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THE LONG-ACTING THERAPEUTICS PATENTS AND LICENCES DATABASE

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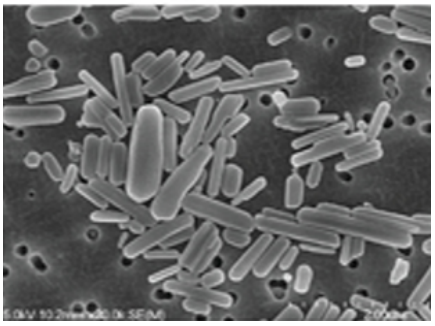

Nanocrystalline Prodrug Technology

Developer(s)

Exavir Therapeutics

Originator

https://exavirtherapeutics.com/

United States of America

Exavir Therapeutics is a spun-out company that originated in 2020 by Alborz and was developed by the University of Nebraska Medical Center. Exavir is specialized in ultra-long-acting drug delivery systems. Exavir has received an NIAD grant in 2023. Exavir currently works on HIV therapeutics off-patent drugs. Howard Gendelman and other researchers play a vital role in Exavir.

Sponsor(s)

University of Nebraska Medical Center

https://www.unmc.edu/

Partnerships

No partner indicated

Technology information

Type of technology

Aqueous drug particle suspension

Administration route

Intramuscular, Subcutaneous

Development state and regulatory approval

Active Pharmaceutical Ingredient (API)

Cabotegravir (CAB)

Development Stage

Pre-clinical

Regulatory Approval

XVIR-110 (Cabotegravir 18 Carbon ester prodrug) is prepared for IND

Description

ProTide Prodrug Technology is an ultra-long-acting nanoformulation. The Pro-Tide technology contains nanocrystals of ester prodrug of the API. Further, the duration of the formulation is dependent on the carbon length of the ester fatty acid. In addition to that, the lipophilicity of the prodrug depends on the physiochemical properties of the fatty acid and the location of the fatty acid attached. Also, this nanoformulation has no residual solvents.

Technology highlight

1) ProTide prodrugs have controlled hydrolysis of the ester chain. The length of the carbon chain can be customizable based on the API. 2) Tissue penetrance can be overcome. 3) Prolonged drug release, plasma circulation rate, and tissue binding of API. 4) Poloxamer 407 is used as a stabilizer; thus, the formulation is stable for 98 days in vivo.

Technology main components

1) ProTide prodrug (14 to 18 carbon ester-linked API) 2) Poloxamer 308 and/or 407 3) Other excipients such as surfactants.

Information on the raw materials sourcing, availability and anticipated price

Not provided

Delivery device(s)

No delivery device

APIs compatibility profile

API desired features

Water-soluble molecules

Water-insoluble molecules

Small molecules

The ProTide formulation targets non-nucleotide reverse transcriptase inhibitors and integrase strand transfer inhibitors such as cabotegravir, tenofovir, dolutegravir, and nevirapine.

Additional solubility data

The solubility of each ProTide can be tailored by modifying the physicochemical properties of the API through adjustments to the hydrophilic or hydrophobic nature of the ester chain, specifically by varying the length of the fatty acid moiety.

Additional stability data

Not provided

API loading: Maximum drug quantity to be loaded

75-90 wt%

API co-administration

1 single API :

LogP

Min: -1.6 Max: 4

Scale-up and manufacturing prospects

Scale-up prospects

The Exavir does not have its own manufacturing facilities.

Tentative equipment list for manufacturing

Avestin EmulsiFlex-C3 High-pressure homogenizer

Manufacturing

1. Disperse solid drug/prodrug in a poloxamer 407 solution at a drug/prodrug to surfactant ratio of 10:1 w/w in endotoxin-free water to form a presuspension. 2. Homogenize the presuspension using an Avestin EmulsiFlex-C3 high-pressure homogenizer at 20,000 ± 1000 PSI until the desired particle size is achieved. 3. Characterize formulations for particle size, polydispersity index (PDI), and zeta potential using DLS with a Malvern Zetasizer Nano-ZSP. 4. Quantify drug loading using LC-MS. 5. Assess endotoxin concentrations using a Charles River Endosafe Nexgen system.

