq. ft. lab/office space in Princeton South Corporate Center (NJ) with 74 employees (60 Ph.D.).



EQUIPMENT

Maipl Therapeutics (Maipl)

The shared facilities of JLABS contain over 90 pieces of equipment. These shared facilities include core biology and chemistry facilities, tissue culture rooms, and medical device prototype rooms. The individual lab units come equipped with features such as central RODI water and vacuum lines, fume hoods, emergency showers/eye wash stations, HazMat storage cabinets, 110V and 220V power supplies for instruments and emergency power outlets. Capabilities are summarized below:

Private and shared chemistry labs with built-in fume hoods

Private and shared Cell Culture Labs (up to BSL2) w/in-house gases (CO2 & N2)

Shared analytical lab

Regulated ventilation system for proper laboratory grade air flow

4, -30, -80 and cryo storage space allocated base on footprint; all cold storage is monitored and available for monitoring

PCR/ qPCR Systems

Fragment Analyzers

Flow Cytometers

Cell Sorter

Spectrophotometer, UV/VIS

HPLC Systems

University of Pennsylvania School of Medicine (Beers Lab)

The main laboratory and adjacent rooms for the Beers Lab within the Penn-CHOP Lung Biology Institute (LBI) are equipped with the following: Biosafety cabinets (3), CO2 tissue culture incubators (4), ultra-, super- and high-speed centrifuges, spectrophotometers (2), gel scanner and image quantitation software, rodent ventilators and perfusion facilities, capillary surfactometer, DNA thermal cyclers, -80°_freezers (7) and -20°_freezers (5), Two (2) Olympus inverted phase fluorescence microscopes with digital CCD camera, live cell imaging stages and IMAGE 1 software, electrophoresis equipment, microplate readers (2), microbalances (3) , pH meters, an autoclave, and LN2 cryostorage.

The PCLBI Human Lung Pipeline core lab in the Stemmler building also possesses additional equipment including a Miltenyi Biotec MACS Tissue dissociator, a Quant7 Q PCR machine, a Lynx Superspeed centrifuge, a LICOR Chemidoc, a Nanodrop spectrophotometer, a FlexiVent rodent pulmonary measurement device and a 12-color BD Fortessa FACS machine.

HDBiosciences

Equipment and capabilities include:

CRISPR centered toolbox for gene editing

KO/KI cell line generation including primary immune cells and iPSC

1,000+ tumor cell lines for drug sensitivity profiling

MOA studies

Comprehensive iPSC platform

Diversified assay format and technology to support hit ID, H2L, lead discovery and biomarker analysis

Biochemical and cellular

Phenotypic & functional

Flow cytometry

High content imaging

LC-MS and Biophysical

High throughput screening with 384-and 1536-well plate options

Compound management support

~300k WuXi compound library

Animal models including PK/PD/biodistribution, Non-GLP toxicology, Oncology, CNS, Fibrosis, Metabolic, Inflammation/autoimmune

Comprehensive Oncology service with broad choice of xenograft, syngeneic, orthotopic, metastatic, and humanized models

Integrated ex vivo analysis and histopathology

Labcorp

The extensive Labcorp facilities and capabilities are described in the Facilities and Other Resources document. Animal housing is compliant with the Guide to the Care and Use of Laboratory Animals, 8th edition and the facility is AAALAC accredited. The more than 330 animal rooms are capable of housing preclinical test animals including mice, rats, hamsters, ferrets, rabbits, canines, minipigs, and primates. They are well equipped for the proposed PK/toxicology studies.

TCG GreenChem

Extensive equipment is located on site to route design and synthesis of complex molecules and scaling up of these compounds under GMP conditions to support pre-clinical and clinical studies for the pharma, biotech, and generic industries. Dynamic capabilities include characterizing these molecules using state-of-the-art instrumentation, working closely with the R&D team and the engineers to then scale these processes in a safe and robust manner and transfer them to the pilot plant and commercial facilities. They leverage the capabilities of the Automated Reaction Design and Engineering Lab ("ARDEL") and the Continuous Flow Lab ("CFL") to accelerate the experiments for reaction screening, route scouting, optimization, process safety and preparation of intermediates, RSMs and APIs. Their five cGMP Kilo Labs, each with two walk-in hoods, support manufacture of Phase I & Phase IIa API: certified cGMP by large Pharma and Biotech. They are a Development Partner with the National Center for Translational Sciences (NCATS) of the NIH.

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator						
Prefix:	First Name*:	Yong	Middle Name G.	Last Name*:	Yue	Suffix:
Position/Title*:	President & CEO					
Organization Name*:	MAIPL THERAPEUTICS, INC.					
Department:						
Division:						
Street1*:	18 CIRCLE RD					
Street2:						
City*:	NEW YORK					
County:						
State*:	NY: New York					
Province:						
Country*:	USA: UNITED STATES					
Zip / Postal Code*:	105835322					
Phone Number*:	000-000-0000		Fax Number:			
E-Mail*:	yong.yue@maipltx.com					
Credential, e.g., agency login: YONGYUE						
Project Role*:	PD/PI		Other Project Role Category:			
Degree Type:	PhD, MS, BS		Degree Year: 1994, 1987, 1984			
Attach Biographical Sketch*:	File Name:		1_Bio_Yue_2024.03.26.pdf			
Attach Current & Pending Support:	File Name:					

PROFILE - Senior/Key Person						
Prefix:	First Name*:	Yoshiyuki	Middle Name	Last Name*:	Fukase	Suffix:
Position/Title*:	Co-Founder and Vice President					
Organization Name*:	MAIPL THERAPEUTICS, INC.					
Department:						
Division:						
Street1*:	18 CIRCLE RD					
Street2:						
City*:	NEW YORK					
County:						
State*:	NY: New York					
Province:						
Country*:	USA: UNITED STATES					
Zip / Postal Code*:	105835322					
Phone Number*:	000-000-0000		Fax Number:			
E-Mail*:	yoshiyuki.fukase@maipltx.com					
Credential, e.g., agency login: YOSHIFUKASE						
Project Role*:	Co-Investigator		Other Project Role Category:			
Degree Type:	PhD, BS		Degree Year: 2001, 1996			
Attach Biographical Sketch*:			File Name:	2_Bio_Fukase_2024.03.26.pdf		
Attach Current & Pending Support:	File Name:					

PROFILE - Senior/Key Person							
Prefix:	First Name*:	MICHAEL	Middle Name	FRANCIS	Last Name*:	BEERS	Suffix:
Position/Title*:	Professor of Medicine						
Organization Name*:	UNIVERSITY OF PENNSYLVANIA						
Department:							
Division:							
Street1*:	Pulmonary & Critical Care Div						
Street2:	Translational Research Center						
City*:	Philadelphia						
County:							
State*:	PA: Pennsylvania						
Province:							
Country*:	USA: UNITED STATES						
Zip / Postal Code*:	191040000						
Phone Number*:	215-898-9106		Fax Number:				
E-Mail*:	MFBEERS@PENNMEDICINE.UPENN.EDU						
Credential, e.g., agency login: mfbeers							
Project Role*:	Other (Specify)		Other Project Role Category: Subaward PI				
Degree Type:	MD, AB		Degree Year: 1985, 1981				
Attach Biographical Sketch*:			File Name:	3_Bio_Beers_2024.02.20.pdf			
Attach Current & Pending Support:	File Name:						

PROFILE - Senior/Key Person						
Prefix:	First Name*:	Clavert	Middle Name	Last Name*:	Louden	Suffix:
Position/Title*:	Consultant					
Organization Name*:	GSG Path-Tox Consultants					
Department:						
Division:						
Street1*:	1031 Redtail Rd					
Street2:						
City*:	Audubon					
County:						
State*:	PA: Pennsylvania					
Province:						
Country*:	USA: UNITED STATES					
Zip / Postal Code*:	194031844					
Phone Number*:	000-000-0000		Fax Number:			
E-Mail*:						
Credential, e.g., agency login: CLOUD						
Project Role*:	Other (Specify)		Other Project Role Category: Other Significant Contributor			
Degree Type:	PhD, DVM, BS		Degree Year: 1992, 1986, 1980			
Attach Biographical Sketch*:	File Name:		4_Bio_Louden_2024.03.26.pdf			
Attach Current & Pending Support:	File Name:					

PROFILE - Senior/Key Person						
Prefix:	First Name*:	Ying	Middle Name	Last Name*:	Zhang	Suffix:
Position/Title*:	DMPK Consultant					
Organization Name*:	MAIPL THERAPEUTICS, INC.					
Department:						
Division:						
Street1*:	3857 Pell Place					
Street2:						
City*:	San Diego					
County:						
State*:	CA: California					
Province:						
Country*:	USA: UNITED STATES					
Zip / Postal Code*:	921304139					
Phone Number*:	000-000-0000		Fax Number:			
E-Mail*:						
Credential, e.g., agency login: YZDMPK						
Project Role*:	Other (Specify)		Other Project Role Category: Other Significant Contributor			
Degree Type:	PhD, MS, BS		Degree Year: 2016, 2005, 2000			
Attach Biographical Sketch*:	File Name:		5_Bio_Zhang_2024.03.26.pdf			
Attach Current & Pending Support:	File Name:					

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Yong G. Yue

ERA COMMONS USER NAME (credential, e.g., agency login): YONGYUE

POSITION TITLE: President and CEO

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Zhejiang University, Hangzhou, China	BS	06/1984	Agronomy
Zhejiang University, Hangzhou, China	MS	06/1987	Biophysics
Virginia Tech, Blacksburg, VA	PhD	05/1994	Genetics

A. Personal Statement

Drawing upon my extensive 20-year experience in the pharmaceutical industry across multiple therapeutic areas such as immunology, oncology, metabolic diseases, neuroscience, and reproductive health, I am positioned exceptionally to serve as the Principal Investigator for this NIH Phase II SBIR grant. My career, characterized by my contributions to innovative drug discovery strategies, evidences my ability to lead complex projects successfully. These experiences underscore my capability to bring together multidisciplinary teams to drive innovation within the constraints of rigorous research and development environments. Moreover, it highlights my adeptness at leveraging advanced technology and science to solve pressing challenges in drug discovery, reflecting an ability to adapt and excel in dynamic scientific landscapes.

I am confident that my expertise, coupled with my proven track record of leadership, innovation, and scientific acumen, positions me ideally as the Principal Investigator for this project. My commitment to advancing healthcare through cutting-edge research and development will ensure the success of this initiative and contribute significantly to the field of biomedicine.

B. Positions, Scientific Appointments, and Honors**Positions**

2023 – Present	President & CEO, Maipl Therapeutics, Inc. Scarsdale, NY
2020 – 2023	Senior Director, Ferring Pharmaceuticals, San Diego, CA
2019 – 2020	Senior Director, Camp4 Therapeutics Inc, Cambridge, MA
2018 – 2019	Senior Director, Flagship Pioneering, New York, NY
2015 – 2018	Director, Boehringer Ingelheim Pharmaceutical Inc., Ridgefield, CT
2012 – 2015	Research Advisor & Group Leader, Eli Lilly and Company, Indianapolis, IN
2012 – 2015	Head of Bioinformatics, ImClone Systems, Eli Lilly and Company, Indianapolis, IN
2010 – 2012	Principal Research Scientist of Human Genetics, Eli Lilly and Company, Indianapolis, IN
2007 – 2010	Principal Research Scientist of Functional Genomics, Eli Lilly and Company, Indianapolis, IN
2005 – 2007	Principal Research Scientist of Bioinformatics, Eli Lilly and Company, Indianapolis, IN
2004 – 2005	Senior Research Scientist, Eli Lilly and Company, Indianapolis, IN
2000 – 2004	Research Scientist, Eli Lilly and Company, Indianapolis, IN

1998 – 2000	Senior Research Biologist, Dow AgroSciences, Indianapolis, IN
1996 – 1998	Research Scientist, Union Camp Corporation, Princeton, NJ

Honors

2004	Lilly Research Laboratory (LRL) President's Award, Eli Lilly and Company
2004	Regional Solution Achievement Award, Eli Lilly and Company
2003	Enabling Biology Elite Award, Eli Lilly and Company
2001	Change the World Award, Eli Lilly and Company
1999	Discovery Recognition Award, Dow AgroSciences
1996	Award for Technological Creativity, Union Camp Cooperation
1994	Gerald O. Mott Meritorious Graduate Student Award, Crop Science Society of America
1994	Charles I. Rich Graduate Fellowship, Virginia Tech

C. Contributions to Science

1. **Lipid Metabolism and Cardiovascular Research.** My work has contributed to understanding the genetic and biochemical underpinnings of lipid processing and its implications for heart health. Specifically, the functional differentiation of the MGAT3 gene between mice and rats revealed species-specific mechanisms of lipid metabolism, while a genome-wide analysis uncovered factors influencing the secretion of Apolipoprotein A-I, a key molecule in lipoprotein transport. These studies open avenues for targeted interventions in metabolic disorders and cardiovascular diseases.
 - a. **Yue YG**, Chen YQ, Zhang Y, Wang H, Qian YW, Arnold JS, Calley JN, Li SD, Perry WL, Zhang HY, Konrad RJ, Cao G. (2011) The acyl coenzymeA:monoacylglycerol acyltransferase 3 (MGAT3) gene is a pseudogene in mice but encodes a functional enzyme in rats. **Lipids**. 46(6):513-20
 - b. Miles RR, Perry W, Haas JV, Mosior MK, N'Cho M, Wang JW, Yu P, Calley J, **Yue Y**, Carter Q, Han B, Foxworthy P, Kowala MC, Ryan TP, Solenberg PJ, Michael LF. (2013) Genome-wide screen for modulation of hepatic apolipoprotein A-I (ApoA-I) secretion. **J Biol Chem**. 288(9):6386-96.
2. **Cancer Genomics and Therapy Research.** My contributions to cancer genomics and therapy research have been multifaceted, addressing the genetic heterogeneity of tumors, identifying druggable cancer driver genes, and exploring the efficacy of targeted therapies. Through comprehensive genomic analyses—including whole-genome sequencing—I have helped to delineate the complex genetic landscapes of gastric adenocarcinoma and lung cancer, particularly highlighting the genetic heterogeneity within these cancers. Additionally, my work in co-targeting oncogenic pathways, such as BRAF and cyclin-dependent kinases, provides novel therapeutic avenues for treating BRAF mutant cancers, further advancing personalized medicine in oncology.
 - a. Chen S-H, Zhang Y, Van Horn RD, Yin T, Buchanan S, Yadav V, Mochalkin I, Wong SS, **Yue YG**, Huber L, Conti I, Henry JR, Starling JJ, Plowman GD, Peng S-B. (2016) Oncogenic BRAF deletions that function as homodimers and are sensitive to inhibition by RAF dimer inhibitor LY3009120. **Cancer Discovery** 6:300-315
 - b. Cristescu R, Lee J, Nebozhyn M, Kim K-M, Ting JC, Wong SS, Liu J, **Yue YG**, Wang J, Yu K, Ye XS, Do I-G, Liu S, Gong L, Fu J, Jin JG, Choi MG, TS, Lee JH, Bae JM, Kim ST, Park SH, Tan P, Chen R, Hardwick J, Kang WK, Ayers M, Dai H, Reinhard C, Aggarwal A, Kim S, Loboda A. (2015) Molecular analysis of gastric cancer identifies discrete subtypes associated with distinct clinical characteristics and survival outcomes: the ACRG (Asian Cancer Research Group) study. **Nature Medicine** 21: 449–456
 - c. Yadav V, Chen S-H, **Yue YG**, Buchanan S, Beckman RP, Peng S-B. (2015) Co-targeting BRAF and cyclin dependent kinases 4/6 for BRAF mutant cancers. **Pharmacology & Therapeutics** 149:139-49

- d. Krishnan VG, Ebert PJ, Ting JC, Lim E, Wong SS, Teo ASM, **Yue YG**, Chua HH, Ma X, Loh GSL, Lin Y, Tan JHJ, Yu K, Zhang S, Reinhard C, Tan DSW, Peters BA, Lincoln SE, Ballinger DG, Larami JM, Nilsen GB, Barber TD, Tan P, Hillmer AM, and Ng PC (2014) Whole-genome sequencing of Asian lung cancers: second-hand smoke unlikely to be responsible for higher incidence of lung cancer among Asian never-smokers. **Cancer Res** 74: 6071–81
- 3. **Single Cell Genomics.** With the advent of single-cell technologies, my focus has extended to developing computational tools that empower researchers to unlock the potential of single-cell RNA-seq data. The Single Cell Explorer suite of tools is designed to facilitate collaborative research and enable the deep exploration of large-scale single-cell datasets. This work supports the growing need for precise and comprehensive analyses at the single-cell level, serving a broad range of applications from basic biological research to clinical diagnostics and therapeutic development.
 - a. Feng D, Whitehurst CE, Shan D, Hill JD, **Yue YG**. (2019) Single cell explorer, collaboration-driven tools to leverage large-scale single cell RNA-seq data. **BMC Genomics** 20: 676

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Yoshiyuki Fukase

ERA COMMONS USER NAME (credential, e.g., agency login): YOSHIFUKASE

POSITION TITLE: Co-Founder and Vice President

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Osaka University, Suita, Japan	BS	03/1996	Chemistry
Osaka University, Suita, Japan	PhD	03/2001	Organic Chemistry
Harvard University, Cambridge, MA	Postdoc	06/2004	Organic Chemistry

A. Personal Statement

I have an extensive background in medicinal chemistry, small molecule drug discovery, and leadership in both project management and team development. During the last 19 years, I've held pivotal roles leading both internal teams and external CRO teams. In these roles, I have overseen comprehensive drug discovery processes from conceptualization to preclinical stages. Notable achievements under my guidance include the successful delivery of preclinical drug candidates, the establishment of a new research organization merging academia and industry expertise, and the innovation in Fragment Based Drug Discovery leading to clinical testing agents. These experiences have honed my aptitude for effective design solutions in drug discovery, emphasizing robust research strategy delivery, drug candidate delivery, and fostering collaborative interdisciplinary interactions.

I am eager to apply my capabilities toward advancing the objectives of this NIH Phase II SBIR grant. My vision for this endeavor is to leverage my comprehensive expertise in drug discovery, my proven leadership skills, and my passion for impactful research to drive innovations that will address pressing healthcare needs.

Patents (sampling of most recent patents from a total of 18)

1. "Inhibitors of ENL/AF9 YEATS" T. Khan, N. Liverton, **Y. Fukase**, M. Michino, A. Stamford, M. Miller, D. Huggins, P. Meinke, PCT Int. Appl., **2021**, WO 2021127166.
2. "Pyridinone- and pyridazinone-based compounds and medical uses thereof" T. Hla, I. Jilishitz, P. Meinke, A. Stamford, M. Foley, A. Sato, Y. Wada, **Y. Fukase**, A. Kina, H. Takahagi, H. Igawa, W. Polvino, PCT Int. Appl., **2019**, WO 2019173790.
3. "Agents and methods for treating dysproliferative diseases" **Y. Fukase**, M. Duggan, H-G. Wendel, K. Singh, PCT Int. Appl., **2019**, WO 2019161345.
4. "Pyrazoloquinazoline antitumor agents" T. Kapoor, **Y. Fukase**, Y. Hirata, Y. Tanaka, S. Morimoto, H. Furukawa, Y. Yoshitomi, M. Foley, PCT Int. Appl., **2018**, WO 2018213712.

B. Positions, Scientific Appointments, and Honors**Positions**

2024 – Present Co-founder & Vice-president, Maipl Therapeutics Inc., New York, NY

2022 – 2023	Director, Ferring Pharmaceuticals Inc., San Diego, CA
2020 – 2022	Director of Chemistry, Tri-institutional Therapeutics Discovery Institute Inc., New York, NY
2017 – 2020	Associated Director, Takeda Pharmaceutical Company Limited, New York, NY
2014 – 2017	Principal Scientist, Tri-institutional Therapeutics Discovery Institute Inc., New York, NY
2009 – 2014	Principal Scientist, Takeda Pharmaceutical Company Limited, Osaka/Kanagawa, Japan
2004 – 2009	Scientist, Takeda Pharmaceutical Company Limited, Osaka, Japan

Scientific Appointments

2002 – 2004	Post-doctoral Research Fellow, Harvard University, Cambridge, MA
2001 – 2002	Research Fellow, Osaka University, Osaka, Japan

Honors

2015	Takeda Research Senior Director's Award, Discovery of Clinical Candidate TAK-828
2009	Takeda Research Senior Director's Award, Discovery of Clinical Candidate TAK-272
2002	Young Investigator Award, The Japanese Society of Carbohydrate Research

C. Contributions to Science

1. Cancer and Tumor Biology. My research focused on understanding and targeting molecular mechanisms behind cancer progression, particularly through the inhibition of specific protein interactions or signaling pathways critical for tumor cell survival and proliferation. This work has contributed to the development of potential therapeutic agents that can selectively target tumor cells without causing significant harm to normal tissues.

- a. "Targeting eIF4A Dependent Translation of KRAS Signaling Molecules" K. Singh, J. Lin, N. Lecomte, P. Mohan, A. Gokce, V. R. Sanghvi, M. Jiang, O. Grbovic-Huezo, A. Burcul, S. G. Stark, P. B. Romesser, Q. Chang, J. P. Melchor, R. K. Beyer, M. Duggan, **Y. Fukase**, G. Yang, O. Ouefelli, A. Viale, E. de Stanchina, A. W. Stamford, P. T. Meinke, G. Rätsch, S. D. Leach, Z. Ouyang, H-G. Wendel, *Cancer Res.* **2021**, 81(8), 2002-2014.
- b. "Design and Synthesis of Conformationally Constrained ROR γ t Inverse Agonists" A. Sato, **Y. Fukase**, M. Kono, A. Ochida, T. Oda, Y. Sasaki, N. Ishii, Y. Tomata, S. Fukumoto, Y. N. Imai, K. Uga, A. Shibata, M. Yamasaki, H. Nakagawa, M. Shirasaki, R. Skene, I. Hoffman, B-C. Sang, G. Snell, J. Shirai, S. Yamamoto, *ChemMedChem* **2019**, 14, 1917-1932.
- c. "Discovery of [cis-3-((5R)-5-[(7-Fluoro-1,1-dimethyl-2,3-dihydro-1H-inden-5-yl)carbamoyl]-2-methoxy-7,8-dihydro-1,6-naphthyridin-6(5H)-yl]carbonyl)cyclobutyl]acetic Acid (TAK-828F) as a Potent, Selective, and Orally Available Novel Retinoic Acid Receptor-Related Orphan Receptor γ t Inverse Agonist" M. Kono, A. Ochida, T. Oda, T. Imada, Y. Banno, N. Taya, S. Masada, T. Kawamoto, K. Yonemori, Y. Nara, **Y. Fukase**, T. Yukawa, H. Tokuhara, R. Skene, B.-C. Sang, I. Hoffman, G. Snell, K. Uga, A. Shibata, K. Igaki, Y. Nakamura, H. Nakagawa, N. Tsuchimori, M. Yamasaki, J. Shirai, S. Yamamoto, *J. Med. Chem.* **2018**, 61(7), 2973-2988.

2. Cardiovascular and Metabolic Diseases. I have explored the molecular underpinnings of cardiovascular and metabolic diseases, such as the role of α V β 3 integrin in angiogenesis and the regulation of blood pressure through renin inhibitors. This research is crucial for the discovery of novel therapeutic agents that can manage or reverse the effects of these prevalent conditions.

- a. "Novel Pure α V β 3 Integrin Antagonists That Do Not Induce Receptor Extension, Prime the Receptor, or Enhance Angiogenesis at Low Concentrations" L. Jihong, **Y. Fukase**, Y. Shang, W. Zou, J. Munoz-Felix, L. Buitrago, J. van Agthoven, Y. Zhang, R. Hara, Y. Tanaka, R. Okamoto, T. Yasui, T. Nakahata, T. Imaeda, K. Aso, Y. Zhou, C. Locuson, D. Nesic, M. Duggan, J. Takagi, R. Vaughan, T. Walz, K. Hodivala-Dilke, S. Teitelbaum, A. Arnaout, M. Filizola, M. Foley, B. Coller, *ACS Pharmacol. Transl. Sci.* **2019**, 2, 387-401.
- b. "Discovery of Benzimidazole Derivatives as Orally Active Renin Inhibitors: Optimization of 3,5-Disubstituted Piperidine to Improve Pharmacokinetic Profile" H. Tokuhara, Y. Imaeda, **Y. Fukase**,

- K. Iwanaga, N. Taya, K. Watanabe, R. Kanagawa, K. Matsuda, Y. Kajimoto, K. Kusumoto, M. Kondo, G. Snell, C. Behnke, T. Kuroita, *Bioorg. Med. Chem.* **2018**, 26(12), 3261-3286.
- c. "Discovery of TAK-272: A Novel, Potent, and Orally Active Renin Inhibitor." Y. Imaeda, H. Tokuhara, **Y. Fukase**, R. Kanagawa, Y. Kajimoto, K. Kusumoto, M. Kondo, G. Snell, C. Behnke, T. Kuroita, *ACS Med. Chem. Lett.*, **2016**, 7(10), 933-938.
- 3. Drug Discovery and Development.** My work in screening and developing new small molecule inhibitors for various therapeutic targets aimed to identify promising compounds that can progress into clinical development stages, ultimately offering new treatment options across different diseases.
- "Deglycase-Activity Oriented Screening to Identify DJ-1 Inhibitors" I. Maksimovic, E. Finkin-Groner, **Y. Fukase**, O. Zheng, S. Sun, M. Michino, D. Huggins, R. Myers, Y. David, *RSC Med. Chem.* **2021**, 12, 1232-1238.
 - "Targeting Allostery in the Dynein Motor Domain with Small Molecule Inhibitors" C. Santarossa, K. Mickolajczyk, J. Steinman, L. Urnavicius, N. Chen, Y. Hirata, **Y. Fukase**, N. Coudray, D. Ekiert, G. Bhabha, T. Kapoor, *Cell Chemical Biology* **2021**, 28, 1460-1473.
 - "Chemical Structure-Guided Design of Dynapyrazoles, Cell-Permeable Dynein Inhibitors with a Unique Mode of Action" J. Steinman, C. Santarossa, R. Miller, L. Yu, A. Serpinskaya, H. Furukawa, S. Morimoto, Y. Tanaka, M. Nishitani, M. Asano, R. Zalyte, A. Ondrus, A. Johnson, F. Ye, M. Nachury, **Y. Fukase**, K. Aso, M. Foley, V. Gelfand, J. Chen, A. Carter, T. Kapoor, *eLife*, **2017**, 6, 1-e25174/36.
- 4. Immunology and Inflammatory Diseases.** Our work in this field involved identifying and validating new therapeutic targets for treating immunological and inflammatory conditions. By modulating specific components of the immune system such as ROR γ t, we aimed to develop therapies that can effectively manage autoimmune diseases and inflammation without compromising immune function.
- "Identification of Novel Quinazolinedione Derivatives as ROR γ t Inverse Agonist" **Y. Fukase**, A. Sato, Y. Tomata, A. Ochida, M. Kono, K. Yonemori, K. Koga, T. Okui, M. Yamasaki, Y. Fujitani, S. Yamamoto, *Bioorg. Med. Chem.* **2018**, 26(3), 721-736.
 - "Discovery of Orally Efficacious ROR γ t Inverse Agonists, Part 2: Design, Synthesis, and Biological Evaluation of Novel Tetrahydroisoquinoline Derivatives" M. Kono, T. Oda, M. Tawada, T. Imada, Y. Banno, N. Taya, T. Kawamoto, H. Tokuhara, Y. Tomata, N. Ishii, **Y. Fukase**, S. Yamamoto, *Bioorg. Med. Chem.* **2018**, 26(2), 470-482.
 - "Discovery of Orally Efficacious ROR γ t Inverse Agonists, Part 1: Identification of Novel Phenylglycinamides as Lead Scaffolds" J. Shirai, Y. Tomata, M. Kono, A. Ochida, **Y. Fukase**, A. Sato, S. Masada, T. Kawamoto, K. Yonemori, R. Koyama, S. Yamamoto, *Bioorg. Med. Chem.* **2018**, 26(2), 483-482.
- 5. Synthetic and Computational Chemistry.** My earlier work in the synthesis of complex molecules and computational chemistry focused on exploring the structural basis of their biological activities. Our work not only contributed to the foundational understanding of how molecular structures influence biological functions but also helped guide the design of more effective therapeutic agents.
- "Synthesis of Rubrivivax gelatinosus Lipid A and Analogues for Investigation of the Structural Basis for Immunostimulating and Inhibitory Activities." **Y. Fukase**, Y. Fujimoto, Y. Adachi, Y. Suda, S. Kusumoto, K. Fukase, *Bull. Chem. Soc. Jpn.*, **2008**, 81(7), 796-819.
 - "Divergent Structural Complexity from a Linear Reaction Sequence: Synthesis of Fused and Spirobicyclic γ -Lactams from Common Synthetic Precursors." C. E. Masse, P. Y. Ng, **Y. Fukase**, M. Sanchez-Rosello, J. T. Shaw, *J. Combi. Chem.*, **2006**, 8(3), 293-296.
 - "New Efficient Route for Synthesis of Lipid A by Using Affinity Separation." **Y. Fukase**, S.-Q. Zhang, K. Iseki, M. Oikawa, K. Fukase, S. Kusumoto, *Synlett*, **2001**, 11, 1693-1698.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Michael Francis Beers

ERA COMMONS USER NAME (credential, e.g., agency login): mfbeers

POSITION TITLE: Robert L Mayock and David A. Cooper Professor of Medicine

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Pennsylvania - Philadelphia, PA	A.B.	05/1981	Biophysics
University of Pennsylvania - Philadelphia, PA	M.D.	05/1985	Medicine

A. Personal Statement

Over the past 30 years, I have acquired the scientific expertise, investigative experience, and leadership skills necessary to successfully perform the proposed work. During pre-doctoral and post-doctoral training I first developed a strong background in both basic cell biology/biochemistry and lung biology, with specific training and expertise in many key research areas needed for this application. My laboratory in the Pulmonary Division at PENN has since established and maintained a long-standing interest in surfactant component metabolism, alveolar epithelial cell biology, and lung injury/repair with a track record of independent peer-reviewed funding to support a collaborative discovery program which encompasses biochemistry, cell biology, immunology and pulmonary pathophysiology extending from molecule to cell to mouse to man, literally from bench to bedside.

As a lung cell biologist, I have recognized expertise in understanding the molecular mechanisms utilized by the alveolar epithelia for expression of surfactant protein components in health and disease. Initially this work was focused defining, in detail, the biosynthetic life-cycle of the hydrophobic Surfactant Proteins (SP) SP-B and SP-C elucidating the critical targeting motifs, chaperones, and AT2 epithelial cell specific factors (e.g. proteases, Nedd4-2 E3 ligase, etc.) required in these processes. During the current funding cycle, this project built upon these discoveries to extend our focus to defining the role of epithelial cell dysfunction and aberrant cell quality control in the pathogenesis of interstitial lung disease (ILD) using the first two published preclinical mouse models of spontaneous pulmonary fibrosis that expressed murine homologues of clinical ILD SP-C (SFTPC) mutations.

Complimentary to this application and related to mechanisms of injury/repair we have focused on the role of AT2 dysfunction in a variety of lung injury models including hyperoxia, bleomycin, LPS inhalation, and coronaviruses, we recently extended this to understanding the role of the UPR / ER Stress and metabolism in promoting pathologic AT2 cell endophenotypes including the transitional cell state.

**** I HAVE NOT published or created research products under another name.**

This program has had continuous extramural support (NIH, Dept of Veterans Affairs, Foundations, and Industry) since 1993. **Ongoing support that I would like to highlight include:**

NIH R01 HL145408 (Beers - PI)

06/01/19– 5/31/2024

“Alveolar Epithelial Cell Dysfunction in Pulmonary Fibrosis: Leveraging SFTPC Mutations for Discovery of Molecular and Cellular Targets”

NIH U01 HL152970 (Beers-PI)

12/01/2020-11/30/2024

Surfactant Protein C Mouse Models: A Fit For Purpose Preclinical Platform For Advancing Discovery In And Treatment Of Idiopathic Pulmonary Fibrosis”

Dept Veterans Affairs Merit Review 2I01BX001176-09 (Beers-PI)

4/01/21 – 3/31/29

Surfactant Protein C Mutations and Interstitial Lung Disease

Publications relevant to current proposal and highlighting the success of my recent trainees include:

- a. Nureki SI, Tomer Y, Venosa A, Katzen J, Russo SJ, Jamil S, Barrett M, Nguyen V, Kopp M, Mulugeta S, and research program has had continuous extramural support (NIH, Dept of Veterans Affairs, Foundations, and Industry **MF Beers**. Expression of Mutant Sftpc in Murine Alveolar Epithelia Drives Spontaneous Lung Fibrosis. *Journal of Clinical Investigation* 128(9):4008-4024. 2018. PMCID: PMC6118576
- b. Katzen J, Wagner BD, Venosa A, Kopp M, Tomer Y, Russo SJ, Headen AC, Basil MC, Stark JM, Mulugeta S, Deterding RR, and **MF Beers**. A SFTPC BRICHOS Mutant Links Epithelial ER Stress and Spontaneous Lung Fibrosis. *JCI Insight* 2019 JCI Insight 4(6):e126125. 2019. PMCID: PMC6483196.
- c. Alysandatos KD, Russo SJ, **DN Kotton*** and **Beers MF***. Patient-specific iPSCs carrying an SFTPC mutation reveal the intrinsic alveolar epithelial dysfunction at the inception of interstitial lung disease. *Cell Reports* Aug 31;36(9):109636. 2021 doi. PMCID: PMC8432578
- d. Katzen J, Rodriguez L, Tomer Y,.....⁺¹⁴....., and **Beers MF**. Disruption of Proteostasis Causes IRE1 Mediated Reprogramming of Alveolar Epithelial Cells. *Proc. Natl Acad. Sci* 119(43): e2123187119 2022 PMCID: PMC9618079

B. Positions, Scientific Appointments, and Honors

Training and Faculty Positions

2008-	Professor of Medicine <i>with tenure</i> , University of Pennsylvania School of Medicine Philadelphia, PA
2001-2008	Associate Professor of Medicine <i>with tenure</i> , Univ. of Pennsylvania School of Medicine
1993-2001	Assistant Professor of Medicine, University of Pennsylvania School of Medicine
1992-1993	Instructor in Medicine, Department of Medicine, University of Pennsylvania
1992-1993	Research Associate, Institute for Environmental Medicine, University of Pennsylvania
1990-1992	Research Fellow, Institute for Environmental Medicine, University of Pennsylvania
1988-1990	Fellow in Pulmonary Medicine, Cardiovascular Pulmonary Division, Hospital of the University of Pennsylvania
1985-1988	Intern and Resident, Department of Medicine, Hospital of the University of Pennsylvania

Other Experience And Professional Memberships

2019	Standing Member Department of Veterans Affairs ORD PULM Study Section
2018-	Member Medical and Scientific Advisory Board Alpha-1-Antitrypsin Foundation
2016-	Chair Research Review Committee Pulmonary Fibrosis Foundation
2013-	Director of Research PENN Interstitial Lung Disease Center
2007-2012	Associate Editor, <i>Journal of Clinical Investigation</i>
2006-2019	Associate Director Pulmonary and Critical Care Fellowship (Research-Basic)
2004-	Attending Physician, Pulmonary and Critical Care Services, Philadelphia VAMC
1992-2004	Attending Physician, Medical Intensive Care Unit, Hospital of the Univ. of Pennsylvania

Honors

2022	Association of American Physicians
2020-2028	US Department of Veterans Affairs Senior Clinician Investigator Award
2019-	Fellow American Physiological Society
2018-	Robert L. Mayock and David A. Cooper Endowed Chair In Pulmonary Medicine
2013-2015	Albert Rose Established Investigator of the Pulmonary Fibrosis Foundation
2009	European Respiratory Society Visiting Professorship, Berne Switzerland
1993-1998	American Heart Association Clinician Investigator Award
1993-1998	NIH KO8 Clinician Investigator Development Award
1991-1993	Ruth Kirschstein F32 Individual NIH National Research Scientist Award

C. Contributions to Science

My collective body of scientific work represents a comprehensive program in *Discovery, Target ID, Target Validation and Translational Proof of Concept* built around understanding the alveolar epithelial cell in health and disease and its role in lung injury/repair. Areas where I have made significant contributions include:

1. *Understanding Surfactant and Alveolar Type 2 Cell Biology* - Throughout my career I have made important observations related to the biosynthetic metabolism of surfactant components including Surfactant Proteins SP-B and SP-C. Using novel reagents and techniques developed in my lab (e.g. first epitope specific proSP-C antibodies) we characterized surfactant protein synthesis, secretion, and endocytosis using a variety of model systems and made many seminal observations to the field including:

- a. **Beers MF** and Moodley Y. When Is An Alveolar Type 2 Cell An Alveolar Type 2 Cell? A Conundrum for Lung Stem Cell Biology and Regenerative Medicine. *Am J Resp Cell Mol Biol* 57:18-27 2017 PMCID: PMC5516281
- b. Kotorashvili A, Russo SJ, Mulugeta S, Guttentag S, and **Beers MF**. Anterograde transport of surfactant protein C proprotein to distal processing compartments requires PPDY mediated association with NEDD4 ubiquitin ligases. *J. Biol. Chem.* 284 (24):16667-16678 2009. PMCID:PMC2713532
- c. Wang W-J, Russo SJ, Mulugeta S, and **Beers MF**. Biosynthesis of surfactant protein C: Sorting of SP-C proprotein involves oligomeric association via a signal anchor domain. *J Biol. Chem.* 277:19929-37 2002.
- d. **Beers MF**, Russo SR, and Lomax CA. Processing of rat proSP-C by alveolar epithelial cells: The COOH-terminus is required for post-translational targeting and proteolysis. *J. Biol. Chem.* 273:15287-293 1998.

