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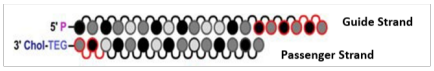


INTASYL self-delivery technology

Developer(s)

Phio Pharmaceuticals, Ltd.

Originator

https://phiopharma.com/

United States of America

Phio Pharmaceuticals, founded in 2011 and headquartered in Marlborough, Massachusetts, is a biotechnology company specializing in RNA-based immuno-oncology therapies. Initially named RXi Pharmaceuticals, it rebranded in 2018 to reflect its focus on self-delivering RNAi technology. The company develops tumor-targeting therapeutics, leveraging cutting-edge RNAi platforms.

Sponsor(s)

Triton Funds

https://www.tritonfunds.com/

Partnerships

Glycostem Ltd.

https://www.glycostem.com/

Helmholtz Zentrum München

https://www.helmholtz-munich.de/

Medigene AG

https://medigene.com/

Technology information

Type of technology

Chemically modified siRNA for self-delivery

Administration route

Intratumoral, Intra-vitreal

Development state and regulatory approval

Active Pharmaceutical Ingredient (API)

PH-762

Development Stage

Phase I

Regulatory Approval

FDA has cleared the IND application for PH-762

Description

INTASYL™ Technology is a proprietary self-delivering RNA interference (sd-rxRNA®) platform designed for precise gene silencing in immuno-oncology. Unlike traditional RNAi therapies, INTASYL allows direct cellular uptake without requiring complex delivery systems. Engineered for immune cells, it enhances anti-tumor responses while ensuring safety, stability, and efficiency. The sd-rxRNA molecules are chemically modified with hydrophobic and hydrophilic elements, enabling passive diffusion into cells. These modifications also provide stability and resist disintegration.

Technology highlight

1. Chemically modified siRNA structure and self-delivery system 2. Cellular uptake mechanism via direct membrane penetration 3. Intracellular processing and RNA-induced silencing complex (RISC) Activation 4. Gene silencing and Immuno-oncology applications 5. Target specificity

Technology main components

Chemically modified siRNA

Information on the raw materials sourcing, availability and anticipated price

Not provided

Delivery device(s)

No delivery device

APIs compatibility profile

API desired features

Proteins

INTASYL self-delivery technology utilizes siRNA to specifically target and silence a range of immuno-oncology proteins, including PD-1, BRD4, CTLA4, TIGIT, LAG3, TIM3, CBLB, SHP-1, STAT-3, MDM2, ADORA2, MMP-1, CD96, CISH, CSK, DGKα, DGKζ, DNMT3A, HK2, IL-6, KLRC1, PD-L1, PRDM, PTEN, TBX21, TET2, and other related proteins involved in immune regulation and tumor evasion. Additionally, it targets dermatology-related proteins such as CTGF, COX2, TGFB1, TGFB2, SPP1, TYR, and MMP1, as well as BRD4, contributing to therapeutic strategies in both immuno-oncology and dermatological conditions.

Additional solubility data

Not provided

Additional stability data

Not provided

API loading: Maximum drug quantity to be loaded

75-90 wt%

API co-administration

2 different APIs : Two APIs should target different genes simultaneously

LogP

Not provided

Scale-up and manufacturing prospects

Scale-up prospects

Not provided

Tentative equipment list for manufacturing

Mermade 12 DNA/RNA Synthesizer

Manufacturing

Manufacturing Process of INTASYL (cGMP): 1. Oligonucleotide Synthesis (via Mermade 12 DNA/RNA Synthesizer) 2. Cleavage and Deprotection 3. Purification (via ion exchange chromatography) 4. Sense Strand Purification 5. Desalting and Concentration 6. Analysis by HPLC and ESI-MS.

Specific analytical instrument required for characterization of formulation

1. HPLC analysis on a Shimadzu Prominence system. 2. Electrospray Ionization Mass Spectrometry (ESI-MS) analysis using Promass Deconvolution for Xcalibur.

Clinical trials

PHIO-762-2301

Identifier

NCT06014086

Link

https://clinicaltrials.gov/study/NCT06014086

Phase

Phase I

Status

Recruiting

Sponsor

Phio Pharmaceuticals Inc.

