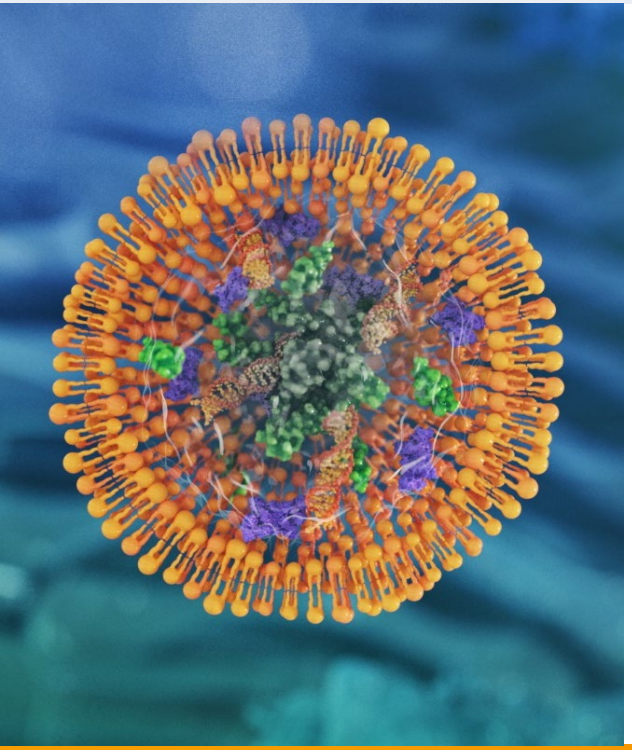

altamira
therapeutics
DELIVERING RNA – BEYOND THE LIVER
Company Presentation
Winter 2025

Forward-Looking Statements

This presentation may contain statements that constitute "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Forward-looking statements are statements other than historical facts and may include statements that address future operating, financial or business performance or Altamira's strategies or expectations. In some cases, you can identify these statements by forward-looking words such as "may", "might", "will", "should", "expects", "plans", "anticipates", "believes", "estimates", "predicts", "projects", "potential", "outlook" or "continue", or the negative of these terms or other comparable terminology. Forward-looking statements are based on management's current expectations and beliefs and involve significant risks and uncertainties that could cause actual results, developments and business decisions to differ materially from those con-templated by these statements. These risks and uncertainties include, but are not limited to, the clinical utility of Altamira's product candidates, the timing or likelihood of regulatory filings and approvals, Altamira's intellectual property position and Altamira's financial position. These risks and uncertainties also include, but are not limited to, those described under the caption "Risk Factors" in Altamira's Annual Report on Form 20-F for the year ended December 31, 2023, and in Altamira's other filings with the Securities Ex-change Commission ("SEC"), which are available free of charge on the SEC's website at: www.sec.gov. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those indicated. All forward-looking statements and all subsequent written and oral forward-looking statements attributable to Altamira or to persons acting on behalf of Altamira are expressly qualified in their entirety by reference to these risks and uncertainties. You should not place undue reliance on forward-looking statements. Forward-looking statements speak only as of the date they are made, and Altamira does not undertake any obligation to update them in light of new information, future developments or otherwise, except as may be required under applicable law.

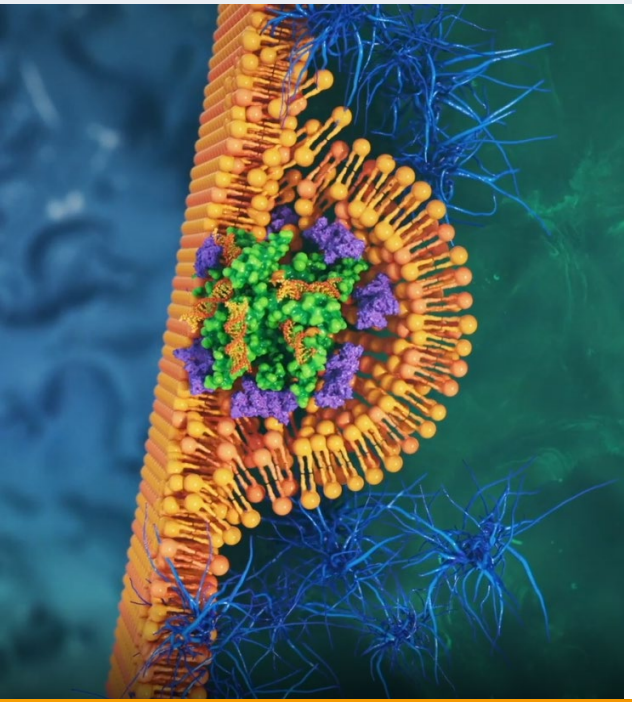
Disruptive, Proprietary RNA Delivery Technology Platform



