altamira therapeutics

Targeting important unmet medical needs

Corporate Presentation

H.C. Wainwright BioConnect Conference, January 10, 2022

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Altamira Therapeutics at a Glance

Legacy programs provide potential opportunity to unlock value for investors in the medium-term via spinoff/divestiture

Respiratory - Altamira Medica:

- Bentrio™ (AM-301) for protection against airborne viruses and allergens

Neurotology - Auris Medical:

- AM-125 for treating acute vertigo
- Sonsuvi® (AM-111) for treating acute inner ear hearing loss
- Keyzilen® (AM-101) for treating acute inner ear tinnitus

Transformative acquisition and merger in Summer 2021

- Acquired Trasir Therapeutics (WU spinoff) and subsequently merged into Auris Medical

Repositioning around RNA therapeutics

- Trasir – pioneer in extrahepatic oligonucleotide delivery
- > 15 years of NIH funded research
- Versatile peptide-based OligoPhore™ / SemaPhore™ platform

Initiated preclinical development of first RNA pipeline program off OligoPhore™ platform

- AM-401 for treatment of mutant KRAS-driven cancer

Altamira Group

altamira medica

Medical devices for protection against airborne allergens and viruses

Auris Medical
Cochlear therapies

Therapeutics for inner ear disorders

altamira therapeutics

RNA therapeutics for extrahepatic targets

Leadership Team

Thomas Meyer | PhD

CEO and Chairman

Founder Auris Medical
14 years with Disetronic Group
incl. CEO and BoD member
>20% sales CAGR
$3 bn market cap

Samuel Wickline | MD

Chief Scientific Officer

Prof. of Cardiovascular Sciences,
Molecular Physiology and Pharmacology,
Medical Engineering at USF
Former Prof. of Medicine, Physics,
Biomedical Engineering, Cell Biology
and Physiology at Wash U

Marcel Gremaud | CPA

Chief Financial Officer

~30 years' experience
in controlling and accounting in
international pharma companies
and start-ups

Our Respiratory Business

- OTC nasal spray (AM-301; Bentrio™)
- Drug-free, preservative free medical device
- Protection against airborne viruses and allergens
  - Confirmed activity also against SARS-CoV-2 Delta variant, Omicron to be confirmed
- Launched in Europe (CE mark) in selected EU countries
- FDA acceptance for Bentrio 510(k) application (allergy)
- Ramping up international sales through distributor network – eight Asian countries covered so far
- Addressing multibillion $ markets

Protects

as a physical barrier
the nasal mucosa

Traps

airborne particles through
electrostatic effects

Humidifies

the nasal mucosa and thus
aids its functionality

Protects for ≥ 3 hours

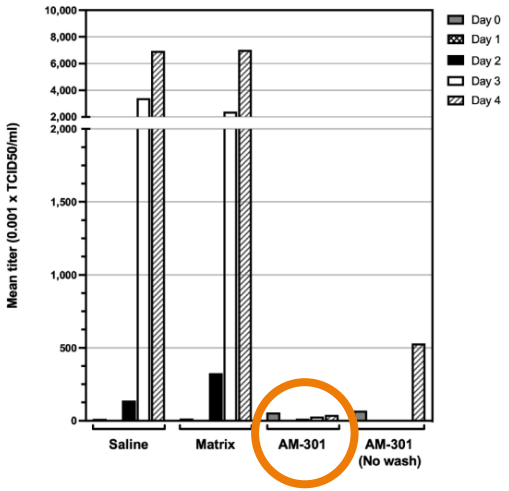
Gel designed for extended
nasal residence time

Efficacy in SARS-CoV-2 and Influenza

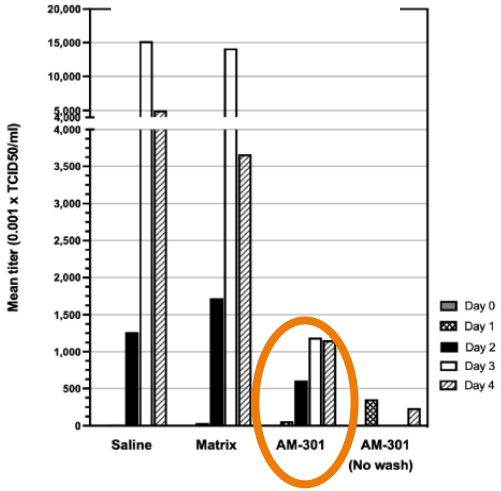
Reconstituted human nasal epithelium model