More details

The goal of this clinical trial is to evaluate the safety and tolerability of intratumoral injections of PH-762 in squamous cell carcinoma, melanoma, or Merkel cell carcinomas of the skin, to understand what the body does to the PH-762, and to observe how the tumor responds to the drug. Participants will receive four injections of PH-762 at weekly intervals, into a single tumor, followed by surgical removal of the tumor approximately two weeks later.

Purpose

Intratumoral PH-762 for Cutaneous Carcinoma

Interventions

Intervention 1

PH-762

Countries

United States of America

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2023-11-07

Anticipated Date of Last Follow-up

2025-01-24

Estimated Primary Completion Date

2025-06-01

Estimated Completion Date

2025-09-01

Actual Primary Completion Date

Not provided

Actual Completion Date

Not provided

Studied populations

Age Cohort

- Adults
- Older Adults

Genders

- All

Accepts pregnant individuals

Unspecified

Accepts lactating individuals

Unspecified

Accepts healthy individuals

No

Comments about the studied populations

Key Inclusion Criteria: * Histologically confirmed cutaneous squamous cell carcinoma (cSCC), melanoma, or Merkel cell carcinoma, meeting one of the following criteria: * cSCC, resectable local tumors: must be Stage II or lower, amenable to curative resection and in a location where acceptable surgical margins are anticipated * cSCC, unresectable local tumors: must be Stage II or lower, tumor has been unresponsive to prior radiation therapy or is not a candidate for curative radiation therapy * cSCC, metastatic disease: disease has progressed during or following prior checkpoint inhibitor therapy (anti-PD-1 or anti-PD-L1 antibody) * Melanoma, metastatic disease: Stage IV disease with a cutaneous lesion that has progressed during or following checkpoint inhibitor therapy.

Health status

Not provided
Other health status: Cutaneous Carcinoma

Study type

Interventional (clinical trial)

Enrollment

30

Allocation

Not provided

Intervention model

Single group assignment

Intervention model description

Not provided

Masking

Open label

Masking description

Not provided

Frequency of administration

Weekly

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Other(s) : "Intratumoral "

Use case

Treatment

Key resources

Not provided

RXI-109-1501

Identifier

NCT02599064

Link

https://clinicaltrials.gov/study/NCT02599064

Phase

Phase I/II

Status

Unknown status

Sponsor

RXi Pharmaceuticals, Corp.

More details

This study is designed to evaluate the safety, tolerability and clinical activity of RXI-109 administered by intravitreal injection to reduce the progression of subretinal fibrosis in subjects with advanced neovascular age-related macular degeneration (NVAMD).

Purpose

Evaluating RXI-109 to Reduce the Progression of Subretinal Fibrosis in Subjects With NVAMD

Interventions

Intervention 1

RXI-109

Countries

United States of America

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2015-11-01

Anticipated Date of Last Follow-up

2018-02-22

Estimated Primary Completion Date

2018-04-01

Estimated Completion Date

2018-05-01

Actual Primary Completion Date

Not provided

Actual Completion Date

Not provided

Studied populations

Age Cohort

- Adults
- Older Adults

Genders

All

Accepts pregnant individuals

Unspecified

Accepts lactating individuals

Unspecified

Accepts healthy individuals

No

Comments about the studied populations

Inclusion Criteria: * Subjects presenting with advanced NVAMD in the study eye with BCVA ≤20/100 potentially due to subretinal fibrosis involving the fovea * BCVA ≥20/800 in the contralateral eye and better than the study eye * ≥50 years of age * Subfoveal choroidal neovascularization (CNV) of any type Exclusion Criteria: * Presence of other causes of CNV including pathologic myopia, ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, and multifocal choroiditis * Evidence of inflammation (Grade 1 or higher) in the anterior or posterior chamber.