OligoPhore™ (siRNA) SemaPhore™ (mRNA) CycloPhore™ (circRNA)	• Proprietary 21 amino acid peptide (nanoparticles) • Efficient delivery of RNA into extrahepatic target cells
RNA Market Taking Off	• Rapidly growing number of RNA therapeutics • Active M&A, licensing environment
'Picks and Shovels' Platform Strategy	• Partner delivery platforms with pharma & biotech • Initiated first collaborations
Two Flagship Programs for Demonstration	• KRAS-driven cancers (AM-401) - IND expected in 2026 • Rheumatoid arthritis (AM-411) - IND expected in 2026
Divesting / Partnering Legacy Assets	• Unlock intrinsic value of inner ear & OTC assets • Extra, non-dilutive funding potential

How Our Technology Works

OligoPhore/ SemaPhore/ CycloPhore nanoparticles comprise a proprietary peptide + RNA payload designed to enable safe and effective delivery by systemic administration.



Stability	RNA complexed in nanoparticle format and only released inside of cells after uptake
Extrahepatic delivery	Not sequestered in liver as is common with conventional RNA-based therapies; permeates inflamed pathological tissues (passive targeting)
Endosomal escape	Efficient release within target cell, about 10-fold increase over LNPs, the current industry standard
Selectivity	Acts on targets in diseased tissues only
Safety	No immune response to nanoparticle components or RNA after multiple serial doses, and no organ toxicities in mice

RNA Delivery is One of the Key Challenges

Exemplary listing of companies active in RNA therapeutics and delivery (list not exhaustive)

Silence gene expression

- Short interfering RNA (siRNA)
- Antisense oligonucleotides (ASOs)

Alnylam, arrowhead pharmaceuticals, AstraZeneca, IONIS, Lilly, NOVARTIS, novo nordisk, ProQR THERAPEUTICS, SAREPTA THERAPEUTICS, SILENCE THERAPEUTICS, sylentis, STOKE THERAPEUTICS

Promote protein expression

- Messenger RNA (mRNA)

ARCTURUS Therapeutics, AstraZeneca, BIONTECH, CUREVAC the RNA people, Lilly, MERCK, moderna, novo nordisk, Pfizer, sanofi, Translate BIO, ultragenyx

Deliver RNA therapeutic to target

- Lipid nanoparticles
- Virus-based vectors
- Ligand conjugates
- Peptide-based nanoparticles

sirnaomics Advancing RNAi Therapeutics, altamira therapeutics, Arbutus BIOPHARMA, entrada THERAPEUTICS, Dicerna a Novo Nordisk company, PepGen

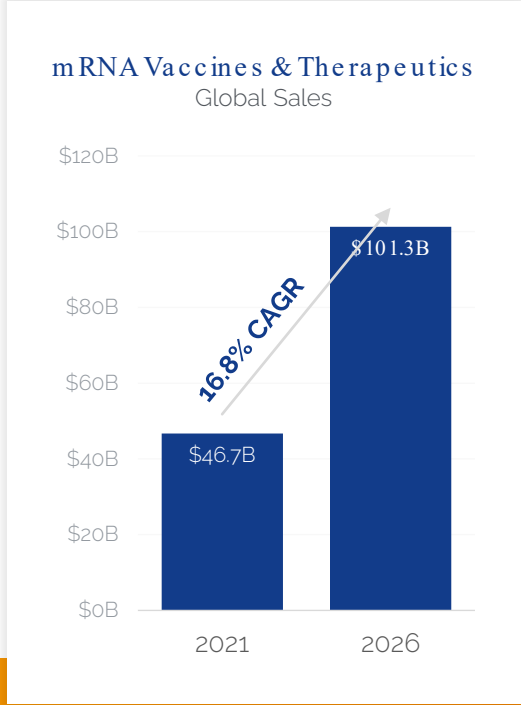
Disruptive Technology Growth Opportunities