- Functional nasal mucosa
- Without help from immune system or mucociliary clearance
- Median Tissue Culture Infectious Dose, TCID50, in Vero cells
- Daily treatment with Bentrio™

Prevention
Start 10' Before



Mitigation
Start 30 hrs After



Highly effective protection

- >99% reduction in viral titer

Activity also post infection

- Significant deceleration of viral titer growth

New study also showing protection against the Delta variant of SARS-CoV-2

- 83-85% reduction in viral titer

Recent study showing significant protection also in influenza (H1N1), both with prophylaxis and treatment

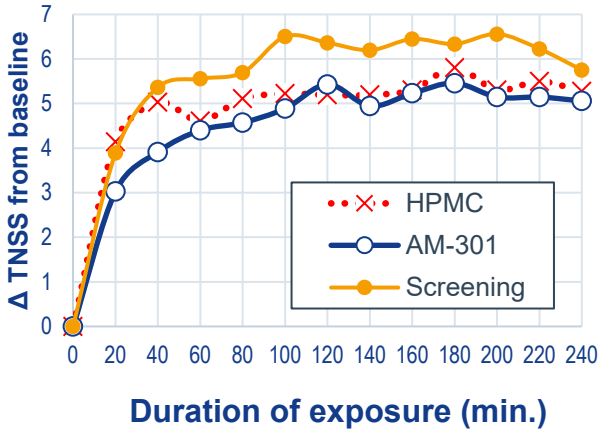
- Viral titer ↓ 84% and 77%

Efficacy in Allergy

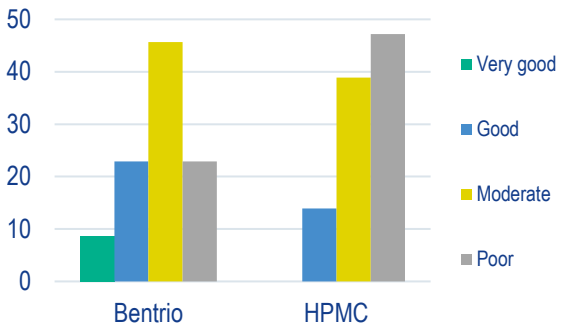
- Clinical pollen chamber study
- Open-label randomized cross-over study
- 36 patients with allergic rhinitis to grass pollen
- Single dose of Bentrio™ or HPMC powder spray prior to 4 hours of controlled pollen exposure

- Study met primary efficacy endpoint = substantial equivalence to predicate device for 510(k)
- Fast onset – significantly better at 20' and 40' timepoints
- Protective effect for 4 hours

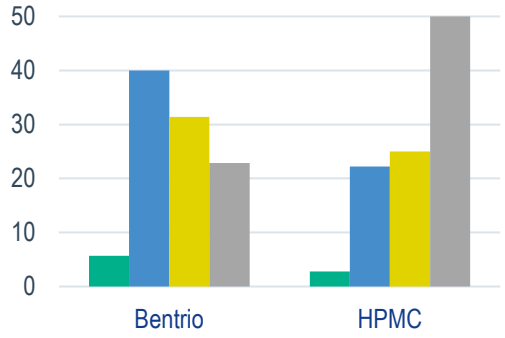
Mean change from baseline



Efficacy rated by subjects (%)



Efficacy rated by clinicians (%)