Health status

Not provided

Other health status: Advanced neovascular age-related macular degeneration

Study type

Interventional (clinical trial)

Enrollment

Not provided

Allocation

Not provided

Intervention model

Single group assignment

Intervention model description

Not provided

Masking

Open label

Masking description

Not provided

Frequency of administration

Monthly

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Other(s) : "Intravitreal "

Use case

Treatment

Key resources

Not provided

Excipients

Proprietary excipients used

No proprietary excipient used

Novel excipients or existing excipients at a concentration above Inactive Ingredients Database (IID) for the specified route of administration

No novel excipient or existing excipient used

Residual solvents used

No residual solvent used

Additional features

Other features of the technology

Not provided

Release properties

When the INSTACYL formulation is administered locally, i.e., intratumorally, the chemically modified siRNA undergoes spontaneous cellular uptake due to the interaction of the lipophilic functional group (e.g., sterol group) with the cell membrane. Thus, the cellular uptake of INSTACYL does not require facilitated transport systems or carriers.

Injectability

INSTACYL formulation is designed for intratumoral and intravitreal route of adminstration.

Safety

The INSTACYL products were well tolerated in the clinical phase 1 studies. One of such study on PH-762 once weekly (for 4 weeks) indicate that there was no No dose-limiting toxicities or clinically significant treatment-emergent adverse effects have been reported.

Stability

Not provided

Storage conditions and cold-chain related features

Not provided

Potential application(s)

Therapeutic area(s)

Oncology

Use case(s)

Treatment

Use of technology

Ease of administration

- Administered by a community health worker
- Administered by a nurse
- Administered by a specialty health worker

Frequency of administration

Weekly

User acceptance

Not provided

Targeted user groups

Age Cohort

- Adults
- Older Adults

Genders

- All

Pregnant individuals

Unspecified

Lactating individuals

Unspecified

Healthy individuals

Unspecified

Comment

Not provided

Potential associated API(s)

PH-762

Class(es)

PD-1 protein silencer

Development stage

Phase I

Clinical trial number(s)

NCT06014086

Foreseen/approved indication(s)

Cutaneous carcinoma

Foreseen user group

Not provided

Foreseen duration between application(s)

Once weekly

Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

FDA has cleared the IND application for PH-762

PH-894

Class(es)

BRD4 protein silencer

Development stage

Pre-clinical

Clinical trial number(s)

Not provided

Foreseen/approved indication(s)

Melanoma

Foreseen user group

Not provided

Foreseen duration between application(s)

Once weekly

Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

Not provided

Patent info

Description

Chemically modified oligonucleotides

Brief description

The disclosure relates, in some aspects, to methods and compositions for production of immunogenic compositions. In some embodiments, the disclosure provides host cells which have been treated ex vivo with one or more oligonucleotide agents capable of controlling and/or reducing the differentiation of the host cell. In some embodiments, compositions and methods described by the disclosure are useful as immunogenic modulators for treating cancer.

Representative patent

AU2018313149B2

Category

Not provided

Patent holder

Phio Pharmaceuticals Corp

Exclusivity

Not provided

Expiration date

August 7, 2038

Status

Active

Description

Reduced size self-delivering RNAi compounds

Brief description

A method for delivering a nucleic acid to a remote target tissue in a subject in need thereof, comprising systemically administering to the subject an sd-rxRNA® in an effective amount to promote RNA interference by the sd-rxRNA® in the remote target tissue, wherein the sd-rxRNA® comprises a guide strand and a passenger strand, wherein the sd-rxRNA® includes a double-stranded region and a single stranded region wherein the double stranded region is from 8-15 nucleotides long, wherein the single stranded region is at the 3′ end of the guide strand and is 4-12 nucleotides long, wherein the single stranded region contains 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 phosphorothioate modifications, wherein at least 40% of the nucleotides of the sd-rxRNA® are modified, and wherein at least two Us.

Representative patent

US10240149B2

Category

Not provided

Patent holder

Phio Pharmaceuticals Corp

Exclusivity

Not provided

Expiration date

March 24, 2031

Status

Active

Description

Phagocytic cell delivery of RNAI

Brief description

The present invention provides a particulate delivery system for delivering an RNAi construct to phagocytic cells such as macrophages, comprising various configurations of a complex comprising a phagocytic cell-targeting moiety and an RNAi construct. The invention further provides methods of making the delivery system, and their uses, such as treating phagocytic cell-associated disease conditions.