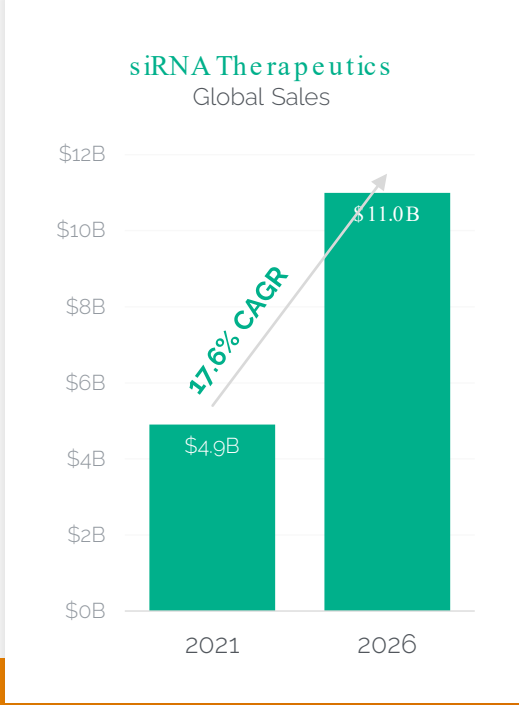
Frontiers in Bioengineering and Biotechnology, March 2021

The Limitless Future of RNA Therapeutics

Tulsi Ram Damase[1], Roman Sukhovershin[1], Christian Boada[2], Francesca Taraballi[3,4], Roderic I. Pettigrew[2] and John P. Cooke[1]

- High specificity
- Cost effective
- Relatively simple to manufacture
- Can target previously undruggable pathways
- Disruptive technology





STRONG GROWTH—STARTING IN 2018

ONLY THE BEGINNING!

*Research and Markets; Allied Market Research

Corporate RNA Strategy

Strong strategy based on external collaborations and in-house programs

Leverage versatility of technology
- Demonstrated to work in multiple disease areas (tested in 17 models….)
- Suitable for siRNA, mRNA, circRNA, ASOs,

Particularly well-suited for indications in oncology and inflammatory disorders

Selecting two therapeutic indications to showcase technology
- KRAS driven cancers – AM-401
- Rheumatoid arthritis – AM-411
- Partner upon IND or Phase 1

OligoPhore™ has been tested *in vivo* …

- Pancreatic and colorectal cancer (KRAS)
- Ovarian cancer (TAM: AXL)
- Lung cancer (ETV-2)
- Metastatic melanoma (NF-κB)
- Adult T cell leukemia/lymphoma (NF-κB)
- Sarcoma (MYCT-1)
- Sarcoma and breast cancer (MYCT-1)
- Necrotizing enterocolitis (NF-κB)
- Rheumatoid and osteoarthritis (NF-κB)
- Atherosclerosis (JNK2)
- Metabolic syndrome/Obesity (ASXL2)
- Aortic aneurysm (NF-κB)