Specific analytical instrument required for characterization of formulation

1. Scanning Electron Microscope (SEM) 2. Dynamic Light Scattering + Malvern Zetasizer Nano-ZSP 3. Ultra-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) 4. Charles River Endosafe Nexgen system

Clinical trials

Not provided

Excipients

Proprietary excipients used

Not provided

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

Not provided

Residual solvents used

Not provided

Additional features

Other features of the technology

- At least 1 year shelf life

Release properties

Nanocrystals facilitate drug delivery to macrophages by forming intracellular and tissue drug reservoirs within endosomes. This intracellular sequestration shields the drug from systemic circulation, thereby extending the half-life of the API. The prodrug undergoes biotransformation into its active form through intracellular kinase-mediated activation.

Injectability

ProTide formulations are injected via intramuscular injection via a 20-25 gauge needle.

Safety

No safety concerns were observed in the preclinical toxicology studies. Further, clinical safety studies are yet to be conducted.

Stability

In preclinical stability studies of the CAB 18-carbon ester ProTide prodrug nanoparticles, the prodrug demonstrated approximately 100% stability, with negligible drug release observed from the intact nanoparticles over the course of one year of storage.

Storage conditions and cold-chain related features

Studies show that the formulation can maintain its integrity over 98 days under various storage conditions.

Potential application(s)

Therapeutic area(s)

Other(s) : "Opoid Use Disorder"

HIV

Use case(s)

Not provided

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

Once every 6 months, Yearly

User acceptance

Not provided

Targeted user groups

Age Cohort

- Adults
- Older Adults

Genders

- Male
- Female

Pregnant individuals

Unspecified

Lactating individuals

Unspecified

Healthy individuals

Unspecified

Comment

Not provided

Potential associated API(s)

Cabotegravir (CAB)

Class(es)

HIV integrase strand transfer inhibitor

Development stage

Pre-clinical

Clinical trial number(s)

Not provided

Foreseen/approved indication(s)

HIV Treatment and PrEP

Foreseen user group

Not provided

Foreseen duration between application(s)

Once yearly

Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

XVIR-110 (Cabotegravir 18 Carbon ester prodrug) is prepared for IND

Dolutegravir (DTG)

Class(es)

HIV integrase inhibitors

Development stage

Pre-clinical

Clinical trial number(s)

Not provided

Foreseen/approved indication(s)

HIV treatment and PrEP

Foreseen user group

Not provided

Foreseen duration between application(s)

Once yearly

Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

Not provided

Tenofovir (TFV)

Class(es)

Nucleoside reverse transcriptase inhibitors (NRTIs)

Development stage

Pre-clinical

Clinical trial number(s)

Not provided

Foreseen/approved indication(s)

HIV Treatment and PrEP

Foreseen user group

Not provided

Foreseen duration between application(s)

Once yearly

Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

Not provided

Rilpivirine (RPV)

Class(es)

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Development stage

Pre-clinical

Clinical trial number(s)

Not provided

Foreseen/approved indication(s)

HIV Treatment and PrEP

Foreseen user group

Not provided

Foreseen duration between application(s)

Once yearly

Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

Not provided

Bictegravir (BIC)

Class(es)

HIV integrase strand transfer inhibitor (INSTI)

Development stage

Pre-clinical

Clinical trial number(s)

Not provided

Foreseen/approved indication(s)

HIV Treatment and PrEP

Foreseen user group

Not provided

Foreseen duration between application(s)

Six monthly

Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

Not provided

Patent info

Description

Antiviral prodrugs compounds and crystalline nanoparticle formulations

Brief description

Prodrug compounds of cabotegravir (CAB), raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG), bictegravir (BIC), BI 224436, and MK-2048. Crystalline nanoparticle formulations comprising one of the prodrugs listed above and and at least one polymer or surfactant. Method of use of said formulation for treating HIV

Representative patent

WO2020086555

Category

Compound/Formulation/Method of treatment

Patent holder

Board of regents of the University of Nebraska

Exclusivity

Not provided

Expiration date

October 22, 2039

Status

Granted: CN, US, MX, EP (BE, CH, CY, DE, ES, FI, FR, GB, HU, IE, IT, LI, LU, MC, MT, NL, RO), SA, EA (AM, AZ, BY, KG, KZ, RU, TJ, TM), Pending: AU, BR, CA, EG, HK, ID, IL, JP, KR, MY, NZ, PH, SG Not in force: AT, BG, CZ, DK, EE, GR, HR, IS, LT, LV, NO, PT, RS, SE, SI, SK, SM, TR, IN, , KH, MA, MD, TN, BA, ME