Market Potential for Bentrio™

Addressing Common Conditions

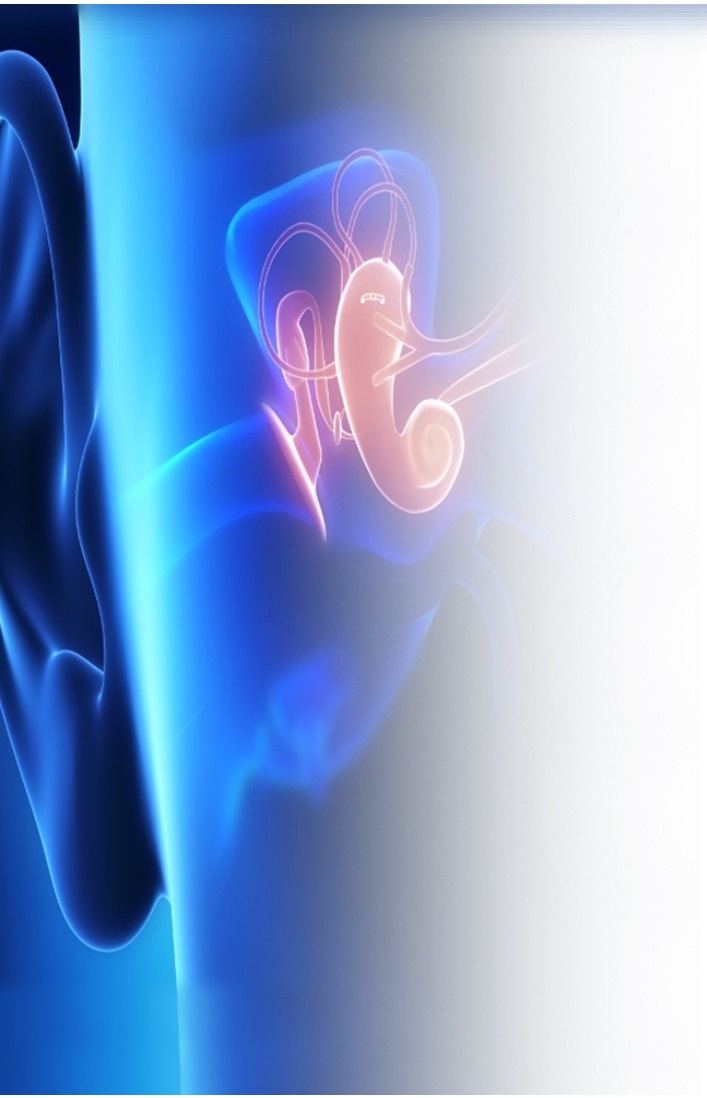
Viral Infection

- Human rhinovirus (HRV) is most common cause of upper respiratory tract infection
- US revenues for could and cough remedies: > $12 billion in 2021[1]
- Influenza resulted in 9-45 million illnesses, 140,000-810,000 hospitalizations and 12,000-61,000 deaths annually since 2010[2]
- COVID-19: 174 million cases and 3.74 million deaths to date

Allergies

- About 7.8% of people 18 and over in the US have hay fever 11.1 million visits to physician offices with primary diagnosis allergic rhinitis[3]
- $4 billion market size for OTC allergy medicines in US in 2020[4]
- Air pollution
  - > 90% of the world's population exposed to unhealthy air, 5th highest mortality risk factor globally[5]
  - E.g. causing 1.8 m premature deaths p.a. in China[6]

[1] *www.statista.com*
[2] *Centers for Disease Control and Prevention*
[3] *Schiller et al., 2010*
[4] *www.ibisworld.com*
[5] *WHO*
[6] *Global Alliance on Health and Pollution*



Our Neurotology Business

- Rx nasal spray (AM-125)
- Reformulated betahistine for vertigo
- Superior bioavailability vs. oral form
- Global market size (oral, ex US) = $450 mm
- Currently in Phase 2
- Phase 3 programs in hearing loss (AM-111) and tinnitus (AM-101) designated for partnering

Intranasal Betahistine for Treating Vertigo

AM-125 Acts as a Vestibular Stimulant

35.4% of the US population ≥ 40 years experience vestibular dysfunction[1]

Lifetime prevalence of vertigo interfering with daily activities is 3-8%[2]

Betahistine – unique vestibular stimulant

- World-wide SOC, but no longer marketed in US
- Current worldwide annual sales ~$450 million[3]

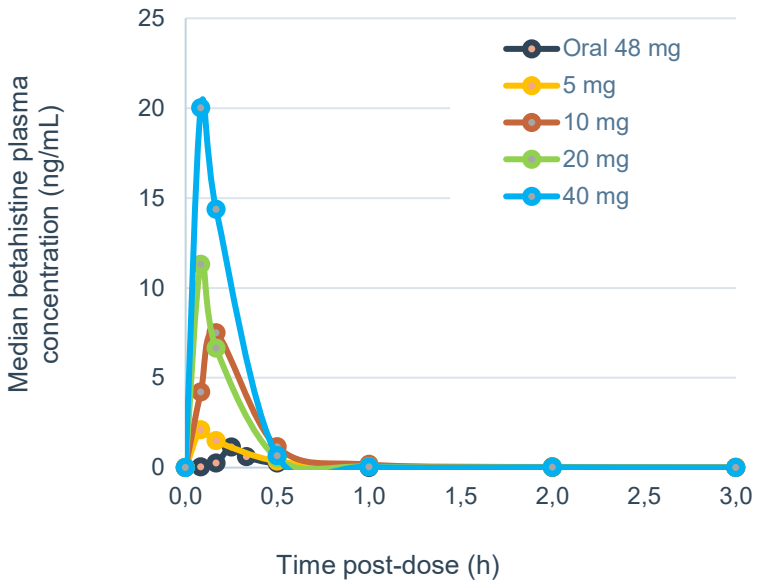
Rx options in US essentially limited to vestibular suppressants