These studies were extended to include mechanisms for abnormal surfactant metabolism and function that occur in both congenital and acquired lung diseases, including acute lung injury, allergic asthma, and BPD.

2. *Epithelial Cell Quality Control and Interstitial Lung Disease: Non-BRICHOS SP-C Mutations* - Over 50 mutations in the *SFTPC* gene have been described in patients with pulmonary fibrosis. My group was the first to report on cases of ILD in children carrying heterozygous mutant SP-C alleles in the linker domain of *SFTPC*. One of these, SP-C^{I73T}, accounts for ~30% of all *SFTPC* mutations and appears in both adult and pediatric cohorts. We went on to define the consequences of their expression using SP-C^{I73T} as the prototype showing it is mistargeted to plasma membrane and endosomes. We also made the novel observation that these mutants induce a late block in autophagy resulting in disrupted cell quality control and impaired mitophagy. We have now causally linked these events to the human disease by developing knock-in SP-C^{I73T} mouse, which acquires clinical, pathological, and biomarker features of human pulmonary fibrosis. Key publications include:

- a. Nureki SI, Tomer Y,and **MF Beers**. Expression Of A Surfactant Protein C Mutant In Alveolar Epithelial Cells Drives Spontaneous Lung Fibrosis *J. Clinl Inv.* 128(9):4008-24 2018C
- b. Hawkins A, Guttentag SH, Deterding R,, Mulugeta S, and **Beers MF**. A non-BRICHOS *SFTPC* mutant (SP-C^{I73T}) linked to interstitial lung disease promotes a late block in macroautophagy disrupting cellular proteostasis and mitophagy. *Am J Phys: Lung Cell Mol Phys.* 308: L33-47 2015 PMCID: PMC4281696
- c. **Beers MF**, Hawkins A, Maguire JA, Kotorashvili A, Zhao M, Newitt JL, Ding W, Russo SJ, Guttentag S, Gonzales L, and S Mulugeta. A non-aggregating Surfactant Protein C mutant is misdirected to early endosomes and disrupts phospholipid recycling. *Traffic* 9:1196-1210 2011 PMCID: PMC3155663
- d. Brasch F,, Mulugeta S, Müller KM, Bauhau M, and **Beers MF**. Interstitial lung disease in a baby with a *de novo* mutation of the *SFTPC* gene. *European Respiratory Journal* 24 (1): 30-39 2004.

3., *Proteostasis and Epithelial Dysfunction In Parenchymal Lung Disease: BRICHOS SFTPC Mutations* - We were able to leverage our basic discovery studies on SP-C biosynthesis to show that a second subset of these mutations in the distal proSP-C COOH terminus (the BRICHOS domain) induces formation of misfolded intracellular aggregates. We demonstrated, using *in vitro* models, that SP-C BRICHOS mutants induce a generalized unfolded protein response (UPR) gene expression, cytokine elaboration, and epithelial apoptosis. The translational relevance and importance of this work was first validated by reports of the identical molecular signatures and pathway activation identified in patients with familial (SP-C related) and sporadic forms of IPF.

Subsequently, we developed and published a BRICHOS SP-C mutant knock-in mouse termed SP-C^{C121G}. that demonstrates cellular, biochemical, clinical, pathological, and biomarker features that mimic human pulmonary fibrosis. Representative examples of some of our seminal observations include:

- a. Katzen J, Wagner BD, Venosa A, Kopp M, Tomer Y, Russo SJ, Headen AC, Basil MC, Stark JM, Mulugeta S, Deterding RR, and **MF Beers**. A SFTPC BRICHOS Mutant Links Epithelial ER Stress and Spontaneous Lung Fibrosis. *JCI Insight* 2019 JCI Insight 4(6):e126125. 2019. PMCID: PMC6483196.
- b. Maguire JA, Mulugeta S, and **MF Beers**. Multiple ways to die: Delineation of the unfolded protein response and apoptosis induced by Surfactant Protein C BRICHOS mutants. *Int. J. Biochem. and Cell Biol* 44(1) 101-112 2012. PMCID:PMC3243113.
- c. Maguire JA, Mulugeta S, and **MF Beers**. Endoplasmic reticulum stress induced by Surfactant Protein C BRICHOS mutants promotes proinflammatory signaling by epithelial cells. *Am J Resp Cell Mol Biol* 2011.

44: 404-414 2011. PMCID: PMC3095939.

d. Mulugeta S, Maguire JA,, and **MF Beers**. Misfolded BRICHOS SP-C mutant proteins induce apoptosis via caspase 4 and cytochrome c related mechanisms. *Am J Phys: Lung Cell Mol Phys* 293: L720-29 2007.

4. *Innate Host Defense and Lung Inflammation: The Role of Pulmonary Collectins* - Another area in which I have made critical contributions to the field and which has been supported by several major funding initiatives has been our studies related to the role of surfactant in innate host defense. Initially this work focused on mouse models of *P. carinii* lung infection in immunodeficient and surfactant protein knockout mice. This work was then extended conceptually to new studies on the role of surfactant collectin proteins SP-A and SP-D in the modulation of lung inflammation in other models of lung injury including hyperoxia, bleomycin, lipopolysaccharide inhalation, and allergic antigen challenges. Most recently this has pivoted to understanding the impact of coronavirus infection on lung epithelial cell homeostasis and lung injury. Representative publications demonstrating the breadth of this work include:

- a. Atochina-Vasserman EN, Gow AJ, Abramova H, Guo C-J, Tomer Y, Preston AM, Beck JM, and **MF Beers**. Immune reconstitution during *Pneumocystis* lung Infection: disruption of surfactant component Expression and Function by S-Nitrosylation. *J. Immunology* 182:2277-87 2009. *PMCID: PMC4016818*.
- b. Jain D, Atochina-Vasserman EN, Tomer Y, Kadire H and **MF Beers**. Surfactant Protein D Protects Against Acute Hyperoxic Lung Injury. *Am J Respir Crit Care Med.* 178: 805-813 2008. *PMCID: PMC256679*
- c. Casey J, Kaplan J, Atochina-Vasserman EN, Gow AJ, Kadire H, Tomer Y, Fisher JH, Hawgood S, Savani RC, and **MF Beers**. Alveolar Surfactant Protein D Content Modulates Bleomycin Induced Lung Injury. *Am J Resp. Crit. Care Med* 172: 869-877 2005.
- d. Nguyen LC, Renner DM,.....⁺²⁰....., **Beers MF**, Rosner MR, Oakes SA, and SR Weiss. SARS-CoV-2 diverges from other betacoronaviruses in only partially activating the IRE1a/XBP1 ER stress pathway in human lung cells. *mBio* 13(5):e0241522 2022 *PMCID9600248*.

Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/michael.beers.1/bibliography/41159624/public/?sort=date&direction=descending>

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Calvert Louden

ERA COMMONS USER NAME (credential, e.g., agency login): CLOUD

POSITION TITLE: Consultant

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Tuskegee University, Tuskegee, AL	BS	06/1980	Animal Genetics & Breeding
Tuskegee University, Tuskegee, AL	DVM	06/1986	Veterinary Medicine
Michigan State University, East Lansing, MI	Residency	06/1987	Anatomic & Clinical Pathology
Michigan State University, East Lansing, MI	PhD	06/1992	Pathology & Environmental Toxicology

A. Personal Statement

I am an energetic, passionate, Board Certified (ACVP) Veterinary Anatomic Pathologist who is committed to staff development with a long-term view of nurturing talent through mentoring, coaching and feedback that builds organizational diversity and capabilities that shape and meet the challenges of the future. My mission is to deliver hypothesis driven, decision enabling translational sciences (efficacy/safety) data, that influence the discovery, development, and registration of transformational medicines through robust, end to end scientific partnerships internally and externally. My three strategic pillars are to collaborate with Toxicologists to deliver on the portfolio (time & quality) with a laser focus on translational patient safety & efficacy, to support Toxicologists efforts (mechanistic/investigative studies) to integrate data that empowers Global Project Teams to drive transformation of project risk into successful mitigation strategies, and to transform Pathology function, from descriptive to evidence-based mechanism-of-action to determine alignment (translational) with clinical efficacy and adverse-outcome (pathway analysis). I have a deep knowledge of the pharma industry, extensive expertise in disease pathophysiology, predictive and translational biomarkers of safety/efficacy, tumor models, drug safety evaluation (cradle to grave) of small molecules and biotherapeutics, successful regulatory interactions and strong external network with industry and academic tox-path KOLs. I look forward to engaging as a consultant on the proposed Phase II SBIR.

B. Positions, Scientific Appointments, and Honors**Positions**

2023 – Present	CSG Path-Tox Consultants, Norristown, PA
2020 – 2023	Vice President, Global Non-Clinical Translational Safety Sciences, Ferring Pharmaceuticals, San Diego, CA
2011 – 2020	Sr. Scientific Director, Global Head of Pathology, Pre-Clinical Development & Safety, Janssen Research and Development LLC, Spring House, PA

2010 – 2011	Senior Director, Pathology, Drug Safety Sciences, Johnson & Johnson Pharmaceuticals, Raritan, NJ
2008 – 2010	Senior Director and East Coast Head of Pathology, Global Pre-Clinical Development, Tox Path & Laboratory Animal Medicine, Johnson & Johnson Pharmaceuticals, Raritan, NJ
2006 – 2008	Global Pathology Head and Global Discipline Leader, AstraZeneca Pharmaceuticals, Wilmington, DE
2005 – 2008	Head of Anatomic & Clinical Pathology, Safety Assessment, AstraZeneca Pharmaceuticals, Cambridge, UK
2001 – 2005	Associate Director and Section Head of Pathology & Clinical Pathology, Safety Assessment, AstraZeneca Pharmaceuticals, Wilmington, DE
2000 – 2001	Senior Principal Research Scientist, DuPont Pharmaceuticals, Newark, DE
1995 – 2000	Senior Pathologist, SmithKline Beecham Pharmaceuticals, King of Prussia, PA
1992 – 1995	Staff Pathologist, SmithKline Beecham Pharmaceuticals, King of Prussia, PA

C. Contributions to Science

1. Discovering Biomarkers for Drug-Induced Vascular Injury

The identification of vascular injury caused by drug toxicity has been a challenge due to the subtle and complex nature of vascular tissue responses. Before our work, there was a significant gap in identifying specific biomarkers that could indicate drug-induced vascular injuries early in drug development. Our team identified novel biomarkers such as von Willebrand Factor (vWF), vWF propeptide, and smooth muscle cell markers that significantly advanced the detection of drug-induced vascular injury. This work demonstrated the potential of these biomarkers to serve as early indicators of vascular damage. These findings have substantially impacted the pharmaceutical industry and regulatory practices by providing tools for the early identification of vascular toxicities in drug development, thus enhancing patient safety. I co-authored the foundational studies that identified and evaluated these biomarkers' effectiveness in signaling vascular injury, contributing to the experimental design and data analysis.

- a. **Louden C. S.**, Brott D., Gould S., Katein A., Kelley, T and Jones H. Novel Biomarkers of Drug-induced vascular injury. *The Toxicologist*, 2006, Abstract 1857.
- b. Brott D, Katein A, Ershaw K, Kelly T, Evans G, Jones H, Gould S, Betton G, Valentin JP, Richardson RJ, **Louden C.** Evaluation of plasma vWF and vWF propeptide in drug-induced vascular injury. *The Toxicologist* CD, 2005.
- c. Katein A, Brott D, **Louden C.** von Willebrand factor as a biomarker of endothelial cell perturbation in rats and dogs. *ASVCP*, 2005.

2. Understanding the Role of Caveolin-1 in Vascular Injury

Caveolin-1's role in vascular biology and pathology had been incompletely understood, particularly its relationship with drug-induced vascular injury. Through our investigations, we were integral in uncovering the role of Caveolin-1 in the pathophysiology of drug-induced vascular injury. Demonstrating its critical role has helped elucidate the molecular mechanisms underpinning vascular responses to drug toxicity. This work contributed to a deeper understanding of vascular injury's molecular basis, aiding in the design of safer therapeutic agents by targeting or sparing Caveolin-1 pathways. My contributions included conceptualizing the study, executing the experimental protocols, and collaborating on data analysis and manuscript preparation.

- a. D. Brott, A. Katein, L. Foster-Brown, J. Morelli, G. Evans, H. Jones, S. Gould, G. Betton, S. Bjurstrom, H. Prior, J-P. Valentin, **C. Louden**. Role of Caveolin-1 in Drug-induced Vascular Injury. *The Toxicologist* CD, 2004, Abstract 1817.

3. Elucidating the Mechanism of Drug-Induced Coronary Artery Lesions

Coronary arterial lesions pose a significant risk to health, yet the specific mechanisms by which some drugs induce these lesions were not well understood. Our research shed light on the mechanisms by which endothelin receptor blockade induces coronary arterial lesions. This included the discovery of connections to endothelin receptor distribution and blood flow disparities in affected regions. These insights have informed drug development and risk assessment processes, emphasizing the careful evaluation of endothelin receptor interactions. In this pivotal study, I served as the principal investigator, directing the research focus, methodology, and interpretation of results.

- a. **Louden C.**, Tierney, L., Branch, C., Schwartz, L., Solleveld, H. Coronary arterial lesions in dogs caused by endothelin receptor blockade are associated with regional differences in endothelin receptor distribution and blood flow. *FASEB J*, 1999.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Ying Zhang

ERA COMMONS USER NAME (credential, e.g., agency login): YZDMPK

POSITION TITLE: DMPK Consultant

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
China Pharmaceutical University, Nanjing, China	BS	06/2000	Pharmacy
University of Bristol, Bristol, UK	MS	05/2005	Chemistry
University of Geneva, Geneva, Switzerland	PhD	01/2016	Pharmaceutical Science
University of California San Diego, San Diego, CA	Certificate	08/2019	ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicology)
University of California San Diego, San Diego, CA	Certificate	08/2022	Drug Discovery & Development

A. Personal Statement

As an accomplished and highly motivated scientist specializing in bioanalysis, drug metabolism, and pharmacokinetics (DMPK), I have developed a deep and extensive expertise in the pharmaceutical and biopharmaceutical industries. I have extensive experience in leading the experimental design and execution of ADMET/DMPK studies, including *in vitro* ADME characterization and *in vivo* pharmacokinetic profiling and modeling. My expertise in discovery and target proteomics, coupled with my knowledge of analytical technologies, such as HPLC, LC-MS, and high-resolution mass spectrometry, further reinforces my capabilities in the field. Together with my strong critical thinking, problem-solving skills, and experience in direct management, supervising, and mentoring research associates, I am well-equipped to navigate the complex landscape of drug development and contribute as a consultant on Maipl's SBIR project.

B. Positions, Scientific Appointments, and Honors**Positions**

2024 – present	DMPK Consultant, Maipl Therapeutics, Scarsdale, NY
2022 – Present	Associate Director, Janux Therapeutics Inc, San Diego, CA
2018 – 2022	Senior Scientist, Ferring Research Institute, San Diego, CA
2016 – 2017	Scientist I, Ferring Research Institute, San Diego, CA
2016 – 2016	Research Scientist, Wuxi AppTec, East Windsor, NJ
2009 – 2011	Senior Research Associate, Synta Pharmaceuticals, Lexington, MA
2007 – 2009	Research Associate II, Synta Pharmaceuticals, Lexington, MA
2007 – 2007	Research Associate, Takeda Pharmaceuticals, San Diego, CA
2006 – 2007	Senior Analytical Chemist, Silliker JR Laboratories ULC, Burnaby, BC, Canada
2001 – 2005	Analytical Chemist I – III, Silliker JR Laboratories ULC, Burnaby, BC, Canada

C. Contributions to Science

1. **Pharmacology and Drug Development.** In my recent research endeavors, I have delved into two significant areas of pharmaceutical science. Firstly, my work contributed to a comprehensive study on FE 205030, a potent, fast-acting injectable CGRP receptor antagonist designed for the acute treatment of episodic migraines. This work involved an extensive characterization of the drug's pharmacological, pharmacokinetic, pharmacodynamic, and physicochemical properties, underscoring its potential as an effective migraine treatment. Secondly, I explored a novel high-throughput strategy for assessing the aqueous solubility of peptides and proteins prone to gelation. This innovative approach facilitated the discovery of new antibacterial Teixobactin analogues, addressing a critical challenge in drug development related to solubility issues. Together, these studies not only advance our understanding of a promising migraine treatment but also pioneer a methodological breakthrough in peptide and protein solubility assessment, highlighting my commitment to addressing complex problems in drug development and pharmacology.
 - a. K. Srinivasan, K. Kozminski, **Y. Zhang**, K. Wisniewski, T. Kohout, H. Wisniewska, G. Harris, B. Lindstrom, and D. Hargrove, Pharmacological, pharmacokinetic, pharmacodynamic and physicochemical characterization of FE 205030: A potent, fast acting, injectable CGRP receptor antagonist for the treatment of acute episodic migraine, *J Pharm Sci*, 2022, 111, 247-261
 - b. **Y. Zhang**, D. Carney, A. Henninot, and K. Srinivasan, Novel high-throughput strategy for the aqueous solubility assessment of peptides and proteins exhibiting a propensity for gelation: Application to the discovery of novel antibacterial Teixobactin analogues, *Mol. Pharmaceutics*, 2021, 18, 469-474
2. **Biochemistry and Chemical Biology.** My work in this area detailed the total chemical synthesis of a biologically active and homogeneous analog of Human Growth Hormone, achieved through sequential native chemical ligation. This endeavor not only demonstrated the synthetic feasibility of complex protein analogs but also opened new avenues for the study of protein functions and therapeutic applications. My earlier work in the field focused on the rapid cloning and expression of a fungal polyketide synthase gene crucial for Squalestatin biosynthesis. This work underscored the potential for manipulating natural biosynthetic pathways to produce valuable compounds, contributing to the understanding of fungal genetics and the development of cholesterol-lowering drugs.
 - a. J. Sueiras-Diaz, **Y. Zhang**, A. Velentza, B. Santoso and S. Yang, Total chemical synthesis of a biologically active and homogeneous analog of Human Growth Hormone [Nle14,125,170,Glu29,91,Gln74,Asn107,Asp109]hGH-NH₂ by sequential native chemical ligation, *Tetrahedron Letters*, 2017, 58, 2448-2455
 - b. R. J. Cox, F. Glod, D. Hurley, C. M. Lazarus, T. Nicholson, B. Rudd, T. J. Simpson, B. Wilkinson and **Y. Zhang**, Rapid cloning and expression of a fungal polyketide synthase gene involved in Squalestatin biosynthesis, *Chemical Communications*, 2004, 20, 2260-2261
3. **Proteomics and Mass Spectrometry.** My work in the optimization of mass spectrometry (MS) techniques for protein analysis led to the introduction of an innovative approach using variable Q1 isolation windows to enhance the selectivity in LC-SWATH-MS acquisition. This work significantly improved the detection and quantification of proteins in complex biological samples. Concurrently, we focused on optimizing the sample preparation process for human dendritic cells, aiming to refine mass spectrometry-based proteomic studies. This optimization was crucial for ensuring accurate and reproducible results in our analyses. Additionally, we developed a method for ranking fragment ions based on outlier detection, which further improved the accuracy of label-free quantification in data-independent acquisition LC-MS/MS. Together, our work has helped in advancing the methodologies for proteomic analysis, enhancing both the precision and reliability of mass spectrometry in identifying and quantifying proteins in various biological contexts.
 - a. **Y. Zhang**, A. Bilbao, T. Bruderer, J. Luban, C. Strambio-De-Castillia, F. Lisacek, G. Hopfgartner and E. Varesio, The use of variable Q1 isolation windows improves selectivity in LC-SWATH-MS acquisition, *Journal of Proteome Research*, 2015, 14, 4359-4371

- b. **Y. Zhang**, D. Bottinelli, F. Lisacek, J. Luban, C. Strambio-De-Castillia, E. Varesio and G. Hopfgartner, Optimization of human dendritic cell sample preparation for mass spectrometry-based proteomic studies, *Analytical Biochemistry*, 2015, 484, 40-50
- c. A. Bilbao, **Y. Zhang***, E. Varesio, J. Luban, C. Strambio-De-Castilla, F. Lisacek and G. Hopfgartner, Ranking fragment ions based on outlier detection for improved label-free quantification in data-independent acquisition LC-MS/MS, *Journal of Proteome Research*, 2015, 14, 4581-4593 (*: co-first author)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

UEI*: UKYVLM1WKBK7

Budget Type*: Project Subaward/Consortium

Enter name of Organization: MAIPL THERAPEUTICS, INC.

Start Date*: 12-01-2024

End Date*: 11-30-2024

Budget Period: 1

A. Senior/Key Person												
Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Yong	G.	Yue		PD/PI	200,000.00	1.8			30,000.00	7,500.00	37,500.00
2.	Yoshiyuki		Fukase		Co-Investigator	150,000.00	1.2			15,000.00	3,750.00	18,750.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	56,250.00
--------------------------------	------------	-------------------------	-----------

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel				Total Other Personnel		0.00
					Total Salary, Wages and Fringe Benefits (A+B)		56,250.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

UEI*: UKYVLM1WKBK7

Budget Type*: Project Subaward/Consortium

Organization: MAIPL THERAPEUTICS, INC.

Start Date*: 12-01-2024

End Date*: 11-30-2024

Budget Period: 1

C. Equipment Description		Funds Requested (\$)*
List items and dollar amount for each item exceeding \$5,000		
Equipment Item		
Total funds requested for all equipment listed in the attached file		
	Total Equipment	0.00
Additional Equipment: File Name:		

D. Travel		Funds Requested (\$)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)		
2. Foreign Travel Costs		
	Total Travel Cost	0.00

E. Participant/Trainee Support Costs		Funds Requested (\$)*
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees		Total Participant Trainee Support Costs
		0.00

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

UEI*: UKYVLM1WKBK7

Budget Type*: Project Subaward/Consortium

Organization: MAIPL THERAPEUTICS, INC.

Start Date*: 12-01-2024

End Date*: 11-30-2024

Budget Period: 1

F. Other Direct Costs		Funds Requested (\$)*
1. Materials and Supplies		
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		179,374.00
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		0.00
8. Data Management and Sharing Costs		
9. HD BioSciences		230,364.00
10. TCG GreenChem		200,000.00
	Total Other Direct Costs	609,738.00

G. Direct Costs		Funds Requested (\$)*
Total Direct Costs (A thru F)		665,988.00

H. Indirect Costs		Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
Indirect Cost Type	1 . MTDC	40.0	511,614.00	204,646.00
Total Indirect Costs				204,646.00
Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs		Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)		870,634.00

J. Fee		Funds Requested (\$)*
		60,944.00

K. Total Costs and Fee		Funds Requested (\$)*
		931,578.00

L. Budget Justification*	File Name: BudJustification_20240326.pdf
--------------------------	--

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

UEI*: UKYVLM1WKBK7

Budget Type*: Project Subaward/Consortium

Enter name of Organization: MAIPL THERAPEUTICS, INC.

Start Date*: 12-01-2025

End Date*: 11-30-2026

Budget Period: 2

A. Senior/Key Person												
Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Yong	G.	Yue		PD/PI	200,000.00	1.8			30,000.00	7,500.00	37,500.00
2.	Yoshiyuki		Fukase		Co-Investigator	150,000.00	1.2			15,000.00	3,750.00	18,750.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	56,250.00
--------------------------------	------------	-------------------------	-----------

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel				Total Other Personnel		0.00
					Total Salary, Wages and Fringe Benefits (A+B)		56,250.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

UEI*: UKYVLM1WKBK7

Budget Type*: Project Subaward/Consortium

Organization: MAIPL THERAPEUTICS, INC.

Start Date*: 12-01-2025

End Date*: 11-30-2026

Budget Period: 2

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment

0.00

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost

0.00

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs

0.00

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

UEI*: UKYVLM1WKBK7

Budget Type*: Project Subaward/Consortium

Organization: MAIPL THERAPEUTICS, INC.

Start Date*: 12-01-2025

End Date*: 11-30-2026

Budget Period: 2

F. Other Direct Costs		Funds Requested (\$)*
1. Materials and Supplies		
2. Publication Costs		28,800.00
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		151,344.00
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Data Management and Sharing Costs		0.00
9. LabCorp PK		192,500.00
	Total Other Direct Costs	372,644.00

G. Direct Costs		Funds Requested (\$)*
	Total Direct Costs (A thru F)	428,894.00

H. Indirect Costs		Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
Indirect Cost Type				
1 . MTDC		40.0	277,550.00	111,020.00
				Total Indirect Costs
				111,020.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs		Funds Requested (\$)*
	Total Direct and Indirect Institutional Costs (G + H)	539,914.00

J. Fee		Funds Requested (\$)*
		37,794.00

K. Total Costs and Fee		Funds Requested (\$)*
		577,708.00

L. Budget Justification*		File Name: BudJustification_20240326.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

UEI*: UKYVLM1WKBK7

Budget Type*: Project Subaward/Consortium

Enter name of Organization: MAIPL THERAPEUTICS, INC.

Start Date*: 12-01-2026

End Date*: 11-30-2027

Budget Period: 3

A. Senior/Key Person												
Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Yong	G.	Yue		PD/PI	200,000.00	1.8			30,000.00	7,500.00	37,500.00
2.	Yoshiyuki		Fukase		Co-Investigator	150,000.00	1.2			15,000.00	3,750.00	18,750.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	56,250.00
--------------------------------	------------	-------------------------	-----------

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel				Total Other Personnel		0.00
					Total Salary, Wages and Fringe Benefits (A+B)		56,250.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

UEI*: UKYVLM1WKBK7

Budget Type*: Project Subaward/Consortium

Organization: MAIPL THERAPEUTICS, INC.

Start Date*: 12-01-2026

End Date*: 11-30-2027

Budget Period: 3

C. Equipment Description		Funds Requested (\$)*
List items and dollar amount for each item exceeding \$5,000		
Equipment Item		
Total funds requested for all equipment listed in the attached file		
	Total Equipment	0.00
Additional Equipment: File Name:		

D. Travel		Funds Requested (\$)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)		
2. Foreign Travel Costs		
	Total Travel Cost	0.00

E. Participant/Trainee Support Costs		Funds Requested (\$)*
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees		Total Participant Trainee Support Costs
		0.00

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

UEI*: UKYVLM1WKBK7

Budget Type*: Project Subaward/Consortium

Organization: MAIPL THERAPEUTICS, INC.

Start Date*: 12-01-2026

End Date*: 11-30-2027

Budget Period: 3

F. Other Direct Costs		Funds Requested (\$)*
1. Materials and Supplies		
2. Publication Costs		108,000.00
3. Consultant Services		
4. ADP/Computer Services		0.00
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Data Management and Sharing Costs		0.00
9. LabCorp Tax		192,500.00
	Total Other Direct Costs	300,500.00

G. Direct Costs		Funds Requested (\$)*
	Total Direct Costs (A thru F)	356,750.00

H. Indirect Costs		Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
Indirect Cost Type				
1 . MTDC		40.0	356,750.00	142,700.00
				Total Indirect Costs
				142,700.00
Cognizant Federal Agency				
(Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs		Funds Requested (\$)*
	Total Direct and Indirect Institutional Costs (G + H)	499,450.00

J. Fee		Funds Requested (\$)*
		34,962.00

K. Total Costs and Fee		Funds Requested (\$)*
		534,412.00

L. Budget Justification*		File Name: BudJustification_20240326.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

BUDGET JUSTIFICATION

Upon careful review of the budget required to complete the Aims as outlined, and review of the eligible waiver topics, we respectfully request the following budget outlined that is in excess of the hard cap. This document justifies the budget and provides a basis for inclusion of the waiver topics. On 6 May 2023, the NIH published the guidance entitled "Health and Human Services (HHS) Approved SBIR/STTR Topics for Awards over Statutory Budget Limitations". NHLBI will consider A. Biomedical technologies (medical devices, instruments, pharmaceuticals, drugs, gene editing/delivery, therapeutics, vaccines, molecular imaging agents, diagnostics and biologics) for heart, lung, blood, and sleep related diseases and disorders requiring Federal regulatory approval (FDA) or clearance to be commercialized; B. Small and large animal testing of products of tissue engineering and regenerative medicine, drugs, medical devices, therapeutics, molecular imaging agents, and biologics and studies involving in vivo animal experiments for heart, lung, blood, and sleep-related diseases and disorders; and D. Therapeutics (drugs, devices, gene therapy, or other biologics) development for heart, lung, blood, and sleep-related diseases and disorders. Due to both the therapeutic development and preclinical testing nature of this proposal, we request the budget waiver on this topic.

PERSONNEL (Y1: \$56,250; Y2: \$56,250; Y3: \$56,250)

Senior/Key Personnel

Yong Yue, PhD, PD/PI (Y1: 1.8 months; Y2: 1.8 months; Y3: 1.8 months) will serve as PD/PI on this project. He will coordinate all research activities. He will also prepare final reports to the funding agency. Dr. Yue has more than 20 years of pharmaceutical industry and bioinformatics experience in multiple therapeutic areas, including immunology, oncology, metabolic diseases, neuroscience, and reproductive health. He has built and led teams of bioinformatics and data scientists at pharma giants like Eli Lilly, Boehringer Ingelheim, and Ferring Pharmaceuticals, as well as in startup biotech companies. Dr. Yue is a co-founder and CEO for Maipl Therapeutics.

Yoshi Fukase, PhD, Co-I (Y1: 1.2 months; Y2: 1.2 months; Y3: 1.2 months) will serve as co-investigator on this project. Dr. Fukase brings 19 years of industry and academic/biotech research experience to the company. He previously served as Director of Medicinal Chemistry at Ferring Pharmaceuticals, where he made the breakthrough discovery of the FP antagonist. Dr. Fukase serves as VP of Medicinal Chemistry for Maipl Therapeutics.

The fringe benefits for Employees are 25.0% of the funds requested.

Consultants (Y1: \$0; Y2: \$28,800; Y3: \$108,000)

Calvert Louden (Y1: \$0; Y2: \$0; Y3: \$50,400) has 25+ years of pharmaceutical experience from SmithKline Beecham, AstraZeneca, Johnson and Johnson and served as Ferring Pharmaceuticals VP of Global Nonclinical Safety Sciences. He will provide pathology and toxicology advice and support Maipl with the proposed nonclinical toxicology testing strategy and in the conduct and execution of FIH enabling nonclinical safety studies.

Ying Zhang, PhD (Y1: \$0; Y2: \$28,800; Y3: \$57,600) is an accomplished and highly motivated bioanalytical and DMPK scientist with extensive knowledge and working experience in the pharmaceutical and biopharmaceutical industries. She will work closely with Dr. Yue to help Maipl in its PK studies and liaison with Toxicology to successfully accomplish the proposed studies.

Consortium (Y1: \$179,374; Y2: \$151,344; Y3: \$0)

University of Pennsylvania Medical Center Beers Lab (Y1: \$179,374; Y2: \$151,344; Y3: \$0) will conduct Aims 1.2, 2.1, and 2.2 efficacy and transcriptomic work (refer to their included detailed budget and budget justification for details).

Other Direct Costs

Fee for Service (Y1: \$430,364; Y2: \$192,500; Y3: \$192,500)

HD Biosciences (Y1: \$230,364; Y2: \$0; Y3: \$0) will conduct Aim 1.1 BLM IPF mouse model efficacy studies. This amount represents the total cost quoted by HD Biosciences for each compound (see attached quote).

TCG GreenChem (Y1: \$200,000; Y2: \$0; Y3: \$0) will provide CDMO services for Aim 3.1 API and formulation work (see attached Quote). This amount represents ~30% of the total cost quoted by TCG GreenChem (see attached quote), with Maipl covering the additional cost with private funds.

Labcorp (Y1: \$0; Y2: \$192,500; Y3: \$192,500) will conduct Aims 3.2 and 3.3 PK and toxicology studies (see attached Quote). This amount represents ~70% of the total cost quoted by labcorp (see attached quote), with Maipl covering the additional cost with private funds.

Indirect costs

Indirect cost rate of 40% has been applied to all direct costs. This rate corresponds to the current indirect cost rate under which the company operates.

Fee

A fee of 7% is requested which we believe demonstrates a reasonable profit margin for for-profit organizations for R&D work. The proposed fee is consistent with the rate the company is currently charging on other R&D projects.

Work Order

Supported by a GRANT

WORK ORDER NUMBER (MPL24FIBRO001-uc2)

This work order (the "Work Order") is dated 01 March 2024 ("Effective Date") and is between **Mapl Therapeutics Inc.** ("Client"), with its principal office at 18 Circle Road, Scarsdale, New York 10583 on behalf of itself and its Affiliates (together "Client"), and **HD Biosciences Inc.** ("Provider"), an affiliate of WuXi AppTec (Hong Kong) Limited ("WXAT HK"), with its principal office at 6122 Nancy Ridge Drive, San Diego, CA 92121, USA.

1. SERVICES INFORMATION

1.1 Title

Evaluation of Compounds Efficacy in the Bleomycin Induced IPF Mouse Model

1.2 Description, Price and Estimated Timeline

Description	Subtotal (USD)	Timeline (Weeks)																																																	
<p>Compounds efficacy in Bleomycin induced IPF mice model (n=72, 12 mice; 6 male and 6 female per group, 6 groups, Control, Model, Model plus Nintedanib 60mpk/po/qd, Model plus TA with 3 different doses po/qd or BID)</p> <p>1. Order 78 C57BL6 (39 male and 39 female) mice, 6-8 weeks old, CR and acclimate 3-7 days</p> <p>2. In-Life duration: 22 days, 72 mice</p> <p>3. Disease induction of bleomycin induced lung fibrosis model Day 1: Bleomycin 0.66 mg/Kg in 50 uL, intra-tracheal. One group is dosed with saline to serve as negative control.</p> <p>4. Randomization by body weight on day 6</p> <p>5. Treatment from Day 6-day22 as indicated in Table 1</p>	\$54,642	5-7																																																	
<p>Table1: Treatment Groups</p> <table border="1"> <thead> <tr> <th>Group</th><th>N</th><th>Bleomycin</th><th>TX</th><th>Dose</th><th>Route</th><th>Regimen</th></tr> </thead> <tbody> <tr> <td>1</td><td>12</td><td>No</td><td>vehicle</td><td>NA</td><td>PO</td><td>QD from D6-D22</td></tr> <tr> <td>2</td><td>12</td><td>yes</td><td>Vehicle</td><td>NA</td><td>PO</td><td>QD or BID from D6-D22</td></tr> <tr> <td>3</td><td>12</td><td>yes</td><td>Nintedanib</td><td>60mpk</td><td>PO</td><td></td></tr> <tr> <td>4</td><td>12</td><td>yes</td><td>TA</td><td>low</td><td>PO</td><td></td></tr> <tr> <td>5</td><td>12</td><td>yes</td><td>TA</td><td>medium</td><td>PO</td><td></td></tr> <tr> <td>6</td><td>12</td><td>yes</td><td>TA</td><td>high</td><td>PO</td><td></td></tr> </tbody> </table> <p>6. Body weight: prior start of dosing and then twice weekly</p>	Group	N	Bleomycin	TX	Dose	Route	Regimen	1	12	No	vehicle	NA	PO	QD from D6-D22	2	12	yes	Vehicle	NA	PO	QD or BID from D6-D22	3	12	yes	Nintedanib	60mpk	PO		4	12	yes	TA	low	PO		5	12	yes	TA	medium	PO		6	12	yes	TA	high	PO			
Group	N	Bleomycin	TX	Dose	Route	Regimen																																													
1	12	No	vehicle	NA	PO	QD from D6-D22																																													
2	12	yes	Vehicle	NA	PO	QD or BID from D6-D22																																													
3	12	yes	Nintedanib	60mpk	PO																																														
4	12	yes	TA	low	PO																																														
5	12	yes	TA	medium	PO																																														
6	12	yes	TA	high	PO																																														

7. Tissue collection on day 22, 2 hours post last dose a-BALF and plasma b-animal perfusion after BALF collection c-Left lungs will be fixed in formalin solution for histology d-Right lungs will be placed in a pre-cooled EP tube and snap frozen in liquid nitrogen and stored at -80 °C from lung hydroxyproline measurement.		
8. Hydroxyproline measurement: 72 samples Tissue lysis and assay (2 dilutions)	\$9440	1-2
9. BALF cytology: total cells, monocytes, neutrophils, lymphocytes	\$15,840	1-2
10. BALF cytokines: TGF-b, IL-10, IL-1b, IL-6 (2 dilutions)	\$8000	1-2
11. BALF: soluble collagen measurement (2 dilutions)	\$4400	1-2
12. Histology: 72 FFPE blocks, H&E staining, Masson Trichrome and modified Ashcroft score α-SMA IHC staining and analysis	\$24,360	4-8
13. Report	\$2,000	1-2
TOTAL (USD)	\$118,682	14-25

1.3 Reporting and Transfer of Results

Data and results will be provided as it becomes available. The final report shall be delivered within [30] days of completion of the Services to which such report relates.

1.4 Additional Requirements

If Applicable

[Any additional requirements such as REAGENT PROVISION, DELIVERABLES et al]

2. TERM

This Work Order shall expire after 90 days from the date of generation.

3. FEES; PAYMENT SCHEDULE

3.1 **Service Fee.** The Service Fee will be USD \$116,682. Provider shall invoice Client for the Service Fee in accordance with the payment schedule below, and Client shall pay such invoices as indicated below.

- 50% of the Total Price will be invoiced upon execution of the quotation.



CONFIDENTIAL

- 50% of the Total Price must be paid at completion of the study.
- When there is an extension of the study, 40% of the project cost will be invoiced upon extension request.
- Client will pay for the cost of shipment of all materials between the Provider and Client or its third parties.

HD Biosciences experienced scientists execute each study with utmost attention and strive to achieve the best possible results. Desired scientific outcomes are not guaranteed.