Representative patent

US8815818B2

Category

Not provided

Patent holder

Phio Pharmaceuticals Corp

Exclusivity

Not provided

Expiration date

August 16, 2029

Status

Active

Supporting material

Publications

** Maxwell, M., Holton, K., Looby, R. J., Byrne, M., & Cardia, J. (2024). Self-Delivering RNAi Compounds for Reduction of Hyperpigmentation. Clinical, cosmetic and investigational dermatology, 17, 3033–3044. https://doi.org/10.2147/CCID.S498987 **

Purpose: Abnormal melanin synthesis causes hyperpigmentation disorders like melasma and lentigines, impacting psychological well-being. RNA interference (RNAi) uses small RNA molecules to inhibit gene expression by targeting specific mRNA, silencing genes involved in undesirable cellular functions. This study assessed INTASYL compounds, self-delivering RNAi molecules, designed to target and reduce tyrosinase gene expression to decrease pigmentation.

Methods: 36 INTASYL compounds were designed to target and reduce TYR gene expression and tested in a screening assay. RXI-231, the lead compound, was tested in normal human epithelial melanocytes and the MelanoDerm™ model, a 3D reconstituted human epidermal culture. RXI-231 was evaluated for its ability to reduce tyrosinase mRNA expression, in vitro dopachrome formation, and melanin content. Penetration of fluorescently labeled INTASYL compounds through the stratum corneum into the epidermis was tested in cultured porcine skin explants using a DermaPen® microneedle device and a proprietary mixture of penetration enhancers. RXI-231 was also tested for skin irritation in the MatTek EpiDerm™ model to determine its non-irritant profile.

Results: RXI-231 significantly reduced tyrosinase mRNA expression, dopachrome formation, and melanin content in both normal human melanocytes and the MelanoDerm model. Application of INTASYL compounds every other day visibly

reduced pigmentation in the 3D epidermal cultures. Penetration studies showed efficient delivery into the epidermis, overcoming the stratum corneum barrier. RXI-231 showed no irritation, with viability above 50% in the MatTek EpiDerm model, confirming its non-irritant profile.

** Cuiffo, B., Maxwell, M., Yan, D., Guemiri, R., Boone, A., Bellet, D., Rivest, B., Cardia, J., Robert, C., & Fricker, S. P. (2024). Self-delivering RNAi immunotherapeutic PH-762 silences PD-1 to generate local and abscopal antitumor efficacy. Frontiers in immunology, 15, 1501679. https://doi.org/10.3389/fimmu.2024.1501679 **

Objective: Immunotherapeutic inhibition of PD-1 by systemically administered monoclonal antibodies is widely used in cancer treatment, but it may cause severe immune-related adverse events (irSAEs). Neoadjuvant PD-1 inhibition before surgery has shown promise in reducing recurrence by stimulating durable antitumor immunity. Local intratumoral (IT) immunotherapy is a potential strategy to minimize irSAEs, but antibodies have limited tumor penetration, making them less suitable for this approach. Therapeutic self-delivering RNAi (INTASYL) is an emerging modality well-suited for neoadjuvant immunotherapy. This study presents preclinical proof-of-concept for PH-762, an INTASYL designed to silence PD-1, currently in clinical development for advanced cutaneous malignancies (ClinicalTrials.gov#NCT06014086).

Methods and analysis: PH-762 pharmacology was characterized *in vitro*, and *in vivo* antitumor efficacy was evaluated using a murine analogue (mPH-762) in syngeneic tumor models with varying PD-1 responsiveness. Bilateral Hepa1-6 models assessed abscopal effects of local treatment. Ex vivo analyses explored mechanisms of direct and abscopal efficacy.

Results: PH-762 was rapidly internalized by human T cells, silencing PD-1 mRNA and decreasing PD-1 surface protein, enhancing TCR-stimulated IFN-γ and CXCL10

secretion. *In vivo*, IT mPH-762 provided robust antitumor efficacy, local and lymphatic biodistribution, and was well tolerated. Ex vivo analyses revealed that IT mPH-762 depleted PD-1 protein, promoted leukocyte and T cell infiltration, and correlated with tumor control. IT mPH-762 also demonstrated efficacy against untreated distal tumors (abscopal effect) by priming systemic antitumor immunity.