AM-125 addresses betahistine's weak point = poor oral bioavailability (~1%)

- Capture part of existing oral betahistine market
- Bring betahistine back to US

[1] *Agrawal et al., 2009*
[2] *Murdin et al., 2015*
[3] *Oral betahistine, manufacturer prices (IMS).*

Superior Bioavailability Using Intranasal Route



- Betahistine targets the histaminergic system
  - Increases inner ear and cerebral blood flow
  - Increases histamine turnover and enhances histamine release in CNS
  - Enhances release of acetylcholine, dopamine and norepinephrine in CNS
- Relative bioavailability of AM-125 vs. oral betahistine (daily dose) = 5 to 29 x

AM-125 Development & Milestones

Development Plan

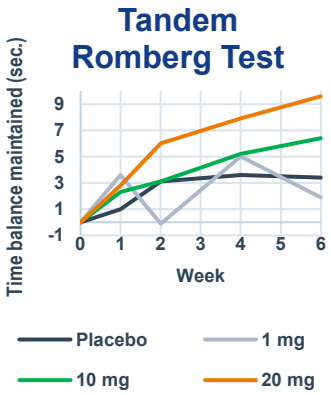
Target indication and patient benefit

- Treatment of acute peripheral vertigo
- Enhance vestibular function
- Improve and accelerate vestibular compensation
- Get patients back on their feet asap!

Clinical Milestones

- First Ph1 trial in 40 healthy volunteers (2015)
- Second Ph1 trial in 72 healthy volunteers (2018)
  - Both showing significantly higher bioavailability vs. oral delivery
  - Treatment safe and well tolerated (maximum 40 mg t.i.d.)
  - Ph2 trial in 118 acute vertigo patients (ongoing)
    - Acute vertigo following neurosurgery
    - Treatment for 4 weeks, 2-week treatment-free follow-up
    - Battery of balance tests + HRQOL questionnaires

Recent and Upcoming Milestones



Interim results from TRAVERS Phase 2 trial Part A in 31 patients suffering from acute vertigo following neurosurgery, treated t.i.d. for four weeks

- Part A: dose dependent improvement in balance + other outcomes
- Continuing with 10 and 20 mg t.i.d. in Part B
- Data read-out in Q1 2022
- IND and start Phase 3 in H1 2022

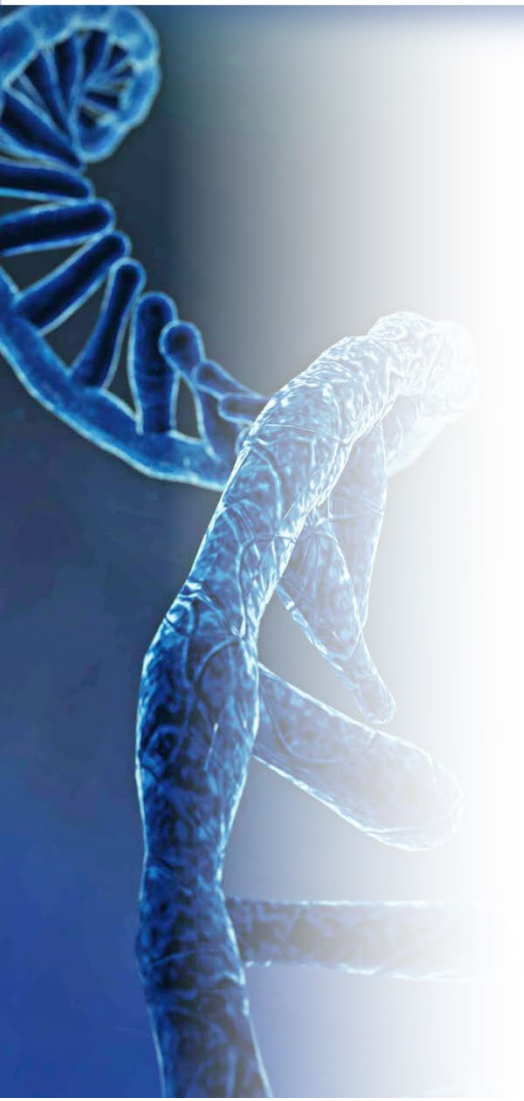
Sonsuvi® (AM-111) and Keyzilen® (AM-101)