3.2 Milestones. If Applicable.

3.3 Payment Instructions. Unless an invoice provides otherwise, Client shall pay the invoice in USD to the account listed below:

HD Biosciences Inc.
6122 Nancy Ridge Drive
San Diego, CA 92121, USA

REMITTANCE ADDRESS

Client will send payment to the following address:

Remit US\$ Check to:
HD Biosciences Inc.
29666 Network Place
Chicago, IL 60673-1296

Remit US\$ ACH to:
JPMorgan Chase Bank NA
Account #229001125
ABA Routing #021000021

Remit US\$ Wire to:
JP Morgan Chase Bank NA
Account#229001125
ABA Routing #021000021
SWIFT Code: CHASUS33

4. COMMUNICATIONS

All communications required under this work order are to be sent via reputable international courier or email and addressed as follows:

If to Client:	If to Provider:
<p>MAIPL THERAPEUTICS INC. 18 Circle Road, Scarsdale, New York 10583</p> <p>Attn: Aritro Sen</p>	<p>HD BIOSCIENCES INC. 6122 Nancy Ridge Drive San Diego, CA 92121</p>



CONFIDENTIAL

UPON SIGNATURE by authorized representatives of the parties, the parties hereto have entered into this Work Order as Effective Date.

MAIPL THERAPEUTICS INC.	HD BIOSCIENCES INC.
By: _____ Name: _____ Title: _____ Date: _____	By: _____ Name: Hong Xin Title: VP and Site Head Date: _____

[REMAINDER OF THE PAGE LEFT BLANK INTENTIONALLY]



CONFIDENTIAL

STANDARD TERMS

The client (“**Client**”) and WuXi AppTec (Hong Kong) Limited (“**Provider**”) have prepared a quote or similar document that describes pricing and technical terms for a project (the “**Purchase Order**”). The Purchase Order and these Standard Terms constitute the agreement between Client and Provider for the project (the “**Agreement**”).

1. DEFINITIONS

1.1 “**Affiliate**” of a person means any other person that directly or indirectly Controls, is Controlled by, or is under common Control with, the person.

1.2 “**Confidential Information**” of a party (the “**Disclosing Party**”) means all information and materials disclosed by or on behalf of the party to the other party (the “**Receiving Party**”) or its Related Persons in connection with the Agreement that is reasonably considered to be confidential. The Confidential Information of both parties includes the existence, terms and objectives of the Agreement, and the nature of any dispute and the outcome of any arbitration proceedings arising out of or in connection with the Agreement.

1.3 “**Control**” over a person means (a) owning 50% or more of the voting securities or other ownership interests of the person or (b) having the power to direct the management or policies of the person.

1.4 “**Intellectual Property**” means patents and patent applications, trademarks, trade names, service marks, domain names, copyrights and copyright applications and registrations, schematics, industrial models, inventions, know-how, trade secrets, computer software programs and other intangible proprietary information.

2. SERVICES

2.1 **Purchase Order.** Provider shall provide certain services (the “**Services**”) to Client pursuant to the Purchase Order. If there is a contradiction between a provision of these Standard Terms and the Purchase Order, then the provision will take precedence unless the Purchase Order specifically states that it takes precedence over the provision.

2.2 **Affiliates.** Provider may delegate or subcontract the Services to an Affiliate. If the Services are provided by an Affiliate, then references to Provider in these Standard Terms will be deemed to be references to the Affiliate with the necessary modifications. Provider shall be liable for the performance of the Affiliate to the same extent as if the performance was that of Provider.

3. SERVICE FEE; PAYMENT

3.1 **Service Fee.** Client shall pay Provider a service fee in the amount and manner provided in the Purchase Order (the “**Service Fee**”).

3.2 **Expenses.** Client shall reimburse Provider for reasonable expenses that are (a) authorized by Client, (b) described in the Purchase Order, or (c) described in these Standard Terms, including Sections 5.1, 5.2, 5.3, 7.1(b), 9.3 and 12.

3.3 **Milestones.** If the Purchase Order includes a payment for completion of a project stage or other kind of milestone, then Provider shall notify Client promptly after the milestone is achieved. Client will be deemed to have agreed that the milestone was achieved unless it notifies Provider otherwise within ten business days. Each milestone payment is designed to reflect fair value of the corresponding Services, and is not dependent on any other milestone unless otherwise specified in the Purchase Order.

3.4 **Payment.** Client shall pay each of Provider’s invoices within 30 days of receipt by wire transfer to the account designated by Provider. Payment must be made without set-off or other deduction of any nature. The Service Fee is exclusive of, and Client shall pay, any applicable taxes (other than taxes on Provider’s income) and other fees of any nature imposed by or under the authority of any government authority.

3.5 **Payment Instructions.** Payment Instructions. Unless an invoice provides otherwise, Client shall pay the invoice in USD by wire transfer to the account listed below:

Name	HD Biosciences Inc.
Address	6122 Nancy Ridge Drive, San Diego, CA 92121, USA
Account	229001125
Currency	USD
Beneficiary Bank	JPMorgan Chase Bank NA
SWIFT Code	CHASUS33
Correspondent Bank	JPMorgan Chase Bank N.A., New York Branch
Remit US Check to	29666 Network Place, Chicago, IL 60673-1296
Correspondent Fed wire ABA	021000021

3.6 **No Claw backs.** Service Fee and other payments under this Section are non-cancelable and non-refundable.

3.7 **Payment Default.** In the event of an overdue payment (a “**Payment Default**”), (a) interest of 0.33% will be accrued daily (12% per annum) of the overdue payment as of the date of the Payment Default and (b) Provider may suspend the provision of the Services until the Payment Default is rectified by Client. If the Payment Default is not rectified within 30 days, then it will be deemed an incurable material breach of the Agreement, and Provider may terminate the Agreement pursuant to Section 11.1(b).

4. PROVISION OF SERVICES

- 4.1 **Specifications.** Provider shall provide the Services in accordance with the specifications of the Purchase Order.
- 4.2 **Qualifications.** Provider shall ensure that the persons that provide the Services (the “**Personnel**”) (a) have the appropriate skills, training and experience and (b) are bound by confidentiality obligations consistent with the terms of the Agreement.
- 4.3 **Compliance.** Provider shall provide the Services in compliance with applicable law and applicable GxP in all material respects.
- 4.4 **On-Site Monitoring.** Representatives of Client may, upon reasonable notice and at times reasonably acceptable to Provider, visit the facilities where the Services are provided and consult informally during such visits with appropriate Personnel in order to monitor the Services. The representatives will be bound by rules applicable to the facilities and may, at the reasonable discretion of Provider, be prohibited from entering or only given limited access to certain areas within the facilities. Provider may require that Client or the representatives execute an agreement that regulates the representatives’ conduct during their visit. Client shall be responsible for all expenses incurred in connection with such visits.

5. SOURCING OF MATERIAL

- 5.1 **Materials.** Provider shall, at Client’s expense or as otherwise specified in the Purchase Order, purchase all materials necessary for the Services (the “**Materials**”). If a Material is not commercially available, then Client may elect to (a) supply the Material to Provider or (b) amend the Purchase Order to permit the use of a commercially available substitute.

5.2 **Client Materials.** If a Material is to be supplied by Client (a “**Client Material**”), then Client shall provide the Client Material at its expense in a timely manner and provide such information as may be required by Provider or applicable law concerning the stability, storage and safety requirements. Provider shall ensure that the Client Material will be (a) used solely for the purpose of providing the Services, (b) only distributed to Personnel on a need-to-know basis for the provision of the Services and (c) preserved and protected in a manner consistent with the specifications of the Purchase Order and any relevant standard operating procedures or other instructions provided by Client.

5.3 **Unused Client Materials and Other Materials.** Provider shall, at Client’s option and expense, return, destroy or otherwise dispose of unused Client Materials promptly after the earlier of (a) completion of the Services for which the Client Materials were provided, (b) termination of the Agreement, or (c) receipt of written instructions from Client pertaining to their disposition. Provider may dispose of other unused Materials at its sole discretion.

6. RECORDS

6.1 **Storage.** All materials, data and documentation obtained or generated by Provider in the course of providing the Services, including all computerized records and files (“**Records**”), will be maintained in a secure area in accordance with industry standards. The Records are the sole and exclusive property of Client.

6.2 **Retention.** Upon termination of the Agreement, Provider shall, at Client’s option, (a) destroy the Records, (b) deliver the Records to Client, or (c) retain the Records for three years and then destroy them. If the Records are to be destroyed, then Provider shall give 30-days’ written notice to Client, and Client may elect during the 30-day period to have the Records transferred to it. Notwithstanding the foregoing, the Records may be retained as required by applicable law or as otherwise necessary for regulatory or insurance purposes.

7. INTELLECTUAL PROPERTY

7.1 **Ownership.** (a) Except as otherwise provided in the Standard Terms, (i) Provider has no rights in any Intellectual Property that is owned by or licensed to Client or any of its Affiliates (“**Client IP**”) and (ii) Client has no rights in any Intellectual Property that is owned by or licensed to Provider or any of its Affiliates (“**Provider IP**”). (b) Provider shall ensure that each of the Personnel vests in Provider any and all rights that such person might otherwise have in the Intellectual Property created or developed in connection with the provision of the Services (“**Project IP**”). Provider hereby assigns and shall assign all right, title and interest in Project IP to Client. Client will, at its expense, have sole control of filing and prosecuting applications for, and maintenance and enforcement of, patents for Project IP. Provider shall, at Client’s expense, use reasonable efforts to assist Client to obtain, maintain and enforce the patents. Client shall promptly notify Provider of any patents granted for Project IP. Provider is responsible for all payments to be made to Personnel in accordance with applicable law requiring remuneration for inventions. (c) Notwithstanding the foregoing, Intellectual Property created or developed in connection with the provision of the Services that is derivative of Provider IP or that relates to experimental methods is Provider IP and not Project IP. (d) Unless otherwise provided for in the Purchase Order, Project IP and Records may only be used for research purposes. Other uses such as in connection with regulatory filings are prohibited.

7.2 **Licenses.** (a) Client hereby grants, and shall ensure that each applicable Affiliate will promptly grant, to Provider and its Affiliates the limited right to use Client IP and Project IP for the purpose of providing the Services. (b) Provider hereby grants, and shall ensure that each applicable Affiliate will promptly grant, to Client and its Affiliates the limited right to use Provider IP for the purpose of using Project IP.

8. REPRESENTATIONS AND WARRANTIES

8.1 **Mutual.** Each party represents and warrants that (a) it validly exists under the laws of the jurisdiction in which it was organized, (b) it has the full power, right and authority to execute and deliver the Agreement and to perform its obligations under the Agreement, (c) the Agreement once executed will constitute a legal, valid and binding agreement enforceable against it and (d) its performance of the Agreement will not conflict with any obligations it may have to any other person.



CONFIDENTIAL

8.2 Infringement. Each party represents and warrants that, to the best of its knowledge, the Services will not infringe the Intellectual Property rights of any third party.

8.3 Debarment. Provider represents and warrants that neither it nor any of the Personnel has been debarred, or, to the best of its knowledge, is under consideration for debarment, by the United States Food and Drug Administration from working in or providing services to any pharmaceutical or biotechnology company pursuant to the Generic Drug Enforcement Act of 1992 or any other governmental authority pursuant to analogous laws.

8.4 Compliance with Law. Each party (a) represents and warrants that neither it nor any of its Affiliates violated any applicable law in connection with actions leading up to entry into the Agreement and (b) shall, and shall ensure that each applicable Affiliate will, comply with all applicable law in connection with performance of the Agreement. Each party shall immediately notify the other party upon becoming aware of a breach of this Section. Breach of this Section with respect to the U.S. Foreign Corrupt Practices Act or any other anti-bribery law will be deemed an incurable material breach for purposes of Section 11.1(b).

9. INDEMNIFICATION; LIMITATION ON LIABILITY; INSURANCE

9.1 Third Party Claims. Each party shall defend, indemnify and hold the other party and its Affiliates and its and their directors, officers, employees, agents and consultants and legal, financial, accounting and other advisors (“Related Persons”) harmless from and against any and all liabilities and damages (including reasonable attorneys’ fees) (“Losses”) resulting from any third party claims, demands, suits or proceedings (“Claims”) to the extent arising out of or relating to (a) in the case that Provider is the indemnifying party, its performance of the Services, (b) in the case that Client is the indemnifying party, its use of Project IP or deliverables produced under the Agreement, (c) a material breach of the Agreement by the indemnifying party, (d) a material violation of applicable law by the indemnifying party or any of its Related Persons or (e) the negligence, recklessness or willful misconduct of the indemnifying party or any of its Related Persons during the course of activities carried out in connection with the Agreement. The indemnification obligations set forth in this Section 9.1 do not apply to the extent that the Loss arises in whole or in part from the negligence, recklessness or willful misconduct of the indemnified party or any of its Related Persons.

9.2 Intellectual Property Claims. Client shall defend, indemnify and hold Provider and its Related Persons harmless from and against Losses resulting from Claims arising out of or related to infringement of any Intellectual Property rights in connection with the Services other than Claims that are solely based on Provider IP independent of the Services. Provider shall defend, indemnify and hold Client and its Related Persons harmless from and against Losses resulting from Claims arising out of or related to infringement of any Intellectual Property rights in connection with the Services and that are solely based on Provider IP independent of the Services.

9.3 Defense. Each party shall notify the other party promptly upon learning of a Claim that is subject to indemnification pursuant to Section 9.1 or 9.2. The indemnifying party may control, at its own expense, the defense of the Claim in good faith with counsel of its choice as long as such counsel is reasonably acceptable to the indemnified party. The indemnified party shall use reasonable efforts to cooperate in the defense and may participate at its own expense using its own counsel. No compromise or settlement of any Claim may be made by the indemnifying party without the indemnified party’s written consent unless (a) there is no finding or admission of any violation of law or any violation of the rights of any person and no effect on any other claims that may be made against the indemnified party, (b) the sole relief provided is monetary damages that are paid in full by the indemnifying party and (c) the indemnified party’s rights under the Agreement are not adversely affected.

9.4 Limitations on Liability. Except for Losses resulting from Claims for which a party has indemnification obligations or damages arising from breach of confidentiality obligations or from a party’s gross negligence or willful misconduct: (a) neither party will be liable to the other party for breach-of-contract damages that (i) the breaching party could not reasonably have foreseen on entry into the Agreement or (ii) result from special circumstances of the non-breaching party; and (b) Provider’s maximum aggregate total liability in connection with the Agreement will not exceed the total payments received under the Agreement.

9.5 Insurance. Each party shall ensure that insurance coverage is carried and maintained with a financially sound and reputable insurer against loss from such risks and in such amounts as is sufficient to support its obligations under the Agreement. Each party shall provide a copy of the applicable insurance policy if requested by the other party.

10. CONFIDENTIALITY AND PUBLICITY

10.1 Confidentiality. Subject to Section 10.2, during the term of the Agreement and for five years thereafter, the Receiving Party shall, and shall ensure that its Related Persons will, (a) maintain the Confidential Information in confidence, (b) not use the Confidential Information other than in connection with the Agreement and (c) not disclose the Confidential Information to any third party other than (i) those of its Related Persons that have a need to know the Confidential Information in connection with the Services and are obligated to maintain the Confidential Information in confidence and (ii) to the extent required by applicable law or reasonably necessary to prosecute or defend litigation or arbitration, and, in either case, only after the Receiving Party gives the Disclosing Party reasonable advance notice of such disclosure and uses reasonable efforts to secure confidential treatment of the Confidential Information. Notwithstanding the foregoing, the existence of the Agreement and its non-technical terms may be disclosed confidentially in connection with a potential financing or acquisition.

10.2 Exceptions to Confidentiality. The obligations of Section 10.1 do not apply to Confidential Information if (a) the Confidential Information is public knowledge or becomes public knowledge after disclosure through no fault of the Receiving Party or any of its Related Persons, (b) the Confidential Information can be shown by the Receiving Party to have been in its or any of its Related Persons’ possession prior to disclosure, (c) the Confidential Information was received from a third party that was not obligated to the Disclosing Party or any of its Related Persons to maintain the Confidential Information in confidence, or (d) the Receiving Party can show that equivalent information was



CONFIDENTIAL

developed independently by the Receiving Party or any of its Related Persons without recourse to the Confidential Information.

10.3 Return of Confidential Information. Upon termination of the Agreement, and if requested in writing by the Disclosing Party within 30 days thereafter, the Receiving Party shall cause all Confidential Information to be promptly destroyed or returned to the Disclosing Party; provided, however, that (a) the Receiving Party may retain a single secure copy of any Confidential Information for legal archival purposes and (b) electronic back-up files that have been created by routine archiving and back-up procedures need not be deleted.

10.4 Publicity. Each party shall not, and shall ensure that its Related Persons will not, use the name, symbols or marks of the other party or any of its Affiliates in any advertising or publicity material or make any form of representation or statement that would constitute an express or implied endorsement by the other party or any of its Affiliates of any commercial product or service without the other party's or Affiliate's prior written consent.

11. TERM AND TERMINATION

11.1 Agreement. The term of the Agreement commences on the Effective Date and will terminate upon completion of the Services. Notwithstanding the foregoing, either party may terminate the Agreement: (a) at any time with three months' advance notice to the other party; or (b) immediately upon notice to the other party if (i) a material breach of the Agreement by the other party remains uncured 30 days after notice of the material breach was received by the other party and (ii) the material breach was not caused by the party terminating the Agreement or any of its Affiliates.

11.2 Survival. Upon termination of the Agreement, all outstanding rights and obligations between the parties arising out of or in connection with the Agreement will immediately terminate, other than any obligations that (a) matured prior to the effective date of the termination or (b) by their nature are intended to survive.

11.3 Termination Fee. If the Agreement is terminated, then Client shall pay Provider for the Services rendered and all non-cancelable obligations in connection with the Services. If the Agreement is terminated by Provider pursuant to Section 11.1(b), then Provider may charge Client a termination fee equal to 25% of the remaining value of the Agreement as non-exclusive liquidated damages in connection with the redeployment of reserved personnel and production capacity.

12. SHIPPING

12.1 All materials to be provided by Provider to Client will be delivered FCA (carrier named by Client) (Incoterms 2010), including deliverables produced under the Agreement, returned Client Materials, returned Records and returned Confidential Information. For the avoidance of doubt, FCA (carrier named by Client) means Provider is responsible for handing over the materials, cleared for export, to a carrier named by Client. Client assumes risk at hand over and pays all costs.

12.2 All materials to be provided by Client to Provider will be delivered DDP (site designated by Provider) (Incoterms 2010), including Materials provided by Client and Client Materials. For the avoidance of doubt, DDP (site designated by Provider) means Client is responsible for delivery to and unloading at the site designated by Provider and pays all costs including import duties and taxes.

13. MISCELLANEOUS

13.1 Force majeure. Neither party shall be liable for non-fulfilment of its obligations under the Agreement if such non-fulfilment is due to an occurrence of force majeure. Each party shall use reasonable efforts to mitigate adverse consequences.

13.2 Assignment. The Agreement may not be assigned by a party without the prior written consent of the other party; provided, however, that a party may assign the Agreement to an Affiliate with a net worth or insurance commensurate with the obligations to be assumed. Any purported assignment in violation of this Section is void.

13.3 Notices. All notices, requests, demands and other communications required under the Agreement must be in writing and will be deemed to have been given or made and sufficient in all respects when delivered by reputable international courier to the following addresses: (a) if to Client, then to the address provided in the Purchase Order and (b) if to Provider, then to WuXi AppTec, Building 1, 288 Fute Zhong Road, Waigaoqiao Free Trade Zone, Shanghai, China 200131, attention: Commercial Contracts Office, telephone: +86 21 5046 1111, with a copy to WuXi AppTec (HongKong) Limited, Unit 826, 8/F, Ocean Centre, Harbour City, 5 Canton Road, Tst, Kowloon, Hong Kong.

13.4 Independent Contractor. The parties are independent contractors, and nothing contained in the Agreement may be deemed or construed to create a partnership, joint venture, employment, franchise, agency, fiduciary or other relationship between the parties.

13.5 Non-Solicitation. During the term of the Agreement and for one year thereafter, Client shall not induce or solicit (or authorize or assist in the taking of any such actions by any third party) any employee or consultant of Provider or any of its Affiliates to leave his or her employment or business association.

13.6 Governing Law. The laws of Hong Kong, without giving effect to principles of conflict of laws, govern all matters relating to the Agreement.

13.7 Arbitration. The parties shall engage in good faith consultation to resolve any dispute arising out of or in connection with this agreement. Such consultation will begin immediately after one party has delivered to the other party a request for consultation. If the dispute cannot be resolved within 30 days following the date on which the request for consultation is delivered, then either party may submit the dispute to the Hong Kong International Arbitration Centre ("HKIAC") for arbitration to be conducted in accordance with the Arbitration Rules of HKIAC in effect at the time of submission. The place of arbitration will be Hong Kong. The official language of the arbitration will be English. The tribunal will consist of one arbitrator to be appointed by HKIAC. The arbitration proceedings will be confidential, and the arbitrator may issue appropriate protective orders to safeguard each party's Confidential



CONFIDENTIAL

Information. During the course of arbitration, the parties shall continue to implement the terms of this agreement. The arbitral award will be final and binding upon the parties, and the party to the award may apply to a court of competent jurisdiction for enforcement of the award. Notwithstanding the foregoing, each party has the right to institute an action in a court of proper jurisdiction for injunctive or other equitable relief pending a final decision by the arbitrator.

13.8 Entire Agreement; Non-Reliance. The Agreement contains the entire agreement between the parties with respect to the subject matter of the Agreement. Prior agreements are hereby superseded. For the avoidance of doubt, prior confidentiality obligations are superseded to the extent that they cover Confidential Information. Each party disclaims that it is relying on any representations or warranties other than those set forth in the Agreement, and irrevocably waives any rights that it might otherwise have to extra-contractual remedies, including claims in tort relating to communications outside of the Agreement.

13.9 Amendment. No modification or waiver of any term of the Agreement or any other form of amendment to the Agreement will be binding unless made expressly in writing and signed by both parties.

13.10 No Third Party Beneficiaries. The provisions of the Agreement are for the sole benefit of the parties.

13.11 Waiver. The waiver by either party of any breach of any term of the Agreement will not constitute a waiver of any other breach of the same or any other term. Failure or delay on the part of either party to fully exercise any right under the Agreement will not constitute a waiver or otherwise affect in any way the same or any other right.

13.12 Severability. If any provision in the Agreement is held to be invalid, illegal or unenforceable in any respect, then (a) the provision will be replaced by a valid and enforceable provision that achieves as far as possible the intention of the parties and (b) all other provisions of the Agreement will remain in full force and effect as if the original Agreement had been executed without the invalidated, illegal or unenforceable provision.

[REMAINDER OF THE PAGE LEFT BLANK INTENTIONALLY]



CONFIDENTIAL

STUDY PLAN

Quote # 1293

Route Scouting for TAR-1000 and TAR-0988A

Submitted to:

Yoshiyuki Fukase

**TCG GreenChem, Inc.
A Contract Innovator Organization**

**701 Charles Ewing Boulevard
Ewing, New Jersey 08628**



TCG GreenChem, Inc. Fit and Value Proposition:

TCG GreenChem, Inc. was founded by former big-pharma pharmaceutical executives with a track record in the development of hundreds of New Chemical Entities (NCE) into the clinic and commercialization of several well-known pharmaceutical products for Boehringer-Ingelheim, Sepracor, and Merck & Co, Inc. TCG GreenChem, Inc., based in Princeton South NJ, and Richmond VA, brings the experience, technological expertise, and know-how, which is required to meet all objectives of drug development. TCG GreenChem Research and Development Center at Princeton South has state of the art process research labs, analytical capabilities, and cGMP Kilo Laboratories to manufacture and release API. TCG GreenChem is positioned as a Contract Innovator Organization TM with a unique modus operandi in the space of pharmaceutical R&D. TCG

GreenChem is the Drug Development Engine that accelerates “Molecules to Medicines” by delivering novel solutions to difficult and highly complex synthetic organic problems to support the cGMP manufacturing of API for enabling tox studies and Phase I/IIA clinical supplies. Moreover, through strategic collaborations with a select group of technology companies based in the USA, we can ensure “line of sight” from kilo lab to pilot plant and beyond. In addition, alliances with CDMOs in North America and Asia, we ensure reliability to meet today’s regulatory and supply-chain challenges for the commercial manufacturing of API.

TCG GreenChem, Inc. in the United States is a subsidiary of TCG Lifesciences Pvt Ltd. TCG Lifesciences is a private limited firm (formerly “Chembiotek Research International”), leading global Contract Research and Manufacturing Services (CRAMS) and CDMO company in the area of drug discovery, development and commercialization. TCG Lifesciences currently has its presence in the United States, Europe, and Japan. TCG Lifesciences has a strong talent pool of 1200+ qualified and trained scientists (including 200+ PhDs), drawn from the best domestic and international institutes and industry. TCG Lifesciences’s services span chemistry, in vitro and in vivo pharmacology, analytical development and validation, and specialty chemicals. Its research infrastructure includes world-class chemistry and biology laboratories, animal facility, electrophysiology laboratory, BSL 2 laboratory (AAALAC accreditation), and cGMP facilities at their R&D centers. **This project will be executed at our New Jersey facilities.**

Introduction and Scope of Work:

Within the auspices of this proposal, Maipl Therapeutics, Inc. will be referred to as Maipl and TCG GreenChem, Inc., will be referred to as TCG GC. The molecules of interest will be referred to as TAR-1000 and TAR-0988A or target molecules.

Maipl is seeking a qualified Contract Manufacturing Organization, with proven experience in the process research, development, and manufacture of investigational drug substances and related substances for use in development and pre-clinical studies. The request for proposal was for generation of 200 g and 300 g each of TAR-100 and TAR-0988A with additional activities as mentioned below.

1. Salt screening of the 2 compounds (both carboxylic acid) by using pharmaceutically acceptable bases.

2. Crystallinity and stability analysis of the salts.
3. Pre-clinical formulation by using pharmaceutically acceptable vehicles.

For the salt and cocrystal screening the following are the list of activities that TCG GC will evaluate

Scope and Execution

1. Review existing information and obtain solubility of the target molecules TAR-1000 and TAR-0988A (free molecule), existing salts and/or co-crystals and salt/co-crystal co-former candidates in 4 – 6 system systems.
2. Conduct in-silico solubility prediction to assess solubility landscape of free molecules, salts/co-crystals, salt/co-crystal conformer candidates, with in-house prototype AI software “Blizzard”. Based upon the solubility assessment, literature recommendations, and in-house expertise, select **top 10** conformers and **8-10** solvent systems for experimentation.
3. Prepare analytical instruments for material characterization: HPLC, NMR & GC (for chemical identity/purity, residual solvents), and XRPD, DSC, TGA, and PLM (for crystal form). DVS will be outsourced as needed.
4. Conduct 80-100 screening experiments (tens of mg scale/experiment). These experiments will be solvent-mediated reactive crystallization under periodic sonication at selected temperature for a period of 3-5 days to facilitate salt and/or cocrystal formation.

At this stage of salt/co-crystal crystal formation screening, solvent mediated approach with periodic sonication is the preferred technique over other techniques such as anti-solvent, evaporation, drying, heat/cool, etc. After discovering crystals from different conformers, all these techniques will be explored in the subsequent polymorph screening to identify all polymorph from the specific conformer.

5. Characterize the resulting solids (amorphous or crystalline, anhydrate/hydrates or non-solvates/solvates) and its chemical identity (salt and/or co-crystals, free molecules, conformer or degradates)
6. Final report submission

TCG GreenChem team has demonstrated a thorough prior experience and history in handling and delivering processes from early-stage R&D to large scale deliveries of complex heterocycles. The

demonstrated examples of which may be found in the published literature, wherein the team have developed safe and “scalable” batch as well as continuous flow processes for delivery on Kg scales. Based on the route of synthesis provided by Maipl, the following sequence of milestones will emanate during the generation of the material.

1. Firstly, process familiarization will be explored with the conditions shared by Maipl and the proof of principle will be established on 5-10 g scale.
2. This will be followed by a fit to purpose optimization that involves an expedited identification of the critical process parameters and TCG GC requests Maipl to share any available information on the critical process parameters (CPP) for the processes.
3. Based on the process documents shared by Maipl and the scale at which the process was executed (low yields are reported at various stages), TCG GC recommends a fit to purpose optimization wherein the robustness of the process will be evaluated before embarking on scale-up. Post this milestone, TCG GC will scale-up in kilo lab to deliver 200 g and 300 g of each of the target molecules.
4. The supply of 200 g to 300 g of target molecules requires access to Kilo Lab facilities (for earlier steps as it is a long synthesis comprising of 14 steps for TAR-1000 and 11 steps for TAR-0988A). The following activities will be a part of the exercise before executing in kilo lab,
 - ❖ Process safety studies for each step on the finalized conditions and isolation protocols.
 - ❖ Prepare Laboratory Process Transfer Documents (LPTDs) and other technology transfer documents.
 - ❖ Conduct Process Safety and Operability Review (PSOR) to transfer the process to the kilo lab
 - ❖ Fit for purpose analytical methods will be developed and used for IPC and release.

General Assumptions

1. Authentic target products will be supplied from the client.
2. The client will aid with the available analytical methods as mentioned in the RFP for the release.
3. Any changes needed to be made in the provided process will lead to additional development and will be taken as an added scope.

4. Fit for purpose analytical methods will be used for analysis of IPC, intermediate and final. (Maipl is requested to share the analytical methods and the respective standards and markers for each of the target molecules).
5. Raw materials will be assessed based on use test and will be released on supplier COA.
6. Any scope of work in addition to the current understanding will be taken as added scope and will have an impact on timeline and cost.

TCG GC has also noticed that the existing process can be further improved with respect to yield at various stages of the synthetic route. More importantly, chromatography, trituration, and prep-HPLC techniques were utilized for purification. TCG GC has extensive experience in developing processes with crystallization for purification enabling a robust and scalable operation for scale-up. A selected list of areas for process improvement (based on the documents shared by Maipl) are listed below and TCG GC has demonstrated examples in the literature in addressing these challenges for the development of a robust process. Hence, TCG GC proposes to collaborate beyond this delivery for the development of a safe, scalable, robust, and cost-effective process for subsequent kilogram deliveries.

S. No	TAR-1000	TAR-0488A
1	Chromatography utilized for the purification of compounds 1-2 and BCO ketone and compound D .	Common intermediates like compounds 1-2 and BCO ketone and compounds 1, 2, 3 , and TAR-0988A are purified by using chromatography or prep-HPLC.
2	Trituration was used for purification for compounds 1, 2, 3 , and TAR-1000	
3	Low yields observed for all the steps in the synthesis of BCO ketone	

Table-1: Areas for process improvement identified for synthesis of TAR-1000 and TAR-0988A.

Outline of Analytical and QC Activities

100g non-GMP Campaign:*

- Development of assay and impurity methods (fit-for-purpose/phase appropriate) for starting material, intermediates, and the target molecules (maximum of 10 methods). Analytical methods beyond proposed above (10 methods) extends beyond the scope of this proposal
- Continuous optimization of assay and impurity test methods (fit-for-purpose) based on the process changes.
- The fit-for-purpose methods developed during the program will not be validated or qualified. Validation/qualification/feasibility will constitute a change of scope.
- Forced degradation studies to show “stability indicating” is not covered within the scope of this proposal.
- Development report for any of the test analytical methods is not within the scope of this proposal.
- At the end of the campaign, Certificate of Test Results (CoTR) will be released for both TAR-1000 and TAR-0988A.
- The scope of the work does not cover informal stability or holding study.

The overall cost of the program and the relevant details are included below for the generation of 200 g and 300 g of each of the target molecules.

S. No	Activity	TAR-1000	TAR-0988A
1	200 g material generation*	\$263,000	\$266,000
2	300 g molecule generation*	\$300,000	\$300,000

* Inclusive of process familiarization and fit for purpose optimization.

Reimbursements:

Any third-party bills as actuals for reimbursement will be submitted.

Dr. Chris Senanayake, and Dr. Bo Qu will manage the program

*Timelines and prices are our best estimate. Any unanticipated issues that jeopardize the process will be addressed during the program and could result in a change in the activities.

Point of Contact: Dr. Gopal Sirasani

Shipping, Packing, handling and custom charges: TCG will arrange the shipment (under suitable condition) of the target compound to the address provided by Maipl and TCG will get reimbursed all the costs in this regard.

Communication: TCG will communicate with Maipl through bi-weekly written project progress reports and a conference call will be held between TCG and Maipl representatives. Maipl will be notified by phone/email immediately of any relevant findings or other circumstances that could impact agreed timelines. Maipl will own all intellectual property and improvements that develop from our effort.

Payment Schedule

- 40 % Downpayment is required immediately after the project approval to cover cost of project assessment and initiation.
- 60 % will be paid NET 30 Days after the completion of the project.

Proposal to Provide Services (PPS) Content from TCG – CrystalPharmaTech

1. Project Summary

TCG GreenChem is supporting the synthesis and scale up of TAR1000 and TAR0988A. The client is looking to perform a salt selection for both compounds and identify candidates with high crystallinity with suitable stability. Both compounds contain a carboxylic acid group, and the salt screening should focus on utilizing pharmaceutically acceptable bases. Following the salt screening, Crystal Pharmatech will perform a vehicle screening and evaluation to identify an acceptable preclinical formulation to use in future PK studies.

Crystal Pharmatech suggests the following workflow:

- Salt Screening and Selection
- Vehicle Evaluation and Selection

2. Specific Activities

Salt Screening and Selection

The intent of this study is to screen and select a salt form of for TAR1000 and TAR0988A which has higher solubility compared to crystalline free form and desirable characteristics such as higher physical and chemical stability, lower propensity for disproportionation (conversion back to free base), acceptable class of counter ion, negligible/low hygroscopicity.

- 100 salt screening experiments with up to 15 different counterions.
- XRPD will be performed on all hits.
- Further characterization including TGA, DSC and PLM will be completed on up to 5 unique salt forms. More salt forms can be characterized at an additional charge.
- Scale up of up to 1 salt hits (at 100-200 mg each) which are potential anhydrous/hydrate will be prioritized.
- In the case where >3 forms need investigation; an additional charge will apply and be included in a change order.
 - Full characterization on up to 3 scaled up salt hits.
 - Phase origin (i.e., hydrate/solvate/anhydrate) (XRPD, DSC, TGA, KF, GC)
 - Salt stoichiometry (CAD/solution NMR)
 - Hygroscopicity analysis (using DVS)
 - Determine impact of grinding
 - One-week chemical/physical stability on optimal hit
 - 25°C/60%RH and 40°C/75%RH, 60°C for 1 week of the recommended crystal form
 - Solid placed at 70/70%RH for 1 week - test for degradation.
 - All the samples will be tested for purity (HPLC) and form conversion (XRPD).
- Solubility evaluation on optimal hit in water, SGF, FaSSIF, FeSSIF based on the confirmation with client, XRPD/HPLC test.
 - Solubility higher than 20 mg/mL just report that it is greater than 20mg/mL.
 - Kinetic solubility will be performed at 1, 2, and 24-hour marks.
- Scale up the selected salt form for TAR1000 and TAR0988A to support the vehicle evaluation and selection study.

Vehicle Evaluation and Selection

- Approximate solubility in ~10 vehicles (including aqueous and non-aqueous formulation).
- Chemical and physical stability for 3 time points in ~5 lead vehicles prepared in duplicate or triplicate if material permitting (timepoints TBD by client).
 - Solubility and stability analyzed by HPLC.
 - Form change tested by XRPD and PLM.

- Record image/video for doseability; confirm flow through a standard rodent gavage needle for gavagability of suspensions.
- For 2-3 lead vehicles, test the redispersibility in SGF, FaSSIF, and FeSSIF
 - Concentration and form content analyzed (If solid remaining/available) after 1 hour (volumes chosen based on client determined species)
- For 1 lead vehicle, perform a 2-stage dissolution of SGF-FaSSIF.
 - Test concentration and crystal form change (if sufficient solids available) at the desired time points.

Table 1: Recommended Cost, Timing, and Material Needed				
Activity	Cost per Compound	Number of Compounds	Timeline (Weeks)	Material per Compound (g)
Salt Selection	\$54,000	2	8	4
Vehicle Evaluation and Selection	\$9,900	2	3	4
Total	\$127,800		11*	8

**Work for both compounds will be performed in parallel.*

3. Desired Material and Background Information

Client will provide Crystal Pharmatech with material as requested in Table 1

Client will also provide:

- All solubility data collected to date.
- All background characterization or phase understanding data available to date
- All stability data collected to date is relevant to the execution of this proposal.
- Detailed HPLC method for the determination of compound integrity, if needed.
- Material Safety Data Sheet (MSDS). For highly potent compound (OEL < 1 µg/m³) and/or compound with known or predicted cytotoxic activity, Crystal Pharmatech will review MSDS and handling procedures and accept or reject to work on the compound after evaluation. Therefore, it is highly recommended that the client provides the MSDS and handling information to Crystal Pharmatech BEFORE approving the proposal and shipping the compound.

4. Timelines

Crystal Pharmatech will start the workflow within 3 business days after the material is received. Subsequently, a kickoff meeting for project discussion will be given by the project manager unless the client requests to start prior to the sample's arrival. The desired work will be completed according to Table 1. Any work in addition to the above workflow will incur extra time and will be clearly communicated to Client through e-mail.

5. Sample Shipping/Disposal/Storage/Return

After the client confirms the acceptance of the final report, Crystal Pharmatech will reach out to the client for sample disposal/return. Please choose one of the followings,

- a. Sample Disposal: Crystal Pharma will dispose the samples by following RCRA and Solid/HAZ waste guidelines,
- b. Sample Storage: Crystal Pharmatech will keep samples until client's further notice, or disposal after 12 months if no further notice received from client.
- c. Sample Return: Crystal Pharma will return the samples to the client based on the information provided below.

Crystal Pharmatech is responsible for covering standard or normal shipping costs; however, Crystal Pharmatech is not responsible for expenses related to premium or expensive shipping methods.

