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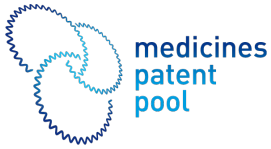
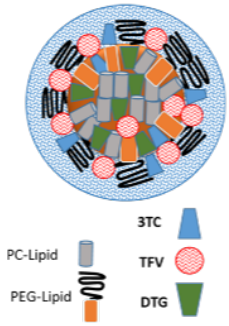




Drug Combination Nanoparticles (DcNP)

Verified by the innovator, on Jul 2021

Developer(s)

Targeted & Long-acting drug Combination (TLC) Program, University of Washington

Originator

https://depts.washington.edu/tlcart/

United States

The purpose of the Targeted Long-acting Combination AntiRetroviral Therapy (TLC-ART) program is to develop one or more safe, stable, scalable and tolerable long acting antiretroviral combinations for treatment of HIV infection.

Sponsor(s)

Unitaid

https://unitaid.org

Partnerships

Clinton Health Access Initiative

https://www.clintonhealthaccess.org/

Medicines Patent Pool

https://medicinespatentpool.org/

Technology information

Type of technology

Based on other organic particles, Aqueous drug particle suspension

Administration route

Subcutaneous

Development state and regulatory approval

Active Pharmaceutical Ingredient (API)

Lamivudine (3TC), Dolutegravir (DTG), Tenofovir (TFV)

Development Stage

Phase I

Regulatory Approval

Not provided

Description

A targeted and long-acting Drug combination Nano-Particle (DcNP) platform that enables transformations of existing and new drug entities from short-acting daily doses to a long-acting drug combination for a maximum therapeutic effect through sustained viral suppression.

Technology highlight

TLC's enabling DcNP technology has been validated to work with a number of current HIV drug combinations using clinics in both pediatric and adult populations. A number of these formulations have been evaluated in non-human primate models to provide both plasma and cell drug levels that persist for weeks after a single subcutaneous injection. This technology has been shown to bring together water soluble (such as tenofovir and lamivudine) and insoluble (such as lopinavir, ritonavir, atezenovir, and dolutegravir) drugs into an all-in-one long-acting injectable product. At least 4 formulations have been tested in NHP to have long-acting plasmakinetics for all drugs and are targeted to enhanced drug levels above plasma drug combinations in HIV host cells-PBMCs.

Technology main components

Drug API and common lipid excipients used in pharmaceutical formulations.

Information on the raw materials sourcing, availability and anticipated price

The existing HIV drug APIs can be sourced through WHO pre-qualified raw material suppliers.

Delivery device(s)

No delivery device

APIs compatibility profile

API desired features

Water-soluble molecules

Water-insoluble molecules

Small molecules

Tenofovir, Lamivudine, Dolutegravir, Lopinavir, Ritonavir, Atazanavir, Efavirenz

Additional solubility data

Not provided

Additional stability data

Not provided

API loading: Maximum drug quantity to be loaded

10-30 wt%

API co-administration

4 different APIs : 2 to 4 different drugs in a single injection are being investigated

LogP

Not provided

Scale-up and manufacturing prospects

Scale-up prospects

Good

Tentative equipment list for manufacturing

Spray-dryer; homogenization; size-reduction

Manufacturing

Injectable cGMP facilties

Specific analytical instrument required for characterization of formulation

Not provided

Clinical trials

First in Human Clinical Trial of a Next Generation, Long-acting Injectable, Combination Antiretroviral Therapy Platform TLC-ART 101 (ACTU 2001)

Identifier

NCT05850728

Link

https://clinicaltrials.gov/study/NCT05850728?intr=TLC-ART&rank=1

Phase

Phase I

Status

Recruiting

Sponsor

NIH

More details

This study is a prospective, open-label, single-site, first-in-human study of a long-acting, injectable combination antiretroviral therapy platform, with a pharmacologically-guided adaptive design for dose escalation, de-escalation, and study duration. The study is designed to learn whether the formulation can be used as a platform for other drugs for treatment of HIV. The formulation is a drug combination nanoparticle (DCNP). The study will be conducted by UW Positive Research. The sample size for this study is 12-16. The study population consists of healthy adults

without HIV. The study duration is 57 days per participant at the start of the study.

Purpose

Safety, tolerability and PK of single subcutaneous injection of TLC-ART 101 in healthy adults

Interventions

Intervention 1

TLC-ART 101 containing lopinavir 15.6mg , ritonavir 4.2 mg, and tenofovir 9.15 mg in a combination nanoparticle suspension of 1.5 mL

Countries

United States of America

Sites / Institutions

Seattle, Washington

Trials dates

Anticipated Start Date

2023-04-01

Actual Start Date

2023-04-01

Anticipated Date of Last Follow-up

Not provided

Estimated Primary Completion Date

2025-10-25

Estimated Completion Date

2025-12-01

Actual Primary Completion Date

Not provided

Actual Completion Date

Not provided

Studied populations

Age Cohort

- Adults
- Older Adults

Genders

- All

Accepts pregnant individuals

No

Accepts lactating individuals

No

Accepts healthy individuals

Yes

Comments about the studied populations

18 Years to 65 Years (Adult, Older Adult) of any sex

Health status

Negative to : HIV, HCV, HBV

Study type

Interventional (clinical trial)

Enrollment

16

Allocation

Non-randomized

Intervention model

Single group assignment

Intervention model description

This study is a prospective, open-label, single-site, first-in-human study of a long-acting, injectable combination antiretroviral therapy platform, with a pharmacologically-guided adaptive design for dose escalation, de-escalation, and study duration. The study is designed to learn whether the formulation can be used as a platform for other drugs for treatment of HIV. The formulation is a drug combination nanoparticle (DCNP). The study will be conducted by UW Positive Research. The sample size for this study is 12-16. The study population consists of healthy adults without HIV. The study duration is 57 days per participant at the start of the study.