Sonsuvi® in Acute Inner Ear Hearing Loss

- Prevents or attenuates hearing loss by protecting hair cell functionality
- Cell-penetrating peptide (brimapitide; JNK inhibitor)
- Single dose by intratympanic injection
- Orphan Drug (FDA and EMA), Fast Track (FDA)
- Phase 3 trial demonstrated significant and clinically relevant improvement in hearing recovery in acute profound hearing loss
- Second Phase 3 trial planned, incorporating regulatory feedback

Keyzilen® in Acute Inner Ear Tinnitus

- Attenuates tinnitus intensity by blocking aberrant excitation of NMDA receptors
- Small molecule (esketamine; NMDA receptor antagonist)
- Three doses by intratympanic injection
- Fast Track
- Two positive Ph2 trials
- Failed to meet endpoints in Ph3 primarily due to design issues
- Ph 2/3 trial planned, incorporating regulatory feedback and learnings from previous trials



We aim to become the leading company for extrahepatic RNA therapeutics

- Versatile peptide-based platform
  - OligoPhore™ (siRNA Payloads)
  - SemaPhore™ (mRNA Payloads)
- KRAS-driven cancer selected as first therapeutic indication for OligoPhore™ platform
- Exploring further potential applications

Select Companies in RNA Therapeutics Space

Company	Ticker	Market Cap (mm) *	Indication	Phase
RNA Therapeutics				
Alnylam Pharmaceuticals, Inc.	ALNY	$23,271	Hereditary ATTR, Acute Hepatic Porphyria	Commercial
Arrowhead Pharmaceuticals, Inc.	ARWR	$7,281	Renal Cell Carcinoma	Ph1/2
Ionis Pharmaceuticals, Inc.	IONS	$4,584	ATTR Amyloidosis, FCS, ALS	Ph3
PTC Therapeutics, Inc.	PTCT	$2,765	Aromatic L-amino acid decarboxylase deficiency	Ph3/Commercial
Dicerna Pharmaceuticals, Inc.	DRNA	2,946	Primary Hyperoxaluria	Ph3
Translate Bio, Inc.	*Acquired*	$3,200	CF	Ph1/2
Arcturus Therapeutics Holdings Inc.	ARCT	$1.240	Ornithine Transcarbamylase Deficiency	Ph2
Arbutus Biopharma Corporation	ABUS	$579	Hepatitis B Virus	Ph1a/1b

** Data from Yahoo Finance as of 12/17/21*

Current Challenges

In Nucleic Acid Delivery

Current state-of-the-art for delivery of nucleic acid therapeutics

- Viral-based vectors
- Pioneer in extrahepatic oligonucleotide delivery
- Lipid nanoparticles (LNPs)
- Ligand conjugates

Delivery technologies remain a key rate-limiting step for unlocking the potential of RNA therapeutics:

- Viral based delivery vectors suffer from lack of transduction efficiency and target specificity
- LNPs and currently available ligand conjugates using GalNac technology preferentially target the liver, and many have suboptimal

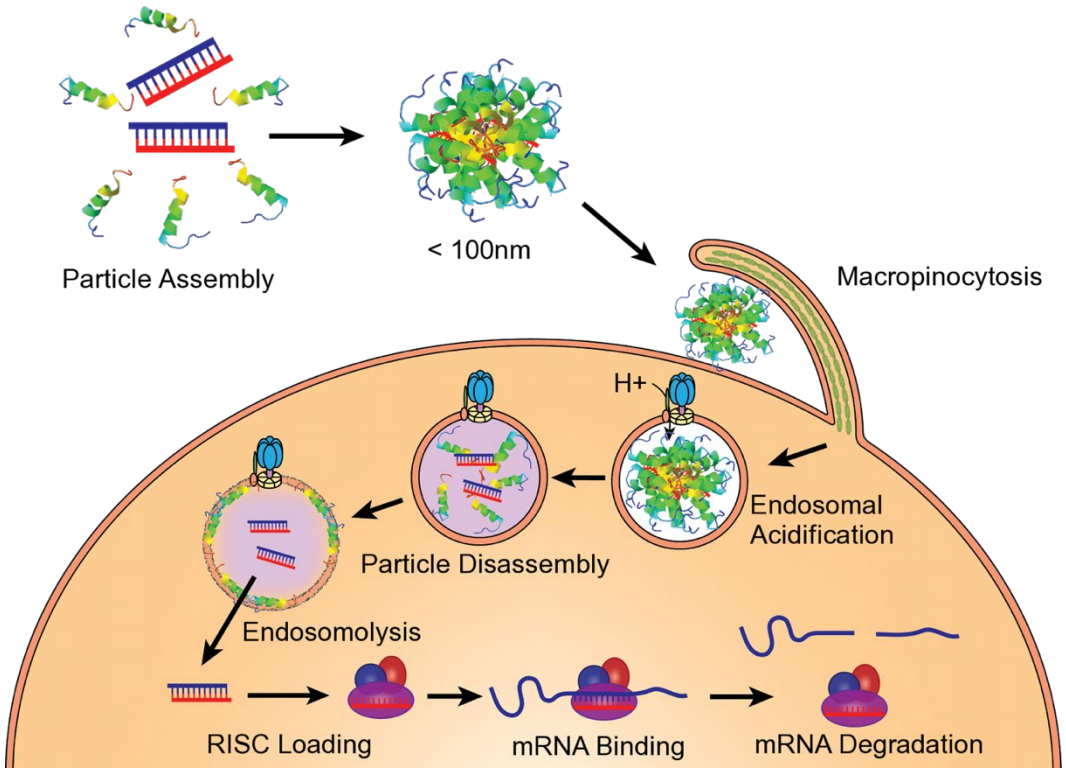
How OligoPhore™ with siRNA Payloads SemaPhore™ with mRNA Payloads Work