6. Communication and Reporting

Crystal Pharmatech will provide regular Project updates and will hold meetings as desired by the Client. At project completion, Crystal Pharmatech will provide a final report including all characterization data and a clear discussion of results. The report will be sent within 4 weeks of the experiment completion date.

7. Pricing

Pricing is outlined in Table 1. Fifty percent (50%) of the service fee is invoiced after the proposal is approved. The remaining service fee will be invoiced upon delivery of the report. Any optional work will result in additional charges as per Table 2, which will be combined with the final invoice. Any deviation that incurs more than 5 hours of scientist time will result in a Change Order. All invoices are due in Net 30 days.

8. Site of Project Execution

The work outlined in this Proposal will be completed at our Cranbury, NJ facility. Please ensure your P.O. reflects our facility information below:

Crystal Pharmatech Inc.
3000 Eastpark Blvd., Ste 500B
Cranbury, NJ 08512

Mapl Acknowledgement

Your signature below indicates your acceptance of the pricing and terms detailed in the quote above.

Signature

PO #

Date

Print Name

Warm Regards,

Gopal Sirasani, Ph.D.

Associate VP, Business Development

TCG GreenChem, Inc.

Phone: 1+ (215) 490-6818

20 March 2024

Yong Yue, PhD, President & CEO
Maipl Therapeutics, Inc. United States

RE: Budgetary Price Estimate to Support Program

Labcorp Quote Number: 801008

Thank you for the opportunity to provide Maipl Therapeutics, Inc. with a budgetary proposal for conducting this important program with Labcorp.

The pricing information provided in this proposal is indicative of estimates for the studies projected to be part of your program. As such all figures provided herein are ballpark in nature and are based on Labcorp's standard practices/designs.

Title	Est Price Low	Est Price High
Rat 2-Phase IV Bolus/SC Single Dose Range-Finding (Phase I) and 7-Day Repeat Dose (Phase II) Toxicity/TK Study with Analytical (Small Molecule)	\$137,600	\$158,200
Dog 2-Phase Oral Gavage Escalating Dose (Phase I) and 7-Day Repeat Dose (Phase II) Toxicity/TK Study with Analytical (Small Molecule)	\$126,000	\$144,900
Collection of Samples for Determination of the Pharmacokinetics of Test Article After Single Oral Dose to Rats with Analytical (Small Molecule)	\$16,700	\$19,300
Collection of Samples for Determination of the Pharmacokinetics of Test Article After Single Oral Dose to Dogs with Analytical (Small Molecule)	\$24,200	\$27,800
Dose Analysis Full Validation in one formulation to support GLP toxicology studies (Small Molecule)	\$24,000	\$27,600
LC-MS/MS Method Development (Rat and dog plasma, single analyte) (Small Molecule)	\$51,400	\$59,100
LC-MS/MS Method Validation in rat plasma, single analyte (Small Molecule)	\$48,500	\$55,800
LC-MS/MS Method Validation in dog plasma, single analyte (Small Molecule)	\$48,500	\$55,800
Total	\$476,900	\$548,500



Quote Assumptions:

- ▶ Analytical support (bioanalytical sample analysis, dose analysis and TK reporting) are included in those stated prices.
- ▶ SEND data reporting is included in those applicable studies.
- ▶ **This document is not a contract.** Pricing outlined herein is ballpark in nature and based on Labcorp's standard practices; therefore, price is subject to change in the future as we refine study design(s) based on your specific requirements.

Here at Labcorp we're confident that we can assist you in accomplishing your development goals and would welcome the opportunity to discuss this program with your team in more detail. If you would like to understand more about Labcorp's Early Development services and/or require a full proposal containing study outlines, refined pricing information and projected project timing, please let us know and we will be happy to prepare a formal quotation.

Thank you once again for considering Labcorp for this important program. We look forward to hearing from you in the near future.

With best regards,

John Morrissey
Inside Sales Manager

Lisa Craig
Business Development Director, Early Development NJ, NY, CT and RI

Pamela Goff
Proposal Manager

Confidentiality Statement

The information in this document contains proprietary information of Labcorp and is supplied in confidence to the recipient. Neither this document nor any of the information contained therein (including any attachments) shall (in part or in whole) be published, reproduced, distributed, disclosed, adapted, used (in each case, in any form by any means) or otherwise made available or accessible in any form or by any means to any other person for any purpose without the express prior written consent of Labcorp.



RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals (\$)
Section A, Senior/Key Person	168,750.00
Section B, Other Personnel	0.00
Total Number Other Personnel	0
Total Salary, Wages and Fringe Benefits (A+B)	168,750.00
Section C, Equipment	0.00
Section D, Travel	0.00
1. Domestic	0.00
2. Foreign	0.00
Section E, Participant/Trainee Support Costs	0.00
1. Tuition/Fees/Health Insurance	0.00
2. Stipends	0.00
3. Travel	0.00
4. Subsistence	0.00
5. Other	0.00
6. Number of Participants/Trainees	0
Section F, Other Direct Costs	1,282,882.00
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	136,800.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	330,718.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Other 1	0.00
9. Other 2	615,364.00
10. Other 3	200,000.00
11. Other 4	0.00
12. Other 5	0.00
13. Other 6	0.00
14. Other 7	0.00
15. Other 8	0.00
16. Other 9	0.00
17. Other 10	0.00
Section G, Direct Costs (A thru F)	1,451,632.00
Section H, Indirect Costs	458,366.00

Section I, Total Direct and Indirect Costs (G + H)	1,909,998.00
Section J, Fee	133,700.00
Section K, Total Costs and Fee (I + J)	2,043,698.00

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

UEI*: GM1XX56LEP58

Budget Type*: Project Subaward/Consortium

Enter name of Organization: University of Pennsylvania

Start Date*: 12-01-2024

End Date*: 11-30-2025

Budget Period: 1

A. Senior/Key Person												
Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Michael	Francis	Beers		Subaward PI		0.6			5,522.00	1,684.00	7,206.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:										Total Senior/Key Person		7,206.00

B. Other Personnel

Number of Personnel*	Project Role*	Calendar	Months	Academic	Months	Summer	Months	Requested	Salary (\$)*	Fringe	Benefits*	Funds Requested (\$)*
	Post Doctoral Associates											
	Graduate Students											
	Undergraduate Students											
	Secretarial/Clerical											
1	Research Specialist		3.96						16,995.00		5,183.00	22,178.00
1	Total Number Other Personnel									Total Other Personnel		22,178.00
Total Salary, Wages and Fringe Benefits (A+B)												29,384.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

UEI*: GM1XX56LEP58

Budget Type*: Project Subaward/Consortium

Organization: University of Pennsylvania

Start Date*: 12-01-2024

End Date*: 11-30-2025

Budget Period: 1

C. Equipment Description		Funds Requested (\$)*
List items and dollar amount for each item exceeding \$5,000		
Equipment Item		
Total funds requested for all equipment listed in the attached file		
	Total Equipment	0.00
Additional Equipment: File Name:		

D. Travel		Funds Requested (\$)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)		
2. Foreign Travel Costs		
	Total Travel Cost	0.00

E. Participant/Trainee Support Costs		Funds Requested (\$)*
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	Total Participant Trainee Support Costs	0.00

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

UEI*: GM1XX56LEP58

Budget Type*: Project Subaward/Consortium

Organization: University of Pennsylvania

Start Date*: 12-01-2024

End Date*: 11-30-2025

Budget Period: 1

F. Other Direct Costs		Funds Requested (\$)*
1. Materials and Supplies		8,000.00
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Animal Housing		2,000.00
9. Next Gen Sequencing		18,000.00
10. Spatial Transcriptomics		43,000.00
11. Internal Other Services		10,000.00
	Total Other Direct Costs	81,000.00

G. Direct Costs		Funds Requested (\$)*
		110,384.00

H. Indirect Costs		Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC			62.5	110,385.00	68,990.00
					Total Indirect Costs 68,990.00
Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)					

I. Total Direct and Indirect Costs		Funds Requested (\$)*
		179,374.00

J. Fee		Funds Requested (\$)*

K. Total Costs and Fee		Funds Requested (\$)*
		179,374.00

L. Budget Justification*		File Name:
		clean_Mail_Beers_BudJust_V1_03-09-2024.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

UEI*: GM1XX56LEP58

Budget Type*: Project Subaward/Consortium

Enter name of Organization: University of Pennsylvania

Start Date*: 12-01-2025

End Date*: 05-31-2026

Budget Period: 2

A. Senior/Key Person												
Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Michael	Francis	Beers		Subaward PI		0.3			2,761.00	842.00	3,603.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:										Total Senior/Key Person		3,603.00

B. Other Personnel

Number of Personnel*	Project Role*	Calendar	Months	Academic	Months	Summer	Months	Requested	Salary (\$)*	Fringe	Benefits*	Funds Requested (\$)*
	Post Doctoral Associates											
	Graduate Students											
	Undergraduate Students											
	Secretarial/Clerical											
1	Research Specialist		1.98						8,837.00	2,695.00		11,532.00
1	Total Number Other Personnel									Total Other Personnel		11,532.00
Total Salary, Wages and Fringe Benefits (A+B)												15,135.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

UEI*: GM1XX56LEP58

Budget Type*: Project Subaward/Consortium

Organization: University of Pennsylvania

Start Date*: 12-01-2025

End Date*: 05-31-2026

Budget Period: 2

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	
Additional Equipment: File Name:	Total Equipment 0.00

D. Travel

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

	Total Travel Cost	0.00
--	--------------------------	-------------

E. Participant/Trainee Support Costs

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

Number of Participants/Trainees	Total Participant Trainee Support Costs	0.00
---------------------------------	---	------

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

UEI*: GM1XX56LEP58

Budget Type*: Project Subaward/Consortium

Organization: University of Pennsylvania

Start Date*: 12-01-2025

End Date*: 05-31-2026

Budget Period: 2

F. Other Direct Costs		Funds Requested (\$)*
1. Materials and Supplies		7,000.00
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Animal Housing		2,000.00
9. Next Gen Sequencing		17,000.00
10. Spatial Transcriptomics		42,000.00
11. Internal Other Services		10,000.00
	Total Other Direct Costs	78,000.00

G. Direct Costs		Funds Requested (\$)*
		Total Direct Costs (A thru F) 93,135.00

H. Indirect Costs			
Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC	62.5	93,136.00	58,209.00
			Total Indirect Costs 58,209.00
Cognizant Federal Agency			
(Agency Name, POC Name, and POC Phone Number)			

I. Total Direct and Indirect Costs		Funds Requested (\$)*
		Total Direct and Indirect Institutional Costs (G + H) 151,344.00

J. Fee		Funds Requested (\$)*

K. Total Costs and Fee		Funds Requested (\$)*
		151,344.00

L. Budget Justification*		File Name:
		clean_Mail_Beers_BudJust_V1_03-09-2024.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

BUDGET JUSTIFICATION

University of Pennsylvania

A. KEY PERSONNEL:

Employee Benefits (EB) are calculated at a rate of 30.5%.

Michael F. Beers, MD, Principal Investigator (Year 1: 0.6 calendar months; Year 2 0.3 Cal Months): Salary support based on his University salary is requested for Dr. Beers who will be responsible for the overall organization and administration of the project specifically related to studies proposed in Aims 1.2 and Aim 2 using mutant SftpcI73T mice. Dr. Beers will also apply his expertise in the laboratory to perform procedures and experiments. As a PI of independent research projects and a 30-year history of extramural support he is well qualified for this role. Dr. Beers currently maintains a laboratory at PENN-CHoP Lung Biology Institute (PCLBI) in the Edward Stemmler building at the University of Pennsylvania.

Dr. Beers is also funded through the Department of Veteran's Affairs for which a partial off-site waiver for work done at the University of Pennsylvania, for which equipment and resources are not available at the PVAMC, has been approved. The joint appointment supported by a signed, formal memorandum of understanding between the University of Pennsylvania (2/8ths) and the Department of Veterans Affairs (6/8ths = 4/8th research and 2/8th clinical) and stating that there is no possibility of dual compensation. The proposed compensation listed represents effort imparted on behalf of the University of Pennsylvania. There is no possibility of dual compensation for the same work, or of an actual or apparent conflict of interest. B. OTHER PERSONNEL:

Employee Benefits (EB) are calculated at a rate of 30.5%.

Katrina Chavez, BS, Research Specialist (Year 1: 4.0 calendar months; Year 2: 2.0 calendar months): Ms. Chavez has 4 years' experience working with the design, execution, and analysis of animal models. She has advanced skills in breeding, genotyping, colony organization, animal surgery, lung physiology measurements, ELISA assays, and qRT- PCR.

She has been with the Beers' lab for 2.5 years playing a critical role in maintenance of the Sftpc mouse colonies and the SOPs for their use in POC intervention studies. Ms. Chavez will work under the direct supervision of Dr. Beers. C. EQUIPMENT: None.

D. TRAVEL: None.

E. PARTICIPANT/TRAINEE SUPPORT COSTS: NONE.

F. OTHER DIRECT COSTS

1. Materials and Supplies: Total \$15,000 is requested to support the following:

General Lab / Tissue Culture Supplies (\$5,000): Support is requested for reagents, glassware, and consumable supplies needed for daily lab operations (e.g., plastic ware, pipettes, buffers, dry chemicals, etc.). In addition, reagents for isolation of AT2 cells, including enzymes, magnetic beads, culture media, serum, antibiotics, and transfection reagents.

Molecular Biology / Protein Chemistry Supplies (\$4,000): Support is requested for molecular biologic supplies for a range of assays including qRT-PCR primers, PCR reagents, precast electrophoresis gels, restriction enzymes, Western immunoblotting reagents.

Antibodies and Immunoreagents (\$4,000): Support is requested for antibodies and immunoreagents for FACS and immunohistochemistry.

Mouse Model Supplies (\$2,000): These include tamoxifen, syringes, terminal surgical supplies (utensils, anesthetics, suture), tissue fixatives, protease inhibitors, and cryostorage.

2. Animal Housing (\$4,000): We expect to maintain an average daily census of 10 cages (40-50 mice) of Sftpc mice. Given current per diem charges the estimate to house this average census (~ 100 cages X \$1.1 per cage per day). 3. Next Gen Sequencing Costs (\$35,000) Single Cell RNAseq related costs will be incurred from facility fees

charged by the Next Gen Sequencing Core for the anticipated analysis of the in vivo Maipl compound testing in Aim 2. Services will include preparation of scRNAseq libraries and barcoding from lung cell suspensions provided by the Beers' lab, sequencing, and data storage. The charges cover submission of 12 independent samples (12 "10X lanes") consisting of 3 induced Sftpc mice each treated with vehicle, Maipl compound or Nintedanib analyzed at 1 time point plus 3 control mice.

4. Spatial Transcriptomics Sequencing Costs (\$85,000): The CHOP Single Cell Technology Core will perform spatially resolved transcriptomics profile analysis of 8 samples (1 slide each) prepared by the Beers' lab from induced Sftpc mice (2 per condition) each treated with vehicle, Maipl compound or Nintedanib analyzed at 1 time point plus 2 controls using NanoString GeoMx Digital Spatial Profiler to assess 18,000+ mouse genes. The requested budget is based on estimates provided by the core's technical supervisor

5. Other Internal Services (\$10,000/yr.): Funds are requested annually for user fees for the use of the Fluorescence Activated Cell Sorting (FACS) Facility, Confocal Microscopy Facility, Luminex Immunology Core, and CHOP Histology Core.

NOTES

1) Indirect Cost For Research On Campus: Indirect rate is calculated at 62.5% effective July 2023 in agreement with DHHS Agreement signed 5/25/23.

2. Employee Benefit Rates Until Amended: Employee Fringe Benefit Rates (EB) are calculated at a rate of 30.5% in all years.

3. Modified total direct costs, consisting of all direct salaries and wages, applicable fringe benefits, materials and supplies, services, travel and up to the first \$25,000 of each subaward (regardless of the period of performance of the subawards under the award). Modified total direct costs shall exclude equipment, capital expenditures, charges for patient care, rental costs, tuition remission, scholarships and student aid fellowships, participant support costs and the portion of each subaward in excess of \$25,000. Other items may only be excluded when necessary to avoid a serious inequity in the distribution of indirect costs, and with the approval of the cognizant agency for indirect costs.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals (\$)
Section A, Senior/Key Person	10,809.00
Section B, Other Personnel	33,710.00
Total Number Other Personnel	2
Total Salary, Wages and Fringe Benefits (A+B)	44,519.00
Section C, Equipment	0.00
Section D, Travel	0.00
1. Domestic	0.00
2. Foreign	0.00
Section E, Participant/Trainee Support Costs	0.00
1. Tuition/Fees/Health Insurance	0.00
2. Stipends	0.00
3. Travel	0.00
4. Subsistence	0.00
5. Other	0.00
6. Number of Participants/Trainees	0
Section F, Other Direct Costs	159,000.00
1. Materials and Supplies	15,000.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Other 1	4,000.00
9. Other 2	35,000.00
10. Other 3	85,000.00
11. Other 4	20,000.00
12. Other 5	0.00
13. Other 6	0.00
14. Other 7	0.00
15. Other 8	0.00
16. Other 9	0.00
17. Other 10	0.00
Section G, Direct Costs (A thru F)	203,519.00
Section H, Indirect Costs	127,199.00

Section I, Total Direct and Indirect Costs (G + H)	330,718.00
Section J, Fee	0.00
Section K, Total Costs and Fee (I + J)	330,718.00

Total Direct Costs less Consortium F&A

NIH policy (NOT-OD-05-004) allows applicants to exclude consortium/contractual F&A costs when determining if an application falls at or beneath any applicable direct cost limit. When a direct cost limit is specified in an FOA, the following table can be used to determine if your application falls within that limit.

Categories	Budget Period 1	Budget Period 2	Budget Period 3	Budget Period 4	Budget Period 5	TOTALS
Total Direct Costs less Consortium F&A	596,998	370,685	356,750	0	0	1,324,433

SBIR/STTR Information

Agency to which you are applying (select only one)*

 DOE HHS USDA Other:

SBC Control ID:*

002558613

Program Type (select only one)*

 SBIR STTR Both (See agency-specific instructions to determine whether a particular agency allows a single submission for both SBIR and STTR)

Application Type (select only one)*

 Phase I Phase II Fast-Track Direct Phase II Phase IIA Phase IIB Phase IIC Commercialization Readiness Program (See agency-specific instructions to determine application type participation.)

Phase I Letter of Intent Number:

* Agency Topic/Subtopic:

Questions 1-8 must be completed by all SBIR and STTR Applicants:

1a. Do you certify that at the time of award your organization will meet the eligibility criteria for a small business as defined in the funding opportunity announcement?* Yes No1b. Anticipated Number of personnel to be employed at your organization at the time of award.* 51c. Is your small business majority owned by venture capital operating companies, hedge funds, or private equity firms?* Yes No1d. Is your small business a Faculty or Student-Owned entity?* Yes No2. Does this application include subcontracts with Federal laboratories or any other Federal Government agencies?* Yes No

If yes, insert the names of the Federal laboratories/agencies:*

3. Are you located in a HUBZone? To find out if your business is in a HUBZone, use the mapping utility provided by the Small Business Administration at its web site: <http://www.sba.gov> * Yes No4. Will all research and development on the project be performed in its entirety in the United States?* Yes No

If no, provide an explanation in an attached file. Explanation:*

5. Has the applicant and/or Program Director/Principal Investigator submitted proposals for essentially equivalent work under other Federal program solicitations or received other Federal awards for essentially equivalent work?* Yes No

If yes, insert the names of the other Federal agencies:*

6. Disclosure Permission Statement: If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and email address of the official signing for the applicant organization to state-level economic development organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?* Yes No7. Does the application include a request of SBIR or STTR funds for Technical and Business Assistance (TABA)? If yes, please follow the agency specific instructions to provide the budget request and justification. (Please answer no if you plan to use the agency TABA vendor, which does not require you to include a request for TABA funds in your application.)* Yes No

8. Commercialization Plan: The following applications require a Commercialization Plan: Phase I (DOE only), Phase II (all agencies), Phase I/II Fast-Track (all agencies). Include a Commercialization Plan in accordance with the agency announcement and/or agency-specific instructions.*

Attach File:*

Maipi-CP-V5.pdf

SBIR/STTR Information

SBIR-Specific Questions:

Questions 9 and 10 apply only to SBIR applications. If you are submitting ONLY an STTR application, leave questions 9 and 10 blank and proceed to question 11.

9. Have you received SBIR Phase II awards from the Federal Government? If yes, provide a company commercialization history in accordance with agency-specific instructions using this attachment.*

Yes No

Attach File:*

10. Will the Project Director/Principal Investigator have his/her primary employment with the small business at the time of award?*

Yes No

STTR-Specific Questions:

Questions 11 - 13 apply only to STTR applications. If you are submitting ONLY an SBIR application, leave questions 11 - 13 blank.

11. Please indicate whether the answer to BOTH of the following questions is TRUE:*

Yes No

(1) Does the Project Director/Principal Investigator have a formal appointment or commitment either with the small business directly (as an employee or a contractor) OR as an employee of the Research Institution, which in turn has made a commitment to the small business through the STTR application process; AND

(2) Will the Project Director/Principal Investigator devote at least 10% effort to the proposed project?

12. In the joint research and development proposed in this project, does the small business perform at least 40% of the work and the research institution named in the application perform at least 30% of the work?*

Yes No

13. Provide UEI of non-profit research partner for STTR.*

COMMERCIALIZATION PLAN

A. Value of the SBIR Project, Expected Outcomes, and Impact

Maipl Therapeutics aims to revolutionize idiopathic pulmonary fibrosis (IPF) treatment by targeting the prostaglandin F2alpha (PGF2 α) receptor with their lead candidates, MA-4586 and MA-4604. This novel approach offers a unique value in addressing an unmet medical need in IPF, where current treatments have limited efficacy, significant side effects, and high costs. By focusing on an independent pathway, Maipl Therapeutics' drug candidates are promising more effective and safer therapeutic alternatives for IPF patients. We believe these efforts could lead to a transformative impact on IPF treatment, improving patients' quality of life, and potentially extending their life expectancy.

Project Overview— IPF is a progressive and fatal interstitial lung disease characterized by the excessive formation of scar tissue in the lungs.¹ It primarily affects older individuals and is associated with a poor prognosis, with a median survival of only 3 to 5 years after diagnosis. About 140,000 Americans live with IPF and approximately 40,000-50,000 new cases are diagnosed each year.² The exact cause of IPF is unknown, although it is believed to involve a combination of genetic predisposition, environmental factors, and abnormal wound healing processes in the lung tissue. The disease is characterized by a gradual decline in lung function, leading to increasing dyspnea (shortness of breath) and reduced exercise tolerance.¹

Currently, the two anti-fibrotic treatments for IPF, **pifrenidone** (Esbriet) and **nintedanib** (Ofev), are considered the standard of care that can slow the progression of the disease but do not cure it.³ These drugs target pathways involved in fibrosis and have been shown to reduce the rate of decline in lung function and improve progression-free survival in patients with IPF (**Figure 1**). However, they are not without limitations, as they can cause side effects such as gastrointestinal issues, weight loss, and photosensitivity, which can be challenging for some patients for long time use.⁴

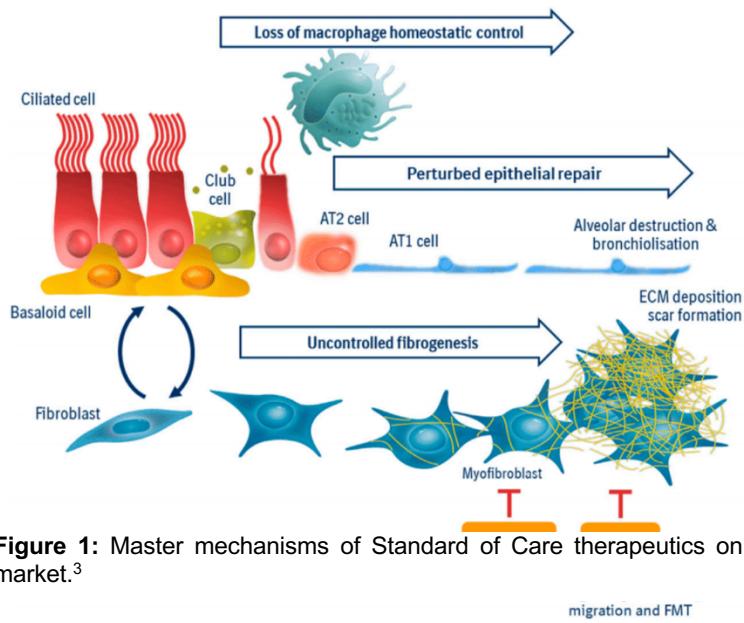


Figure 1: Master mechanisms of Standard of Care therapeutics on the market.³

process. One such approach is the targeting of the prostaglandin F2 alpha (PGF2 α) receptor, which is believed to play a role in the development of fibrosis in the lungs.⁵ Targeting this receptor with specific agents could offer a new and potentially more effective treatment option for patients with IPF.

In this Phase II SBIR grant application, Maipl Therapeutics proposes to evaluate the *in vivo* efficacy of its crystalline formula (MA-4586) and its amorphous formula (MA-4604) in two mice models. These studies are crucial for demonstrating the therapeutic potential of its compounds and will provide valuable insights into their mechanism of action (MOA) and effectiveness in preparation for clinical research. Additionally, Maipl Therapeutics will investigate the effects of PGF2 α intervention on the crosstalk between different cellular environments within the alveolar niche, specifically focusing on fibrotic signaling. Lastly, we plan to conduct exploratory non-GLP toxicology studies in rats and dogs to assess the *in vivo* safety of MA-4586 and MA-4604. These studies are essential for determining the safety profile of the compounds and will be crucial for moving towards Chemistry, Manufacturing, and Controls (CMC), IND-enabling (GLP) studies, IND filing, and Phase I clinical trials. Overall, the proposed studies will provide the necessary data packages to support the further development of MA-4586 and/or MA-4604 as potential treatments for IPF, ultimately benefiting patients suffering from this devastating disease.

Technical Objectives

Maipl Therapeutics' plans to generate pre-clinical evidence to support the development of its novel therapeutic agents for IPF by targeting the PGF2 α receptor (FP). We intend to evaluate the *in vivo* efficacy specifically in IPF disease models, determine the MOA of PGF2 α /FP in IPF disease pathophysiology, and assess *in vivo* (non-GLP) safety of lead candidates, MA-4586 and MA-4604.

Aim 1. Determine the anti-fibrosis efficacy of lead candidates in two IPF disease models. In preparation for IND-enabling studies, we will use two well-established preclinical IPF disease models to determine the efficacy of MA-4586 and MA-4604 (vs nintedanib) - the bleomycin (intra-tracheal)-induced pulmonary fibrosis mouse (C57BL/6) model and a tamoxifem-induced spontaneous lung fibrosis genetic mouse model, I^{ER}-Sftpc^{I73T}. Milestone: Determine ability of the tested compounds to limit significant decrease in body weight, development of lung fibrosis, inflammation, and mortality rate (I^{ER}-Sftpc^{I73T} only).

Aim 2. Determine changes in alveolar niche crosstalk and fibrotic signaling following FP inhibition. This aim will enable determination of which cellular targets our candidates (MA-4586 and MA-4604) hit, what process gets altered, and how this ultimately impacts the effect size of these drugs. We will distinguish the transcriptional signatures of lung cell populations and define fibrotic, alveolar, and regenerative niche dynamics after FP antagonist and nintedanib interventions. These studies will define the MoA of MA-4586 and MA-4604 in IPF disease pathophysiology in support of an IND submission. Milestones: (1) Determine changes in populations dynamics, cell crosstalk, and cell lineage signatures, (2) Identify alterations in spatial niches in the lung associated with profibrotic populations that may be involved in fibrosis.

Aim 3. Establish non-GLP preclinical safety in two species. Following exploratory PK and formulation optimization, we will conduct dose range finding and repeated dose toxicology studies in rodent (rat) and non-rodent (dog) species in preparation for IND-enabling GLP studies. Milestones: (1) Optimize formulation and dose, (2) Establish mean tolerable dose, (3) Determine dose level for no observed (adverse) effects (NOEL and NOAEL) to inform selection of the first dose and dose escalation schema in GLP studies.

Expected Outcomes

Maipl Therapeutics aims to demonstrate the efficacy of its lead candidates, MA-4586 and MA-4604, in preclinical models of IPF. The primary objectives include evaluating fibrotic tissue deposition, lung function, and examining the safety profile of the compounds. Additionally, Maipl seeks to elucidate the MOA of their compounds in the context of IPF pathogenesis, leveraging the expertise of their scientific team. Successful outcomes from these studies will provide valuable data to support further preclinical development, IND filing, and progression into clinical trials for IPF treatment.

Impact— Currently, IPF therapeutics remain a significant unmet need, with the standard of care drugs, pirfenidone and nintedanib, only able to slow disease progression rather than halt or reverse it. In addition, the

typical survival rate for patients with IPF is significantly lower than many forms of cancers with current drugs having little impact on disease progression (**Figure 2**).⁶ These drugs also come with tolerability issues, and patient response to these antifibrotic treatments is heterogeneous (some patients do not respond) and can generate adverse effects. Consequently, Maipl Therapeutics' approach stands out as the majority of drugs currently in development for IPF target a TGF β -dependent pathway. While TGF β is a critical mediator of fibrosis in IPF, **additional TGF β -independent pathways** have a key role in fibrogenesis but there are very few

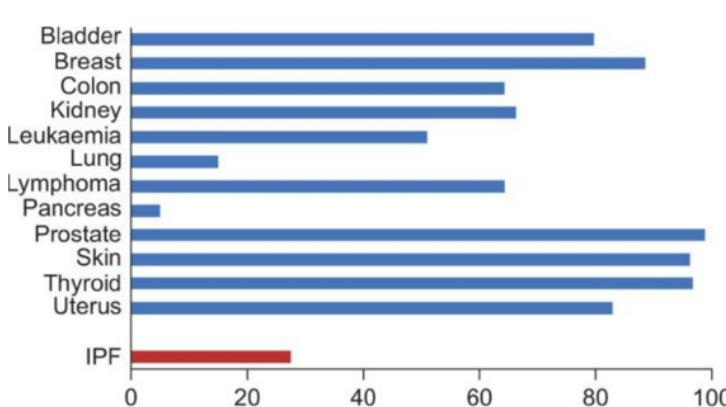


Figure 2: 5-year survival rate for IPF vs different cancers.

drugs targeting TGF β -independent fibrotic pathways.⁵ Maipl Therapeutics is targeting the PGF2 α pathway that has been convincingly implicated as a TGF β -independent signaling hub and its receptor (FP) as a novel drug target for IPF with strong preclinical data. We have discovered a highly selective, potent FP antagonist with preclinical studies indicating promising oral PK, *in vitro* safety profiles, and *in vivo* efficacy (non-IPF model).⁷ This unique approach offers the potential for a more effective and safer alternative for IPF patients. By evaluating the efficacy and safety of its lead candidates, MA-4586 and MA-4604, in preclinical IPF models, Maipl Therapeutics aims to demonstrate the potential of its novel therapeutic approach. If successful, this research

could pave the way for a new class of IPF treatments that could potentially halt or reverse fibrosis progression, addressing a critical gap in current IPF therapeutics.

Position of this SBIR Project in the Product Development and Regulatory Pathway— Completion of this Direct to Phase II SBIR Proposal is a necessary step to proceed to IND-enabling (GLP) studies. Maipl Therapeutics' compounds have successfully completed target validation, proof of concept, and the development of a small molecule antagonist against the target, demonstrating their potential. In addition, we believe successful completion of this project scope lays the framework for CMC, IND-enabling (GLP) studies, IND filing, and a phase I clinical trial for this novel IPF treatment. This is critical for raising the additional funds needed for a Phase 2 clinical trial and attracting a marketing partner. **Figure 3** provides an overview of the development process to date, the positioning of the proposed project in the commercialization pathway, and our anticipated timeline for subsequent development and commercialization.

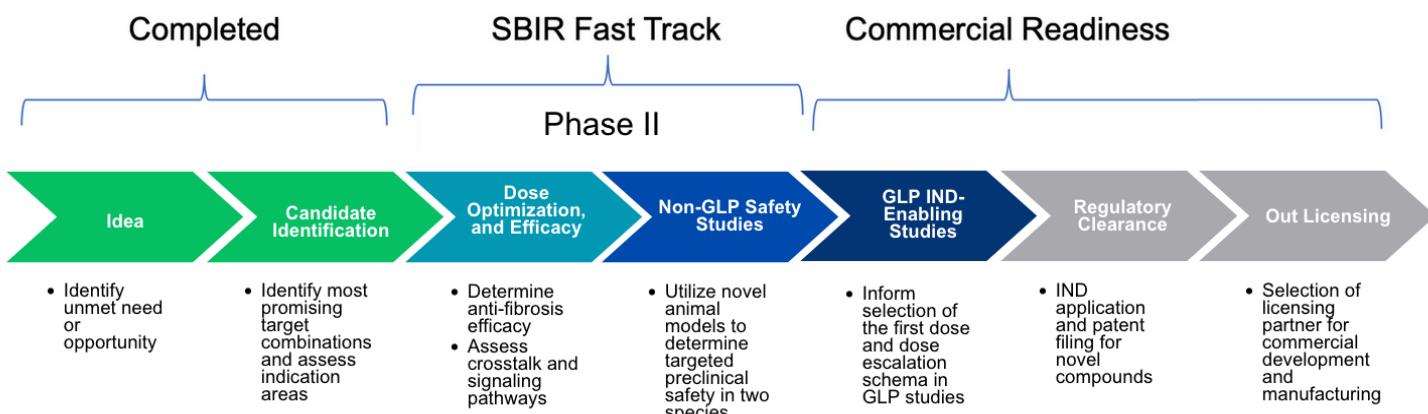


Figure 3: Product development and regulatory pathway process.

B. Company

Corporate Structure and Mission— Maipl Therapeutics was co-founded by three former employees of Ferring Pharmaceuticals: in May 2023, Ferring Pharmaceuticals decided to shift its drug discovery efforts and focus exclusively on external in-licensing and a clinical development model. As a result, Ferring Pharmaceuticals permanently closed the Ferring Research Institute in San Diego. Dr. Yong Yue (CEO), Senior Director of Computational Biology and Data Sciences, and Dr. Yoshiyuki Fukase (VP of Medicinal Chemistry), Chemistry Lead of the FP program, partnered in founding Maipl Therapeutics, in addition to other former Ferring Pharmaceutical employees. Ferring was developing the FP antagonist for pre-term birth, but Maipl pivoted (based on existing published data) to use these compounds for endometriosis-associated menstrual pain and IPF. In December 2023, Maipl formally signed the out-licensed contract with Ferring Pharmaceuticals and received the worldwide rights for a series of 5 FP antagonist compounds.

Maipl Therapeutics is deeply rooted in science and its therapeutic hypothesis is backed by compelling evidence. We are developing first-in-class medicines to treat IPF and other diseases like endometriosis, by focusing on medical conditions related to prostaglandin dysregulation, including pain, fibrosis, and inflammation. Maipl's mission is to provide innovative solutions for these debilitating health issues that affect millions of people worldwide.

Management Team—The leadership team at Maipl Therapeutics has deep expertise in pharmaceuticals and drug discovery in various therapeutic areas, including endocrine and women's health, oncology, and metabolism. Its combined leadership ensures Maipl's dedication to developing innovative medicines for diseases such as idiopathic pulmonary fibrosis and endometriosis.

Co-Founder, CEO and President – Dr. Yong Yue: Dr. Yue has more than 20 years of pharmaceutical industry



and bioinformatics experience in multiple therapeutic areas, including immunology, oncology, metabolic diseases, neuroscience, and reproductive health. He has built and led teams of bioinformatics and data scientists at pharma giants like Eli Lilly, Boehringer Ingelheim, and Ferring Pharmaceuticals, as well as in startup biotech companies. Dr. Yue has a proven ability to partner across functions and focus on organizational priorities at all levels of governance. He has made key strategic and scientific contributions to drug discovery and development portfolios, with a deep knowledge of bioinformatics algorithms, data science, and machine learning. His most recent role was as Senior Director of

Computational Biology and Data Sciences at Ferring Pharmaceuticals, where he was responsible for developing and leading data-driven drug discovery strategies. Dr. Yue also founded a stealth AI startup called Innative Bio.

Co-Founder and VP of Medicinal Chemistry – Dr. Yoshiyuki Fukase: Dr. Fukase brings 19 years of industry



and academic/biotech research experience to the company. He previously served as Director of Medicinal Chemistry at Ferring Pharmaceuticals, where he made the breakthrough discovery of the FP antagonist. Dr. Fukase has led projects that delivered 3 clinical compounds (TAK-272, TAK-828, and Imapikiren) and advanced preclinical development of drug candidates for 4 programs from academia-industry research collaborations and has authored or inventoried over 40 publications and patents. Prior to his role at Ferring Pharmaceuticals, he served as Associate Director of Drug Discovery Chemistry at Takeda Pharmaceuticals and Director of Chemistry at Tri-Institutional

Therapeutics Discovery Institute (MSKCC/Rockefeller U/Weill Cornell Medicine). Dr. Fukase's expertise lies in leading discovery chemistry groups, overseeing internal and external medicinal chemistry resources, and advancing small molecule drug discovery projects to clinical candidate selection. He is adept at recruiting, coaching, and developing internal talents and evaluating and implementing enabling discovery technology for drug discovery.