Masking

Open label

Masking description

Not provided

Frequency of administration

Monthly

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Subcutaneous

Use case

Treatment

Key results

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

- Biodegradable
- Non-removable
- Room temperature storage
- At least 1 year shelf life

Release properties

Intracellular uptake and accessible by cellular enzymes to transform into active metabolites such as TFV-DP and 3TC-TP.

Injectability

Not provided

Safety

Not provided

Stability

Not provided

Storage conditions and cold-chain related features

No cold-chain needed

Potential application(s)

Therapeutic area(s)

HIV

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
- Self-administered

Frequency of administration

Monthly

User acceptance

Not provided

Targeted user groups

Age Cohort

- Adults

Genders

- Male
- Female
- Cisgender female
- Cisgender male
- Transgender female
- Transgender male
- Intersex
- Gender non-binary
- All

Pregnant individuals

Unspecified

Lactating individuals

Unspecified

Healthy individuals

No

Comment

Not provided

Potential associated API(s)

Lamivudine (3TC), Dolutegravir (DTG), Tenofovir (TFV)

Class(es)

Antiviral

Development stage

Phase I

Clinical trial number(s)

Not provided

Foreseen/approved indication(s)

Treatment for people living with HIV

Foreseen user group

People living with HIV

Foreseen duration between application(s)

1 month

Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

Not provided

Lopinavir and ritonavir (LPV/r), Tenofovir (TFV)

Class(es)

antiviral

Development stage

Pre-clinical

Clinical trial number(s)

Not provided

Foreseen/approved indication(s)

Treatment for people living with HIV to provide sustained viral suppression

Foreseen user group

People living with HIV

Foreseen duration between application(s)

1 month

Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

Not provided

Tenofovir-Lamivudine-Dolutegravir (TLD) - long-acting injectable (LAI) (TLD LAI)

Class(es)

Not provided

Development stage

Pre-clinical

Clinical trial number(s)

Not provided

Foreseen/approved indication(s)

HIV treatment

Foreseen user group

Adults living with HIV

Foreseen duration between application(s)

1 month

Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

Not provided

Patent info

Technology patent families

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Antiviral compositions that transform short-acting therapeutic agents into long-acting injectable forms that lasts for many weeks per administration Expiry date: 2041-01-07 The present disclosure describes simple, stable, and scalable antiviral therapeutic agent compositions that transform short-acting antiviral (e.g., anti-HIV) therapeutic agents that would otherwise require daily short-acting oral administration into long-acting injectable forms that lasts for many weeks per administration. A mixture of water-soluble and water-insoluble antiviral therapeutic agents can be present in the long-acting and drug-combination composition.	WO2021142150		University of Washington	Yes	Company

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income
Granted		
Filed	China, Brazil	United States of America
Not in force	World Intellectual Property Organization (WIPO)	World Intellectual Property Organization (WIPO)

MPP Licence(s)

MPP/Uni Washington licence on Drug Combination Nanoparticles (DcNP) - HIV prevention/treatment

https://medicinespatentpool.org/licence-post/long-acting-injectable-drug-combination-for-hiv-treatment-prevention

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Combination pharmaceutical compositions including a combination of hydrophilic and hydrophobic therapeutic agents Expiry date: 2040-01-10 The current invention is about a pharmaceutical formulation with a hydrophilic and hydrophobic drug along with a compatibilizer (lipid). The method of preparation is by dissolving all the components in suitable mixture of solvents, and then evaporating the solvent to get the powder form.	WO2020146788		University of Washington	Yes	Company

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income
Granted	South Africa	
Filed	China, Brazil, India, Nigeria	
Not in force	World Intellectual Property Organization (WIPO)	World Intellectual Property Organization (WIPO), United States of America

MPP Licence(s)

MPP/Uni Washington licence on Drug Combination Nanoparticles (DcNP) - HIV prevention/treatment

https://medicinespatentpool.org/licence-post/long-acting-injectable-drug-combination-for-hiv-treatment-prevention

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Drug Combination Nanoparticles for multiple drugs extended release Expiry date: 2036-06-15 Multi-drug lipid nanoparticles that stably incorporate multiple small molecule drugs with divergent hydrophobic and water solubility characteristics and related methods of making and using the same. The disclosed compositions and methods provide for enhanced stability of lipid nanoparticle drug formulations that can reliably provide drugs addressing different mechanistic targets with prolonged presence in the body for more efficacious treatment and avoidance of single drug resistance.	WO2016205384		The University Of Washington	Yes	Company

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income
Granted		United States of America
Filed	World Intellectual Property Organization (WIPO), China	World Intellectual Property Organization (WIPO)
Not in force		

MPP Licence(s)

MPP/Uni Washington licence on Drug Combination Nanoparticles (DcNP) - HIV prevention/treatment

https://medicinespatentpool.org/licence-post/long-acting-injectable-drug-combination-for-hiv-treatment-prevention

Tenofovir/Dolutegravir/Lamivudine (LAI candidate)