The peptide-based OligoPhore™ / SemaPhore™ technology allows for safe and effective delivery of RNA payloads with systemic administration:

- *Stability:* RNA complexed in nanoparticle format for, and only released inside of cells after uptake
- *Extrahepatic delivery:* not sequestered in liver, but permeates inflamed pathological tissues
- *Endosomal escape:* pH-dependent nanoparticle disassembly, followed by full release of RNA into cytoplasm
- *Selectivity:* silences molecular targets in diseased tissues only
- *Safety:* no cellular or adaptive immune responsivity to nanoparticle components or RNA after multiple serial doses, and no organ toxicities in mice

Phore = Greek fo agent, bearer
Sema = Greek for sign, message

Summary of OligoPhore™ Mechanism of Action



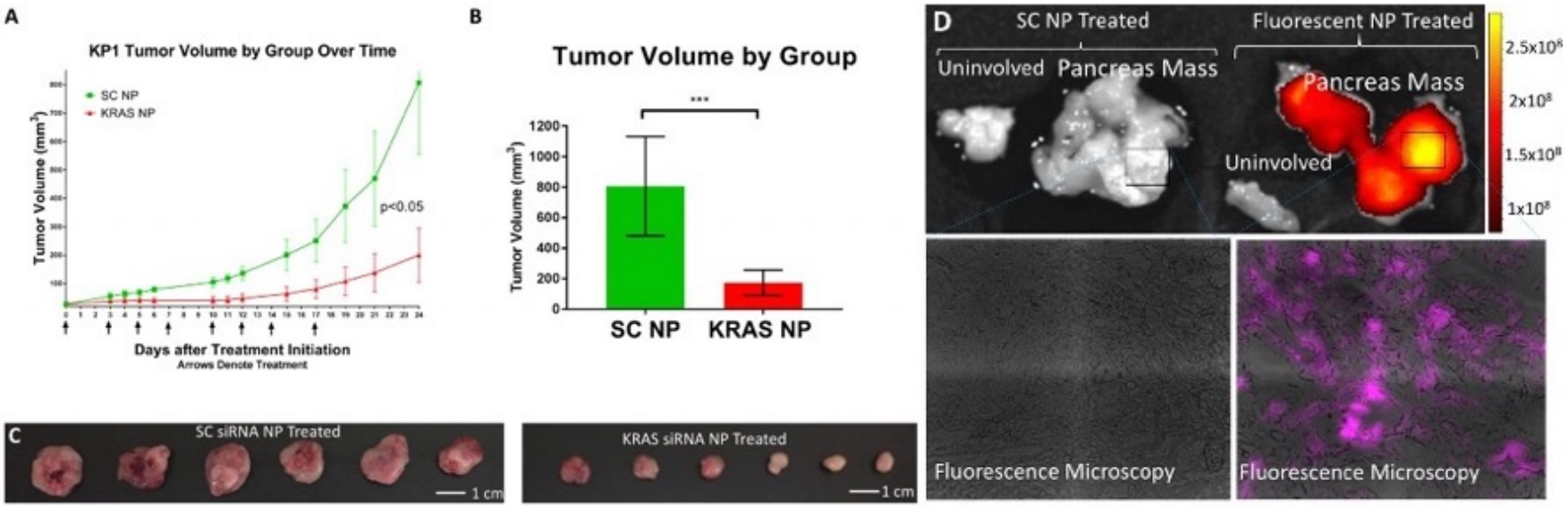
Hou KK et al. A role for peptides in overcoming endosomal entrapment in siRNA delivery - A focus on melittin. Biotechnol. Adv. 2015; 33(6 Pt 1): 931-40.