Consulting Scientific Advisor – Dr. Ying Zhang: Dr. Zhang is an accomplished and highly motivated



bioanalytical and DMPK scientist with extensive knowledge and working experience in the pharmaceutical and biopharmaceutical industries. She has a Ph.D. in Pharmaceutical Science from the University of Geneva, Switzerland, an M.Sc. in Chemistry from the University of Bristol, UK, and a degree in Pharmacy from China Pharmaceutical University, China. Dr. Zhang has a strong background in leading ADMET/DMPK experimental design and execution, *in vitro* ADME characterization, *in vivo* PK profiling and modeling, and attending project strategic discussions and CRO management. She is proficient in small molecular bioanalysis, physicochemical characterization, pre-formulation assessment, *in vitro* ADMET screening assays, and metabolite identification. Dr. Zhang also has

comprehensive knowledge and extensive method development experience in protein/antibody quantitative bioanalysis using state-of-the-art LC-MS/MS technologies and ligand binding assays. She is skilled in analytical technology, pharmacokinetic analysis, modeling, and simulation using WinNonlin, and bioanalytical method development and validation following GLP and ICH guidelines.

Subcontracting Lead Scientist – Dr. Michael Beers: Dr. Michael Francis Beers is world renowned lung



disease expert and a Professor of Medicine at the University of Pennsylvania. He received his A.B. in Biophysics in 1981 and his M.D. in 1985, both from the University of Pennsylvania. Over the past 30 years, Dr. Beers has acquired scientific expertise, investigative experience, and leadership skills necessary for successful research. His laboratory in the Pulmonary Division at the University of Pennsylvania has a long-standing interest in surfactant component metabolism, alveolar epithelial cell biology, and lung injury/repair. Dr. Beers has recognized expertise in understanding the molecular mechanisms utilized by the alveolar epithelia for the expression of surfactant protein components in health and disease. His research extends from molecule to cell to mouse

to man, encompassing biochemistry, cell biology, immunology, and pulmonary pathophysiology. Dr. Beers' work has led to significant discoveries in the biosynthetic life-cycle of hydrophobic surfactant proteins and their role in interstitial lung disease (ILD). His research also focuses on understanding the role of AT2 dysfunction in various lung injury models and the role of the UPR/ER Stress and metabolism in promoting pathologic AT2 cell endophenotypes. Dr. Beers will be conducting the scientific research addressed in Aim 2 of this proposal.

Contract Toxicology Consultant – Dr. Calvert Louden: Dr. Calvert Louden, a seasoned Veterinary Anatomic Pathologist, brings over 20 years of experience in pathology to his role. He is deeply committed to delivering hypothesis-driven translational sciences for transformative medicines. Throughout his career, Dr. Louden has held key leadership positions at top pharmaceutical companies such as AstraZeneca Pharmaceuticals, Johnson & Johnson Pharmaceuticals, and Dupont Pharmaceuticals. Additionally, he is a former employee of Ferring Pharmaceuticals. He has a proven track record of leading global teams with a "modality agnostic approach," focusing on pathology support from early discovery to clinical development. Dr. Louden's expertise lies in disease pathophysiology, biomarkers, and regulatory interactions. He is known for his collaborative approach and his ability to drive innovation in drug development strategies.

Company Advisors

Scientific Advisor - Darryle Schoepp: Dr. Schoepp holds a PhD and has over 30 years of experience in Neuroscience therapeutics in the pharmaceutical industry. He has served as the former Senior VP and Neuroscience Head at Merck & Co and former VP of Neuroscience Research and Early Clinical Development at Eli Lilly & Co. Dr. Schoepp has made significant contributions to the field with over 200 publications and 15 US patents. He has been involved in the discovery and introduction of over 20 novel first-in-class agents for psychiatric and neurological diseases, including compounds investigated for migraine, pain, cognition, anxiety disorders, and schizophrenia.

Scientific Advisor - Frank F. Tu: Dr. Tu, MD, MPH, is a board-certified obstetrician/gynecologist with extensive research expertise in menstrual pain. He currently serves as a Clinical Professor in the Department of Obstetrics and Gynecology at the University of Chicago and is the Director of the Division of Gynecological Pain & Minimally Invasive Surgery at the Northshore Research Institute. Dr. Tu provides multidisciplinary, cutting-edge care to women in the Midwest region with benign pelvic conditions such as fibroids, endometriosis, pelvic pain, and ovarian cysts. Dr. Tu has also held leadership positions, serving as President in 2014 and Scientific Program Chair from 2009 to 2011 for the International Pelvic Pain Society.

History of Funding— Maipl Therapeutics has successfully raised \$400,000 with an initial friends and family investment and is currently raising ~\$1 million in a Pre-Seed round / early Seed round and with the intention to close on an additional \$6 million. These funds will be dedicated to the development phase of several compound indications (such as endometriosis-associated menstrual pain), including establishing efficacy in pre-clinical IPF animal models as well as performing MOA and toxicological studies necessary for IND-enabling research.

Plan to Develop from a Small BioTechnology R&D Business to a Successful Commercial Entity—As illustrated in **Figure 3** of our commercialization pathway, we are currently approximately three years away from advancing our lead compounds, MA-4586 and MA-4604, for IPF, with an estimated five years until product launch. While this timeline aligns with standard pharmaceutical development, it presents challenges for a small business without revenue-generating products. To navigate this transition successfully and become a thriving commercial entity within 7 to 10 years, we are focusing on three key activities. **First**, we are developing an indication-specific plan for Maipl Therapeutics, detailing the development and commercialization of the lead compounds for both IPF and endometriosis-associated menstrual pain. This plan will outline critical activities and milestones, including conducting preclinical studies to demonstrate efficacy and safety, determining MOA, and evaluating pharmacokinetics (PK) and absorption, distribution, metabolism, and excretion (ADME). From there, we will be submitting an additional Phase III SBIR grant to progress from IND-enabling studies to IND-filing and Phase I clinical trials. We will work closely with regulatory agencies to ensure compliance and expedite the development process, including preparing and submitting an Investigational New Drug (IND) application. **Second**, we are actively seeking funding from various sources to support our pipeline's further development and commercialization. This includes pursuing bridge investments, non-dilutive funding like the Direct to Phase II SBIR, and securing licensing deals or other partnerships to support future manufacturing needs. **Lastly**, we are exploring other use-cases for several of our compounds and generating data specific to endometriosis-associated menstrual pain, following a similar pathway.

These additional areas in preclinical development provide additional commercial potential. Through these activities, we expect to successfully develop, test, and commercialize multiple therapeutics. Diversifying our pipeline to include multiple compounds and more than one indication for each compound ensures that our commercial future is not tied to a single success or failure. Like most start-up pharmaceutical firms, we expect the most likely path to commercial success with these compounds will be through licensing and marketing partnerships, and demonstrating safety and efficacy is the best path toward securing these agreements. This

Direct to Phase II application will have the potential to carry us into the security of a strong partnership for our novel IPF therapeutics.

C. Market, Customer, and Competition

Market Size—As of January 2024, the current U.S. market size for IPF is estimated at \$5.9 billion, with the global market projected to reach \$11.7 billion by 2031, with a compound annual growth rate (CAGR) of 7.3% over the forecast period.⁸ This growth is driven by factors such as increasing prevalence and incidence with age, the availability of premium-priced drugs, and the rapid approval of new treatments. Current projections expect this global market to dramatically grow (Figure 4).⁹

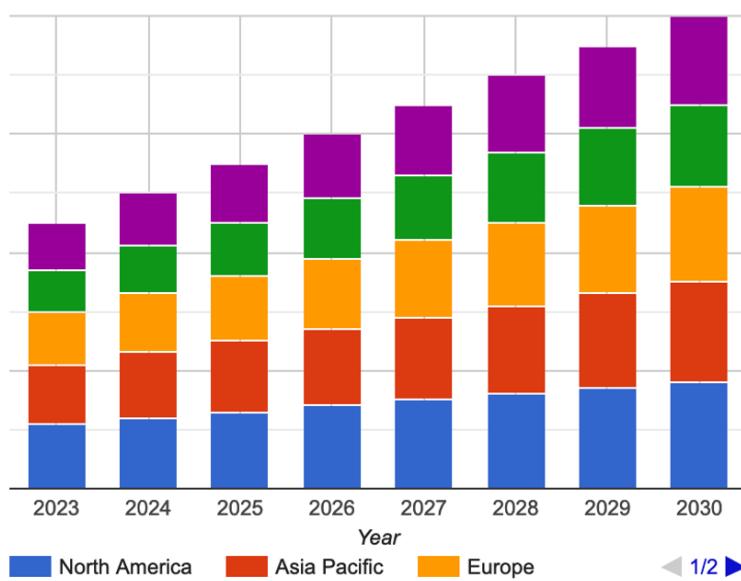


Figure 4: Global Idiopathic Pulmonary Fibrosis Market by Region

Currently, North America dominates the IPF market, thanks to its well-established healthcare infrastructure, high awareness about IPF among healthcare professionals and patients, and a strong focus on research and development.⁸ The region is home to several key pharmaceutical companies actively involved in developing and marketing IPF therapies. Favorable reimbursement policies and early adoption of novel treatments also contribute to North America's dominance in the IPF market, substantiating our current first-effort focus on establishing Maipl Therapeutics in this market.

Additionally, Asia Pacific is experiencing the fastest growth in the IPF market, driven by rapid economic development, increasing healthcare spending, and a growing geriatric population.⁸ Improved healthcare access and facilities, along with rising awareness about IPF, are leading to earlier diagnosis and better disease management

in the region. We believe targeting the Asia Pacific market may prove a sound commercialization effort.

Notably, one of the primary concerns in developing novel therapies for IPF is the lack of adequate animal models. **Thus, for its drug development, Maipl Therapeutics is using a novel genetic mouse model, IER-SftpcI73T mice, which is derived from an IPF-associated gene and spontaneously develops lung fibrosis.** This model closely mimics key aspects of human IPF, making it highly translationally relevant to the human condition. By using this model, Maipl can study the progression of lung fibrosis and evaluate the efficacy of its compounds in a context that closely resembles human IPF. We believe this will provide a better understanding of the underlying mechanisms of IPF pathogenesis, ultimately enhancing the data we can extrapolate from our next phase of research.

Customer

As Maipl Therapeutics is currently preclinical, we are sharply focused on identifying licensing opportunities to strategic partners and larger pharmaceutical companies. These partners could be interested in collaborating on the development and commercialization of our therapeutics. We believe partnerships with companies like Johnson & Johnson, AbbVie, Eli Lilly, and Boehringer Ingelheim could bring expertise, resources, and funding to support the drug's advancement through clinical trials and regulatory approval.

As the drug progresses through clinical trials, potential customers may also include investors interested in supporting the company's growth and development. These investors could include venture capital firms, private equity investors, and potentially larger pharmaceutical companies looking to acquire or continue to license the drug. There is precedent for both venture capital financing and strategic acquisitions in the IPF space.

Market Entry Challenges

Current Treatments: The standard of care for IPF includes two main FDA-approved medications: pirfenidone (sold under the brand name Esbriet) and nintedanib (sold under the brand name Ofev). These medications have been shown to slow disease progression and are often used in combination with supportive care measures such as supplemental oxygen, pulmonary rehabilitation, and management of comorbid conditions. However, they face significant shortfalls in treating patients with IPF. While these drugs can slow the decline in lung function, they

do not cure or reverse the fibrosis. The extent of their effect varies among individuals, and they do not work for everyone.

1. **Side Effects:** Both pirfenidone and nintedanib can cause side effects that may be intolerable for some patients. These can include gastrointestinal issues (such as nausea, diarrhea, and vomiting), liver enzyme abnormalities, and skin rashes.
2. **Cost:** These medications can be expensive, exceeding \$350 in monthly prescription costs, which may limit access for some patients, especially in regions without adequate insurance coverage or healthcare support.
3. **Progression of Disease:** Despite treatment, IPF can still progress in some patients, highlighting the need for more effective therapies.
4. **Limited Options:** Currently, pirfenidone and nintedanib are the only FDA-approved medications for IPF, leaving a gap in treatment options for patients who do not respond well to these drugs or experience intolerable side effects. No other drugs have been FDA approved for IPF since 2014.

Impact of PGF2 α Target: Maipl Therapeutics chose to explore the PGF2 α pathway for treating IPF because of its distinct role in promoting fibrosis in the lung independent of traditional pathways like TGF- β or fibroblast growth factor receptor.¹⁰ Research has shown that PGF2 α is abundant in the bronchoalveolar lavage fluid of IPF patients and is associated with disease severity and prognosis. Additionally, preclinical studies have demonstrated that PGF2 α induces pulmonary fibrosis independently of TGF β , a well-known pro-fibrotic factor. These findings suggest that targeting the PGF2 α pathway could offer a novel and potentially more effective approach to treating IPF compared to targeting traditional pathways. Moreover, clinical evidence shows its abundance in bronchoalveolar lavage fluid (BALF) of IPF subjects, with significant association of plasma concentrations of its metabolite and IPF disease severity.¹¹

PGF2 α has been established as a key player in promoting fibrosis in the lung: preclinical studies demonstrate that PGF2 α induces pulmonary fibrosis by promoting fibroblast proliferation and collagen production via PGF2 α receptor (FP) activation, reprogramming fibroblasts to an “inflammatory/transitional” cell state.¹⁰ Mouse knockout studies in disease models further validate this, showing that loss of the PGF2 α receptor, FP, reduces pulmonary fibrosis.¹²

Unfortunately, there are no drugs targeting FP currently on the market. Previous efforts from Bayer, Merck Sereno, and Alcon have failed to generate results showing strong pharmacological potential.⁵ However, Maipl Therapeutics has developed a highly selective, potent FP antagonist with excellent oral pharmacokinetics and safety profile, making it a promising candidate for clinical development. Preliminary comparison studies have been conducted to these previously developed FP antagonists; however, Maipl Therapeutics’ compounds show superior potency, specificity, and efficacy. The company has in-licensed a series of FP antagonist compounds and is developing two of them for IPF, namely MA-4586 and MA-4604. These compounds have shown high potency and selectivity for FP in preclinical studies.

Maipl’s FP antagonist drug program has achieved early drug discovery milestones and is ready to initiate development for IPF, potentially leading to IND-enabling studies, IND submission, and Phase 1 clinical trials. Its innovative approach not only targets IPF but also opens avenues for other indications where PGF2 α plays a significant role, such as endometriosis and preterm birth.

Competition— Several novel compounds are currently under investigation in clinical trials for IPF, potentially posing competition to Maipl Therapeutics (**Table 1**). While these therapeutics show potential in treating IPF, focusing on PGF2 α as a target may provide a more optimal approach due to the robust evidence supporting its role in fibrosis and the validation of the FP receptor as a drug target for IPF; Maipl Therapeutics, with its highly selective and potent FP antagonist, may have a competitive advantage in this regard, especially considering the limitations and challenges faced by other compounds in clinical development.

Moreover, Maipl Therapeutics aims to establish itself as a pioneer in treating IPF through a novel, more effective target. Led by Dr. Yong Yue, former research lead at Ferring Pharmaceuticals, Maipl leverages its scientific expertise and collaboration with Ferring to build credibility and access resources. Our marketing strategy focuses on highlighting this unique approach, scientific leadership, and partnership with Ferring to attract investors and establish thought leadership in the field. With a clear regulatory strategy and market research insights, Maipl aims to transition to clinical development and address unmet medical needs in IPF treatment at an appropriate time.

Our established network will enable us to access resources, expertise, and existing relationships for future research and commercialization efforts. We believe this will facilitate Maipl Therapeutics’ initiatives in

building a strong foundation for future commercialization and success in the treatment of IPF.

Competitive Advantages—To date, there is no other PGF2 α receptor antagonist that is being developed to treat IPF. Furthermore, to the best of our knowledge, there are currently no clinically available small molecule antagonists for FP, making Maipl's compound series the sole FP antagonists in development. This poses Maipl Therapeutics at a competitive edge to provide treatment through a novel target. However, there are other clinical organizations examining other potential targets for pharmaceutical development. These drugs and their targets are listed below:

Monoclonal antibodies targeting specific proteins:

Pamrevlumab (FG-3019) by FibroGen

Recombinant proteins or peptides:

PRM-151 by Promedior, Inc.

Small molecule inhibitors:

GLPG1690 by Galapagos NV

BI 1015550 by Boehringer Ingelheim

PBI-4050 by Prometic Life Sciences Inc.

PLN-74809 by Pellino3 Pharma

BMS-986020 by Bristol-Myers Squibb

TD139 by Novartis

INS018_055 by Insilico

Table 1 provides additional descriptions.

Table 1. Potential Competing Technologies

Potential Competitor	Product Description
Pamrevlumab	A monoclonal antibody that inhibits connective tissue growth factor (CTGF), which plays a key role in fibrosis by promoting extracellular matrix production.
PRM-151	A recombinant form of pentraxin-2, which modulates macrophage activity and reduces fibrosis by inhibiting the transformation of fibroblasts into myofibroblasts.
GLPG1690	A selective autotaxin inhibitor that reduces lysophosphatidic acid (LPA) levels, which are implicated in fibrosis and inflammation.
BI 1015550	A small molecule inhibitor of phosphodiesterase 4B (PDE4B), an enzyme involved in inflammation and fibrosis.
PBI-4050	A synthetic analog of a molecule called FBLN3, which has anti-inflammatory and antifibrotic effects.
PLN-74809	A small molecule inhibitor targeting lysophosphatidic acid receptor 1 (LPA1), which is involved in fibrosis-related pathways.
BMS-986020	A lysophosphatidic acid receptor 1 (LPA1) antagonist that reduces fibrosis and inflammation.
TD-139	A galectin-3 inhibitor, targeting a protein involved in fibrosis and inflammation.
INS018_055	RAF2- and NCK-interacting kinase (TNIK) as an anti-fibrotic target.

D. Intellectual Property (IP) Protection

To protect our intellectual property (IP) resulting from our IPF therapeutic innovation, we are employing several strategies: We maintain strict confidentiality around key processes or formulations as trade secrets and implement measures such as non-disclosure agreements (NDAs) to help safeguard our IP. Additionally, we are considering entering into licensing agreements with other companies for the use of our IP, allowing us to generate revenue while maintaining control over our innovations. Enforcement of our IP rights is crucial, and we work closely with legal counsel to monitor and take legal action against any infringement. These strategies will help us establish and maintain a strong IP portfolio, providing us with a competitive advantage and barriers to entry for others in the IPF therapeutic market. Additionally, Maipl Therapeutics' investigators will assert copyright in scientific and technical articles based on data produced under the grant where necessary, but we will also make every effort to keep technologies developed as a result of this research project widely available and accessible to the research community. If additional patents are filed and the technology licensed, we will only seek exclusivity in cases where this approach is determined to be the best route for successful development of the

technology for public use and benefit.

Licensed IP: The following patents have been filed by Ferring Pharmaceuticals on the chemical composition of the matter and their salt forms. These patients, and additional filings on selective FP antagonists, are licensed exclusively to Maipl Therapeutics for all uses worldwide.

Small Molecule Prostaglandin F Receptor Antagonists

Ferring Patent Reference	Country	Status	Filed Date	Application Number
P3055DK01PRI	Denmark	Application	2023-09-19	PA 2023 30220
P3055EP01PRI	European Patent	Application	2023-09-07	EP 23196026.1
P3055US02PRI	United States	Application	2023-07-26	USSN 63/529,092

Salt Form Patent

Invention ID	Invention Reference	Invention	Status
81172314	P3095	Specific salt form with improved solubility	Filed

New and/or Arising IP: Possible areas of development at Maipl Therapeutics for generating additional IP may include 1) formulation, 2) indication, secondary endpoints, 3) dosing regimen, and 4) patient sub-populations.

A joint patent committee (the “JPC”) between Maipl and Ferring has the responsibility to (a) review and discuss the status of the Licensed Patents and Arising Patents; (b) discuss any material Arising IP that has arisen since the prior meeting of the JPC; (c) discuss and determine whether patent applications should be filed based on Arising Know-How, including in which countries such patent applications would be filed; (d) discuss any open enforcement or defense actions; and (e) other IP matters.

Freedom to operate (FTO): An initial FTO search focus on identifying PCT, US, and EPO patents and patent applications is planned. The initial FTO search will focus on the compounds per se (such as the 6 main compounds), with follow up searches on other aspects of the product (e.g., on formulations) carried out in the future. Towards this end, a European partial search report was issued January 2, 2024; further search request filed and awaiting issuance of complete search report. We are waiting for the issuance of search report from Danish Patent Office.

E. Finance Plan

Financing—Maipl Therapeutics is exploring additional fundraising efforts and expects the key deliverables funded via this grant application, namely validation of our IPF MA-4586 and MA-4604 compounds, will further de-risk the development program and will enable the company to raise a combination of non-dilutive and private financing. Published PoC studies have established FP as a promising drug target for IPF and Maipl Therapeutics has developed a series of highly potent and selective FP antagonists with excellent oral PK and DMPK/ADME properties preferable for an oral drug. These studies will enable Maipl Therapeutics to move to CMC, IND-enabling (GLP) studies, IND-filing and phase I clinical trial for the Phase III SBIR phase, moving forward our plans for commercialization.

To note, these compounds have a strong foundation in research, with six years and roughly \$7 million spent by Ferring Pharmaceuticals before transferring the program to Maipl Therapeutics. This extensive background research not only underscores the scientific validity of these compounds but also highlights their potential as effective candidates for further study. Maipl’s focus on developing these compounds for treating IPF and other indications, such as endometriosis-associated menstrual pain, builds upon a robust foundation of idea generation, target identification, target validation, target-to-lead, and lead optimization, including *in vivo* efficacy in a non-IPF model.

Exit Strategy—Maipl Therapeutics’ feels confident that its revolutionary therapeutics for IPF position it to be highly attractive for acquisition by several key players in the pharmaceutical industry, including AbbVie, Eli Lilly, Johnson & Johnson, Boehringer Ingelheim, and Genentech:

AbbVie’s active internal discovery program in IPF is focused on developing novel therapies for the treatment of this debilitating lung disease. AbbVie has been conducting research to identify and validate new targets and

pathways involved in the pathogenesis of IPF, with the goal of developing innovative treatments that can slow or halt the progression of the disease. The company is leveraging its expertise in drug discovery and development to advance promising drug candidates through preclinical and clinical development, with the ultimate aim of bringing new therapies to patients with IPF. AbbVie's commitment to advancing research in IPF underscores the importance of addressing this unmet medical need and improving outcomes for patients with this progressive disease. This makes it a likely contender for acquiring smaller pre-clinical stage companies focused in this therapeutic area like Maipl Therapeutics. In 2022, AbbVie acquired UK-based biotechnology company DJS Antibodies for \$255 million that was in a preclinical development stage of a drug DJS-002 targeting LPAR1 for IPF.

Johnson & Johnson's focus on pulmonary hypertension therapeutics suggests that the company may have a strategic interest in expanding its portfolio to include therapies for pulmonary hypertension, a condition that shares some similarities with IPF in terms of lung function and respiratory difficulties. By leveraging its expertise and resources in the pulmonary hypertension therapeutics area, Johnson & Johnson may be well-positioned to develop innovative treatments for IPF that target similar pathways or mechanisms involved in both conditions. This adjacency underscores the potential synergies between pulmonary hypertension and IPF therapeutics, making our therapeutic an attractive opportunity for Johnson & Johnson to acquire.

Additionally, **Boehringer Ingelheim** and **Genentech** are expected to face patent expirations on their IPF drugs: nintedanib (Ofev) is heading for patent expiry in 2029, and pirfenidone (Esbriet), filed in the U.S. in 2014, was granted seven years of orphan drug exclusivity, which expired in 2021.^{14,15} However, Genentech still holds 19 Orange Book-listed patents purportedly covering Esbriet issued between 2009 and 2014 and set to expire between 2026 and 2033. Acquiring Maipl's innovative compounds could then be a strategic move for Boehringer Ingelheim and Genentech. By acquiring Maipl, either company could replenish their pipelines with new, potentially more effective therapies for IPF. This could help them maintain a competitive edge in the market and continue to meet the needs of patients with IPF. Additionally, the novel mechanism of action of Maipl's compounds could offer a differentiated treatment option compared to existing therapies, potentially allowing Boehringer Ingelheim and Genentech to capture a larger market share and maintain themselves as leaders in the IPF space.

Maipl has been selected to join JLABS (Johnson & Johnson Labs), a life science incubator in San Diego to expand its business strategy and network. This relationship could open the potential develop new partnerships with the goal of licensing out its compounds to maximize their impact in the market.

F. Production and Marketing Plan

Production—Maipl Therapeutics plans to partner with HD BioSciences, LabCorp, and TCG GreenChem as the CDMO/CROs for certain aspects of its research. In addition, Pearl Pathways will serve as our consulting regulatory and quality compliance partner. As we progress through the Direct to Phase II study, this will lay the framework for Chemistry, Manufacturing, and Controls (CMC), IND-enabling (GLP) studies, IND filing, and a phase I clinical trial for this novel IPF treatment. Our next development strategy involves licensing the compounds to a qualified biopharmaceutical company for next steps. This partner would need to have the capability to conduct clinical Phase II/III studies, handle manufacturing, obtain worldwide registration, oversee commercial launch, and manage subsequent promotion. This approach allows Maipl to leverage the expertise and resources of a larger partner for the later stages of development and commercialization.

Marketing— We plan to leverage Maipl's relationship with Ferring Pharmaceuticals, as well as Dr. Yue's (CEO) relationship with Eli Lilly and Boehringer Ingelheim (previously worked in these companies) to establish credibility and access key networks. For example, we will focus on building relationships with key opinion leaders and experts in the field, as well as engaging with patient advocacy groups to raise awareness about our research and potential therapies. Additionally, we will incorporate dedicated business development team members into these efforts to help facilitate discussions with potential partners or acquirers, demonstrating the value of their innovative compounds and the potential for collaboration or acquisition. During this time, Maipl's leadership will attend relevant conferences (i.e., previously attended conferences include SF BIO, JP Morgan healthcare conference, Women's Health Innovation Summit, Endocrine Society conference, Pulmonary Fibrosis Foundation Conference, and more) and events to showcase the potential of its compounds and network with potential stakeholders in the industry.

G. Revenue Stream

General Revenue Estimates and Strategy—For the IPF indication, after successfully completing the Phase II

SBIR project, Maipl intends to apply for a Phase III SBIR grant (and/or utilize funds raised through other funding mechanisms like Seed/Series A funding) to complete IND-enabling studies, IND filing and Phase I studies. Thereafter, Maipl plans to license its lead compounds to a biopharmaceutical company capable of completing the clinical development program to successfully launch the product. Maipl does not expect any revenue related to commercialization until a licensing or other structured transaction is made with a strategic partner, which is anticipated to occur once the Phase I data becomes available. Additionally, Maipl may consider licensing the compound at the time of IND submission if a suitable opportunity arises.

Revenue Projections—It is challenging to ascertain strict revenue projections without some clinical data in hand, but we anticipate a successful completion of our Pre-Seed/Seed funding round of \$4-5M and expect to obtain successful data that would allow us to complete a next round of financing of \$20M along with two anticipated SBIRs (**Table 2**). If Phase 1 trial results are positive, we expect to partner this asset thereafter in late 2028.

Table 2: Current and 5-year Projections

Financial Forecast (USD)	2024 Forecast	2025 Forecast	2026 Forecast	2027 Forecast	2028 Forecast
Revenue					
Upfront & Milestone	\$ -	\$ -	\$ -	\$ 20,000,000	\$ 50,000,000
Partner Sales Milestone and Royalties	\$ -	\$ -	\$ -	\$ -	\$ -
Product Sales by Maipl	\$ -	\$ -	\$ -	\$ -	\$ -
Total Revenue	\$ -	\$ -	\$ -	\$ 20,000,000	\$ 50,000,000
Cost of Revenue					
Upfront & Milestone to Ferring	\$ -	\$ -	\$ -	\$ 750,000	\$ 12,000,000
Sales Milestone and Royalties to Ferring	\$ -	\$ -	\$ -	\$ -	\$ -
Cost of Sales by Maipl	\$ -	\$ -	\$ -	\$ -	\$ -
Total Cost	\$ -	\$ -	\$ -	\$ 750,000	\$ 12,000,000
Gross Profit	\$ -	\$ -	\$ -	\$ 19,250,000	\$ 38,000,000
Expenses					
R&D Personnel	\$ 1,090,000	\$ 1,140,000	\$ 1,710,000	\$ 1,881,000	\$ 2,069,100
R&D Lab	\$ 1,250,000	\$ 1,375,000	\$ 1,512,500	\$ 1,663,750	\$ 275,000
R&D CRO and External	\$ 1,640,000	\$ 4,610,000	\$ 18,500,000	\$ 20,350,000	\$ 22,385,000
General and Admin	\$ 80,000	\$ 100,000	\$ 110,000	\$ 121,000	\$ 133,100
Legal	\$ 150,000	\$ 165,000	\$ 181,500	\$ 199,650	\$ 219,615
Total Expense	\$ 4,210,000	\$ 7,390,000	\$ 22,014,000	\$ 24,215,400	\$ 25,081,815
Profit / Loss	\$ (4,210,000)	\$ (7,390,000)	\$ (22,014,000)	\$ (4,965,400)	\$ 12,918,185

COMMERCIALIZATION PLAN REFERENCES

1. Wolters PJ, Collard HR, Jones KD. Pathogenesis of Idiopathic Pulmonary Fibrosis. *Annu Rev Pathol*. 2014;9:157–179. PMCID: PMC4116429
2. Association AL. Why We Need Idiopathic Pulmonary Fibrosis Research Now More Than Ever [Internet]. [cited 2024 Mar 9]. Available from: <https://www.lung.org/blog/why-we-need-ipf-research>
3. White ES, Thomas M, Stowasser S, Tetzlaff K. Challenges for Clinical Drug Development in Pulmonary Fibrosis. *Front Pharmacol*. 2022 Jan 31;13:823085.
4. Moor CC, Mostard RLM, Grutters JC, Bresser P, Aerts JGJV, Dirksen CD, Kimman ML, Wijsenbeek MS. Patient expectations, experiences and satisfaction with nintedanib and pirfenidone in idiopathic pulmonary fibrosis: a quantitative study. *Respiratory Research*. 2020 Jul 23;21(1):196.
5. Beck H, Thaler T, Meibom D, Meininghaus M, Jörißen H, Dietz L, Terjung C, Bairlein M, Von Bühler CJ, Anlauf S, Fürstner C, Stellfeld T, Schneider D, Gericke KM, Buyck T, Lovis K, Münster U, Anlahr J, Kersten E, Levilain G, Marossek V, Kast R. Potent and Selective Human Prostaglandin F (FP) Receptor Antagonist

- (BAY-6672) for the Treatment of Idiopathic Pulmonary Fibrosis (IPF). *J Med Chem.* 2020 Oct 22;63(20):11639–11662.
6. Vancheri C, Bois RM du. A progression-free end-point for idiopathic pulmonary fibrosis trials: lessons from cancer. *European Respiratory Journal.* European Respiratory Society; 2013 Feb 1;41(2):262–269. PMID: 22903965
 7. Hamshaw I, Straube A, Stark R, Baxter L, Alam MT, Wever WJ, Yin J, Yue Y, Pinton P, Sen A, Ferguson GD, Blanks AM. PGF2 α induces a pro-labour phenotypical switch in human myometrial cells that can be inhibited with PGF2 α receptor antagonists. *Front Pharmacol.* 2023 Dec 14;14:1285779. PMCID: PMC10752971
 8. Global Idiopathic Pulmonary Fibrosis (IPF) Market Analysis Report 2023-2029: Enhancing R&D Operations for Development of Novel Treatments and Improving Access to Treatment - ResearchAndMarkets.com [Internet]. 2023 [cited 2024 Mar 9]. Available from: <https://www.businesswire.com/news/home/20231214483693/en/Global-Idiopathic-Pulmonary-Fibrosis-IPF-Market-Analysis-Report-2023-2029-Enhancing-RD-Operations-for-Development-of-Novel-Treatments-and-Improving-Access-to-Treatment---ResearchAndMarkets.com>
 9. Global Idiopathic Pulmonary Fibrosis Market Size and Forecast to 2030 [Internet]. [cited 2024 Mar 9]. Available from: <https://www.skyquestt.com/report/idiopathic-pulmonary-fibrosis-market>
 10. Li K, Zhao J, Wang M, Niu L, Wang Y, Li Y, Zheng Y. The Roles of Various Prostaglandins in Fibrosis: A Review. *Biomolecules.* 2021 May 24;11(6):789. PMCID: PMC8225152
 11. Vantaggiato L, Shaba E, Cameli P, Bergantini L, d'Alessandro M, Carleo A, Montuori G, Bini L, Bargagli E, Landi C. BAL Proteomic Signature of Lung Adenocarcinoma in IPF Patients and Its Transposition in Serum Samples for Less Invasive Diagnostic Procedures. *International Journal of Molecular Sciences.* Multidisciplinary Digital Publishing Institute; 2023 Jan;24(2):925.
 12. Rodriguez LR, Tang SY, Barboza WR, Murthy A, Tomer Y, Cai TQ, Iyer S, Chavez K, Das US, Ghosh S, Dimopoulos T, Babu A, Connelly C, FitzGerald GA, Beers MF. Disruption of Prostaglandin F2 α Receptor Signaling Attenuates Fibrotic Remodeling and Alters Fibroblast Population Dynamics in A Preclinical Murine Model of Idiopathic Pulmonary Fibrosis. *bioRxiv.* 2023 Jun 7;2023.06.07.543956. PMCID: PMC10274762
 13. Priyan V. AbbVie to bolster neuroscience pipeline with Mitokinin acquisition [Internet]. *Pharmaceutical Technology.* 2023 [cited 2024 Mar 9]. Available from: <https://www.pharmaceutical-technology.com/news/abbvie-mitokinin-acquisition/>
 14. Seeking Ofev successor, Boehringer takes PDE4B drug into phase 3 [Internet]. *pharmaphorum.* [cited 2024 Mar 9]. Available from: <https://pharmaphorum.com/news/seeking-ofev-successor-boehringer-takes-pde4b-drug-into-phase-3>
 15. Genentech v. Sandoz: Patents claiming methods of managing side effects found invalid or not infringed [Internet]. *Patently-O.* 2022 [cited 2024 Mar 9]. Available from: <https://patentlyo.com/patent/2022/12/genentech-claiming-infringed.html>

PHS 398 Cover Page Supplement

1. Vertebrate Animals Section

Are vertebrate animals euthanized? Yes No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

Yes No

If "No" to AVMA guidelines, describe method and provide scientific justification

.....

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

Yes No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period *Anticipated Amount (\$) *Source(s)

3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? Yes No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Human Fetal Tissue Section

*Does the proposed project involve human fetal tissue obtained from elective abortions? Yes No

If "yes" then provide the HFT Compliance Assurance

If "yes" then provide the HFT Sample IRB Consent Form

5. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: Yes No

If the answer is "Yes" then please answer the following:

*Previously Reported: Yes No

6. Change of Investigator/Change of Institution Section

Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

Change of Grantee Institution

*Name of former institution:

PHS 398 Research Plan

Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	
Research Plan Section	
2. Specific Aims	SA-MaipI-V4.1.pdf
3. Research Strategy*	RS-MaipI-V4.1.pdf
4. Progress Report Publication List	
Other Research Plan Section	
5. Vertebrate Animals	Vertebrate_Animals-MaipI-2024.03.26.pdf
6. Select Agent Research	
7. Multiple PD/PI Leadership Plan	
8. Consortium/Contractual Arrangements	MaipI_SOW_LOI_merged_2024.03.26.pdf
9. Letters of Support	LOS_Merged_20240326.pdf
10. Resource Sharing Plan(s)	RSP-MaipI-2024.03.26.pdf
11. Other Plan(s)	DMSP-MaipI-2024.03.26.pdf
12. Authentication of Key Biological and/or Chemical Resources	Authentication_MaipI_2024.03.26.pdf
Appendix	
13. Appendix	

SPECIFIC AIMS

Maipl Therapeutics (Maipl) specializes in addressing medical conditions related to inflammation, pain, and fibrosis. We are developing first-in-class medications to treat idiopathic pulmonary fibrosis (IPF) by taking advantage of a highly novel target, the prostaglandin F2 alpha (PGF2 α) receptor, FP.

Problem and Significance: IPF is an interstitial lung disease of unknown etiology that is irreversible, chronic, and progressive.^{1,2} Approximately 140,000 Americans live with IPF and ~40,000-50,000 new cases are diagnosed each year.³ IPF prognosis is similar to that of many types of cancers, with worse survival prognosis and increasing incidence worldwide.^{4,5} According to a study of Medicare beneficiaries, medical costs to the U.S. healthcare system attributed to IPF (excluding medications) are estimated at \$2B.⁶

Unmet Need: IPF symptoms progress from cough and dyspnea (out of breath sensation) to end-stage respiratory failure. Apart from lung transplantation, currently there is no curative treatment for IPF primarily due to poor understanding of disease etiology involving a number of factors like cellular proliferation, interstitial inflammation, fibrosis, or a combination of these within the alveolar wall without full understanding of underlying causes. There are currently two FDA-approved antifibrotic drugs, pirfenidone (transforming growth factor- β [TGF- β] inhibitor) and nintedanib (tyrosine kinase inhibitor) that are effective in slowing disease progression and are the standard of care (SoC) for IPF.⁷⁻⁹ However, these drugs have severe side effects limiting sustainability, are expensive, and some IPF patients are non-responsive.¹⁰ Since 2014, no new drug has been approved for IPF. There are a number of molecules against various targets that are currently being developed and/or are in clinical trials, with some positive results for IPF.¹¹⁻¹³ However, given the complexity of the IPF pathogenic process, and the heterogeneous patient population, there is a substantial unmet need for drugs targeting various pathways, as combination therapies are likely to be most effective, as is the case with most respiratory diseases.