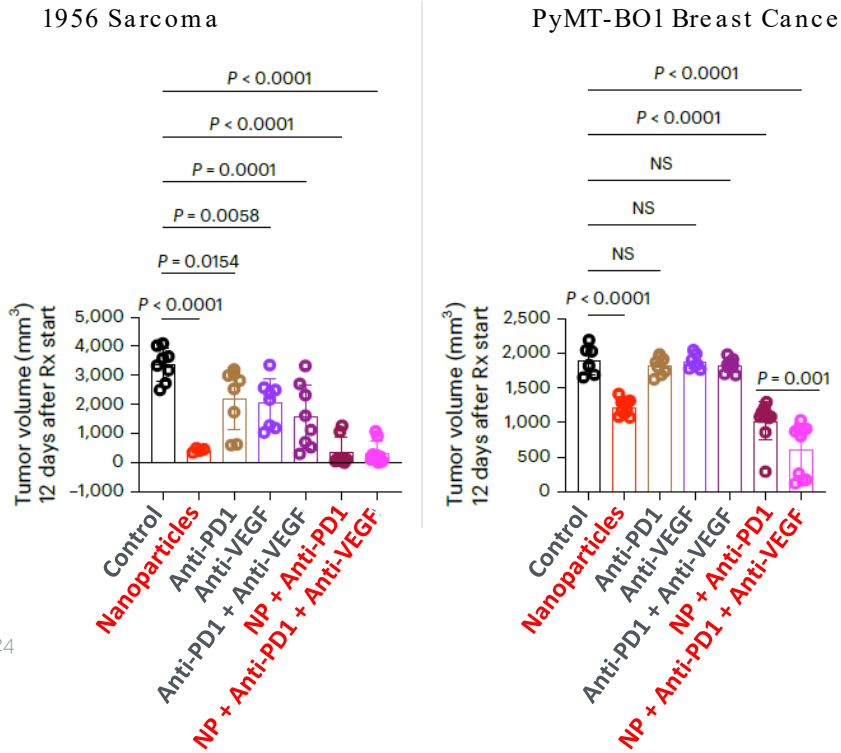
SemaPhore™ has been tested *in vivo* …

- Osteoarthritis (WNT16)
- Atherosclerosis ($p27^{Kip1}$)
- Aortic aneurysm (SOD2)
- Osteoarthritis (DNMT3B)
- Tumor microenvironment (ZBTB46)

Use Case: Enhancing the Potential of Anti-PD1 Therapy

Delivering SemaPhore™ *Zbtb46* mRNA
in sarcoma and metastatic breast cancer models.

- Work by Choi Lab at WashU
- Cancers form defective blood vessels that feed the tumor
- Defective vasculature blocks access to tumor infiltrating T cells
  - Limits effectiveness of anti-PD1 therapy
- *Zbtb46 mRNA* nanoparticles normalized tumor vessels and enhanced antitumor immunity
  - Highly significant reduction in tumor growth (p<0.0001)
  - Effects potentiated when combined with anti-PD1
- "Remarkably, *Zbtb46* nanoparticles induced dramatic anti-PD1 response in both anti-PD1-responsive [..] and anti-PD1-refractory [..] tumor models, generating long-term complete remission of tumor in many of the treated animals."

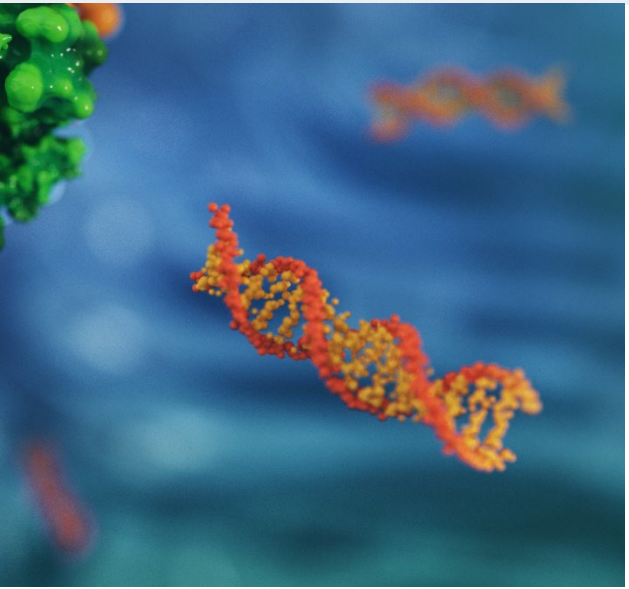


Kabir et al., 2024

nature immunol

Leveraging the Platforms

License technology to biotechs / pharmas for use with their own RNA molecules



- Active business development program
- First two collaborators signed up

HEQET THERAPEUTICS

- Evaluate OligoPhore™ + certain non-coding RNAs in the regeneration of damaged heart tissue following myocardial infarction

Univercells Biologics for all

- Evaluate SemaPhore™ + mRNA vaccine(s)
- Lower mRNA loss during cell entrance may allow for using lower doses and thus result in potentially more effective and efficient vaccines

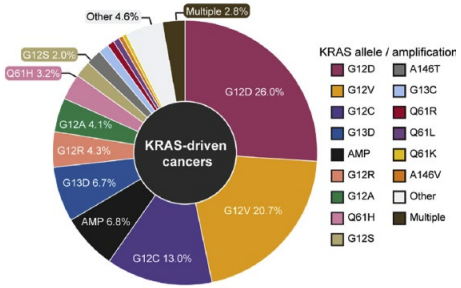
AM-401: Stop the "Beating Heart" of Tumors