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Emtricitabine and lamivudine compounds Expiry date: 2010-02-08 Novel substituted 1,3-oxathiolane cyclic compounds having pharmacological activity, to processes for and intermediates of use in their preparation, to pharmaceutical compositions containing them, and to the use of these compounds in the antiviral treatment of mammals.	CA2009637	Compound	Biochem Pharma Inc, Iaf Biochem International, Inc	No	Health Canada

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income

Granted		United States of America, Australia, Germany, Spain, Finland, Ireland, Portugal
Filed		United States of America, Australia, Cyprus, Germany, Denmark, Spain, Greece, Hungary, Ireland, Japan, Luxembourg, Latvia, Netherlands, New Zealand, Poland, Singapore, Slovenia, Slovakia
Not in force	Bosnia and Herzegovina, Yugoslavia/Serbia and Montenegro, China, Honduras, South Africa, Botswana, Ghana, Gambia (the), Kenya, Lesotho, Malawi, Sudan, Eswatini, Uganda, Zambia, Zimbabwe, Burkina Faso, Benin, Central African Republic, Congo, Côte d'Ivoire, Cameroon, Gabon, Guinea, Mali, Mauritania, Niger, Senegal, Chad, Togo, Malaysia, Philippines, Armenia, Kyrgyzstan, Tajikistan, Sri Lanka, Dominican Republic, Georgia, Uzbekistan, Mexico, Moldova, Republic of, Ukraine	Canada, United States of America, Austria, Germany, Denmark, Spain, Greece, Hong Kong, Croatia, Israel, Japan, Korea, Republic of, Luxembourg, Netherlands, Norway, Belgium, Switzerland, France, United Kingdom, Italy, Liechtenstein, Sweden, Uruguay, Saudi Arabia

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Emtricitabine and lamivudine - process for preparing Expiry date: 2012-12-21 The present invention relates to processes for preparing substituted 1,3-oxathiolanes with antiviral activity and intermediates of use in their preparation.	WO9414802	Process	Biochem Pharma Inc	No	EPO (extended family)

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income
Granted		
Filed		Denmark, Spain, Portugal
Not in force	World Intellectual Property Organization (WIPO)	Canada, Austria, World Intellectual Property Organization (WIPO), Australia, Germany, Denmark, Spain, Hungary, Japan, Portugal, Belgium, Switzerland, France, United Kingdom, Greece, Ireland, Italy, Liechtenstein, Luxembourg, Monaco, Netherlands, Sweden

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Lamivudine compound Expiry date: 2011-05-02 (-)-4-Amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one, its pharmaceutically acceptable derivatives, pharmaceutical formulations thereof, methods for its preparation and its use as an antiviral agent are described.	WO9117159	Compound	Iaf Biochem International Inc	No	Health Canada

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income
Granted		United States of America
Filed		United Kingdom, Australia, Finland, Hungary, Japan, Korea, Republic of, New Zealand, Poland, Singapore, Slovenia
Not in force	World Intellectual Property Organization (WIPO), Bosnia and Herzegovina, Yugoslavia/Serbia and Montenegro, China, Morocco, Moldova, Republic of, Tunisia, South Africa, Botswana, Ghana, Gambia (the), Kenya, Lesotho, Malawi, Sudan, Eswatini, Uganda, Zambia, Zimbabwe, Burkina Faso, Benin, Central African Republic, Congo, Côte d'Ivoire, Cameroon, Gabon, Guinea, Mali, Mauritania, Niger, Senegal, Chad, Togo, Egypt, Ukraine, Malaysia, Georgia	Canada, United Kingdom, World Intellectual Property Organization (WIPO), Bulgaria, Hong Kong, Croatia, Ireland, Israel, Japan, Korea, Republic of, Norway, Portugal, Romania, Slovakia, Taiwan, Province of China, United States of America, Austria, Belgium, Switzerland, Germany, Denmark, Spain, France, Greece, Italy, Liechtenstein, Luxembourg, Netherlands, Sweden

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Lamivudine crystal forms Expiry date: 2012-06-02 (-)$i(cis)-4-Amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(IH)-pyrimidine-2-one in crystalline form, in particular as needle-shaped or bipyramidyl crystals, pharmaceutical formulations thereof, methods for their preparation and their use in medicine.	WO9221676	Polymorphs	Glaxo Group Limited	No	Health Canada, US FDA

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income
Granted		United States of America
Filed		United Kingdom, Austria, Australia, Denmark, Ireland, Iceland, Portugal, Singapore
Not in force	Mexico, South Africa, Botswana, Ghana, Gambia (the), Kenya, Lesotho, Malawi, Sudan, Eswatini, Uganda, Zambia, Zimbabwe, Burkina Faso, Benin, Central African Republic, Congo, Côte d'Ivoire, Cameroon, Gabon, Guinea, Mali, Mauritania, Niger, Senegal, Chad, Togo, Philippines, Ukraine, Pakistan, Georgia, World Intellectual Property Organization (WIPO)	Canada, United Kingdom, Austria, Bulgaria, Germany, Denmark, Hong Kong, Ireland, Israel, Japan, Korea, Republic of, Norway, New Zealand, Portugal, Russian Federation, Slovakia, Taiwan, Province of China, Belgium, Switzerland, Spain, France, Greece, Italy, Liechtenstein, Luxembourg, Monaco, Netherlands, Sweden, World Intellectual Property Organization (WIPO)