Preclinical Data From 13 Murine Disease Models So Far

OligoPhore™ with siRNA Payloads

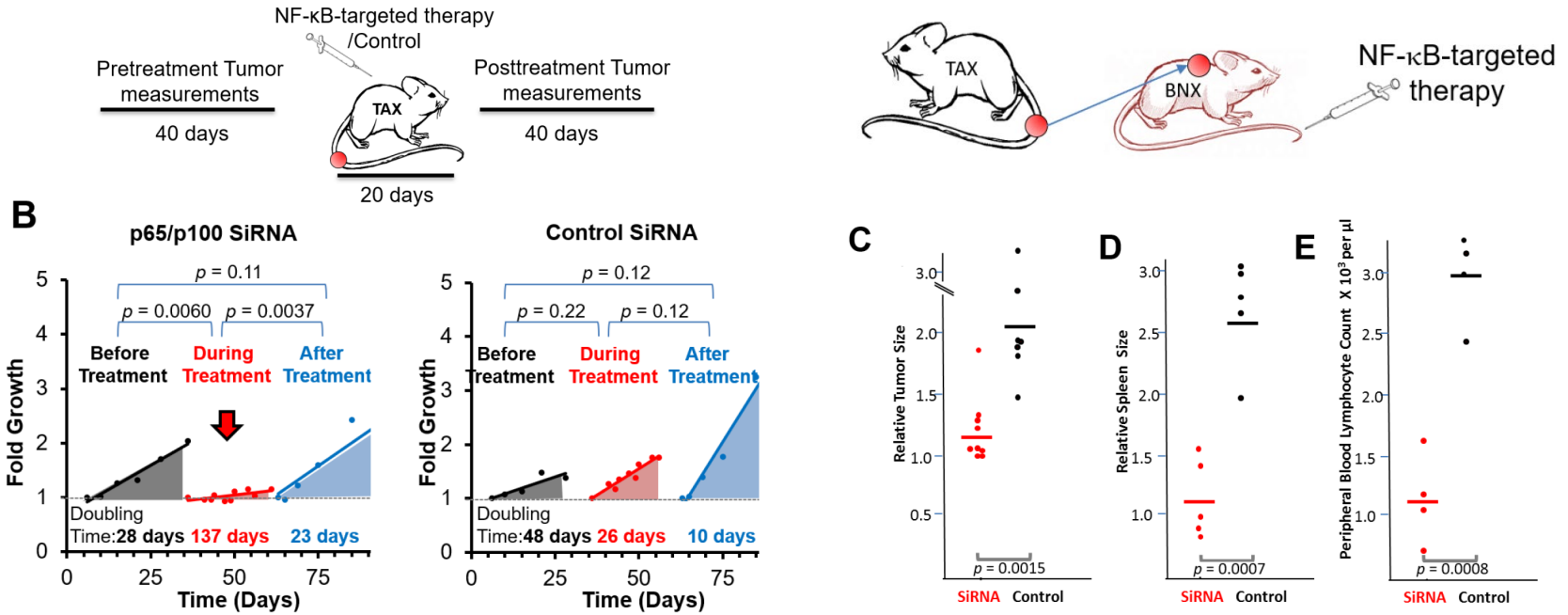
- Pancreatic and colorectal cancer (KRAS)
- Ovarian cancer (TAM: AXL)
- Lung cancer (ETV-2)
- Metastatic Melanoma (NFkB)
- Adult T Cell Leukemia / Lymphoma (NFkB)
- Sarcoma (MYCT-1)
- Necrotizing enterocolitis (NFkB)
- Rheumatoid and osteoarthritis (NFkB)
- Atherosclerosis (JNK2)
- Metabolic syndrome/Obesity (ASXL2)
- Aortic Aneurysm (NFkB)

Pancreatic Tumor Inhibition With KRAS siRNA



Strand MS et al. Precision delivery of RAS-inhibiting siRNA to KRAS driven cancer via peptide-based nanoparticles. Oncotarget. 2019;10:4761-4775.