Knock down various KRAS mutations with *poly* KRAS^{mut} OligoPhore nanoparticles

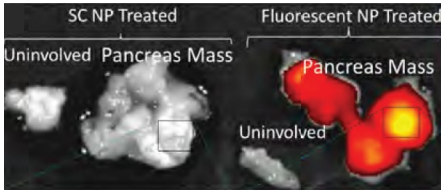
to inhibit cell proliferation in KRAS driven colorectal, pancreatic, or non-small cell lung cancer.

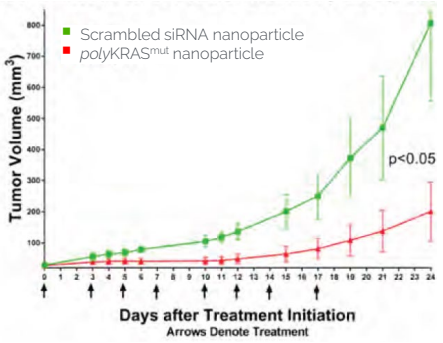
- Mutated KRAS may cause cancer to grow
- Found in 1/5 of all human cancers, particularly in:
  - Pancreatic cancer (85-90%)
  - Colorectal cancer (40%)
  - Non-small cell lung cancer (30-35%)
- 150,000 cases diagnosed in US p.a.
- ~1M deaths per year world-wide
- Considered "undruggable" for decades

Many mutations known, G12D, G12V, and G12C accounting for >50%



OligoPhore *poly* KRAS^{mut} siRNA transfects tumor cells, not healthy or uninvolved cells





OligoPhore *poly* KRAS^{mut} significantly reduces pancreatic tumor volume growth

KPC pancreatic tumor model in mice; Strand et al., 2019

*KPC pancreatic tumor model in mice; Strand et al., 2019

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AM-401

KRAS driven cancer
IND targeted for 2026

- High unmet medical need – most aggressive tumors
- Small molecule G12C inhibitors approved in NSCLC
  - Sotorasib (Lumakras, Amgen), Adagrasib (Krazati, Mirati)
- Multiple other small molecule inhibitors under development (G12C, G12D…), but few competing RNA projects (G12D or KRAS modulators)

AM-401 KEY DIFFERENTIATING FACTORS

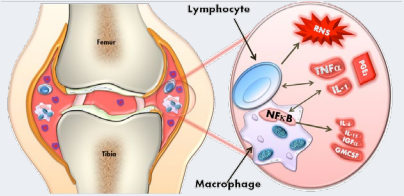
*poly*KRAS^{mut} allows to target different mutations and is thus **polyvalent**
G12C, G12V, G12D, G12R, G12A, and A146T, covering 90.9% of KRAS mutations in pancreatic, 65.3% in colorectal, 80.0% in non-small cell lung cancer

Blocking production of KRAS by degrading mRNA to cause **less resistance** than inhibition of KRAS

Small molecule inhibitors have significant side effects, particularly when combined with other agents
OligoPhore **targets specifically** tumor cells

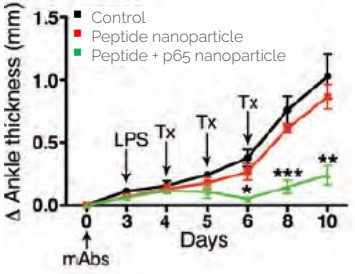
AM-411: Block Inflammation in Rheumatoid Arthritis

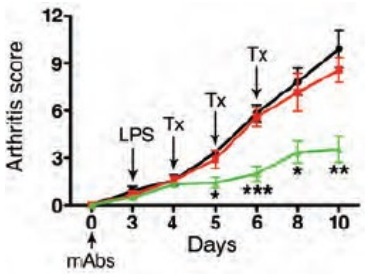
Knock down NF-κB (p65),
a key checkpoint in RA inflammation.