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Tenofovir disoproxil compounds Expiry date: 2017-07-25 The present invention relates to intermediates for phosphonomethoxy nucleotide analogs, in particular intermediates suitable for use in the efficient oral delivery of such analogs.	WO9804569	Compound	Gilead Sciences, Inc	No	Health Canada, US FDA, MPP Licence

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income
Granted		Luxembourg, United Kingdom
Filed		
Not in force	China, India, World Intellectual Property Organization (WIPO)	Canada, Austria, Australia, Germany, Denmark, Spain, Hong Kong, Japan, Korea, Republic of, Luxembourg, Netherlands, New Zealand, Portugal, Taiwan, Province of China, United States of America, Belgium, Switzerland, Finland, France, Greece, Ireland, Italy, Liechtenstein, Monaco, Sweden, Chile, World Intellectual Property Organization (WIPO), Singapore

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Tenofovir disoproxil fumarate (TDF) Expiry date: 2018-07-23 The invention provides a composition comprising bis(POC)PMPA and fumaric acid (1:1). The composition is useful as an intermediate for the preparation of antiviral compounds, or is useful for administration to patients for antiviral therapy or prophylaxis. The composition is particularly useful when administered orally. The invention also provides methods to make PMPA and intermediates in PMPA synthesis. Embodiments include lithium t-butoxide, 9-(2-hydroxypropyl) adenine and diethyl p-toluenesulfonylmethoxy-phosphonate in an organic solvent such as DMF. The reaction results in diethyl PMPA preparations containing an improved by-product profile compared to diethyl PMPA made by prior methods	WO9905150	Compound, Salt	Gilead Sciences, Inc	No	Health Canada, US FDA, MPP Licence

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income
Granted		
Filed		Portugal

Patent status/countries	Low, Low- middle and upper-middle	High income
Not in force	Brazil, China, India, Mexico, Indonesia, World Intellectual Property Organization (WIPO), Albania	Canada, United States of America, Austria, Australia, Germany, Denmark, Spain, Hong Kong, Japan, Korea, Republic of, New Zealand, Portugal, Singapore, Slovenia, Taiwan, Province of China, Belgium, Switzerland, Cyprus, Finland, France, United Kingdom, Greece, Ireland, Italy, Liechtenstein, Luxembourg, Monaco, Netherlands, Sweden, World Intellectual Property Organization (WIPO), Lithuania, Latvia, Romania

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Tenofovir alafenamide fumarate (TAF) Expiry date: 2021-07-20 A novel method is provided for screening prodrugs of methoxyphosphonate nucleotide analogues to identify prodrugs selectively targeting desired tissues with antiviral or antitumor activity. This method has led to the identification of novel mixed ester-amidates of PMPA for retroviral or hepadnaviral therapy, including compounds of structure (5a) having substituent groups as defined herein. Compositions of these novel compounds in pharmaceutically acceptable excipients and their use in therapy and prophylaxis are provided. Also provided is an improved method for the use of magnesium alkoxide for the preparation of starting materials and compounds for use herein.	WO0208241	Compound	Gilead Sciences, Inc	No	Health Canada, US FDA

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income

Granted	Ukraine, Albania, Ethiopia, Fiji, Grenada, Kiribati, Solomon Islands, Saint Lucia	Australia, Bulgaria, Denmark, Estonia, Hong Kong, Croatia, Hungary, Israel, Iceland, Japan, Korea, Republic of, Poland, Slovenia, United States of America, Russian Federation, Belgium, Switzerland, Cyprus, Germany, Finland, France, United Kingdom, Greece, Italy, Liechtenstein, Luxembourg, Netherlands, Sweden, Lithuania, Romania, Latvia, Brunei Darussalam, Czechia, Anguilla, Bermuda, Falkland Islands (Malvinas), Montserrat, Turks and Caicos Islands, Virgin Islands (British), Saint Helena, Ascension and Tristan da Cunha, Singapore, Cayman Islands, Gibraltar, Guernsey
Filed	Jamaica	Australia, Denmark, Spain, Norway, Portugal, Slovenia, Cyprus, Finland, France, Lithuania
Not in force	China, Mexico, Türkiye, South Africa, Ghana, Gambia (the), Kenya, Lesotho, Malawi, Mozambique, Sudan, Sierra Leone, Eswatini, Tanzania, United Republic of, Uganda, Zimbabwe, Armenia, Azerbaijan, Belarus, Kyrgyzstan, Kazakhstan, Moldova, Republic of, Tajikistan, Turkmenistan, Burkina Faso, Benin, Central African Republic, Congo, Côte d'Ivoire, Cameroon, Gabon, Guinea, Equatorial Guinea, Guinea-Bissau, Mali, Mauritania, Niger, Senegal, Chad, Togo, India, Indonesia, Viet Nam, World Intellectual Property Organization (WIPO), North Macedonia, Albania, Congo, democratic Republic of the, Haiti, Nepal, Tuvalu, Brazil	Canada, Australia, Denmark, Spain, Hong Kong, Croatia, Japan, Norway, New Zealand, Portugal, Slovenia, United States of America, Austria, Belgium, Switzerland, Cyprus, Germany, Finland, France, United Kingdom, Greece, Ireland, Italy, Liechtenstein, Luxembourg, Monaco, Netherlands, Sweden, World Intellectual Property Organization (WIPO), Lithuania, Romania, Latvia, Czechia, Guyana, Seychelles, Jersey