Proposed Solution: The majority of drugs currently in development for IPF target a TGF β -dependent pathway. While TGF β is a critical mediator of fibrosis in IPF, additional **TGF β -independent pathways** have a key role in fibrogenesis but there are few drugs targeting TGF β -independent fibrotic pathways. Maipl Therapeutics is targeting the PGF2 α pathway via its receptor (FP) that has been clearly implicated as a TGF β -independent signaling hub; a promising new drug target for IPF.¹⁴⁻¹⁶ We have developed a highly selective, potent FP antagonist with preclinical studies indicating promising oral PK, *in vitro* safety profiles and *in vivo* efficacy (non-IPF model). The objective of this Direct to Phase II SBIR proposal is to evaluate the *in vivo* efficacy specifically in IPF disease models, determine the mechanism of action (MoA) of PGF2 α /FP in IPF disease pathophysiology, and assess *in vivo* (non-GLP) safety of our lead candidates, MA-4586 and MA-4604. Both MA-4604 and MA-4586 are composed of 2-phenyl-quinoline scaffold connecting to branched unique hydrocarbon moieties. Each branched moiety has a unique side chain, carbon-carbon linkage for MA-4604 and oxime linkage for MA-4586, which contribute to favorable high potency and DMPK profiles. Proposed Specific Aims include:

Aim 1. Determine the anti-fibrosis efficacy of lead candidates in two IPF disease models. In preparation for IND-enabling studies, we will use two well-established preclinical IPF disease models to determine the efficacy of MA-4586 and MA-4604 (vs nintedanib) - the bleomycin (intra-tracheal)-induced pulmonary fibrosis mouse (C57BL/6) model and a tamoxifem-induced spontaneous lung fibrosis genetic mouse model, I^{ER}-Sftpc^{I^{73T}}. **Milestone:** Determine ability of the tested compounds to limit significant decrease in body weight, development of lung fibrosis, inflammation, and mortality rate (I^{ER}-Sftpc^{I^{73T}} only).

Aim 2. Determine changes in alveolar niche crosstalk and fibrotic signaling following FP inhibition. This aim will enable determination of which cellular targets our candidates (MA-4586 and MA-4604) hit, what process gets altered, and how this ultimately impacts the effect size of these drugs. We will distinguish the transcriptional signatures of lung cell populations and define fibrotic, alveolar, and regenerative niche dynamics after FP antagonist and nintedanib interventions. These studies will define the MoA of MA-4586 and MA-4604 in IPF disease pathophysiology in support of an IND submission. **Milestones:** (1) Determine changes in population dynamics, cell crosstalk, and cell lineage signatures, (2) Identify alterations in spatial niches in the lung associated with profibrotic populations that may be involved in fibrosis.

Aim 3. Establish non-GLP preclinical safety in two species. Following exploratory PK and formulation optimization, we will conduct dose range finding and repeated dose toxicology studies in rodent (rat) and non-rodent (dog) species in preparation for IND-enabling GLP studies. **Milestones:** (1) Optimize formulation and dose, (2) Establish mean tolerable dose, (3) Determine dose level for no observed (adverse) effects (NOEL and NOAEL) to inform selection of the first dose and dose escalation schema in GLP studies.

Impact and Future Work: The proposed studies lay the framework for Chemistry, Manufacturing, and Controls (CMC), IND-enabling (GLP) studies, IND filing, and a phase I clinical trial for this novel IPF treatment.

SIGNIFICANCE—*Maip Therapeutics is developing a first-in-class drug for IPF against a highly novel target, prostaglandin F2 alpha (PGF2 α) receptor (FP), that is unique to any other drugs under development for IPF.*

Idiopathic pulmonary fibrosis (IPF) is an irreversible, chronic, progressive, degenerative age-related pulmonary condition of unknown etiology. Current IPF prognosis is similar to that of many types of cancers, with worse survival prognosis than all cancers except lung and pancreas, and increasing incidence worldwide^{4,5} (currently 11-17/100,000).^{17,18} Apart from lung transplantation, there are no curative treatments for IPF primarily due to poor understanding of disease etiology involving a number of factors like cellular proliferation, interstitial inflammation, fibrosis, or a combination of these within the alveolar wall without any underlying cause. The current FDA approved standard of care (SoC), single drug anti-fibrotic therapies pirfenidone and nintedanib, only slow the deterioration in pulmonary function.¹⁹⁻²¹ In addition, real world experience has repeatedly demonstrated that both these therapies are fraught with debilitating side effects that occur in a significant portion of patients. These side effects, including GI intolerance, often require discontinuation of therapy or engagement of a cumbersome mitigation/management protocol that includes dose reductions.¹⁴⁻¹⁷ No drug has been approved for IPF since 2014 and **an effective new IPF therapeutic option is a significant unmet need** for this disease

There are many molecules against various targets that are currently being developed and/or are in clinical trials with some positive results for IPF. However, given the complexity of the pathogenic process and the heterogeneous patient population, investigating drugs targeting various pathways is required to ensure multiple therapeutic target options are available. A combination of multi-target therapies is likely to be more effective, as is already the case with most respiratory chronic diseases and lung cancer.

Pathophysiology and Etiology of IPF: The pathophysiology of IPF involves the destruction of normal lung architecture along with inflammation and fibrosis. While the role of fibrosis is now well-established in IPF, inflammation remains controversial primarily due to the failure of multiple anti-inflammatory therapies as IPF treatments.^{22,23} Although the cause of IPF is largely unknown, in recent years several factors like genetic mutations (mutations in MUC5B)²⁴⁻²⁶ in genes encoding for surfactant protein C, SF-C²⁷⁻²⁹ and telomerase reverse transcriptase, TERT,^{30,31} external/environmental factors like smoking,³²⁻³⁴ exposure to occupational irritants and infections like EBV, CMV, HHV-7/8,^{35,36} and SARS-Co-V-2,³⁷ and premature aging have been identified as predisposing factors that increase the risk of developing IPF. The sequence of IPF pathogenesis can be subdivided into three pathophysiological stages (Fig. 1):³⁸

- 1) The predisposition stage is where genetic mutations, external factors, infection or other unknown factors lead to epithelium dysfunction. Not all individuals in this stage necessarily develop clinically relevant disease which depends on the degree and duration of exposure to these factors.
- 2) The initiation stage involves epithelial cell dysfunction by molecular mediators such as endoplasmic reticulum (ER) stress, excessive TGF- β activation, and growth factor, chemokine, or ligand secretion (e.g., Wnt, BMP4) that lead to fibroblast recruitment/activation/differentiation causing lung epithelial cells to undergo epithelial-to-mesenchymal transition (EMT).
- 3) The progression stage involves release of abnormal types and quantities of extracellular matrix proteins by mesenchymal cells that remodel and scar the lung leading to progressive fibrosis and disruption of alveolar architecture.

The IPF lung is characterized by the pathognomonic histology of Usual Interstitial Pneumonitis (UIP) marked by temporally and spatially heterogeneous areas of fibroblast/myofibroblast accumulation coupled with extracellular matrix deposition, disrupted alveolar architecture, and subpleural honeycombing.³⁹⁻⁴¹ For IPF patients, the progression of symptoms is marked from cough and dyspnea (out of breath sensation) to end-stage respiratory failure leading to either lung-transplantation or death within 3-5 years of diagnosis.^{18,42}

IPF drugs—Present and Future:

At present two anti-fibrotic drugs, pirfenidone and nintedanib, approved by the FDA in 2014, are the current SoC for IPF that slow down functional decline.⁷⁻⁹ Pirfenidone is a modified pyridine small molecule with antifibrotic, anti-inflammatory, and antioxidant properties that inhibit TGF β as well

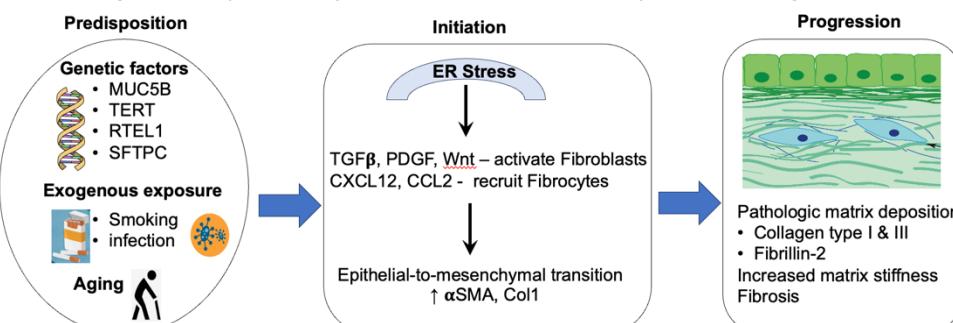


Figure 1. Pathophysiological stages of IPF. MUC5B: Mucin 5B; RTEL1: regulator of telomere length 1; SFTPC: surfactant protein C; TERT: telomerase reverse transcriptase; TGF β : transforming growth factor β ; PDGF: Platelet-derived growth factor; α SMA: alpha smooth muscle actin; Col1 – collagen 1

as block the production of inflammatory cytokines such as tumor necrosis factor alpha (TNF α), interleukin-1 (IL-1), IL-4, and IL-13. Nintedanib is a tyrosine kinase inhibitor that specifically targets platelet derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and vascular endothelial growth factor receptor (VEGFR). Both pirfenidone and nintedanib are disease-modifying drugs providing an effective therapeutic option for IPF. However, due to the complexity of the disease, response to these antifibrotic treatments is heterogeneous (some patients do not respond) and are limited by side effects. This necessitates the need to establish novel therapeutic approaches, and development of new drugs against unique targets. Moreover, in both preclinical models and clinical practice, neither pirfenidone nor nintedanib completely attenuate either fibrotic endpoints or loss of lung function, suggesting contributing roles of additional pathways in fibrogenesis.^{19,20,43,44}

Several investigational drugs for the treatment of IPF are in ongoing and recently completed clinical trials.^{13,45} These candidates target epithelial cell injury and death or aberrant wound healing responses, including immune system dysregulation, fibroblast accumulation, myofibroblast differentiation, and extracellular matrix deposition and stiffening.^{11,12} However, there are very few drugs that target the TGF β -independent fibrotic pathway or pathologic fibroblast subsets. Aim 2 focuses on defining the underlying pathways and fibroblast subtypes in IPF and, if successful in preclinical models, could provide equipoise for combination therapy.

Role of PGF2 α in fibrosis and IPF – Proof of concept (PoC) and validation of FP as a drug target:

Years of research have established that PGF2 α promotes lung fibrosis independent of TGF β . Clinical evidence includes (i) PGF2 α abundance in bronchoalveolar lavage fluid (BALF) of IPF patients,¹⁴ and (ii) significant association of plasma PGF2 α metabolite (15-keto-13,14-dihydro PGF2 α) levels and IPF disease severity and prognosis.¹⁵

Mechanism of Action (MoA) preclinical studies indicate that (i) PGF2 α induces pulmonary fibrosis independently of TGF- β by promoting fibroblast proliferation and collagen production via FP activation,¹⁴ and (ii) PGF2 α / FP signaling reprograms adventitial fibroblasts to an “inflammatory/transitional” cell state leading to fibrosis.¹⁶

PoC mouse knockout studies in disease models

indicate that Loss of FP (FP knockout, *Ptgfr*^{-/-}) attenuates pulmonary fibrosis in (i) bleomycin-induced pulmonary fibrosis model (Fig. 2),¹⁴ and (ii) a genetic model, *I^{ER}-Sftpc^{173T}* (Fig. 3A),¹⁶ (*I^{ER}-Sftpc^{173T}* is a spontaneous epithelial-driven lung fibrosis mouse model that recapitulates the pathological and clinical features of human IPF⁴⁶). (iii) Knockout of FP in *I^{ER}-Sftpc^{173T}* models significantly increases survival rate (Fig. 3B).¹⁶

Proof of Concept (PoC) pharmacology studies

indicate that (i) A selective FP antagonist, BAY6672, developed by Bayer showed anti-inflammatory and antifibrotic effects in a silica-induced lung fibrosis mouse model,⁴⁷ and (ii) PGF2 α inhibition by BAY6672 and OBE022 (another selective FP antagonist developed by Obseva) blocked fibrotic endpoints and decreased lung fibrosis similar to nintedanib in bleomycin-induced pulmonary fibrosis model (Fig. 4).¹⁶ The above studies clearly establish the role of PGF2 α signaling in the pathophysiology of IPF and validate FP as a drug target for IPF. **Unfortunately, to date there are no drugs targeting FP.**

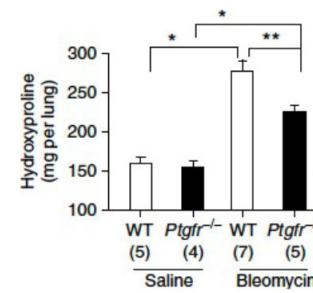


Figure 2. Effect of FP knockout (Ptgr^{-/-}) in bleomycin-induced pulmonary fibrosis mouse model. Nat Med. 2009 Dec; 15(12): 1426-30.

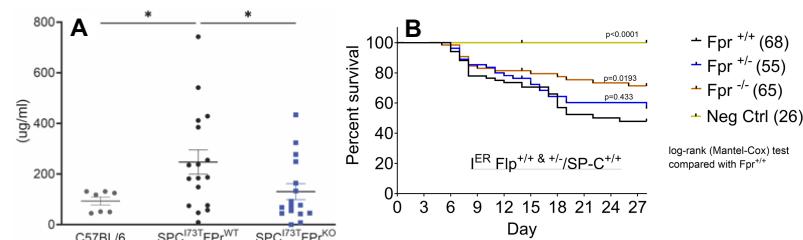


Figure 3. (a) Effect of FP knockout (FPr^{KO}) in Sftpc^{173T} genetic mouse model of IPF – BALF soluble collagen (Sircol); (b) Effect of FP knockout (Ptgr^{-/-}) on survival of Sftpc^{173T} animals – Kaplan Meier. JCI Insight. 2023;8(24):e172977 including our collaborator Dr. Beers.

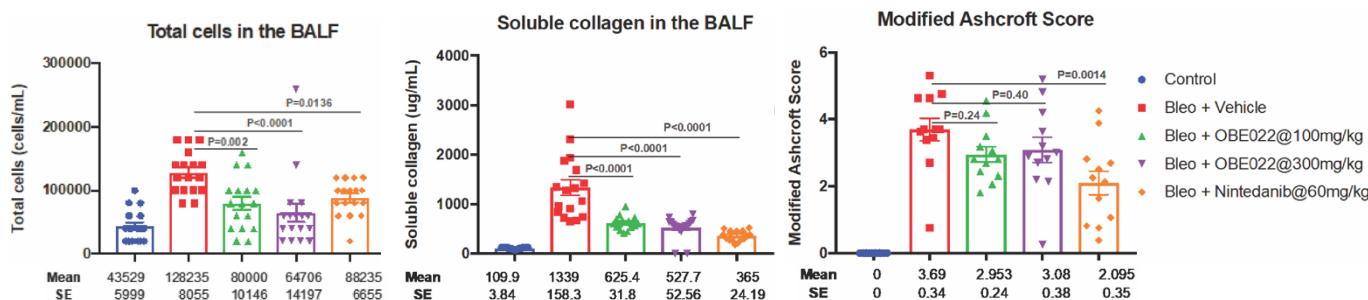


Figure 4. Pharmacological inhibition of FP in bleomycin-induced pulmonary fibrosis mouse model. JCI Insight. 2023;8(24):e172977 (BAY-6672 data can be found here).

FP Antagonist: Given the underlying role of PGF2 α in various diseases, much effort has been placed on development of drugs against FP:

- The first-generation FP antagonist, AL-8810, was a PGF2 α analogue with FP inhibitory properties (partial agonist) developed by Alcon. AL-8810 has been studied in a large number of preclinical studies in different diseases areas.⁴⁸ AL-8810 failed to achieve drug-like properties and was terminated.
- The second generation of FP antagonists were oligopeptides, THG113, PDC31 and PDC113.824 (allosteric modulators) developed by PDC Biotech for preterm birth^{49,50} and primary dysmenorrhea.⁵¹ This program was terminated at phase 1 since the modality (peptide) was not conducive for the target indications.
- The third generation of FP antagonists involved small molecules, AS604872, discovered by Merck Sereno⁵² that were licensed and developed by ObsEva as OBE022 (and out-licensed to Organon) for preterm birth.^{53,54} Bayer developed another FP antagonist, BAY-6672, for IPF⁴⁷ but the BAY-6672 program has been terminated in early preclinical stages due to poor DMPK/ADME properties incompatible for an oral drug. OBE022 is the only drug that has gone to phase 2 clinical trials (for preterm birth) but has now been terminated due lack of efficacy in preventing preterm birth.

Summary: Given the complexity of IPF, it is recognized that to develop effective therapies, a clear understanding of the interrelationship between various molecular pathways at each stage of IPF is needed. This will not only help to identify stage specific targets, but also simultaneously target different molecular pathways as an effective therapy to slow disease progression. Maipl Therapeutics is the only company that has developed a highly selective (over other prostaglandin receptors), potent (*in vitro* and *in vivo*) FP antagonist, with excellent ADME, *in vitro* safety, and oral pharmacokinetic (PK) profiles that have desirable characteristics of a clinical drug.

Strength and success of the Maipl team. Maipl Therapeutics is a biotech startup specializing in addressing medical conditions related to inflammation, pain, and fibrosis and is developing radically different, first-in-class medicines to treat endometriosis-associated menstrual pain and IPF. The company is a spinoff from Ferring Pharmaceuticals formed by senior members of Ferring's Global Drug Discovery and is based on a series of small molecules in-licensed from Ferring Pharmaceuticals. At Ferring, **Dr. Yong Yue** was Senior Director of Computational Biology and Data Sciences and a member of the global senior leadership team. He is a co-founder and CEO of Maipl and will lead the proposed studies as the PI of this grant. The lead medicinal chemist of the FP program at Ferring, **Dr. Yoshiyuki Fukase**, is now the VP of Medicinal Chemistry at Maipl Therapeutics. An extensive description of the team is provided in the **Commercialization Plan**. We have also secured the participation of **Dr. Michael Beers**, Robert L Mayock and David A. Cooper Professor of Medicine at the University of Pennsylvania and a leading authority on preclinical modeling of parenchymal lung disease. He will lead studies at U Penn in Aim 1 using his genetic PF models and experiments in Aim 2 to define the impact of Maipl compounds of niche crosstalk.

INNOVATION—MA-4586 and MA-4604 represent several key innovations over past attempts by others:

- **Novel candidates:** Both MA-4604 and MA-4586 are composed of 2-phenyl-quinoline scaffold connecting to branched unique hydrocarbon moieties. Each branched moiety has a unique side chain, carbon-carbon linkage for MA-4604 and oxime linkage for MA-4586, which contribute to favorable high potency and DMPK profiles to be developed as oral drug.
- **Novel target:** FP is a novel (TGF β -independent) therapeutic target for IPF. Currently, there is no drug development / clinical trial program targeting FP (or the PGF2 α pathway) for IPF.
- **Innovative medicinal chemistry:** Maipl Therapeutics uses innovative medicinal chemistry to become the first company to have developed a series of FP antagonist compounds with all the properties needed for an oral drug; overcoming weaknesses of previous FP antagonists.
- **Applicable to other indications:** A drug targeting FP can be developed beyond IPF for other indications like dysmenorrhea and pre-term birth where PGF2 α plays a major pathophysiological role.
- **Novel models:** A major technical barrier to the development of effective IPF therapies is the dearth of clinically relevant preclinical models. The current murine models utilized to study IPF are limited by issues that complicate feasibility and relevance (reviewed in^{18, 19}) including the use of exogenous injury agents (e.g. bleomycin) to achieve fibrotic endpoints or the overexpression of single genes (e.g. TGF β , TGF- α , IL-13) that may disrupt normal cell-cell crosstalk and skew mechanistic interpretation. Thus, **an additional critical unmet need for IPF is an improved preclinical platform that integrates disease relevant murine models** to close these knowledge gaps, translate pathogenesis, and accelerate discovery. In this proposal, in addition to the BLM model, we are using a novel genetic mouse model (*I^{ER}-Sftpc*^{173T} mice) derived from an

IPF-associated gene that develops spontaneous lung fibrosis and is a highly translationally relevant platform of human IPF.

Intellectual Property (IP) Strategy. Maipl Therapeutics has in-licensed a series of FP antagonist compounds from Ferring Pharmaceuticals. Of the five compounds in-licensed from Ferring, Maipl is developing two of these for a separate indication, endometriosis-associated menstrual pain, while two other compounds, MA-4586 and MA-4604, are being developed for IPF.

PRELIMINARY STUDIES—Medicinal Chemistry: To generate an orally available FP antagonist, a medicinal chemistry approach was taken using BAY-6672 and the publication by Beck *et al.* as the starting point.⁴⁷ BAY-6672 had potent FP antagonistic activity *in vitro*, but it did not show a preferable DMPK profile including membrane permeability, which resulted in discrepancy in efficacy between *in vitro* and *in vivo* studies. To address this issue, conformational analysis by computational modeling was developed to design compounds to improve potency and DMPK profiles. Overlaid modeling of BAY-6672 and compound 1 (another FP antagonist from the BAY-series showing good DMPK profiles with weak FP antagonist activity) allowed us to hypothesize the existence of a plausible hydrophobic space in the binding site of FP, adjacent to the bicyclooctane (BCO) ring of compound 1 (Fig. 5). Introduction of bulky substituent to the position pointing to the new space (FE-252683) successfully enhanced FP antagonist activity by more than 100-fold compared to compound 1 and BAY-6672. Moreover, FE-252683 retained good DMPK profiles of compound 1. An extensive lead optimization campaign based on the newly identified scaffold resulted in development of a series of compounds including FE-1227107 (MA-4604) and FE-254586 (MA-4586).

In vitro Pharmacology: There are five principal bioactive prostaglandins, PGE2, PGF2 α , PGD2, PGI2, and TXA2 (thromboxane) that signal via the G protein-coupled receptors (GPCRs) subfamily comprised of eight members, EP1-4, FP, DP, IP, and TP receptors, respectively. The FP and TP receptor couples to the Gq pathway to induce phospholipase C (PLC) activation and trigger the inositol phosphate (IP) cascade. PLC then cleaves phosphatidylinositol 4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol1,4,5-trisphosphate (IP3), resulting in a transient increase of intracellular calcium. The lifetime of IP3 is very short (< 30 sec) before being transformed into inositol bisphosphate (IP2) and then IP1. IP1 is accumulated in the cell and is stable in the presence of LiCl in StimB buffer. EP4, which is the primary receptor of PGE2, couples to the Gs α pathway to induce adenosine mono phosphate (cAMP) that accumulates stably within a cell and can be measured.

Potency: To measure the antagonist activity of compounds MA-4586 and MA-4604 at the FP, a cell-based IP1 accumulation assay, using human embryonic kidney EBNA derived (HEK-EBNA) cell lines stably expressing the FP receptor from various species (human, mouse, rat), was used.

Selectivity: To determine the selectivity of the compounds, antagonist activity at the EP4 (PTGER4) and TXA2 receptor (TP) were measured. For EP4, a cell-based cyclic cAMP, and for TP, a cell-based myo-inositol 1 phosphate (IP1) accumulation assay, were done in DLD-1 cells derived from human colon transiently expressing the EP4 / TP receptor from various species. Cells were exposed to varying concentrations of test compounds followed by exposure to a submaximal concentration of FP receptor agonist or EP4 selective agonist (TCS2510) or TP receptor agonist. Antagonist inhibition IP1 / cAMP accumulation was then assessed through an HTRF (homogeneous time resolved fluorescence)-based competitive immunoassay and expressed as Kb values (equilibrium dissociation constant of the antagonist-receptor complex), (Table 1). Results show that both MA-4586 and MA-4604 are highly potent (in nM/sub-nM range in different species) and selective (>40x more selective to FP than EP4 and TP).

PK and ADME: PK studies were performed in rat and mouse for intravenous (IV) bolus (1mg/Kg) and oral (PO, 3 mg/Kg)

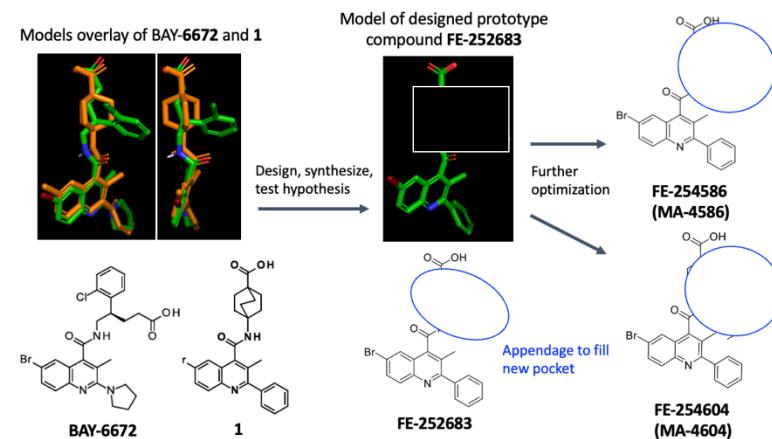


Figure 5. Medicinal chemistry of MA-4586 and MA-4604. Proprietary sections are blocked from view.

Table 1. *In vitro* pharmacology profile of MA-4586 and MA-4604. FP-PGF receptor, EP4-PGE2 α receptor, TP-TXA2 (thromboxane) receptor.

	Measurement	Assay	MA-4586	MA-4604
<i>in vitro</i> pharmacology	Potency (IC ₅₀)	FP Kb nM (human/mouse/rat)	3.1 / 0.07 / 0.04	0.1 / 0.1 / 0.08
		EP4 Kb nM (human)	116	18
		TP Kb nM (human)	141	1
	Selectivity	hFP to hEP4	> 40x	> 100x
		hFP to hTP	> 45x	> 20x

administration and total body clearance (CL; ml/min per kg), terminal half-life ($t_{1/2}$) and steady-state distribution volume (V_{ss} ; ml/Kg) were measured for IV administration, while bioavailability after oral administration (%F) was determined. **Fig. 6** shows the mean plasma concentration of MA-4586 and MA-4604 after IV bolus and PO dosing.

Membrane permeability: Cell permeability of MA-4586 and MA-4604 was measured using the MDR1-MDCK permeability assay, involving a combination of Madin Darby Canine Kidney (MDCK) cells, and the MDR1 gene to encode the efflux protein P-glycoprotein, P-gp. The efflux ratio derived from this assay helps assess whether a compound is subject to efflux. Both compounds demonstrated moderate to high permeability and a low likelihood of being substrates for the P-gp efflux transporter (**Table 2**). Compounds with efflux ratios higher than 3 suggest they could be efflux substrates.

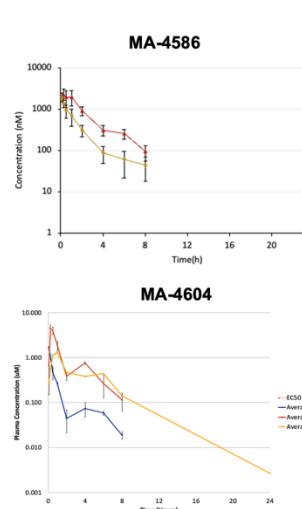
Metabolite stability: Drug metabolism is the major elimination route from the body for most drugs. We have performed a set of *in vitro* tests to evaluate the elimination rate of MA-4586 and MA-4604 metabolized by enzymes (metabolic stability), which can have implications for drug efficacy and safety.

- **Hepatic stability** – Human, mouse, and rat hepatocytes (cryopreserved) were treated with MA-4586 or MA-4604 and extraction ratio (the fraction of drug which is metabolized) was determined by LC-MS/MS. Hepatocytes contain both phase I and phase II drug metabolizing enzymes and provide a valuable *in vitro* model for predicting *in vivo* hepatic clearance.
- **Microsomal stability:** We have also performed microsomal stability assay using human and rat microsomes to determine the intrinsic clearance of MA-4586 or MA-4604.

Data is represented as extraction rates in the table which represent the proportion of drug candidates degraded by liver microsomes and hepatocytes, respectively. Both compounds exhibited moderate metabolic stability in microsomal and hepatocyte systems derived from most tested species.

Plasma protein binding (PPB): We have performed plasma protein binding assays in plasma from three different species (human, mouse, rat) utilizing an equilibrium dialysis method by using the Rapid Equilibrium Dialysis (RED) device followed by LC-MS/MS. The concentrations of free drug (%F) for both compounds were measured to be >2%.

CYP3A4 induction: Pregnenol X receptor



PK Parameters (n=3)		MA-4586 (free)	MA-4604 (free)
Mouse		Female C57BL/6J	Female C57BL/6J
IV	Dose (mg/Kg)	1	1
	C_0 (nM)	2284	2120
	$T_{1/2}$ (h)	2.99	2.1
	V_{dss} (L/Kg)	1.86	2.33
	CL (mL/min/Kg)	13.1	19.72
	$AUC_{0-\text{last}}$ (nM \cdot h)	2181	1200
PO	$AUC_{0-\text{inf}}$ (nM \cdot h)	2398	1300
	$AUC_{0-\text{last}} / Dose$	2181	1300
	Dose (mg/Kg)	3	5
	C_{max} (nM)	2354	4400
	T_{max} (h)	0.5	0.3
	$T_{1/2}$ (h)	1.86	
	$AUC_{0-\text{last}}$ (nM \cdot h)	5118	6600
	$AUC_{0-\text{inf}}$ (nM \cdot h)	5329	6900
	$AUC_{0-\text{last}} / Dose$	1708	1400
	Bioavailability (%)	74.8	106

Figure 6. Mean plasma concentration and PK parameter for MA-4586 and MA-4604 after IV and oral (PO) dosing in mouse. xxx

Table 2. ADME profile of MA-4586 and MA-4604.

Measurement	Assay	MA-4586	MA-4604
Membrane permeability	Papp AB MDCK-MDR1 (10E-6 cm/s)	26	14.6
	Efflux Ratio MDCK-MDR1 (net)	1.1	1.8
Hepatocyte stability	Extraction ratio (human/rat/mouse)	0.79 / 0.69 / 0.65	0.83 / 0.57 / 0.8
Microsomal stability	Human / rat	0.46 / 0.21	0.2 / 0.13
Plasma Protein Binding	PPB (%F)-RED (human/rat/mouse)	1.15 / 1.3 / 0.95	0.3 / 1.12 / 0.56
CYP3A4 induction (% at 10μM)	PXR (at 10μM)	8	53
	CYP 1A2	>50	9.6
	CYP 2B6	N/A	1.9
	CYP 2C8	N/A	52
	CYP 2C9	>50	0
	CYP 2C19	>50	24
	CYP 2D6	6.1	12
	CYP 3A4	>50	9.4

(PXR) activation: We have evaluated PXR activation for MA-4586 and MA-4604 by utilizing stably-transfected human hepatoma cell lines (DPX2) and a luciferase reporter gene assay. This assay evaluates drug metabolism and the potential for drug-drug interactions. Both compounds demonstrated a low risk for CYP3A4 induction.

CYP inhibition: We have performed CYP (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4T) inhibition studies in pooled human liver microsome. MA-4586 does not pose a high risk for inhibiting a panel of major human metabolic CYPs. **Table 2** summarizes the ADME characteristics for MA-4586 and MA-4604 from the above studies. The data shows that the ADME properties for both compounds are preferable for oral administration.

In vitro Toxicology (non-GLP): We have performed a series of comprehensive *in vitro* toxicology and safety pharmacology studies to assess the safety profile of MA-4586 and MA-4604.H

Hepatotoxicity: A liver toxicity profile was performed by (1) High Content Analysis (HCA), (2) Mitochondrial toxicity (Glu/Gla), and (3) Functional mitochondrial toxicity (Seahorse) assay using primary human hepatocytes, HepG2.

Mutagenicity & Genotoxicity: To evaluate the mutagenicity potential of MA-4586 and MA-4604, Ames reverse mutation assay (2 strain Ames-TA98 and TA100; 5 strain Ames – TA98, TA100, TA1535, TA97a and TA102) were performed. For genotoxicity, *in vitro* micronucleus assay (+S9 and -S9) was done in human TK6 cells. The *in vitro* micronucleus was positive for MA-4604 based on an earlier, low-purity batch of this compound. To further mitigate this observation, we have performed a series of tests involving state-of-the-art stem cell (iPSC)-based reporter assays that provides mechanistic insight into genotoxic properties of compounds called ToxTracker ACE (Aneugen Clastogen Evaluation) through a CRO, Toxys (Netherlands). These tests were negative for MA-4604 and the toxicology report shows a very low risk level for genotoxicity for MA-4604. Moreover, in the micronucleus test, late controlled control (-S9) was also positive for MA-4604, suggesting that the positive micronucleus test for MA-4604 may have been due to some impurities in the compound. Importantly, all the other compounds of the same chemical series were negative for micronucleus. Therefore, currently we are in the process of purifying ultra-pure MA-4604 and will repeat the *in vitro* micronucleus assay.

Eurofins SafetyScan 78 Functional assays: This is a functional safety assay involving a panel of targets and pathways which are now well-established as contributors to clinical adverse drug reactions (ADRs). This panel of 78 targets is now routinely used in different stages of drug discovery for early safety evaluation of drug candidates on clinical adverse event predictions.⁵⁵

Cardiac screen: Electrophysiological assays were conducted to profile compounds for activities on voltage-gated sodium (Nav1.5), calcium (Cav1.2), and potassium (hERG) channels using a Qube electrophysiological platform.

Drug-induced Liver Injury (DILI) strategy: DILI is one of the major causes for drugs to fail in clinic and mitigating DILI risks early in drug discovery is critical. Transport of bile acids via bile salt export pump (BSEP) is a rate limiting step of bile formation and flow. BSEP inhibition has been implicated as a risk factor for a drug's DILI potential. Also, the multidrug resistance-associated proteins (MRP) 2, 3 and 4 are postulated to be compensatory hepatic basolateral bile acid efflux transporters when biliary excretion by BSEP is impaired. MRP inhibition is associated with an increased risk of cholestatic potential among BSEP non-inhibitors. Similarly, organic anion transporting polypeptide 1B1 and 1B3 (OATP1B1 and OATP1B3), are liver-specific uptake transporters, which are associated with DILI. Screening and identifying potent OATP inhibitors with little toxicity is of great value in reducing OATP-mediated DILI. Therefore, we have measured BSEP, MRP (2,3 and 4) and ODAO (OATP1B1 and OATP1B3) inhibition in HEK293 cells for MA-4586 and MA-4604.

Finally, based on hepatobiliary transporter inhibition, acyl glucuronide stability, potential hepatic accumulation, Glu/Gal assay Sea Horse assay, assays human hepatocytes, we have developed a DILI de-risking matrix score (Max 6.5-worst) that serves as a basis for DILI prediction of compounds. **Table 3** shows the results of the above toxicology studies for MA-4586 and MA-4604 that demonstrate that both compounds have no toxicological concerns and are relatively safe.

Efficacy Studies: In women, PGF2 α plays a major role in uterine contraction and is critical for parturition.⁵⁶ In fact, FPKO animals do not deliver pups naturally due to lack of uterine contraction (all other aspects are normal in FPKO mice including in-utero fetal development and viable pups can be delivered via C-section at term).⁵⁷ This is the reason FP antagonists historically were being developed for preterm birth and/or severe menstrual pain due to high uterine contractions. Based on the above rationale, we have used uterine contractility as the primary efficacy endpoint for the FP compounds. We have used two studies to determine the efficacy of our compounds:

Table 3. *In vitro* toxicology profile of MA-4586 and MA-4604.

Measurement	Assay	MA-4586	MA-4604
Hepatotoxicity	High Content Analysis, AC50 (uM)	>100 ATP	>100 ATP
	Mitochondrial toxicity (Glu/Gla)	cytotoxicity >100 uM for glucose and galactose	cytotoxicity >100 uM for glucose and galactose
	Functional mitochondrial toxicity (Seahorse)	No effect on mitochondrial functional endpoints	No effect on mitochondrial functional endpoints
Mutagenicity & Genotoxicity	2 strain Ames	Negative (+S9 and -S9)	Negative (+S9 and -S9)
	5 strain Ames	Negative (+S9 and -S9)	Negative (+S9 and -S9)
	<i>in vitro</i> Micronucleus	Negative (+S9 and -S9)	Positive (+S9 and -S9)
	ToxTracker assay DNA damage, Aneugenicity, p53 activation,	N/A	Negative
Functional safety	SafetyScan 78	No predicted adverse effects	No predicted adverse effects
Off target safety panel	47 targets panel screen	No off-target concerns (all <50% inhibition at 10 uM)	No off-target concerns (all <50% inhibition at 10 uM)
Cardiac screen	Electrophysiology for Ikr, Nav1.5, Cav1.2	Not done as there was no concerns based on Safety screen	Overall, no adverse functional effect hERG, Nav1.5 & Cav1.2 > 10uM
DILI	BSEP IC50 (uM)	10.3	14.4
	OATP1B1 IC50 (uM)	0.77	0.757
	OATP1B3 IC50 (uM)	0.9	0.408
	MRP2 IC50 (uM)	<50% inhibition	14.7
	MRP3 IC50 (uM)	9.8	13.4
	MRP4 IC50 (uM)	53	40.6
	Derisking Matrix score (Max 6.5; worst)	2.75	3.00

1. Ex vivo - rat intrauterine pressure (IUP) model:

Intrauterine pressure is a direct measure of uterine contractility. In this model, rats were subjected to 5 challenges of PGF2 α (100 ug/Kg, 5 min IV infusion), 30 minutes apart and IUP was measured using an intrauterine catheter. Five minutes prior to the 4th PGF2 α challenge, animals were treated with vehicle or FP antagonist (10 min IV infusion). Results (Fig. 7) show that MA-4604 is highly efficacious and, in a dose dependent manner, significantly inhibits rat IUP. MA-4586 is equally effective (-88.33 mean % inhibition at 2.3 mg/Kg, IV) in rat IUP model (data not shown).

2. In vivo - mouse parturition study: Pregnant animals (primigravid mice) were treated (oral) twice a day starting from GD16 (pm) up to GD20 (am) with FP antagonist (total 8 administrations) and delay in delivery was determined compared to vehicle. Results (Fig. 8) show that MA-4604 in a dose dependent manner significantly delayed delivery up to 50h compared to vehicle. MA-4586 in a dose dependent manner significantly delayed delivery up to 24h (18 mg/Kg) compared to vehicle.