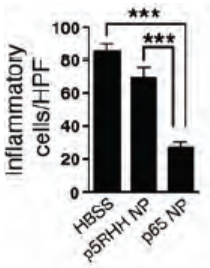
- Chronic autoimmune disease
- Causes joint swelling and pain
  - Reduced QoL and productivity
- Affects 1 out of 28 women / 59 men
- No cure available, but various treatment options:
  - Disease-modifying anti-rheumatic drugs (DMARDs)
  - Non-steroidal anti-inflammatory drugs (NSAIDs)
  - Corticosteroids
- Major shortcomings of therapies:
  - Drug resistance (up to 50% of patients)
  - Systemic adverse reactions (e.g., rash, hair loss, altered liver function, low blood cell counts, nausea, weight loss, increased infections, and neuropathy)

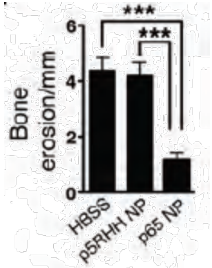
OligoPhore p65 stabilizes ankle swelling and reduces arthritis score





OligoPhore p65 reduces inflammation and protects against bone erosion





Collagen-antibody induced arthritis model in mice, Zhou et al., 2014.

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AM-411

Rheumatoid arthritis
IND targeted for 2026

- High unmet medical need

- Global rheumatoid arthritis market = $57.9 Billion in 2019 → $62.9 Billion in 2027
  - Expiration of patents, biosimilars arriving
  - High hopes for novel Tx class of JAK inhibitors gave way to disappointment due to safety issues

AM-411 KEY DIFFERENTIATING FACTORS

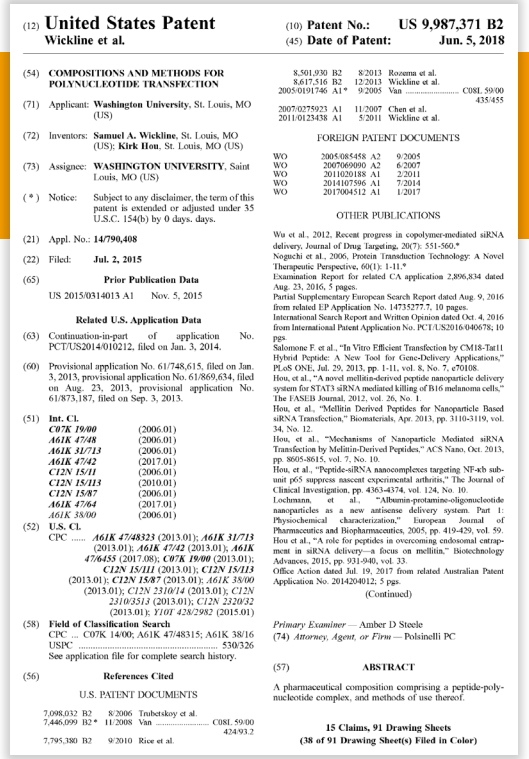
Mediators of inflammation play many physiological roles in healthy tissues – AM-411 targets only inflamed tissues

Reduced systemic side effects

Blocking production of an NF-κB component by degrading mRNA to cause less resistance than inhibition of NF-κB

Less likelihood of resistance

Intellectual Property



(12) **United States Patent**
Wickline et al.

(10) **Patent No.: US 9,987,371 B2**
(45) **Date of Patent: Jun. 5, 2018**

(54) **COMPOSITIONS AND METHODS FOR POLYNUCLEOTIDE TRANSFECTION**

(71) Applicant: **Washington University**, St. Louis, MO (US)

(72) Inventors: **Samuel A. Wickline**, St. Louis, MO (US); **Kirk Hou**, St. Louis, MO (US)

(73) Assignee: **WASHINGTON UNIVERSITY**, Saint Louis, MO (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days. days.

(21) Appl. No.: **14/790,408**

(22) Filed: **Jul. 2, 2015**

(65) **Prior Publication Data**

US 2015/0314013 A1 Nov. 5, 2015

Related U.S. Application Data

(63) Continuation-in-part of application No. PCT/US2014/010212, filed on Jan. 3, 2014.

(60) Provisional application No. 61/748,615, filed on Jan. 3, 2013, provisional application No. 61/869,634, filed on Aug. 23, 2013, provisional application No. 61/873,187, filed on Sep. 3, 2013.