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Dolutegravir and Cabotegravir compounds Expiry date: 2026-04-28 The present invention is to provide a novel compound (I), having the anti-virus activity, particularly the HIV integrase inhibitory activity, and a drug containing the same, particularly an anti-HIV drug, as well as a process and an intermediate thereof. Compound (I) wherein Z<1> is NR<4>; R<1> is hydrogen or lower alkyl; X is a single bond, a hetero atom group selected from O, S, SO, SO2 and NH, or lower alkylene or lower alkenylene in which the hetero atom group may intervene; R<2> is optionally substituted aryl; R<3> is hydrogen, a halogen, hydroxy, optionally substituted lower alkyl etc; and R<4> and Z<2> part taken together forms a ring, to form a polycyclic compound, including e.g., a tricyclic or tetracyclic compound.	WO2006116764	Compound	Glaxosmithkline Llc	Yes	US FDA, Health Canada

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income

Granted	Brazil, China, Morocco, Mexico, Philippines, Ukraine, Viet Nam, South Africa, Türkiye, Armenia, Azerbaijan, Belarus, Kyrgyzstan, Kazakhstan, Moldova, Republic of, Tajikistan, Turkmenistan, Nigeria, Colombia, Indonesia, Malaysia, Algeria	United States of America, Australia, Canada, Cyprus, Hong Kong, Israel, Japan, Korea, Republic of, Luxembourg, Norway, New Zealand, Taiwan, Province of China, Austria, Belgium, Bulgaria, Switzerland, Czechia, Germany, Denmark, Estonia, Spain, Finland, France, United Kingdom, Greece, Hungary, Ireland, Iceland, Italy, Liechtenstein, Lithuania, Latvia, Monaco, Netherlands, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia, Russian Federation, Trinidad and Tobago, Singapore
Filed	Egypt	United States of America, Cyprus, Luxembourg, Norway, Finland, France, Hungary, Lithuania, Netherlands, Slovenia
Not in force	Türkiye, India, World Intellectual Property Organization (WIPO)	United States of America, Cyprus, Hong Kong, Israel, Japan, Luxembourg, Austria, Belgium, Bulgaria, Switzerland, Czechia, Germany, Denmark, Estonia, Spain, Finland, France, United Kingdom, Greece, Hungary, Ireland, Iceland, Italy, Liechtenstein, Lithuania, Latvia, Monaco, Netherlands, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia, World Intellectual Property Organization (WIPO)

MPP Licence(s)

MPP licence on adult formulations of dolutegravir (DTG) and DTG/ABC combinations

https://medicinespatentpool.org/licence-post/dolutegravir-adult-dtg/

MPP licence on paediatric formulations of dolutegravir (DTG)

https://medicinespatentpool.org/licence-post/dolutegravir-paediatrics-dtg/

MPP licence on adult formulations of dolutegravir (DTG) and DTG/ABC combinations in AZ, BY, KZ and MY

https://medicinespatentpool.org/licence-post/dolutegravir-adult-dtg-umics/

Compulsory licence on dolutegravir in Colombia

https://www.statnews.com/wp-content/uploads/2024/04/NC_534_Licencia_obligatoria_aceptada.pdf

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Tenofovir alafenamide hemifumarate (TAF) Expiry date: 2032-08-15 A hemifumarate form of tenofovir alafenamide, and antiviral therapy using tenofovir alafenamide hemifurnarate (e.g., anti-HTV and anti-HBV therapies).	WO2013025788	Salt	Gilead Sciences, Inc	No	US FDA

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income
Granted	Costa Rica, Morocco, Moldova, Republic of, Mexico, Peru, Botswana, Ghana, Gambia (the), Kenya, Liberia, Lesotho, Malawi, Mozambique, Namibia, Rwanda, Sudan, Sierra Leone, Eswatini, Tanzania, United Republic of, Uganda, Zambia, Zimbabwe, Armenia, Azerbaijan, Belarus, Kyrgyzstan, Kazakhstan, Tajikistan, Turkmenistan, Viet Nam, Benin, Cameroon, Burkina Faso, Chad, Guinea-Bissau, Mali, Senegal, Congo, Guinea, Gabon, Niger, Equatorial Guinea, Mauritania, Togo, Côte d'Ivoire, Central African Republic, Bolivia (Plurinational State of), Philippines, South Africa, Ukraine, Brazil, El Salvador, Montenegro, Türkiye, North Macedonia, Albania, Bosnia and Herzegovina, Serbia	United States of America, Australia, Canada, Chile, Hong Kong, Israel, Japan, Korea, Republic of, New Zealand, Singapore, Taiwan, Province of China, Uruguay, Russian Federation, Denmark, Slovenia, Panama, Croatia, San Marino, Cyprus, Bahamas, Belgium, Germany, France, Luxembourg, Netherlands, Switzerland, United Kingdom, Sweden, Italy, Austria, Liechtenstein, Greece, Spain, Monaco, Portugal, Ireland, Finland, Bulgaria, Czechia, Estonia, Slovakia, Hungary, Poland, Iceland, Malta, Norway, Romania, Latvia, Lithuania