Additional documents

No documents were uploaded

Useful links

There are no additional links

Access principles

Collaborate for development

Consider on a case by case basis, collaborating on developing long acting products with potential significant public health impact, especially for low- and middle-income countries (LMICs), utilising the referred to long-acting technology

Not provided

Share technical information for match-making assessment

Provide necessary technical information to a potential partner, under confidentiality agreement, to enable preliminary assessment of whether specific medicines of public health importance in LMICs might be compatible with the referred to long-acting technology to achieve a public health benefit

Not provided

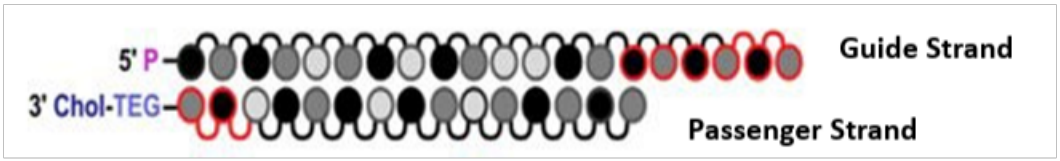
Work with MPP to expand access in LMICs

In the event that a product using the referred to long-acting technology is successfully developed, the technology IP holder(s) will work with the Medicines Patent Pool towards putting in place the most appropriate strategy for timely and affordable access in low and middle-income countries, including through licensing

Not provided

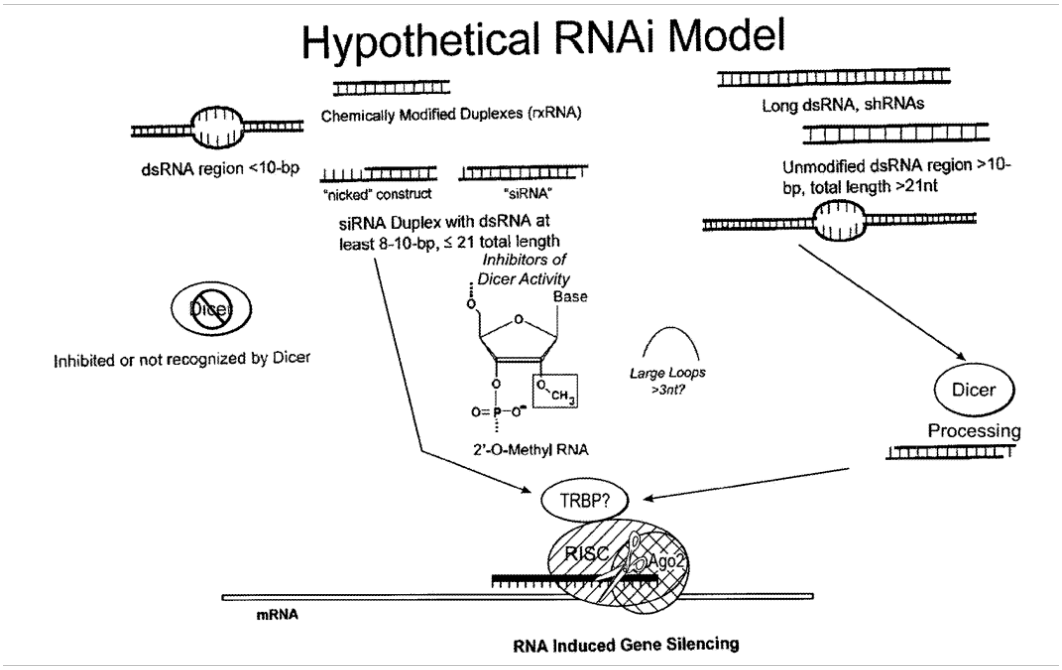
Comment & Information

Illustrations



Guide strand acts as active strand with RISC and the passenger strand is inactive but plays a role in structural integrity.

Phio Pharmaceuticals Corp. (2025). Phio Pharmaceuticals: INTASYL® siRNA Patented Technology. https://d2ghdaxqb194v2.cloudfront.net/2839/196675.pdf



Example of RNAi model and its mechanism of action

Ehrlich, G., & Fenster, M. (2021). Methods and systems for anonymously selecting subjects for treatment against an infectious disease caused by a pathogen. U.S. Patent No. US20210147849A1.