(51) **Int. Cl.**

C07K 19/00	(2006.01)
A61K 47/48	(2006.01)
A61K 31/713	(2006.01)
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C12N 15/113	(2010.01)
C12N 15/87	(2006.01)
A61K 47/64	(2017.01)
A61K 38/00	(2006.01)

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CPC ***A61K 47/48323*** (2013.01); ***A61K 31/713*** (2013.01); ***A61K 47/42*** (2013.01); ***A61K 47/6455*** (2017.08); ***C07K 19/00*** (2013.01); ***C12N 15/111*** (2013.01); ***C12N 15/113*** (2013.01); ***C12N 15/87*** (2013.01); *A61K 38/00* (2013.01); *C12N 2310/14* (2013.01); *C12N 2310/3513* (2013.01); *C12N 2320/32* (2013.01); *Y10T 428/2982* (2015.01)

(58) **Field of Classification Search**
CPC ... C07K 14/00; A61K 47/48315; A61K 38/16
USPC 530/326
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

7,098,032 B2	8/2006	Trubetskoy et al.	
7,446,099 B2 *	11/2008	Van	C08L 59/00 424/93.2
7,795,380 B2	9/2010	Rice et al.	
8,501,930 B2	8/2013	Rozema et al.	
8,617,516 B2	12/2013	Wickline et al.	
2005/0191746 A1 *	9/2005	Van	C08L 59/00 435/455
2007/0275923 A1	11/2007	Chen et al.	
2011/0123438 A1	5/2011	Wickline et al.	

FOREIGN PATENT DOCUMENTS

WO	2005/085458 A2	9/2005
WO	2007069090 A2	6/2007
WO	2011020188 A1	2/2011
WO	2014107596 A1	7/2014
WO	2017004512 A1	1/2017

OTHER PUBLICATIONS

Wu et al., 2012, Recent progress in copolymer-mediated siRNA delivery, Journal of Drug Targeting, 20(7): 551-560.*
Noguchi et al., 2006, Protein Transduction Technology: A Novel Therapeutic Perspective, 60(1): 1-11.*
Examination Report for related CA application 2,896,834 dated Aug. 23, 2016, 5 pages.
Partial Supplementary European Search Report dated Aug. 9, 2016 from related EP Application No. 14735277.7, 10 pages.
International Search Report and Written Opinion dated Oct. 4, 2016 from International Patent Application No. PCT/US2016/040678; 10 pgs.
Salomone F. et al., "In Vitro Efficient Transfection by CM18-Tat11 Hybrid Peptide: A New Tool for Gene-Delivery Applications," PLoS ONE, Jul. 29, 2013, pp. 1-11, vol. 8, No. 7, e70108.
Hou, et al., "A novel mellitin-derived peptide nanoparticle delivery system for STAT3 siRNA mediated killing of B16 melanoma cells," The FASEB Journal, 2012, vol. 26, No. 1.
Hou, et al., "Mellitin Derived Peptides for Nanoparticle Based siRNA Transfection," Biomaterials, Apr. 2013, pp. 3110-3119, vol. 34, No. 12.
Hou, et al., "Mechanisms of Nanoparticle Mediated siRNA Transfection by Melittin-Derived Peptides," ACS Nano, Oct. 2013, pp. 8605-8615, vol. 7, No. 10.
Hou, et al., "Peptide-siRNA nanocomplexes targeting NF-kb subunit p65 suppress nascent experimental arthritis," The Journal of Clinical Investigation, pp. 4363-4374, vol. 124, No. 10.
Lochmann, et al., "Albumin-protamine-oligonucleotide nanoparticles as a new antisense delivery system. Part 1: Physicochemical characterization," European Journal of Pharmaceutics and Biopharmaceutics, 2005, pp. 419-429, vol. 59.
Hou et al., "A role for peptides in overcoming endosomal entrapment in siRNA delivery—a focus on melittin," Biotechnology Advances, 2015, pp. 931-940, vol. 33.
Office Action dated Jul. 19, 2017 from related Australian Patent Application No. 2014204012, 5 pgs.
(Continued)

Primary Examiner — Amber D Steele
(74) *Attorney, Agent, or Firm* — Polsinelli PC

(57) **ABSTRACT**

A pharmaceutical composition comprising a peptide-polynucleotide complex, and methods of use thereof.