Supporting material

Publications

** Kulkarni, T. A., Bade, A. N., Sillman, B., Shetty, B. L. D., Wojtkiewicz, M. S., Gautam, N., Hilaire, J. R., Sravanam, S., Szlachetka, A., Lamberty, B. G., Morsey, B. M., Fox, H. S., Alnouti, Y., McMillan, J. M., Mosley, R. L., Meza, J., Domanico, P. L., Yue, T. Y., Moore, G., Edagwa, B. J., … Gendelman, H. E. (2020). A year-long extended release nanoformulated cabotegravir prodrug. Nature materials, 19(8), 910–920. https://doi.org/10.1038/s41563-020-0674-z **

Long-acting cabotegravir (CAB) extends antiretroviral drug administration from daily to monthly. However, dosing volumes, injection site reactions and health-care oversight are obstacles towards a broad usage. The creation of poloxamer-coated hydrophobic and lipophilic CAB prodrugs with controlled hydrolysis and tissue penetrance can overcome these obstacles. To such ends, fatty acid ester CAB nanocrystal prodrugs with 14, 18, and 22 added carbon chains were encased in biocompatible surfactants named NMCAB, NM2CAB, and NM3CAB and tested for drug release, activation, cytotoxicity, antiretroviral activities, pharmacokinetics, and biodistribution. Pharmacokinetics studies, performed in mice and rhesus macaques with the lead 18-carbon ester chain NM2CAB, showed plasma CAB levels above the protein-adjusted 90% inhibitory concentration for up to a year. NM2CAB, compared with NMCAB and NM3CAB, demonstrated a prolonged drug release, plasma circulation time and tissue drug concentrations after a single 45 mg per kg body weight intramuscular injection. These prodrug modifications could substantially improve CAB's effectiveness.

** Cobb, D. A., Smith, N., Deodhar, S., Bade, A. N., Gautam, N., Shetty, B. L. D., McMillan, J., Alnouti, Y., Cohen, S. M., Gendelman, H. E., & Edagwa, B. (2021). Transformation of tenofovir into stable ProTide nanocrystals with long-acting pharmacokinetic profiles. Nature communications<span style="color: rgb(33, 33,**

**33);">, 12(1), 5458. https://doi.org/10.1038/s41467-021-25690-5 **

Treatment and prevention of human immunodeficiency virus type one (HIV-1) infection was transformed through widespread use of antiretroviral therapy (ART). However, ART has limitations in requiring life-long daily adherence. Such limitations have led to the creation of long-acting (LA) ART. While nucleoside reverse transcriptase inhibitors (NRTI) remain the ART backbone, to the best of our knowledge, none have been converted into LA agents. To these ends, we transformed tenofovir (TFV) into LA surfactant stabilized aqueous prodrug nanocrystals (referred to as NM1TFV and NM2TFV), enhancing intracellular drug uptake and retention. A single intramuscular injection of NM1TFV, NM2TFV, or a nanoformulated tenofovir alafenamide (NTAF) at 75 mg/kg TFV equivalents to Sprague Dawley rats sustains active TFV-diphosphate (TFV-DP) levels ≥ four times the 90% effective dose for two months. NM1TFV, NM2TFV and NTAF elicit TFV-DP levels of 11,276, 1,651, and 397 fmol/g in rectal tissue, respectively. These results are a significant step towards a LA TFV ProTide.

** Deodhar, S., Sillman, B., Bade, A. N., Avedissian, S. N., Podany, A. T., McMillan, J. M., Gautam, N., Hanson, B., Dyavar Shetty, B. L., Szlachetka, A., Johnston, M., Thurman, M., Munt, D. J., Dash, A. K., Markovic, M., Dahan, A., Alnouti, Y., Yazdi, A., Kevadiya, B. D., Byrareddy, S. N., … Gendelman, H. E. (2022). Transformation of dolutegravir into an ultra-long-acting parenteral prodrug formulation. Nature communications, 13(1), 3226. https://doi.org/10.1038/s41467-022-30902-7 **