Patent status/countries	Low, Low- middle and upper-middle	High income
Filed	China, Ecuador, India, Paraguay, Thailand, Venezuela (Bolivarian Republic of), Türkiye, North Macedonia, Albania, Serbia, Egypt	Hong Kong, Denmark, Slovenia, Bahrain, Kuwait, Qatar, Saudi Arabia, Oman, United Arab Emirates, Croatia, San Marino, Cyprus, Belgium, Germany, France, Luxembourg, Netherlands, Switzerland, United Kingdom, Sweden, Italy, Austria, Liechtenstein, Greece, Spain, Monaco, Portugal, Ireland, Finland, Bulgaria, Czechia, Estonia, Slovakia, Hungary, Poland, Iceland, Malta, Norway, Romania, Latvia, Lithuania
Not in force	World Intellectual Property Organization (WIPO), Argentina, China, Colombia, Indonesia, Pakistan, Brazil, Montenegro, Türkiye, North Macedonia, Albania, Bosnia and Herzegovina, Serbia	World Intellectual Property Organization (WIPO), Hong Kong, Israel, Japan, New Zealand, Denmark, Slovenia, Croatia, San Marino, Cyprus, Belgium, Germany, France, Luxembourg, Netherlands, Switzerland, United Kingdom, Sweden, Italy, Austria, Liechtenstein, Greece, Spain, Monaco, Portugal, Ireland, Finland, Bulgaria, Czechia, Estonia, Slovakia, Hungary, Poland, Iceland, Malta, Norway, Romania, Latvia, Lithuania

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
TAF manufacturing process Expiry date: 2032-10-03 Methods for isolating 9-{(R)-2-[((S)-{[(S)-l -(isopropoxycarbonyl)ethyl]amino}phenoxyphosphinyl)methoxy]propyl}adenine:'' (compound 16): a method for preparing, in high diastereomeric purity, intermediate compounds 13 and 15: method for preparing intermediate compound 12: 9-{(R)-2-[((S)-{[(S)-l -(isopropoxycarbonyl)ethyl]amino}phenoxyphosphinyl)methoxy]propyl}adenine has anti-viral properties.	WO2013052094	Process	Gilead Sciences, Inc	No	MPP licence

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income
Granted	China, Colombia, Mexico, Armenia, Azerbaijan, Belarus, Kyrgyzstan, Kazakhstan, Tajikistan, Turkmenistan, Türkiye, Bosnia and Herzegovina, Montenegro	Australia, Canada, Hong Kong, Japan, Korea, Republic of, Taiwan, Province of China, United States of America, Russian Federation, Austria, Belgium, Switzerland, Czechia, Germany, Spain, France, United Kingdom, Greece, Hungary, Ireland, Italy, Liechtenstein, Netherlands, Norway, Poland, Portugal, Sweden, Slovenia, Slovakia, New Zealand, Israel
Filed	China	Hong Kong, Korea, Republic of
Not in force	Argentina, Costa Rica, Peru, Albania, North Macedonia, Serbia, Türkiye, World Intellectual Property Organization (WIPO), Brazil, Bosnia and Herzegovina, Montenegro, Ecuador	Chile, Japan, Uruguay, Bulgaria, Cyprus, Czechia, Denmark, Estonia, Finland, Greece, Croatia, Hungary, Iceland, Lithuania, Luxembourg, Latvia, Monaco, Malta, Norway, Poland, Romania, Slovenia, Slovakia, San Marino, World Intellectual Property Organization (WIPO)

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Dolutegravir/Cabotegravir intermediates production processes & Intermediates Expiry date: 2029-12-09 Processes are provided which create an aldehyde methylene, or hydrated or hemiacetal methylene attached to a heteroatom of a 6 membered ring without going through an olefinic group and without the necessity of using an osmium reagent. In particular, a compound of formula (I) can be produced from (II) and avoid the use of an allyl amine: (formulae I and II) where R, P 1 P3, R3 and Rx are as described herein.	WO2010068262	Intermediates, Process	Shionogi & Co., Ltd, Viiv Healthcare Company	No	MPP Licence

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income
Granted	China, India, Türkiye, North Macedonia	Japan, Korea, Republic of, Singapore, Taiwan, Province of China, United States of America, Portugal, Belgium, Germany, France, Netherlands, Switzerland, United Kingdom, Italy, Liechtenstein, Spain, Finland, Cyprus, Hungary
Filed		Portugal, Spain
Not in force	China, World Intellectual Property Organization (WIPO), Türkiye, North Macedonia, Albania, Bosnia and Herzegovina, Serbia	World Intellectual Property Organization (WIPO), Luxembourg, Sweden, Austria, Greece, Denmark, Monaco, Ireland, Finland, Cyprus, Bulgaria, Czechia, Estonia, Slovakia, Hungary, Poland, Iceland, Malta, Norway, San Marino, Croatia, Romania, Latvia, Lithuania, Slovenia

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Dolutegravir salts, their crystals & process Expiry date: 2029-12-08 A synthesis approach providing an early ring attachment via a bromination to compound I-I yielding compound II-II, whereby a final product such as AA can be synthesized. In particular, the 2,4-difluorophenyl-containing sidechain is attached before creation of the additional ring Q.	WO2010068253	Process, Salt	Glaxosmithkline Llc, Johns, Brian, Alvin, Shionogi & Co., Ltd, Taoda, Yoshiyuki, Yoshida, Hiroshi	Yes	US FDA

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income
Granted	China, Mexico, Indonesia, India	United States of America, Australia, Canada, Switzerland, Germany, Spain, France, United Kingdom, Ireland, Italy, Liechtenstein, Japan, Korea, Republic of, Russian Federation, Singapore, Taiwan, Province of China
Filed	Brazil	Canada
Not in force	World Intellectual Property Organization (WIPO), North Macedonia, Türkiye, India	World Intellectual Property Organization (WIPO), Austria, Belgium, Bulgaria, Switzerland, Cyprus, Czechia, Germany, Denmark, Estonia, Spain, Finland, France, United Kingdom, Greece, Croatia, Hungary, Ireland, Iceland, Italy, Liechtenstein, Lithuania, Luxembourg, Latvia, Monaco, Malta, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia, San Marino, Hong Kong