Tumor Growth Inhibition In Adult T-cell Leukemia / Lymphoma by NF-κB siRNA



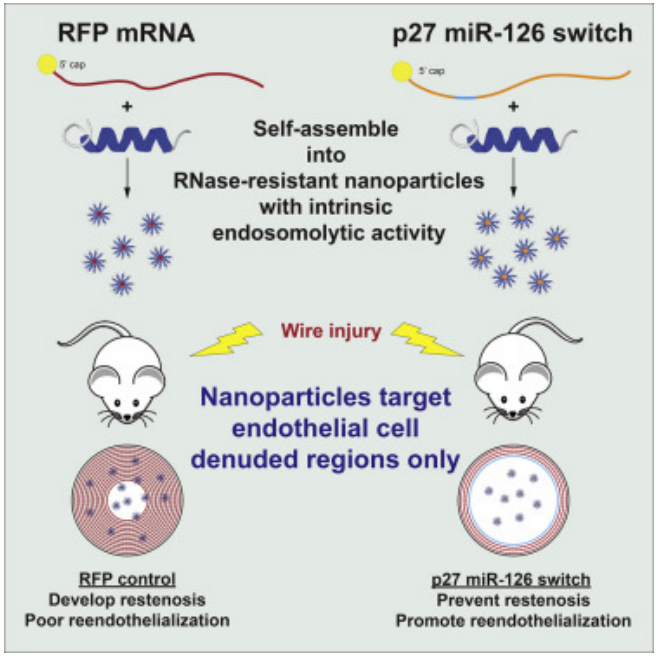
Rauch DA et al. Targeting NF-κB with nanotherapy in a mouse model of adult T-cell leukemia/lymphoma. Nanomaterials 2021, 11(6), 1582.

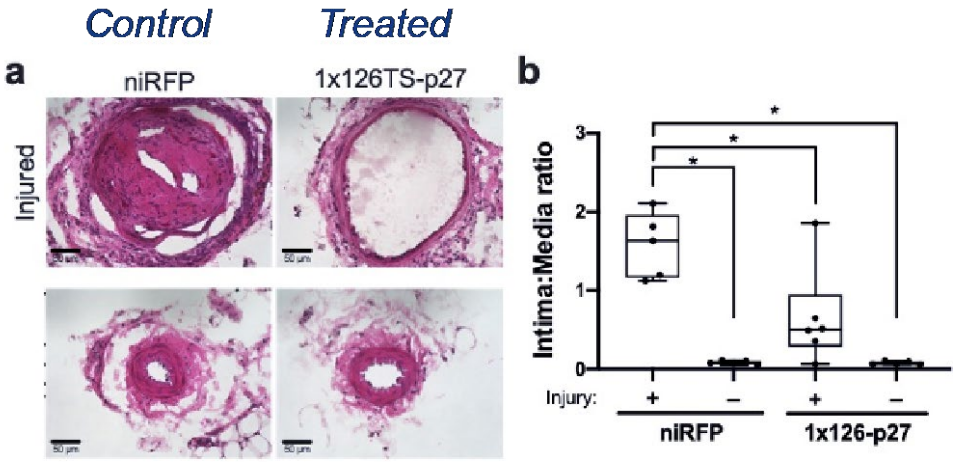
Preclinical Data From 3 Murine Disease Models So Far

- Osteoarthritis (WNT16)
- Atherosclerosis (p27Kip1)
- Aortic Aneurysm (SOD2)

SemaPhore™ with mRNA Payloads

Effective Treatment of Atherosclerosis by $p27^{Kip1}$ mRNA





Lockhart et al. Self-assembled miRNA-switch nanoparticles target denuded regions and prevent restenosis. Mol Ther. 2021; 5;29(5):1744-57.

RNA Development Plan

- Initial focus on siRNA and existing data, while advancing research on mRNA and other payloads
- CMC upscaling and safety package incl. NHP tox study → targeting IND submission by end of 2022
- Team of in-house experts, complemented by network of consultants and CROs in EU and US
- Seeking to explore further therapeutic indications

Multiple Potential Near- and Mid-term Value Inflection Points

Timeline	Q1 2022	Q2 2022	Q3 2022	Q4 2022
Respiratory (Bentrio™)*	510(k) for allergy	Read-out trials in • COVID-19 • House dust mite • Seasonal allergic rhinitis		
Neurotology (AM-125)*	Read-out Ph2	IND	Start Ph3	
RNA Therapeutics (AM-401)	Pre-IND studies			IND submission

*Exploring opportunities to spinoff / divest respiratory and neurotology assets

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