Ultra-long-acting integrase strand transfer inhibitors were created by screening a library of monomeric and dimeric dolutegravir (DTG) prodrug nanoformulations. This led to an 18-carbon chain modified ester prodrug nanocrystal (coined NM2DTG) with the potential to sustain yearly dosing. Here, we show that the physiochemical and pharmacokinetic (PK) formulation properties facilitate slow drug release from tissue macrophage depot stores at the muscle injection site and adjacent lymphoid tissues following single parenteral injection. Significant plasma drug levels are recorded up to a year following injection. Tissue sites for prodrug hydrolysis are dependent on nanocrystal dissolution and prodrug release, drug-depot volume, perfusion, and cell-tissue pH. Each affect an extended NM2DTG apparent half-life recorded by PK parameters. The NM2DTG product can impact therapeutic adherence, tolerability, and access of a widely used integrase inhibitor in both resource limited and rich settings to reduce HIV-1 transmission and achieve optimal treatment outcomes.

** Cobb, D. A., Smith, N., Deodhar, S., Bade, A. N., Gautam, N., Shetty, B. L. D., McMillan, J., Alnouti, Y., Cohen, S. M., Gendelman, H. E., & Edagwa, B. (2021). Transformation of tenofovir into stable ProTide nanocrystals with long-acting pharmacokinetic profiles. Nature communications, 12(1), 5458. https://doi.org/10.1038/s41467-021-25690-5 **

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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