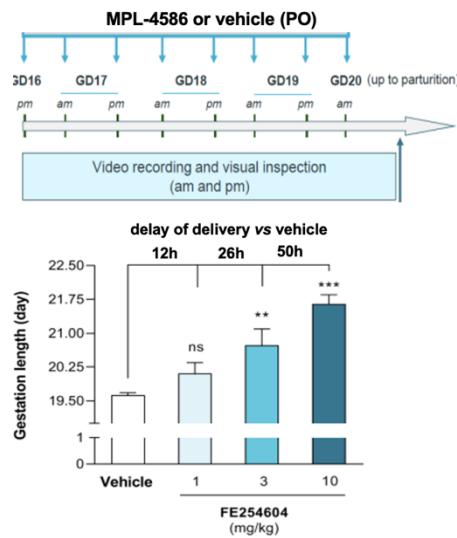


Figure 8. Efficacy study of MA-4586 in mouse parturition model.

high *in vivo* clearance, only moderate selectivity and lacked single agent *in vivo* efficacy (mouse parturition; data not shown).⁵⁸ Moreover, MA-4604 displays efficacy in IUP at doses ~50-100x lower than OBE002 and BAY-6672 (Fig. 9).

APPROACH—The objectives of this Phase II SBIR are to (1) evaluate the *in vivo* efficacy of lead candidates MA-4586 and MA-4604 in two preclinical IPF models (BLM-induced IPF and *I^{ER}-Sftpc^{l73T}*-induced spontaneous lung fibrosis), (2) determine the MoA of PGF2 α /FP in IPF disease pathophysiology, and (3) assess *in vivo* safety (exploratory non-GLP toxicology studies in rat and dog) of MA-4586 and MA-4604. These studies will enable Maipl to move to CMC, IND-enabling (GLP) studies, IND-filing, and phase I clinical trial.

Aim 1. Determine the anti-fibrosis efficacy of lead candidates in two IPF disease models. Rationale: Results from this study will establish efficacy of Maipl's compounds in pre-clinical IPF disease models, the data of which is essential for IND-filing.

Table 4. Aim 1 Milestones

Sub-Aims	Quantitative Success Metric
1.1. Efficacy – BLM IPF mouse model	Ability of the tested compounds to limit significant decrease in body weight, development of lung fibrosis (determined by histopathology, collagen and hydroxyproline levels), inflammation (cytology and cytokine levels in bronchiolar lavage fluid (BALF), plasma, and lung tissue), mortality rate (by Kaplan Meier in <i>I^{ER}-Sftpc^{l73T}</i> only), and (l73T only) lung function by Flexivent, fibrillar collagen deposition using PSR staining, and image analysis, and collagen gene expression by RT PCR). Statistically equal to or better than nintedanib.
1.2. Efficacy – <i>I^{ER}-Sftpc^{l73T}</i> genetic model of spontaneous lung fibrosis	

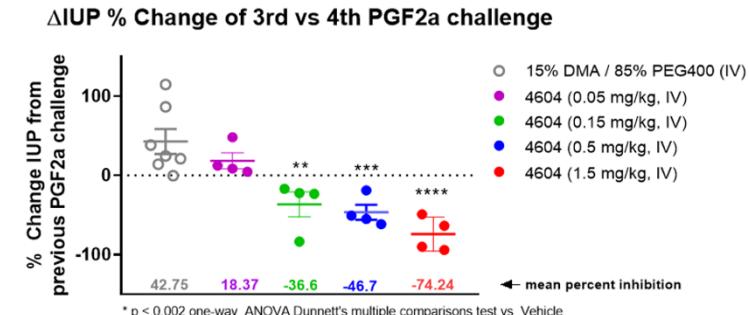


Figure 7. Efficacy study of MA-4604 in rat intrauterine pressure (IUP) model. Δ IUP % change of 3rd vs 4th PGF2 α challenge shows significantly inhibited IUP in rats.

	OBE002	BAY-6672	MA-4604
FP Kb (nM) human / rat	24 / 260	2.2 / 0.84	0.02 / 0.08
Microsomes E _h h / r	0.95 / 0.88	0.33 / 0.84	0.2 / 0.13
Aqueous Solubility (μM)	Pro drug:1 Metabolite: 3	80	89
MDCK Papp A → B 10 ⁻⁶ cm/s (passive permeability)	9.9	2.4	15
MDCK (hepatic) Efflux ratio	3	20	1.8
PPB hu / rat (% free)	0.67 / 0.42	0.06 / 0.18	0.29 / 1.1
in vivo CL (mL/min/kg)	51	13	11
	ND	ND	ND
Rate PK AUC _{0-∞} /dose (μM·hr/mg/kg)	6.9	100	1.7
Prostanoid Selectivity	Only 10-20-fold selectivity for hEP2 and hIP except: 13-fold at TP	100-fold selectivity for all except: 13-fold at TP	>100-fold selective for all except 22-fold at TP

■ Poor ■ Acceptable ■ Best

		Approximate 50% change in rat IUP	Rat FP Kb (nM)	Human FP Kb (nM)
Rat IUP Model	OBE002	Between 19-61 mg/kg	260	24
	BAY-6672	Between 1.54-4.6 mg/kg	0.84	2.2
	MA-4604	Between 0.5-1.5 mg/kg	0.083	0.023

Figure 9. Comparison of OBE002, BAY-6672, and MA-4604.

1.1. Bleomycin (BLM)-induced pulmonary fibrosis mouse model (HD Biosciences) - C57BL/6 mice (male and female, 8 weeks old, n=6/sex) will be acclimatized for 1 week prior to the experiment. Animals will be kept under a standard condition with room temperature at 21-23 °C, 30-70% relative humidity, and a 12 : 12h light : dark cycle. Chow and water will be available *ad libitum*. All the *in vivo* experimental procedures will be approved by the institutional animal care and use committee (IACUC) at HD BioSciences.

Model development: Mice will receive bleomycin on day 1 at a dose of 0.66mg/kg (equivalent to 1U/kg), in a volume of 50ul by intra-tracheal administration. This is a **well-established model** and routinely performed by the CRO (HD BioSciences, San Diego). Animals will be treated with vehicle, nintedanib, and different doses of MA-4586 or MA-4604 (doses are based on *in vivo* efficacy studies in mouse parturition model). Detailed treatments and group design for this study are shown in **Table 5**.

1.2. *I^{ER}-Sftpc^{I73T}* genetic model of spontaneous lung fibrosis (UPenn) – The *I^{ER}-Sftpc^{I73T}* animals express a disease-associated missense mutation in the surfactant protein C (Sftpc) gene. Tamoxifen treatment of *I^{ER}-Sftpc^{I73T}* mice develop an early multiphasic alveolitis and transition to spontaneous fibrotic remodeling by 28 days.^{16,46} This genetic model is **highly translational** and recapitulates the pathological and clinical features of the human IPF disease. This study will be performed in Dr. Michael Beers' laboratory at the University of Pennsylvania where the *I^{ER}-Sftpc^{I73T}* model is well-established.¹⁶ All the proposed *in vivo* procedures will be approved by the IACUC of UPenn.

Model development: Tamoxifen induction (using published doses¹⁶) of adult *I^{ER}-Sftpc^{I73T}* mice will be initiated at 12-14 weeks of age by intraperitoneal (ip) injection. The I73T model does **not** use bleomycin (indiscriminate cell injury) but involves spontaneous fibrosis emanating from selective AT2 injury. There will be 2 tamoxifen injections, one on d0 and another 4 days later. Both male (n=6) and female (n=6) animals will be used. Animals will be treated with vehicle, nintedanib, and different doses of MA-4586 or MA-4604. Detailed treatments and group design for this study are shown in **Table 5**. BID dosing for MA-4586 and MA-4604 will be used as was the case in the parturition studies (based on PK data).

Table 5. Detailed treatment and group design for Sub-Aims 1.1 and 1.2.

Group, compound, and dosing			1.1 BLM-induced PF model				1.2 <i>I^{ER}-Sftpc^{I73T}</i> genetic model			
Grp	n	Compound	Route	Dosing Level	Model Development	Treatment Duration	Take Down	Model Development	Treatment Duration	Take Down
1	12	Vehicle	P.O., QD	NA	Saline, i.t, 50 ul	D6-D22	D22	<i>I^{ER}-Sftpc^{I73T}</i> + saline	D12-D28	D28
2	12	Vehicle	P.O., QD	NA	BLM 0.66mg/Kg, i.t, 50 ul	D6-D22	D22	<i>I^{ER}-Sftpc^{I73T}</i> + Tam	D12-D28	D28
3	12	nintedanib	P.O., QD	60pmk	BLM 0.66mg/Kg, i.t, 50 ul	D6-D22	D22	<i>I^{ER}-Sftpc^{I73T}</i> + Tam	D12-D28	D28
4	12	MA-4586: 4.5mg/Kg MA-4604: 1mg/Kg	P.O., BID	low	BLM 0.66mg/Kg, i.t, 50 ul	D6-D22	D22	<i>I^{ER}-Sftpc^{I73T}</i> + Tam	D12-D28	D28
5	12	MA-4586: 9mg/Kg MA-4604: 3mg/Kg	P.O., BID	mid	BLM 0.66mg/Kg, i.t, 50 ul	D6-D22	D22	<i>I^{ER}-Sftpc^{I73T}</i> + TX	D12-D28	D28
6	12	MA-4586: 18mg/Kg MA-4604: 10mg/Kg	P.O., BID	high	BLM 0.66mg/Kg, i.t, 50 ul	D6-D22	D22	<i>I^{ER}-Sftpc^{I73T}</i> + TX	D12-D28	D28

Endpoint analyses: (i) Body weight will be measured on d1 and d6 (for BLM model) and d12 (for *I^{ER}-Sftpc^{I73T}* model), and once weekly thereafter, (ii) BALF, plasma and lung tissue will be collected 2h post treatment dosing on the day of take down; individual animals will be perfused after BALF collection, (iii) Animal left lungs will be collected and fixed for further histology analysis. Animal right lungs will be snap frozen in liquid nitrogen and stored at -80°C for analysis of hydroxyproline. Histopathological evaluation will include H&E staining and analysis, Masson Trichrome and modified Ashcroft score, and α-SMA (smooth muscle actin) IHC staining and analysis, (iv) BALF measurements including soluble collagen, cytology (total cells, monocyte, neutrophil, lymphocyte, eosinophils), and cytokines (TGF-β1, IL-10, IL-1β, IL-6), (v) Kaplan Meier survival analysis by log rank testing will be done only for the *I^{ER}-Sftpc^{I73T}* model. For the I73T model, we will also measure lung function by Flexivent, fibrillar collagen deposition using PSR staining and image analysis, and collagen gene expression by RT PCR.

Limitations and alternative approaches: Based on published studies reporting a positive effect of inhibiting FP (with OBE022 and BAY6672)^{47,53} on pulmonary fibrosis in preclinical models and the superior compound properties of Maipl's FP antagonist compounds compared to OBE002 and BAY6672 (**Fig 8**), we do not anticipate problems in the proposed studies. However, if we find that MA-4586 and/or MA-4604 have limited effect in the proposed preclinical models, we will use a combinational approach with nintedanib. Given that there are numerous pathways involved in IPF disease pathology, inhibiting more than one pathway may show better

efficacy. This understanding of which cell populations, pathways, and genes in the lungs are affected by PGF2 α /FP (vs targeted pathways by nintedanib) is imperative in determining the pathophysiological effect of PGF2 α and identifying patients who might benefit. This is a key de-risking step for the clinical development of the FP antagonists as a drug for IPF (Aim 2). We may also use other backup compounds from the same chemical series if MA-4586 and/or MA-4604 do not show the desired efficacy. In this proposal, we are using nintedanib as a positive control. Whether MA-4604/4586 is superior in terms of efficacy, tolerability, or sustainability can only be answered in Ph1/2 clinical trials. The focus here is to evaluate if MA-compounds have positive effects in attenuating pulmonary fibrosis in preclinical animal models. Based on *in vitro* toxicity studies, on-target safety, and previous clinical Ph1/2 studies, we believe that the MA-FP antagonists may have a better tolerability or sustainability compared to SoC. Two models will provide validation through concordance as they relate to effect size, biomarkers, and/or cell behaviors. Endpoints biomarkers, and pathways that are affected in both models (and seen in humans), would be the best case scenario with priority given to moving that compound forward.

Aim 2. Determine changes in alveolar niche crosstalk and fibrotic signaling following FP inhibition.

Rationale: While published studies have established the PGF2 α pathway as a potential drug target for IPF, the MoA of PGF2 α in IPF disease pathophysiology is incompletely understood but based on our prior work, likely involves altering the dynamics/function of adventitial and/or transitional/inflammatory fibroblast populations. The main objective of this aim is to determine the pulmonary cell populations that are targeted by PGF2 α to induce fibrosis leading to IPF (and thus will be affected by FP antagonists). These studies will not only enable differentiation of the FP antagonists with the current FDA approved drug, nintedanib, but also enable determination of which targets MA-4586 and MA-4604 hit, what process gets altered, and how this ultimately impacts the effect size of these drugs. These studies are essential for (1) rationalizing the drug target for IND submission (2) developing Ph 2 clinical trial plans including potential clinical biomarkers, (3) stratifying patient populations, (4) dosing optimization, and (5) determining non-specific effect on pathways/cells that may cause toxicity issues in the clinic. These studies will define the MoA of MA-4586 and MA-4604 in IPF disease pathophysiology. Both Sub-Aims will be performed by Dr. Beers at the University of Pennsylvania Core facility.

Table 6. Aim 2 Milestones

Sub-Aims	Quantitative Success Metric
2.1. MoA of FP antagonist vs nintedanib in lung	<ul style="list-style-type: none"> Identify genes and pathways specifically affected by MA-4586 & MA-4604 vs nintedanib in adventitial fibroblasts in an IPF preclinical animal model
2.2. Fibrotic, alveolar, regenerative niche dynamics	<ul style="list-style-type: none"> Identify spatial niches associated with profibrotic populations

2.1. Distinguish transcriptional signatures of lung populations after FP antagonist and nintedanib interventions.

Despite the extensive characterization of lung populations in models of fibrosis through single-cell sequencing, there is little data on the effects of intervention on pulmonary cell population dynamics. The Beers lab (University of Pennsylvania) conducting Aim 2 work recently published a characterization of the fibroblast heterogeneity arising throughout the injury/repair process observed with pulmonary fibrosis and established a role of PGF2 α signaling in pulmonary fibrosis acting through a key mesenchymal cell population, the adventitial fibroblasts.⁵⁹ These studies show FP expression predominantly within an adventitial fibroblast subpopulation which was capable of being selectively reprogrammed to a recently described¹¹ “inflammatory/transitional” cell state in a PGF2 α dependent manner. However, question remains about differences in transitional fibroblast origin, alveolar or adventitial, that further complicates the mechanism by which PGF2 α inhibition slow fibrotic progression. To better resolve these changes, we propose the generation of an adventitial lineage traced mouse that would allow for the following of adventitial derived populations through the development of fibrosis and after intervention. Specifically, we will cross our in-house *Sftpc*^{I73T/I73T}*Rosa26*^{Flp/Tom}*Pdgfra*^{GFP/WT} to the commercially available *Ly6a*^{MerCreMer} which functionally labels all adventitial fibroblasts GFP⁺ and TdTom⁺ upon tamoxifen administration. Using this fibrotic model, we will intervene with daily 60 mg/kg nintedanib, PGF2 α inhibitors MA-4586 or MA-4604 at day 12 (dose determined by the efficacious dose in Aim 1). Through scRNASeq analysis, we will interrogate populations dynamics, cell crosstalk, and adventitial lineage signatures. These studies will determine the exact genes and pathways in specific lung cells that are hit by FP antagonist vs nintedanib.

2.2. Define fibrotic, alveolar, and regenerative niche dynamics after FP antagonist and nintedanib interventions:

Our interpretation of single cell data and preliminary data coupled with published functional organoid assays suggests that the adventitial fibroblast is a regenerative population. We hypothesize that this cell may be recruited to sites of injury to promote epithelial proliferation and serve as a progenitor pool for the transitional fibroblast. To explore this, we will employ the same adventitial reporter mouse used in aim 2.1 and generate tissue slices from the fibrotic time point after intervention with daily 60 mg/kg nintedanib, MA-4586, MA-4604, or vehicle. These tissue slices will be prepared for spatial transcriptomics. Using our single cell data from aim 2.1 as a reference, we will identify spatial niches associated with profibrotic populations as well as those

hypothesized to be involved in repair including transitional and adventitial populations. These studies will establish how the fibrotic niche changes following FP antagonist vs nintedanib treatment. The Beers lab has an established record of next gen transcriptomic analysis combining in-house developed analysis pipelines with advances published in the field.⁵⁹⁻⁶¹ Concurrent to the generation of slides, H&E serial sections will be used to identify regions of cellular infiltration and fibrosis.

Limitations and alternative approaches: Our previous work suggests that the inhibition of PGF2 α inhibits the entry of adventitial fibroblasts into the transition state and alleviates the fibrotic burden in the mouse model. Given the promising PK profile of the Maipl compounds, we expect to reproduce these findings and better define the dynamics of the adventitial fibroblast through the time course of fibrotic development. We expect that preservation of this population will potentially establish regenerative niches in the fibrotic lung through the spatial accumulation of adventitial fibroblasts in proximity to alveolar areas. Though the depth of spatial transcriptomics provides clear resolution of highly different cell states, the similarities in adventitial derived and alveolar derived fibroblasts may not be clearly resolved. If this is the case, we will turn to RNAscope, an established protocol that when combined with the fluorescent reporters in the proposed mouse line allows for higher resolution definition of small transcript numbers. The resulting data will provide a significant insight into the fibroblast heterogeneity in development and potential resolution of fibrosis guiding decisions on candidate molecules that can be moved forward through the drug discovery pipeline.

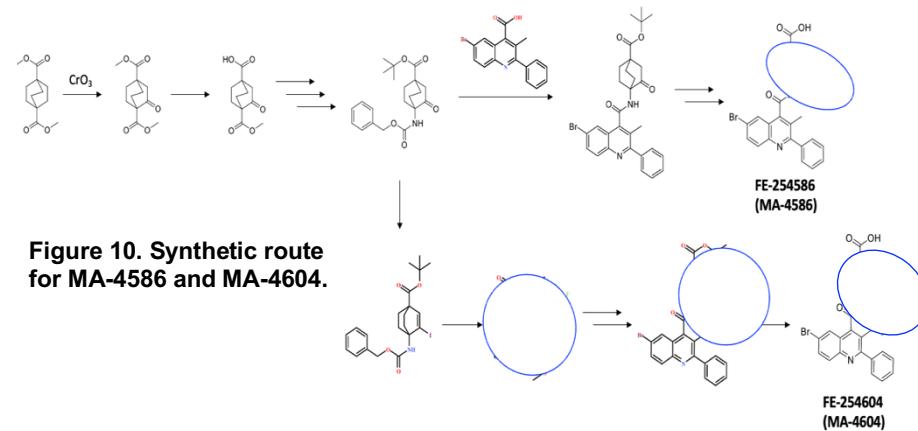
Aim 3. Establish non-GLP preclinical safety in two species. Rationale: Maipl Therapeutics has already established DMPK, ADME, *in vitro* toxicology and *in vivo* efficacy for MA-4586 and MA-4604. In this aim, we will perform exploratory toxicology studies that will enable us to proceed to IND-enabling (GLP) studies. The proposed studies are standard drug discovery PK and exploratory toxicology studies that will be performed by different CROs.

Table 7. Aim 3 Milestones

Sub-Aims	Quantitative Success Metric
3.1. API and Formulation	<ul style="list-style-type: none"> Analytical and bioanalytical methods developed; Formulation analysis methods developed. Solubility ≥ 10 mg/mL in formulation solvent; Stability of API: $\leq 0.2\%$ diminishment in purity (v/v HPLC) after 1 week timepoint under 40°C/75% RH and 60°C (capped). ≥ 200 mg produced for Sub-Aim 3.3.
3.2. <i>In vivo</i> PK	<ul style="list-style-type: none"> Establish PK profile in two species; Establish optimal formulation for follow on preclinical studies.
3.3. Toxicology	<ul style="list-style-type: none"> DRF/MTD: Systemic MTD in rats and dogs determined that will inform repeated dose studies in both species. Repeat Dose: Determine NOEL and NOAEL in preparation for GLP IND-enabling studies. Safety: No pathologies or negative clinical observations attributed to test compounds.

3.1. Active Pharmaceutical Ingredient (API) and Formulation (TCG GreenChem CDMO): The proprietary compound form (crystalline vs amorphous) for MA-4586 and MA-4604 will first be confirmed, particle size determined if crystalline, formulation, and formulation stability assessed, preferably for 3 days and at least 8 days at room temperature and refrigerated (4°C), respectively. Formulation analysis methods will also be developed and validated, as needed for GLP studies. An efficient synthetic route for the lead compounds has been established (Fig. 10) and it enables to produce API in sufficient amounts for exploratory toxicology studies. As MA-4586 and MA-4604 possess carboxylic acid moiety, salt screen will be conducted to identify crystal form with physicochemical properties preferable for further development. Pharmaceutically acceptable bases will be investigated by testing crystallinity, aqueous solubility, and stability under ambient condition including hygroscopicity. Formulation development will be based on the physicochemical properties of the crystal form thus obtained. Pharmaceutically acceptable solvent/vehicle will be examined to identify formulation condition suitable for dosing in *in vivo* toxicology studies based on solubility, stability, and settlement status if suspension.

3.2. *In vivo* PK studies (LabCorp CRO): Single dose formulation PK studies will compare multiple formulations to support formulation development for toxicology studies. MA-4586 and MA-4604 will be prepared in various oral formulations and administered as a single dose and repeat dose (rats and dogs) to evaluate how these formulations affect the drug's PK profile (Table 8). The results derived from this study will help



in identifying the optimal formulation and understand the dose linearity to support future preclinical studies. A single oral dose of MA-4586 / MA-4604 administered to rats under both fed and fasted conditions will evaluate whether the presence of food affects the PK profiles of the drug candidate, which helps investigate potential food and drug interactions and assists in optimizing dosing regimens. The PK profiles of MA-4586 and MA-4604 will be studied after administering its highest dose to both male and female rats to explore potential sex-related differences in drug metabolism to ensure its efficacy and safety across genders. A repeat dose PK study with a single selected formulation will assess its accumulation and steady-state concentration within the body. This study aims to understand the drug's PK behavior over time, aiding in dose optimization and safety assessments. The distribution of the compounds over time in different organs will also be evaluated in rats. These findings will facilitate the understanding of the drug's localization and its potential efficacy or toxicity in the target tissues.

Table 8: Exploratory PK and formulation studies.

Study Type	Species/Strain	Dose Groups	Route	Duration	Endpoints
Single dose formulation	Rat/Sprague Dawley	Main Study: Male 3 dose levels 1-1000 mg/kg; 3 formulations n=3 /formulation/dose	PO	24 hours	Serial bleeding at: 15, 30 min, 1, 2, 4, 7, 24 hr post dosing per animal. PK profile, dose linearity, optimal formulation, , fed vs. fasted
Single dose formulation	Dog/Beagle	Main Study: Male 3 dose levels 1-1000 mg/kg; 3 formulations n=3/dose/formulation	PO	48 hours	Serial bleeding at: 5, 15, 30 min, 1, 2, 4, 6, 8, 24, 48 hr post dosing per animal. PK profile, dose linearity, optimal formulation,
Repeat dose PK	Rat/ Sprague Dawley	Main Study: Male 3 dose levels; single formulation (determined by single dose formulation study) n=3/dose; Total 9 animals	OG	7 days Once daily	Repeat dosing up to 7 days, serial blood sampling on day 7 at 0.25, 0.5, 1, 2, 4, 7, 24, hr after last dose. Body weight and food intake monitoring. PK profile. General health as above. Females at highest dose.
Repeat dose PK	Dog/Beagle	Main Study: Male 3 dose levels; single formulation (determined by single dose formulation study) n=3/dose; total 9 non-naïve animals	OG	7 days Once daily	Repeat dosing up to 7 days, serial blood sampling on day 7 at 0.25, 0.5, 1, 2, 4, 7, 24, hr after last dose. Body weight and food intake monitoring. PK profile. General health.
Rat Tissue distribution	Rat/Sprague Dawley	Main study: Male single dose n=3/time point; total 9 animals 9 rats sacrificed at 3 time points (0.5, 2, 8 hr).	PO	8 hours	11 tissues (brain, liver, spleen, lung, heart, kidney, stomach, small intestine, large intestine, muscle, fat) and blood collected from each animal.at each time point. LC-MS/MS method

3.3. Non-GLP Toxicology studies (LabCorp CRO): Dose range finding (DRF) / maximum tolerated dose (MTD) toxicology studies in rats and dogs will aim at finding the dose that will produce tolerable levels of adverse toxic effects of the 2 tested compounds (**Table 9**). Adverse effects of acute dose administration (single dose escalation) will be determined via oral gavage (OG). Data from this phase will assist in estimating the MTD for a single administration and establish dose for a repeat dose phase. A 14-day (repeat) toxicity study will then investigate toxicity induced by the test compounds (MA-4586 and MA-4604) when given daily for 14 consecutive days (**Table 9**) to define a NOEL (no-observable-effect-level) and NOAEL (no-observed-adverse-effect level). This is considered as a de-risking study before moving to IND-enabling GLP 28-day toxicity studies.

Table 9: Dose range finding and repeat dose tox/TK studies.

Study Type	Species/Strain	Dose Groups	Route	Duration	Endpoints
Dose range finding/MTD	Rat/ Sprague Dawley	Main Study: 5/sex/group L, M, H Vehicle 3/sex	OG	24 hours	Mortality, body weight, clinical observations, food consumption, plasma and whole blood toxicokinetics,
Dose range finding	Dog/Beagle	Main Study: 2/sex/group L, M, H Vehicle 2/sex	OG	24 hours	
Repeat Dose Tox and TK	Rat/ Sprague Dawley	Main Study: 5/sex/group L, M, H Vehicle 3/sex	OG	14 days Once daily	As above plus histopathology, urinalysis, organ weights, gross necropsy.
Repeat Dose Tox and TK	Dog/Beagle	Main Study: 2/sex/group L, M, H Vehicle 2/sex	OG	14 days Once daily	

Endpoint analysis: Clinical observations will be recorded daily and individual body weights at least two times during acclimation, D1, ~weekly thereafter (intervals of 7 days \pm 1), and prior to sacrifice. Body weight gain will be calculated for selected intervals and for the study overall. Individual food consumption will be measured and recorded to coincide with body weight measurements for the animals. Food efficiency will be reported.

Blood samples will be collected for toxicokinetic sample analysis at six time-points (0.5, 1, 2, 4, 7, and 24 hours) after dosing. Vehicle control animals will be sampled once (approximately 3 hours) after dosing on the same days. Approximately 240 μ L of blood will be collected in capillary blood collection tubes treated with heparin. A high-performance liquid chromatography with ultraviolet detection (HPLC-UV) method for the

quantitation of MA-4586 and MA-4604 has already been developed and validated. The validated method will be used for bioanalytical sample analysis of MA-4586 and MA-4604 in rat plasma. Blood samples will be collected from all surviving animals at terminal sacrifice for the evaluation of clinical pathology. Hematological analysis will include mean corpuscular hemoglobin, hemoglobin concentration, erythrocyte count, hematocrit, total white blood cell and differential leukocyte count, mean corpuscular volume, mean corpuscular hemoglobin concentration, nucleated red blood cells, total cholesterol and triglycerides, liver enzymes (alkaline phosphatase-ALP; alanine transaminase- ALT, aspartate transaminase-AST) and total bilirubin. If any test-related findings are found in the high dose group, mid and low dose groups will be assessed sequentially.

All animals will be euthanized after blood collection for clinical pathology. The liver, spleen, heart, and kidneys (combined) of animals will be weighed. The stomach, duodenum, ileum with Peyer's patches, colon, cecum, liver, heart, kidneys (combined), lungs and bone marrow (from femur) will be preserved. Histological examination will be performed on the preserved organs and tissues (control vs high dose groups). In addition, gross lesions of potential toxicological significance noted in the test groups at the time of terminal sacrifice will be examined.

Data analysis: Statistical analysis will be conducted by the statistical division of the CRO.

Statistical Considerations: Significance will indicate a statistically significant difference between the control and the experimental groups and will be judged at $p < 0.05$. For all in-life endpoints that are identified as multiple measurements of continuous data over time (e.g., body weight, body weight gain, food consumption, and food efficiency), treatment and control groups will be compared using a two-way analysis of variance (ANOVA), testing the effects of both time and treatment, with methods accounting for repeated measures in one independent variable. If a significant interaction effect is observed between treatment and time, further analysis of the p value for each individual factor will be conducted ultimately by a post hoc multiple comparisons test (e.g., Dunnett's test) of the individual treated groups to control. If warranted by sufficient group sizes, all endpoints with single measurements of continuous data within groups (e.g., organ and relative organ weight) will be evaluated for homogeneity of variance and normality. Where homogenous variances and normal distribution is observed, treated and control groups will be compared using a one-way ANOVA. When one-way ANOVA is significant, a comparison of treated groups to control will be performed with a multiple comparisons test (e.g., Dunnett's test). Where variance is considered significantly different, groups will be compared using a non-parametric method (e.g., Kruskal-Wallis non-parametric analysis of variance). When non-parametric analysis of variance is significant, a comparison of treated groups to control will be performed (e.g., Dunn's test). TK parameters will be estimated using WinNonlin 7.0 (Certara LP, Princeton, NJ). Parameters include C_{max} , T_{max} , $AUC_{(0-24)}$, V_d , Cl , k_{en} and k_{el} and elimination $T_{1/2}$. When appropriate, statistical analysis of TK data and parameters will be performed using Graphpad Prism. The number of animals used in each study is usual industry standard. Sex will be balanced between treatment groups, comparator, and control efficacy, PK/PD, and toxicology animals. Appropriate statistical analyses will be performed to identify potential sex-related differences in all study endpoints.

Limitations and alternative approaches: The on-target safety for FP is excellent as FP knockout animals are viable and normal (other than they cannot deliver pups normally due to lack of uterine contractions- viable pups can be delivered via C-section at term).⁵⁷ Moreover, first in human, Ph1 (dose escalation) and Ph2a (NCT03369262), placebo-controlled, randomized trials of OBE022⁵³ as well as first-in-human study of PDC31 (NCT01250587) were safe and well tolerated without any safety concerns. Based on these studies and our *in vitro* toxicology studies, we do not anticipate any potential toxicological issues for MA-4586/MA-4604. Should we find unacceptable toxicity, off-target effects, or narrow safety margins, we will initially reconsider a different formulation strategy for slow/sustained release or using a purer compound. Toxicity is also highly species specific and therefore if we find any tolerability issues arising with our compounds, as an alternative approach we will perform the above studies in a different animal species like minipig.

Timeline and next steps: Table 10 provides the proposed timeline for SBIR Phase II milestones. These studies lay the framework for Chemistry, Manufacturing, and Controls (CMC), IND-enabling (GLP) studies (using the superior compound demonstrated in this project), IND filing, and a Ph1 clinical trial for this novel IPF treatment.

Milestone Description	Quarter											
	1	2	3	4	5	6	7	8	9	10	11	12
1.1. Efficacy – BLM induced												
1.2. Efficacy - I ^{ER} -Sftp ^c ^{173T} model												
2.1. MoA investigation												
2.2. Niche dynamics												
3.1. API and Formulation												
3.2. <i>In vivo</i> PK												
3.3. Toxicology												

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001

Expiration Date: 01/31/2026

Use of Human Specimens and/or Data

Does any of the proposed research in the application involve human specimens and/or data *

Yes No

Provide an explanation for any use of human specimens and/or data not considered to be human subjects research.

Are Human Subjects Involved

Yes No

Is the Project Exempt from Federal regulations?

Yes No

Exemption Number

1 2 3 4 5 6 7 8

Other Requested Information

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			

VERTEBRATE ANIMALS

1. Description of Procedures

1.1. Bleomycin (BLM)-induced pulmonary fibrosis mouse model (HD Biosciences). C57BL/6 mice (male and female, 8 weeks old, n=6/sex) will be acclimatized for 1 week prior to the experiment. Animals will be kept under a standard condition with room temperature at 21-23 °C, 30-70% relative humidity, and a 12 : 12h light : dark cycle. Chow and water will be available *ad libitum*. Mice will receive bleomycin on day 1 at a dose of 0.66mg/kg (equivalent to 1U/kg), in a volume of 50µl by intra-tracheal administration. Animals will be treated with vehicle, nintedanib, and different doses of MA-4586 or MA-4604 (doses are based on *in vivo* efficacy studies in mouse parturition model).

1.2. *I^{ER}-Sftpc^{I^{73T}}* genetic model of spontaneous lung fibrosis (UPenn). Tamoxifen induction of adult *I^{ER}-Sftpc^{I^{73T}}* mice will be initiated at 12-14 weeks of age by intraperitoneal (ip) injection. The *I^{73T}* model does **not** use bleomycin (indiscriminate cell injury) but involves spontaneous fibrosis emanating from selective AT2 injury. There will be 2 tamoxifen injections, one on d0 and another 4 days later. Both male (n=6) and female (n=6) animals will be used. Animals will be treated with vehicle, nintedanib, and different doses of MA-4586 or MA-4604. BID dosing for MA-4586 and MA-4604 will be used.

2.1. Distinguish transcriptional signatures of lung populations after FP antagonist and nintedanib interventions. We will cross our in-house *Sftpc^{I^{73T}/I^{73T}}*Rosa26^{Flp/Tom}Pdgfra^{GFP/WT} to the commercially available *Ly6a^{MerCreMer}* which functionally labels all adventitial fibroblasts GFP⁺ and TdTom⁺ upon tamoxifen administration. Using this fibrotic model, we will intervene with daily 60 mg/kg nintedanib, PGF2 α inhibitors MA-4586 or MA-4604 at day 12 (dose determined by the efficacious dose in Aim 1). Through scRNASeq analysis, we will interrogate populations dynamics, cell crosstalk, and adventitial lineage signatures. These studies will determine the exact genes and pathways in specific lung cells that are hit by FP antagonist vs nintedanib.

2.2. Define fibrotic, alveolar, and regenerative niche dynamics after FP antagonist and nintedanib interventions: We will employ the same adventitial reporter mouse used in aim 2.1 and generate tissue slices from the fibrotic time point after intervention with daily 60 mg/kg nintedanib, MA-4586, MA-4604, or vehicle. These tissue slices will be prepared for spatial transcriptomics. Using our single cell data from aim 2.1 as a reference, we will identify spatial niches associated with profibrotic populations as well as those hypothesized to be involved in repair including transitional and adventitial populations. Concurrent to the generation of slides, H&E serial sections will be used to identify regions of cellular infiltration and fibrosis.

3.2. *In vivo* PK studies (LabCorp CRO): MA-4586 and MA-4604 will be prepared in various oral formulations and administered as a single dose and repeat dose (rats and dogs) to evaluate how these formulations affect the drug's PK profile. A single oral dose of MA-4586 / MA-4604 administered to rats under both fed and fasted conditions will evaluate whether the presence of food affects the PK profiles of the drug candidate, which helps investigate potential food and drug interactions and assists in optimizing dosing regimens. The PK profiles of MA-4586 and MA-4604 will be studied after administering its highest dose to both male and female rats to explore potential sex-related differences in drug metabolism to ensure its efficacy and safety across genders. A repeat dose PK study with a single selected formulation will assess its accumulation and steady-state concentration within the body. The distribution of the compounds over time in different organs will also be evaluated in rats.

3.3. Non-GLP Toxicology studies (LabCorp CRO): Dose range finding (DRF) / maximum tolerated dose (MTD) toxicology studies in rats and dogs will aim at finding the dose that will produce tolerable levels of adverse toxic effects of the 2 tested compounds. Adverse effects of acute dose administration (single dose escalation) will be determined via oral gavage (OG). Data from this phase will assist in estimating the MTD for a single administration and establish dose for a repeat dose phase. A 14-day (repeat) toxicity study will then investigate toxicity induced by the test compounds (MA-4586 and MA-4604) when given daily for 14 consecutive days to define a NOEL (no-observable-effect-level) and NOAEL (no-observed-adverse-effect level).

Summary of Animals Used:

Study	Species/Strain	Male	Female
Sub-Aim 1.1	C57BL/6 mice	6	6
Sub-Aim 1.2	<i>I^{ER}-Sftpc^{I^{73T}}</i> mice	6	6
Sub-Aim 2.1	<i>Sftpc^{I^{73T}/I^{73T}}</i> Rosa26 ^{Flp/Tom} Pdgfra ^{GFP/WT} crossed with <i>Ly6a^{MerCreMer}</i> mice	6	6
Sub-Aim 2.2	<i>Sftpc^{I^{73T}/I^{73T}}</i> Rosa26 ^{Flp/Tom} Pdgfra ^{GFP/WT} crossed with <i>Ly6a^{MerCreMer}</i> mice	6	6
Sub-Aim 3.2	Sprague Dawley Rat	45	0
	Beagle Dog	36	0
Sub-Aim 3.3	Sprague Dawley Rat	36	36
	Beagle Dog	16	16

Total Mice	24	24
Total Sprague Dawley Rats	81	36
Total Beagle Dogs	52	16

2. Justifications

The welfare of all study animals is of primary importance. The purpose of the proposed animal studies is to obtain data on the preclinical efficacy, safety/toxicity, and transcriptomics of MA-4586 and MA-4604. The interaction of the test agents with intact animal systems is of crucial importance and we have carried out extensive prior work to justify moving to the proposed studies in mice, rats, and dogs. The principles of refinement, reduction, and replacement will be applied whenever possible. Safety studies follow FDA guidance and CRO recommendations in the selection of a species to characterize the MA-4586 and MA-4604 safety profiles, determine the dose-response relationship, and establish safety margins to guide IND-enabling GLP studies. Alternative models (*in vitro*, computational, invertebrate) that incorporate all required variables are not available. Additionally, toxicology evidence including mammalian species is generally required for safety data to support clinical development. Beagle dogs are typically used in similar studies as the mammal of choice in preparation for GLP toxicology.