15 Claims, 91 Drawing Sheets
(38 of 91 Drawing Sheet(s) Filed in Color)

WORLDWIDE EXCLUSIVE LICENSE FROM WASHINGTON UNIVERSITY

Patent covering OligoPhore™ / SemaPhore™ platform

- Compositions comprising a peptide-polynucleotide complex
- Methods for delivering such nanoplexes
- Coverage until 2034 (+ potential extension)
- Generating further IP (e.g. *poly*KRAS^{mut} and p65 – potential coverage until 2043/4)
- Proprietary manufacturing process

Management Overview

Thomas Meyer, Ph.D.
CEO & CHAIRMAN

- Company founder
- Funded and grew Company since 2003
- 14 years with Disetronic Group including CEO and BoD member (>20% sales CAGR, $3B market cap)

Covadonga Pañeda, Ph.D.
CHIEF OPERATING OFFICER

- Joined as CDO in 2022
- 18 years experience in FDA/EMA drug development
- Non-clinical and clinical study design and regulatory submissions
- 7 years in RNAi for ophthalmology

Marcel Gremaud, CPA
CHIEF FINANCIAL OFFICER

- Working for Company since 2013
- ~30 years experience in controlling and accounting
- International pharma companies and start-ups

Samuel Wickline, MD
CHIEF SCIENTIFIC ADVISER

- Joined in 2021 through acquisition of Trasir Tx
- Prof. of Cardiovascular Sciences, Molecular Physiology and Pharmacology at USF
- Former Prof. of Med., Physics, Biomedical Engr, Cell Biology and Physiology at Wash U

Legacy Programs: Partial Spin-Off of OTC Nasal Spray Business

Bentrio® in Allergic Rhinitis

Protection Against Airborne Particles

- Drug-free, preservative-free formulation, applied as nasal spray
- Four clinical trials demonstrating safety and efficacy in allergic rhinitis
  - Efficacy: close to medicated sprays
  - Tolerability: close to saline sprays
- Commercialized through distributors
- Significant growth expected
  - Launch in additional countries / regions
- Advanced discussions on North America, Europe and other key markets

First Step in Transition Process

- Sale of 51% of Altamira Medica AG in late 2023
  - Cash consideration about $2.3 million
  - Buyer is Swiss private equity investor
  - CYTO retaining 49% of capital
- CYTO also entitled to 25% of:
  - Future license income
  - Medica's value appreciation in case of a sale
- CYTO's overall share of upside: 62%
- Remaining stake to be divested

Legacy Programs: Inner Ear Assets to be Divested / Partnered

Become focused
"Pure play" RNA delivery company

Monetize legacy assets
through divestiture, out-licensing

AM-125 in Acute Vestibular Syndrome

- Rx product, applied as nasal spray
- Reformulation of oral betahistine
  - Global market $450M (ex US) – standard of care for vertigo
  - Poor bioavailability
- Invested $18 million to date
- Proof of concept in Phase 2, ready for Phase 3 trial
- No comparable product in US
- Structured partnering process initiated

Potential Other Indications

- Histamine plays important role in many behavioral and physiological functions:
  - Appetite, drinking, sleep, wakefulness, learning, attention and memory
- Clinical utility of betahistine shown, among others, in:
  - ADHD, cognitive function in dementia, memory loss, antipsychotic-induced weight gain
- Histamine as target, e.g.:
  - Narcolepsy, Tourette syndrome, Prader-Willi syndrome

Investor Summary

RNA technology coming of age

- Disruptive potential in human medicine
- Rapidly growing # of RNA therapeutics

Extensive proof of concept

- Successfully tested *in vivo* in 17 different disease models
- 30+ papers published

Altamira has unique, versatile RNA delivery technology platform

- Patented, under license from Wash U
- Suitable for different types of RNA molecules
- OligoPhore™, SemaPhore™, CycloPhore™

Flagship programs in oncology and rheumatoid arthritis

- First IND expected to be filed in 2026
- Technology platform out-licensing as business model

Addressing major challenges in RNA delivery

- IV administration, reaching extrahepatic targets
- Strong endosomal release (10x compared to lipid nanoparticles)

Divestiture/ partnering of Legacy Assets

- Process started
- Unlock intrinsic value / non-dilutive funding

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DELIVERING RNA – BEYOND THE LIVER