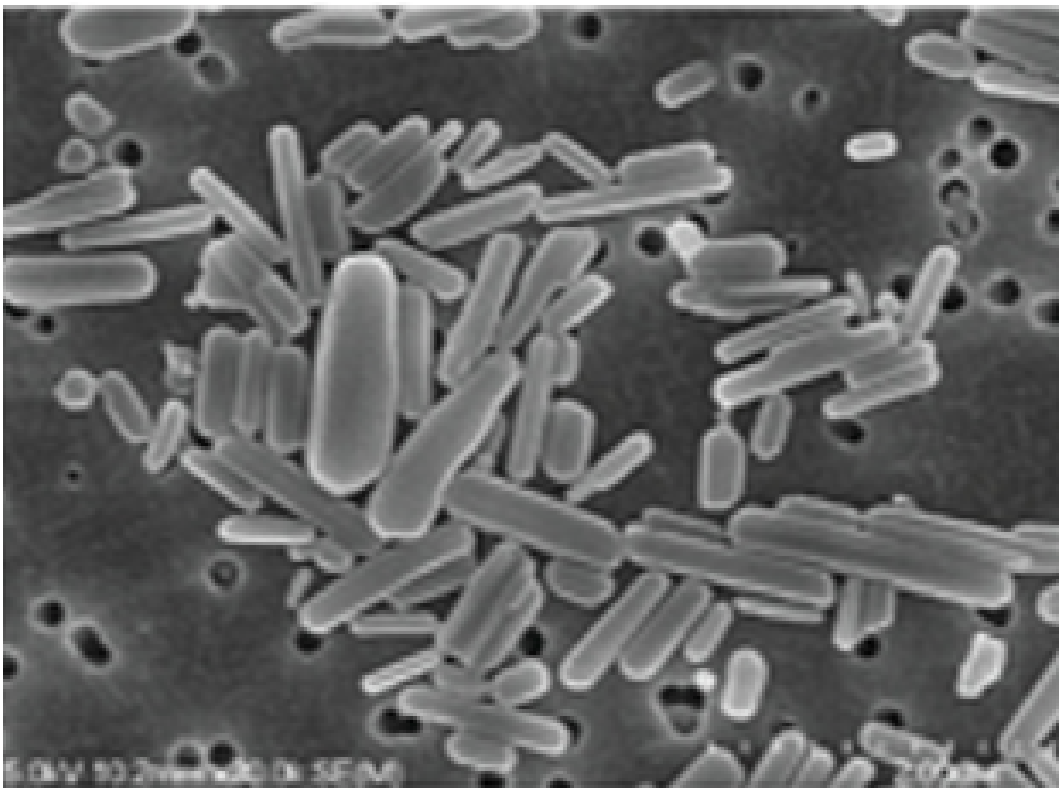
Work with MPP to expand access in LMICs

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

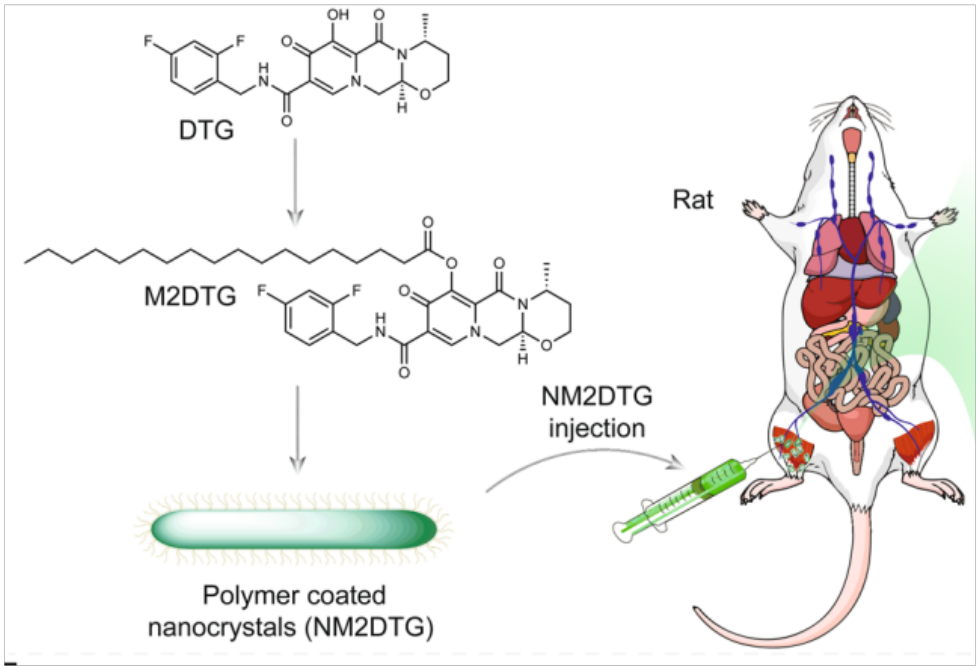
Comment & Information

Illustrations



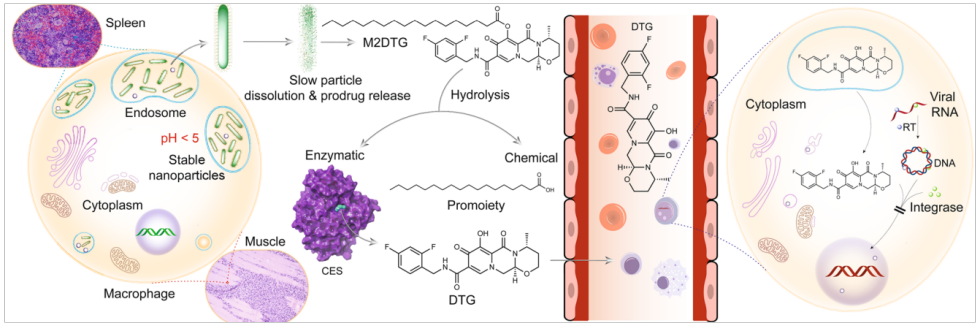
SEM analysis of Cabotegravir 18 carbon ester ProTide prodrug nanocrystals

Kulkarni, T. A., Bade, A. N., Sillman, B., Shetty, B. L. D., Wojtkiewicz, M. S., Gautam, N., Hilaire, J. R., Sravanam, S., Szlachetka, A., Lamberty, B. G., Morsey, B. M., Fox, H. S., Alnouti, Y., McMi



Dolutegravir converted to Prodrug and tested as IM injection in rats

Deodhar S, Sillman B, Bade AN, et al. Transformation of dolutegravir into an ultra-long-acting parenteral prodrug formulation. Nat Commun. 2022;13(1):3226. Published 2022 Jun 9. doi:10.1038/s41467-022



pro-DTG is slowly dissolved from the nanoformulation in the low pH microenvironment in macrophages and then hydrolyzed to release DTG. The slow rate of dissolution of the DTG nanocrystals from tissue

Deodhar S, Sillman B, Bade AN, et al. Transformation of dolutegravir into an ultra-long-acting parenteral prodrug formulation. Nat Commun. 2022;13(1):3226. Published 2022 Jun 9. doi:10.1038/s41467-022