3. Minimization of Pain and Distress

All animals receive humane care in compliance with government and institutional guidelines. Animals may experience pain or distress as a result of treatment or surgical manipulations to be performed. To minimize this, animals will be maintained at a surgical plane of anesthesia. To assess the depth of anesthesia, the loss of toe pinch or pedal withdrawal reflex will be checked regularly.

Animals will be monitored at least daily by staff for such criteria as abnormal posture, changes in respiratory rate, lack of grooming, infection/inflammation at the injection site, eye discharge, piloerection, reduction in activity or response to stimuli. Veterinarians will be consulted if any of the preceding signs are observed to identify the appropriate course of action.

4. Method of Euthanasia

At the completion of the study, all animals will be euthanized using methods consistent with the AVMA *Guidelines for the Euthanasia of Animals: 2020 Edition*.

LITERATURE CITED

1. Lederer DJ, Martinez FJ. Idiopathic Pulmonary Fibrosis. Longo DL, ed. *N Engl J Med.* 2018;378(19):1811-1823. doi:10.1056/NEJMra1705751
2. Koo SM, Uh ST, Kim DS, et al. Relationship between survival and age in patients with idiopathic pulmonary fibrosis. *J Thorac Dis.* 2016;8(11):3255-3264. doi:10.21037/jtd.2016.11.40
3. Pergolizzi JV, LeQuang JA, Varrassi M, Breve F, Magnusson P, Varrassi G. What Do We Need to Know About Rising Rates of Idiopathic Pulmonary Fibrosis? A Narrative Review and Update. *Adv Ther.* 2023;40(4):1334-1346. doi:10.1007/s12325-022-02395-9
4. Hutchinson J, Fogarty A, Hubbard R, McKeever T. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. *Eur Respir J.* 2015;46(3):795-806. doi:10.1183/09031936.00185114
5. Cottin V, Spagnolo P, Bonniaud P, et al. Mortality and Respiratory-Related Hospitalizations in Idiopathic Pulmonary Fibrosis Not Treated With Antifibrotics. *Front Med.* 2021;8:802989. doi:10.3389/fmed.2021.802989
6. Collard HR, Chen SY, Yeh WS, et al. Health Care Utilization and Costs of Idiopathic Pulmonary Fibrosis in U.S. Medicare Beneficiaries Aged 65 Years and Older. *Annals ATS.* 2015;12(7):981-987. doi:10.1513/AnnalsATS.201412-553OC
7. Wakwaya Y, Brown KK. Idiopathic Pulmonary Fibrosis: Epidemiology, Diagnosis and Outcomes. *The American Journal of the Medical Sciences.* 2019;357(5):359-369. doi:10.1016/j.amjms.2019.02.013
8. Mooney J, Reddy SR, Chang E, Broder MS, Gokhale S, Corral M. Antifibrotic therapies reduce mortality and hospitalization among Medicare beneficiaries with idiopathic pulmonary fibrosis. *JMCP.* 2021;27(12):1724-1733. doi:10.18553/jmcp.2021.27.12.1724
9. Shah PV, Balani P, Lopez AR, Nobleza CMN, Siddiqui M, Khan S. A Review of Pirfenidone as an Anti-Fibrotic in Idiopathic Pulmonary Fibrosis and Its Probable Role in Other Diseases. *Cureus.* Published online January 4, 2021. doi:10.7759/cureus.12482
10. Dempsey TM, Payne S, Sangaralingham L, Yao X, Shah ND, Limper AH. Adoption of the Antifibrotic Medications Pirfenidone and Nintedanib for Patients with Idiopathic Pulmonary Fibrosis. *Annals ATS.* 2021;18(7):1121-1128. doi:10.1513/AnnalsATS.202007-901OC
11. Thong L, McElduff EJ, Henry MT. Trials and Treatments: An Update on Pharmacotherapy for Idiopathic Pulmonary Fibrosis. *Life.* 2023;13(2):486. doi:10.3390/life13020486
12. Somogyi V, Chaudhuri N, Torrisi SE, Kahn N, Müller V, Kreuter M. The therapy of idiopathic pulmonary fibrosis: what is next? *Eur Respir Rev.* 2019;28(153):190021. doi:10.1183/16000617.0021-2019
13. Calvello M, Flore MC, Richeldi L. Novel drug targets in idiopathic pulmonary fibrosis. *Expert Opinion on Orphan Drugs.* 2019;7(3):125-146. doi:10.1080/21678707.2019.1590196
14. Oga T, Matsuoka T, Yao C, et al. Prostaglandin F2 α receptor signaling facilitates bleomycin-induced pulmonary fibrosis independently of transforming growth factor- β . *Nat Med.* 2009;15(12):1426-1430. doi:10.1038/nm.2066
15. Aihara K, Handa T, Oga T, et al. Clinical Relevance of Plasma Prostaglandin F2 α Metabolite Concentrations in Patients with Idiopathic Pulmonary Fibrosis. Feghali-Bostwick C, ed. *PLoS ONE.* 2013;8(6):e66017. doi:10.1371/journal.pone.0066017
16. Rodriguez LR, Tang SY, Roque Barboza W, et al. PGF2 α signaling drives fibrotic remodeling and fibroblast population dynamics in mice. *JCI Insight.* 2023;8(24):e172977. doi:10.1172/jci.insight.172977

17. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and Prevalence of Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med.* 2006;174(7):810-816. doi:10.1164/rccm.200602-163OC
18. Flaherty KR, Mumford JA, Murray S, et al. Prognostic Implications of Physiologic and Radiographic Changes in Idiopathic Interstitial Pneumonia. *Am J Respir Crit Care Med.* 2003;168(5):543-548. doi:10.1164/rccm.200209-1112OC
19. Richeldi L, Du Bois RM, Raghu G, et al. Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis. *N Engl J Med.* 2014;370(22):2071-2082. doi:10.1056/NEJMoa1402584
20. King TE, Bradford WZ, Castro-Bernardini S, et al. A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. *N Engl J Med.* 2014;370(22):2083-2092. doi:10.1056/NEJMoa1402582
21. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *The Lancet.* 2011;377(9779):1760-1769. doi:10.1016/S0140-6736(11)60405-4
22. Heukels P, Moor CC, Von Der Thüsen JH, Wijsenbeek MS, Kool M. Inflammation and immunity in IPF pathogenesis and treatment. *Respiratory Medicine.* 2019;147:79-91. doi:10.1016/j.rmed.2018.12.015
23. Inui N, Sakai S, Kitagawa M. Molecular Pathogenesis of Pulmonary Fibrosis, with Focus on Pathways Related to TGF- β and the Ubiquitin-Proteasome Pathway. *IJMS.* 2021;22(11):6107. doi:10.3390/ijms22116107
24. Hancock LA, Hennessy CE, Solomon GM, et al. Muc5b overexpression causes mucociliary dysfunction and enhances lung fibrosis in mice. *Nat Commun.* 2018;9(1):5363. doi:10.1038/s41467-018-07768-9
25. Seibold MA, Wise AL, Speer MC, et al. A Common *MUC5B* Promoter Polymorphism and Pulmonary Fibrosis. *N Engl J Med.* 2011;364(16):1503-1512. doi:10.1056/NEJMoa1013660
26. Moore C, Blumhagen RZ, Yang IV, et al. Resequencing Study Confirms That Host Defense and Cell Senescence Gene Variants Contribute to the Risk of Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med.* 2019;200(2):199-208. doi:10.1164/rccm.201810-1891OC
27. Thomas AQ, Lane K, Phillips J, et al. Heterozygosity for a Surfactant Protein C Gene Mutation Associated with Usual Interstitial Pneumonitis and Cellular Nonspecific Interstitial Pneumonitis in One Kindred. *Am J Respir Crit Care Med.* 2002;165(9):1322-1328. doi:10.1164/rccm.200112-123OC
28. Markart P, Ruppert C, Wygrecka M, et al. Surfactant protein C mutations in sporadic forms of idiopathic interstitial pneumonias. *European Respiratory Journal.* 2006;29(1):134-137. doi:10.1183/09031936.00034406
29. Whitsett JA, Weaver TE. Hydrophobic Surfactant Proteins in Lung Function and Disease. *N Engl J Med.* 2002;347(26):2141-2148. doi:10.1056/NEJMra022387
30. Peljto AL, Blumhagen RZ, Walts AD, et al. Idiopathic Pulmonary Fibrosis Is Associated with Common Genetic Variants and Limited Rare Variants. *Am J Respir Crit Care Med.* 2023;207(9):1194-1202. doi:10.1164/rccm.202207-1331OC
31. Alder JK, Chen JJL, Lancaster L, et al. Short telomeres are a risk factor for idiopathic pulmonary fibrosis. *Proc Natl Acad Sci USA.* 2008;105(35):13051-13056. doi:10.1073/pnas.0804280105
32. Huzen J, Wong LSM, Van Veldhuisen DJ, et al. Telomere length loss due to smoking and metabolic traits. *J Intern Med.* 2014;275(2):155-163. doi:10.1111/joim.12149
33. Milara J, Serrano A, Peiró T, et al. Aclidinium inhibits cigarette smoke-induced lung fibroblast-to-myofibroblast transition. *Eur Respir J.* 2013;41(6):1264-1274. doi:10.1183/09031936.00017712

34. Bellou V, Belbasis L, Evangelou E. Tobacco Smoking and Risk for Pulmonary Fibrosis. *Chest*. 2021;160(3):983-993. doi:10.1016/j.chest.2021.04.035
35. Moore BB, Moore TA. Viruses in Idiopathic Pulmonary Fibrosis. Etiology and Exacerbation. *Annals ATS*. 2015;12(Supplement 2):S186-S192. doi:10.1513/AnnalsATS.201502-088AW
36. Sheng G, Chen P, Wei Y, et al. Viral Infection Increases the Risk of Idiopathic Pulmonary Fibrosis. *Chest*. 2020;157(5):1175-1187. doi:10.1016/j.chest.2019.10.032
37. Wendisch D, Dietrich O, Mari T, et al. SARS-CoV-2 infection triggers profibrotic macrophage responses and lung fibrosis. *Cell*. 2021;184(26):6243-6261.e27. doi:10.1016/j.cell.2021.11.033
38. Wolters PJ, Collard HR, Jones KD. Pathogenesis of Idiopathic Pulmonary Fibrosis. *Annu Rev Pathol Mech Dis*. 2014;9(1):157-179. doi:10.1146/annurev-pathol-012513-104706
39. Flaherty KR, Toews GB, Travis WD, et al. Clinical significance of histological classification of idiopathic interstitial pneumonia. *Eur Respir J*. 2002;19(2):275-283. doi:10.1183/09031936.02.00182002
40. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2018;198(5):e44-e68. doi:10.1164/rccm.201807-1255ST
41. Katzenstein ALA, Myers JL. Nonspecific Interstitial Pneumonia and the Other Idiopathic Interstitial Pneumonias: Classification and Diagnostic Criteria: *The American Journal of Surgical Pathology*. 2000;24(1):1. doi:10.1097/00000478-200001000-00001
42. Nathan SD, Shlobin OA, Weir N, et al. Long-term Course and Prognosis of Idiopathic Pulmonary Fibrosis in the New Millennium. *Chest*. 2011;140(1):221-229. doi:10.1378/chest.10-2572
43. Wollin L, Wex E, Pautsch A, et al. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. *Eur Respir J*. 2015;45(5):1434-1445. doi:10.1183/09031936.00174914
44. Wollin L, Maillet I, Quesniaux V, Holweg A, Ryffel B. Antifibrotic and Anti-inflammatory Activity of the Tyrosine Kinase Inhibitor Nintedanib in Experimental Models of Lung Fibrosis. *J Pharmacol Exp Ther*. 2014;349(2):209-220. doi:10.1124/jpet.113.208223
45. Glass DS, Grossfeld D, Renna HA, et al. Idiopathic pulmonary fibrosis: Current and future treatment. *Clinical Respiratory J*. 2022;16(2):84-96. doi:10.1111/crj.13466
46. Nureki SI, Tomer Y, Venosa A, et al. Expression of mutant Sftpc in murine alveolar epithelia drives spontaneous lung fibrosis. *Journal of Clinical Investigation*. 2018;128(9):4008-4024. doi:10.1172/JCI99287
47. Beck H, Thaler T, Meibom D, et al. Potent and Selective Human Prostaglandin F (FP) Receptor Antagonist (BAY-6672) for the Treatment of Idiopathic Pulmonary Fibrosis (IPF). *J Med Chem*. 2020;63(20):11639-11662. doi:10.1021/acs.jmedchem.0c00834
48. Sharif NA, Klimko PG. Prostaglandin FP receptor antagonists: discovery, pharmacological characterization and therapeutic utility. *British J Pharmacology*. 2019;176(8):1059-1078. doi:10.1111/bph.14335
49. Goupil E, Tassy D, Bourguet C, et al. A Novel Biased Allosteric Compound Inhibitor of Parturition Selectively Impedes the Prostaglandin F2 α -mediated Rho/ROCK Signaling Pathway. *Journal of Biological Chemistry*. 2010;285(33):25624-25636. doi:10.1074/jbc.M110.115196
50. Peri KG, Quiniou C, Hou X, et al. THG113: A novel selective FP antagonist that delays preterm labor. *Seminars in Perinatology*. 2002;26(6):389-397. doi:10.1053/sper.2002.37307

51. Bottcher B, Laterza RM, Wildt L, et al. A first-in-human study of PDC31 (prostaglandin F2 receptor inhibitor) in primary dysmenorrhea. *Human Reproduction*. 2014;29(11):2465-2473. doi:10.1093/humrep/deu205
52. Cirillo R, Tos EG, Page P, et al. Arrest of preterm labor in rat and mouse by an oral and selective nonprostanoid antagonist of the prostaglandin F2 α receptor (FP). *American Journal of Obstetrics and Gynecology*. 2007;197(1):54.e1-54.e9. doi:10.1016/j.ajog.2007.02.010
53. Pohl O, Marchand L, Gotteland J, Coates S, Täubel J, Lorch U. Pharmacokinetics, safety and tolerability of OBE022, a selective prostaglandin F2 α receptor antagonist tocolytic: A first-in-human trial in healthy postmenopausal women. *Brit J Clinical Pharma*. 2018;84(8):1839-1855. doi:10.1111/bcp.13622
54. Täubel J, Lorch U, Coates S, et al. Confirmation of the Cardiac Safety of PGF $_{2\alpha}$ Receptor Antagonist OBE022 in a First-in-Human Study in Healthy Subjects, Using Intensive ECG Assessments. *Clinical Pharm in Drug Dev*. 2018;7(8):889-900. doi:10.1002/cpdd.447
55. Bowes J, Brown AJ, Hamon J, et al. Reducing safety-related drug attrition: the use of in vitro pharmacological profiling. *Nat Rev Drug Discov*. 2012;11(12):909-922. doi:10.1038/nrd3845
56. Li W jiao, Lu J wen, Zhang C yue, et al. PGE2 vs PGF2 α in human parturition. *Placenta*. 2021;104:208-219. doi:10.1016/j.placenta.2020.12.012
57. Sugimoto Y, Yamasaki A, Segi E, et al. Failure of Parturition in Mice Lacking the Prostaglandin F Receptor. *Science*. 1997;277(5326):681-683. doi:10.1126/science.277.5326.681
58. Pohl O, Chollet A, Kim SH, et al. OBE022, an Oral and Selective Prostaglandin F $_{2\alpha}$ Receptor Antagonist as an Effective and Safe Modality for the Treatment of Preterm Labor. *J Pharmacol Exp Ther*. 2018;366(2):349-364. doi:10.1124/jpet.118.247668
59. Rodriguez LR, Tang SY, Barboza WR, et al. *Disruption of Prostaglandin F $_{2\alpha}$ Receptor Signaling Attenuates Fibrotic Remodeling and Alters Fibroblast Population Dynamics in A Preclinical Murine Model of Idiopathic Pulmonary Fibrosis*. Molecular Biology; 2023. doi:10.1101/2023.06.07.543956
60. Katzen J, Rodriguez L, Tomer Y, et al. Disruption of proteostasis causes IRE1 mediated reprogramming of alveolar epithelial cells. *Proceedings of the National Academy of Sciences*. 2022;119(43):e2123187119. doi:10.1073/pnas.2123187119
61. Patient-specific iPSCs carrying an SFTPC mutation reveal the intrinsic alveolar epithelial dysfunction at the inception of interstitial lung disease - PubMed. Accessed March 12, 2024. <https://pubmed.ncbi.nlm.nih.gov/34469722/>

Scope of Work (BEERS Laboratory)

The laboratory of Dr. Michael Beers at University of Pennsylvania will collaborate with the team at Maipl Therapeutics Inc. on Maipl's SBIR grant to develop and commercialize a PGF2a receptor antagonist for treatment of IPF. The Beers' laboratory will be responsible for profiling and phenotyping the genetic mouse models SP-C^{173T} developed by Dr. Beers in response to treatment with Maipl's compounds (Aim 1). In addition, the Beers' laboratory will assess functional and transcriptomic changes in the lung tissue and alveolar epithelial cells of Stpc^{173T} mutant mice treated with Maipl compounds using scRNASeq as well as RNAscope and Vivium 10X spatial transcriptomics (Aim 2). When dictated experimentally, the Beers' lab will extend the studies to include additional functional outcomes in the AT2 cells and mesenchymal populations from these mice in organoid culture. The mutant mice for these studies will be maintained in Dr. Beers' animal colony at UPENN and *in vivo* and *in vitro* experiments outlined in the Experimental Approach of Aim1 and Aim 2 will be performed and analyzed in his laboratory. Data generated from these studies will be shared with Maipl Therapeutics.



Office of Research Services

Subrecipient Statement of Intent

Subrecipient Institution (Sub) Legal Name:	The Trustees of the University of Pennsylvania	Pass-Through Entity (PTE) Legal Name:	MaipI Therapeutics, Inc.
Sub DUNS:	04-225-0712		

Sub Principal Investigator:	MICHAEL F BEERS	PTE Principal Investigator:	
Sub Internal Project Identifier (optional):	PD# 10098639	PTE Internal Project Identifier (optional):	PA-23-230

Project Title:	Prostaglandin F2 receptor, FP antagonism as a therapeutic option for Idiopathic Pulmonary Disease (IPF)		
Prime Awarding Agency:	NATIONAL INSTITUTES OF HEALTH	Complete Project Period:	Start: 01/01/2025 End: 06/30/2026
Total Proposed Amount for Project Period:	\$ 330,718	Cost Sharing Amount for Project Period:	\$

- Federally negotiated F&A rate that matches our FDP Expanded Clearinghouse Pilot Entity Profile
 A reduced F&A rate dictated by the prime awarding agency. Rate: _____ Base Type: _____
 Not applicable (no indirect costs are requested by Sub)

Project Use Information:

Human Subjects <input type="checkbox"/> Yes <input type="checkbox"/> No	Vertebrate Animals <input type="checkbox"/> Yes <input type="checkbox"/> No	Stem Cells <input type="checkbox"/> Yes <input type="checkbox"/> No	Genomic Data Sharing <input type="checkbox"/> Yes <input type="checkbox"/> No
---	---	---	---

Sub Email for Awards:	pennaors@lists.upenn.edu
-----------------------	--------------------------

This proposal has been reviewed and approved by the appropriate official(s) of Subrecipient, and certified to its accuracy and completeness. The appropriate programmatic and administrative personnel of Subrecipient involved in this application are aware of the prime awarding agency's policies, agree to accept the obligation to comply with award terms, conditions and certifications, and are prepared to establish the necessary inter-institutional agreement consistent with that policy.

This letter also serves as certification that the University of Pennsylvania has a conflict of interest policy that is in compliance with the requirements of all applicable regulations, including but not limited to those set forth in 45 CFR Part 94 and 42 CFR Part 50, Subpart F. All financial disclosures have been made related to the activities that may be funded and prior to expenditure of funds or within 30 days the University of Pennsylvania will report to prime institution any identified financial conflict of interest related to the award, and provide an indication whether the conflict has been managed, reduced or eliminated.

Further, the University of Pennsylvania (Penn) is submitting this proposal with the understanding that the scope of work is considered fundamental research. Penn reserves the right to negotiate an agreement that complies with university policies and will permit free publication of results should this proposal be selected for funding. Penn's policies prohibit discrimination based on nationality, country of origin, ethnicity, gender, race or religion. Penn cannot accept any award terms or conditions which would restrict any member of the research group, including faculty, students, and staff from the ability to participate fully in all of the intellectually significant portions of the project.

The following documents are attached to this Statement of Intent:

- | | |
|--|---|
| <input type="checkbox"/> Sub Statement of Work | <input type="checkbox"/> Sub Budget Justification |
| <input type="checkbox"/> Sub Detailed Line Item Budget | <input type="checkbox"/> Other (Specify): _____ |

Michael Carman Jr. Digitally signed by Michael Carman Jr.
 Date: 2024.03.14 15:42:14 -04'00' 03/15/2024

Signature of Subrecipient's Authorized Official

Date

Michael Carman Jr. / Associate Director

Name, Title, and Email of Authorized Official

**3451 Walnut Street 5th Floor, Franklin Building Philadelphia PA
 19104-6205 TEL 215.898.7293 FAX 215.898.9708**



Lung Epithelial Cell Biology Laboratories
Pulmonary, Allergy, and Critical Care Division
Department of Medicine

Michael F. Beers, M.D.
Robert L Mayock and David A Cooper
Professor of Medicine

PENN-CHOP Lung Biology Institute
Hospital of the University of Pennsylvania
Corporal Michael Crescenz VA Medical Center

March 5th, 2024

Dr. Yong Yue
Maipl Therapeutics Inc,
40 W 51ST ST. #5091
New York, NY 10185

Dear Yue,

I write expressing enthusiastic support for the SBIR application by Maipl Therapeutics, Inc. entitled "*Prostaglandin F2a receptor, FP antagonism as a therapeutic option for Idiopathic Pulmonary Disease (IPF)*." I am proud to be your academic partner on such a timely and critical proposal.

As you know, I am a physician scientist in the Pulmonary, Allergy & Critical Care Division of the Department of Medicine at the Perelman School of Medicine with expertise in epithelial dysfunction, surfactant biology, and parenchymal lung disease. My lab has long-standing experience in analysis of pulmonary phenotypes in mice, especially those associated with a variety of injury and remodeling models, such as the *Sftpc^{1/3T}* mutant mice featured in your current proposal, which we originally published in 2018 (Nureki, et al. in *J Clin Invest* 2018 *PMC 6118576*). In addition, my lab has developed a significant interest in PGF2a signaling as a result of our recent publication in *JCI Insight* (Rodriguez, et al 2023 *PMC 10807712*) and I am excited by the library of compounds you have developed targeting this pathway.

For your current proposal, I am delighted to collaborate as the academic partner on a subcontract participating on your SBIR application. My lab and I are really looking forward to work together assessing both the effect size of your compounds in our *Sftpc^{1/3T}* model (Aim 1) as well as a detailed mechanistic evaluation of the cell populations in the fibrotic niche impacted by PGF2 α signals (Aim 2). These studies will provide impactful new data to drive patient stratification based on cellular endophenotypes, promote development of new clinical biomarkers, and allow differentiation from the current standard of care (i.e., Nintedanib) while also promoting new understanding of why some patients do not respond (or have poor response) to Nintedanib and how FP antagonism may be effective.

During the course of your work, you will have access to myself and my team for consultation and brainstorming. I look forward to this impactful collaboration.

Good luck with the proposal.

Kind regards,

A handwritten signature in blue ink that reads "Michael F. Beers M.D."

Michael F. Beers, MD
Robert L. Mayock & David A. Cooper Professor of Medicine

Department of Radiology



*Vagelos College of Physicians and Surgeons
Columbia University Irving Medical Center*

March 17, 2024

Dr. Yong Yue
President & CEO
Maipl Therapeutics, Inc.
18 Circle Road
Scarsdale, NY 10185

Dear Dr. Yue,

I am writing this letter to support Maipl's proposal "Prostaglandin F2a receptor, FP antagonism as a therapeutic option for Idiopathic Pulmonary Disease (IPF)" to be submitted to the NIH's SBIR program.

I am a professor of radiology at Columbia University Irving Medical. My expertise lies in thoracic radiology with a specific focus on interstitial lung diseases. I have dedicated my career to identifying patterns of fibrosis on chest CT and translating the patterns into clinically meaningful implications such as why Usual Interstitial Pneumonitis (UIP), the most common and most lethal of the fibrotic lung diseases, is peripherally located. I have created a visual radiology scoring system that correlates with % DLCO and mortality and allows quantification of the rate of change allowing characterization of patients as rapid progressors who would benefit most from interventions. Cancer is a significant complication for patients with fibrosis, we have described how lung cancer in fibrosis is different than lung cancer in emphysema and are currently working to understand where and why lung cancer occurs in fibrosis.

The incidence of pulmonary fibrosis with its morbidity and mortality is increasing as the population ages. As a leading researcher in the early and accurate diagnosis of idiopathic pulmonary fibrosis, I am uniquely suited to address the need for an IPF treatment on the market. Maipl Tx stands out as the sole enterprise actively engaged in the development and marketing of a prostaglandin F2 alpha receptor antagonist possessing drug-like characteristics intended for IPF treatment. This distinguishes Maipl from its counterparts, as the majority of ongoing drug development efforts are focused on TGF-beta-dependent pathways. By directing its efforts towards the prostaglandin F2 alpha receptor, an independent pathway from TGF-beta, Maipl is strategically targeting a pathway that plays a pivotal role in fibrogenesis. I am confident that Maipl's leadership and team possess the skills necessary to bring to fruition improved outcomes for patients who suffer from this disease given their considerable experience and determination.

I fully support Maipl Tx and its endeavors to provide an improved/novel therapeutic for the treatment of IPF. I look forward to being kept apprised of your developments.

630 West 168th Street MC 28 New York, NY 10032-3784

DocuSign Envelope ID: 87F1684D-9590-4830-9F54-124E78ED1240

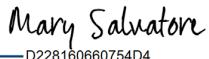
Department of Radiology



Vagelos College of Physicians and Surgeons
Columbia University Irving Medical Center

Sincerely,

DocuSigned by:

 Mary Salvatore

D228160660754D4...

Mary M. Salvatore MD, MBA
Professor of Radiology
Columbia University Irving Medical Center
New York, NY 10032

630 West 168th Street MC 28 New York, NY 10032-3784

From the Desk of
CALVERT LOUDEN

March 20th, 2024

Dr. Yong Yue
President & CEO
Maipl Therapeutics, Inc.
18 Circle Road
Scarsdale, NY 10185

Dear Dr. Yue,,

I am writing this letter to confirm my role as a Pathologist & Toxicologist Consultant in Maipl's SBIR application titled: "*Prostaglandin F2 α receptor, FP antagonism as a therapeutic option for Idiopathic Pulmonary Disease (IPF)*", to be submitted to the NIH in April, 2024.

I have 25+ years of pharmaceutical experience from SmithKline Beecham, AstraZeneca, Johnson and Johnson and served as Ferring Pharmaceuticals vice president of global nonclinical safety sciences. I would be happy to provide pathology and toxicology advise and support to Maipl with the proposed nonclinical toxicology testing strategy and in the conduct and execution of FIH enabling nonclinical safety studies. The hourly rate for my consulting services is \$350/hour and I am willing to commit up to 10h/week for this project (\$14000/month for 1.5 years).

I fully support Maipl Therapeutics and your endeavors to provide an improved therapy for Idiopathic Pulmonary Fibrosis (IPF). Best of luck in securing funding for this important work.

Best Regards.



Calvert Louden
Mar 20, 2024

Calvert Louden, DVM Ph.D, Dip ACVP, FIATP.
Director
CSG Path-Tox Consultants
Norristown, Pennsylvania, USA



March 20th, 2024

Dr. Yong Yue
President & CEO
Maipl Therapeutics, Inc.
18 Circle Road
Scarsdale, NY 10185

Dear Dr. Yue,

I am writing this letter to confirm my role as a DMPK/ADME Consultant in Maipl's SBIR application titled: "*Prostaglandin F2 α receptor, FP antagonism as a therapeutic option for Idiopathic Pulmonary Disease (IPF)*", to be submitted to the NIH in April, 2024.

I have more than 10 years of experience in DMPK/ADME space having worked at various CRO (Wuxi ApTec, NJ), Pharmaceutical (Takeda and Ferring Pharmaceuticals, both in San Diego) and Biotech (Janux Therapeutics, San Diego) companies. I would be happy to help Maipl in its PK studies and liaison with Toxicology to successfully accomplish the proposed studies. The hourly rate for my consulting services is \$300/hour and I am willing to commit up to 5h/week for this project (\$6000/month for 2 years).

I fully support Maipl Therapeutics and your endeavors to provide an improved therapy for Idiopathic Pulmonary Fibrosis (IPF). Best of luck in securing funding for this important work.

Best Regards.

A handwritten signature in black ink that reads "Ying Zhang".

Ying Zhang, Ph.D.
3857 Pell Place, San Diego, CA 92130

Wednesday, March 20, 2024 at 14:30:38 Eastern Daylight Time

Subject: Maipl Therapeutics passes JLABS Final Review!
Date: Wednesday, March 20, 2024 at 1:56:00 PM Eastern Daylight Time
From: Fredericksen, Michelle [US]
To: Yong Yue
Attachments: image001.jpg

Hello Yong,

Great news, we received notice that Maipl Therapeutics has cleared the Final Review stage! We would like to formally invite you to join JLABS - Congratulations!

Now that you've passed final review, there are some items you can get started on:

1. TOUR OF SITE TO SELECT SPACE – Scheduled for March 27th at 2:00pm.
2. REVIEW OF LICENSE AGREEMENT
 - a) Should you have any questions about anything in the attached draft License Agreement, please contact, me.
 - b) Should you have any legal questions, you are responsible for engaging your own attorney for advice.
3. OTHER ACTION ITEMS

To gain occupancy at JLABS you will need to have the following in place, please feel free to get a head start:

a. **Insurance:** The insurance requirements set for in Article XIV and Exhibit C of the License Agreement have typically taken other licensees several weeks to secure with their Insurance agent and insurer, so it is advised that you provide your agent with Exhibit C at your earliest convenience to insure that all requirements set forth therein are met. If at any time, you or your agent has any questions about the insurance requirements, please do not hesitate to contact me. Attached is a list of agents and insurers that have worked with some licensees in securing coverage in JLABS in the event you are having any difficulties.

b. **Business Tax License** (this application will take ten minutes to complete but may take up to two weeks to obtain). You need only submit a copy of the application to me prior to move-in.

c. **California EPA ID:** If you will have a laboratory footprint, please apply for an EPA ID through this link. The SIC code on the application should be 2834, which is the code for all pharma and biotech applications. Eric can also help you complete this form.

LOOKING AHEAD:

At Johnson & Johnson Innovation, we are committed to helping advance health equity – the process of eliminating avoidable differences in health outcomes across historically underserved communities. After you have onboarded, we will invite you to complete a voluntary Health Equity Assessment Tool (HEAT) designed to help early-stage innovators consider ways to integrate health equity into their ways of working. If you'd like to better understand our perspective on health equity, you can check out the module "Unlocking Innovation Through Health Equity".

If you have any questions, please do not hesitate to reach out to myself or any of the JLABS team members.

We look forward to having your team at JLABS!

Warm Regards,

Michelle FREDERICKSEN

Senior Business Operations Manager, North America - JLABS @ San
Diego+1 (760)-566-8628



Getting this email outside of your working hours? At J&J, we are globally connected, committed to Our Credo and work in ways that allow us to meet our commitments at work and at home. We value making time to get enough sleep, eat right, be physically active, and spend time with the people that matter most. I am sending you this email at a time that works for me. I only expect you to respond to it when convenient for you.

RESOURCE SHARING PLAN

Maipl Therapeutics will make the results and accomplishments of this research available to the research community and to the public at large by the timely release and sharing of data. As a means of sharing knowledge, the investigators supported by this grant will seek to publish the original research in primary scientific journals. For each publication that results from the grant-supported research, we will include an acknowledgment of NIH grant support and follow guidelines regarding free access to published materials. Information on each publication resulting from work performed under the NIH grant-supported project will be included in the annual and/or final progress report submitted to the NIH awarding office. Maipl Therapeutics will work with other investigators to respond to requests for data for reanalysis or assistance replicating the research, and all reasonable requests will be accommodated given appropriate data and privacy protections, feasibility of complying with the request, and compliance with the policies of all participating institutions and organizations. Maipl Therapeutics is also open to collaboration with outside groups who express interest in this approach. Maipl Therapeutics defines “reasonable request” for data as requiring: (1) at least 30 days to comply, (2) that it is not a significant burden to prepare, (3) that it is not a significant cost to prepare or host, (4) that it is for research purposes only, and (5) has a sound scientific rationale and purpose including one with a testable and plausible hypothesis or reasonable analysis goals.

INTELLECTUAL PROPERTY RIGHTS

The investigators will assert copyright in scientific and technical articles based on data produced under the grant where necessary, but we will also make every effort to keep technologies developed as a result of this research project widely available and accessible to the research community. If additional patents are filed and the technology licensed, we will only seek exclusivity in cases where this approach is determined to be the best route for successful development of the technology for public use and benefit.

NIH Generated message:

The Other Plan(s) attachment included with the application is not evaluated during the peer review process but will be evaluated prior to a funding decision. Although part of the official submission, the attachment is maintained as a separate document in eRA Commons viewable by authorized users and is not part of this assembled application.

AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES

Overview/General:

All planned experiments will be designed and undertaken with masking of experimental groups where applicable, especially for *in vivo* efficacy studies. Studies will be designed with replicates to assess the variability in the experimental measurements for a given experimental condition. Appropriate statistics (parametric and non-parametric) will be employed for each experiment to assess for statistically significant ($p < 0.05$) difference in experimental groups. Generated raw data files and experimental records will be stored in a secure server within Maipl Therapeutics and the respective partner laboratories.

Specialty chemicals and kits:

For FACS analysis, the following reagents and sources will be used: anti-mouse CD16/32 antibody, eBioscience™ Fixable Viability Dye eFluor™ 780, eFluo450 CD11b (eBiosciences, San Diego, CA); PE-CF594 SiglecF (BD Biosciences, Franklin Lakes, NJ); PE CD43, BB515 CD45, BV711 EpCAM, APC-Cy7 PeCAM, APC MHCI-I, PE-Cy7 CD104, PE CD51, BV705 CD11c, AF700 Ly6G, APC CD64, PE-Cy5 MHC-II and BV510 Ly6C (Biolegend, San Diego, CA).

For the hydroxyproline measurement, the Total Collagen Assay Kit for collagen quantification in tissues will be obtained from QuickZyme. For the BALF cytokines: TGF-b, IL-10, IL-1, IL-6. The U-PLEX Assay Platform will be obtained from Meso Scale Discovery. For the BALF soluble collagen measurement, the Soluble Collagen Assay Kit (ab242291) will be obtained from Abcam.

Other common chemicals are from reputable vendors such as Sigma-Aldrich (St Louis, MO). All common chemical resources used in this study are medical-grade drugs or lab reagents obtained from reputable suppliers and used in the course of medical care or laboratory assessment.

Antibodies:

For Western blotting and IHC, a polyclonal proSP-C antiserum (“NPRO-SP-C”) raised against the Met [10]–Glu domain of rat proSP-C, polyclonal anti-SP-B (“PT3”) raised against bovine surfactant protein B, and polyclonal anti-SP-D (antisera 1754) raised against 2 synthetic SP-D peptides are each produced in rabbits in the Beers’ laboratory and validated extensively as published.

The other antibodies and sources proposed for the Western analysis and IFC studies are from commercial sources and have been validated in rigorously in prior independent publications, in the Beers lab, and independently tested and validated by Investigators that utilize the UPENN CVI Histology and Gene Expression Core (approximately 100,000 slides processed each year, 500 antibodies tested and validated in multiple tissue types to ensure specificity).

Animals:

Animals will be maintained in animal facilities under IACUC approved protocols. Both male and female animals will be used as described in the **Research Strategy** and **Vertebrate Animals** sections. Animal totals include:

Study	Species/Strain	Male	Female
Sub-Aim 1.1	C57BL/6 mice	6	6
Sub-Aim 1.2	<i>IE^R-Sftpc^{J73T}</i> mice	6	6
Sub-Aim 2.1	<i>Sftpc^{J73T/J73T}</i> <i>Rosa26^{Flp/Tom}</i> <i>Pdgfra^{GFP/WT}</i> crossed with <i>Ly6a^{MerCreMer}</i> mice	6	6
Sub-Aim 2.2	<i>Sftpc^{J73T/J73T}</i> <i>Rosa26^{Flp/Tom}</i> <i>Pdgfra^{GFP/WT}</i> crossed with <i>Ly6a^{MerCreMer}</i> mice	6	6
Sub-Aim 3.2	Sprague Dawley Rat	45	0
	Beagle Dog	36	0
Sub-Aim 3.3	Sprague Dawley Rat	36	36
	Beagle Dog	16	16
Total Mice		24	24
Total Sprague Dawley Rats		81	36
Total Beagle Dogs		52	16

Primary Mouse Cells

Cells collected for the proposed studies will be validated in the following ways: (1) Cells will be screened for mycoplasma at the time of collection to ensure genomic integrity for further downstream applications; (2) Primary cells will be adhered to coverslips and stained for contaminating cell types as published; (3) Primary cells will also be sorted via Flow cytometry with validated antibodies that are commercially available and have been extensively validated elsewhere.