MPP Licence(s)

MPP licence on adult formulations of dolutegravir (DTG) and DTG/ABC combinations

https://medicinespatentpool.org/licence-post/dolutegravir-adult-dtg/

MPP licence on paediatric formulations of dolutegravir (DTG)

https://medicinespatentpool.org/licence-post/dolutegravir-paediatrics-dtg/

MPP licence on adult formulations of dolutegravir (DTG) and DTG/ABC combinations in AZ, BY, KZ and MY

https://medicinespatentpool.org/licence-post/dolutegravir-adult-dtg-umics/

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Cabotegravir prodrugs & Cabotegravir and Dolutegravir intermediates and processes Expiry date: 2029-07-23 The present invention features compounds that are prodrugs of HIV integrase inhibitors and therefore are useful in the delivery of compounds for the inhibition of HIV replication, the prevention and/or treatment of infection by HIV, and in the treatment of AIDS and/or ARC.	WO2010011814	Intermediate(s), Process	Glaxosmithkline Llc, Shionogi & Co., Ltd, Viiv Healthcare Company	No	MPP Licence

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income
Granted	China, India	Belgium, Germany, France, Netherlands, Switzerland, United Kingdom, Sweden, Italy, Liechtenstein, Spain, Portugal, Japan, Korea, Republic of, Singapore, United States of America
Filed		Spain, Portugal
Not in force	Türkiye, North Macedonia, Bosnia and Herzegovina, World Intellectual Property Organization (WIPO), Albania, Serbia	Belgium, France, Luxembourg, Netherlands, Switzerland, Sweden, Austria, Liechtenstein, Greece, Denmark, Monaco, Portugal, Ireland, Finland, Cyprus, Bulgaria, Czechia, Estonia, Slovakia, Hungary, Poland, Iceland, Malta, Norway, San Marino, Croatia, Romania, Latvia, Lithuania, Slovenia, World Intellectual Property Organization (WIPO)

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Dolutegravir in combination with lamivudine (3TC) Expiry date: 2031-01-24 The present disclosure relates to combinations of compounds comprising HIV integrase inhibitors and other therapeutic agents. Such combinations may be useful in the inhibition of HIV-1 or potentially the inhibition of HIV replication, or for the prevention and/or treatment of infection by HIV, or in the treatment of AIDS and/or ARC.	CA3003988	Combination	Viiv Healthcare Company	Yes	MPP licence

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income
Granted	Turkmenistan, Belarus, Tajikistan, Kazakhstan, Azerbaijan, Kyrgyzstan, Armenia, Türkiye, North Macedonia, Albania, Bosnia and Herzegovina, Montenegro, Serbia, Mexico	United States of America, Canada, Australia, Russian Federation, Belgium, Germany, France, Luxembourg, Netherlands, Switzerland, United Kingdom, Sweden, Italy, Austria, Liechtenstein, Greece, Spain, Denmark, Monaco, Portugal, Ireland, Finland, Cyprus, Bulgaria, Czechia, Estonia, Slovakia, Hungary, Poland, Iceland, Malta, Norway, San Marino, Croatia, Romania, Latvia, Lithuania, Slovenia, Israel
Filed	Türkiye, North Macedonia, Albania, Bosnia and Herzegovina, Montenegro, Serbia	Singapore, Belgium, Germany, France, Luxembourg, Netherlands, Switzerland, United Kingdom, Sweden, Italy, Austria, Liechtenstein, Greece, Spain, Denmark, Monaco, Portugal, Ireland, Finland, Cyprus, Bulgaria, Czechia, Estonia, Slovakia, Hungary, Poland, Iceland, Malta, Norway, San Marino, Croatia, Romania, Latvia, Lithuania, Slovenia

Patent status/countries	Low, Low- middle and upper-middle	High income
Not in force	Moldova, Republic of, Dominican Republic	United States of America, Australia

MPP Licence(s)

MPP licence on adult formulations of dolutegravir (DTG) and DTG/ABC combinations

https://medicinespatentpool.org/licence-post/dolutegravir-adult-dtg/

MPP licence on paediatric formulations of dolutegravir (DTG)

https://medicinespatentpool.org/licence-post/dolutegravir-paediatrics-dtg/

MPP licence on adult formulations of dolutegravir (DTG) and DTG/ABC combinations in AZ, BY, KZ and MY

https://medicinespatentpool.org/licence-post/dolutegravir-adult-dtg-umics/

Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Dolutegravir or cabotegravir in combination with ABC, 3TC or RPV Expiry date: 2031-01-24 The present invention relates to combinations of compounds comprising HIV integrase inhibitors and other therapeutic agents. Such combinations are useful in the inhibition of HIV replication, the prevention and/or treatment of infection by HIV, and in the treatment of AIDS and/or ARC.	WO2011094150	Combination	Glaxosmithkline Llc, Underwood, Mark Richard	Yes	MPP licence

Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income
Granted	Malaysia, Philippines	Hong Kong
Filed	Algeria, Egypt, Thailand, Malaysia, Philippines, Viet Nam	Oman
Not in force	Costa Rica, Ecuador, Libya, World Intellectual Property Organization (WIPO), Brazil, Tajikistan, Belarus, Azerbaijan, Moldova, Republic of, Turkmenistan, Armenia, Kyrgyzstan, Kazakhstan	Hong Kong, World Intellectual Property Organization (WIPO), Russian Federation

MPP Licence(s)

MPP licence on adult formulations of dolutegravir (DTG) and DTG/ABC combinations

https://medicinespatentpool.org/licence-post/dolutegravir-adult-dtg/

MPP licence on paediatric formulations of dolutegravir (DTG)

https://medicinespatentpool.org/licence-post/dolutegravir-paediatrics-dtg/

MPP licence on adult formulations of dolutegravir (DTG) and DTG/ABC combinations in AZ, BY, KZ and MY

https://medicinespatentpool.org/licence-post/dolutegravir-adult-dtg-umics/

Supporting material

Publications

** Qingxin Mu, Jesse Yu, Lisa A. McConnachie, John C. Kraft, Yu Gao, Gaurav K. Gulati & Rodney J. Y. Ho (2018) Translation of combination nanodrugs into nanomedicines: lessons learned and future outlook Journal of Drug Targeting, 26:5-6, 435-447, DOI: 10.1080/1061186X.2017.1419363 **

The concept of nanomedicine is not new. For instance, some nanocrystals and colloidal drug molecules are marketed that improve pharmacokinetic characteristics of single-agent therapeutics. For the past two decades, the number of research publications on single-agent nanoformulations has grown exponentially. However, formulations advancing to pre-clinical and clinical evaluations that lead to therapeutic products has been limited. Chronic diseases such as cancer and HIV/AIDS require drug combinations, not single agents, for durable therapeutic responses. Therefore, development and clinical translation of drug combination nanoformulations could play a significant role in improving human health. Successful translation of promising concepts into pre-clinical and clinical studies requires early considerations of the physical compatibility, pharmacological synergy, as well as pharmaceutical characteristics (e.g. stability, scalability and pharmacokinetics). With this approach and robust manufacturing processes in place, some drug-combination nanoparticles have progressed to non-human primate and human studies. In this article, we discuss the rationale and role of drug-combination nanoparticles, the pre-clinical and clinical research progress made to date and the key challenges for successful clinical translation. Finally, we offer insight to accelerate clinical translation through leveraging robust nanoplatform technologies to enable implementation of personalised and precision medicine.

** John C. Kraft, Lisa A. McConnachie, Josefin Koehn, Loren Kinman, Jianguo Sun, Ann C. Collier, Carol Collins, Danny D. Shen, Rodney J.Y. Ho, <a href="https://www.sciencedirect.com/science/article/abs/pii/S0168365918300634?via**

**rel="noopener noreferrer" target="_blank">Mechanism-based pharmacokinetic (MBPK) models describe the complex plasma kinetics of three antiretrovirals delivered by a long-acting anti-HIV drug combination nanoparticle formulation Journal of Controlled Release, Volume 275, 2018, Pages 229-241, ISSN 0168-3659, https://doi.org/10.1016/j.jconrel.2018.02.003. **

Existing oral antiretroviral (ARV) agents have been shown in human studies to exhibit limited lymph node penetration and lymphatic drug insufficiency. As lymph nodes are a reservoir of HIV, it is critical to deliver and sustain effective levels of ARV combinations in these tissues. To overcome lymph node drug insufficiency of oral combination ARV therapy (cART), we developed and reported a long-acting and lymphocyte-targeting injectable that contains three ARVs—hydrophobic lopinavir (LPV) and ritonavir (RTV), and hydrophilic tenofovir (TFV)—stabilized by lipid excipients in a nanosuspension. A single subcutaneous (SC) injection of this first-generation formulation of drug combination nanoparticles (DcNPs), named TLC-ART101, provided persistent ARV levels in macaque lymph node mononuclear cells (LNMCs) for at least 1 week, and in peripheral blood mononuclear cells (PBMCs) and plasma for at least 2 weeks, demonstrating long-acting pharmacokinetics for all three drugs. In addition, the lymphocyte-targeting properties of this formulation were demonstrated by the consistently higher intracellular drug concentrations in LNMCs and PBMCs versus those in plasma. To provide insights into the complex mechanisms of absorption and disposition of TLC-ART101, we constructed novel mechanism-based pharmacokinetic (MBPK) models. Based upon plasma PK data obtained after single administration of TLC-ART101 (DcNPs) and a solution formulation of free triple-ARVs, the models feature uptake from the SC injection site that respectively routes free and nanoparticle-associated ARVs via the blood vasculature and lymphatics, and their eventual distribution into and clearance from the systemic circulation. The models provided simultaneous description of the complex long-acting plasma and lymphatic PK profiles for all three ARVs in TLC-ART101. The long-acting PK characteristics of the three drugs in TLC-ART101 were likely due to a combination of mechanisms including: (1) DcNPs undergoing preferential lymphatic uptake from the subcutaneous space, (2) retention in nodes during lymphatic first-pass, (3) subsequent slow release of ARVs into blood

circulation, and (4) limited extravasation of DcNP-associated ARVs that resulted in longer persistence in the circulation.

Keywords: Mechanism-based pharmacokinetic modeling; Long-acting; Antiretrovirals; HIV drug combination treatment; Lymphatic targeted drug delivery; Lymphatic drug insufficiency

** Mu Q, Yu J, Griffin JI, Wu Y, Zhu L, McConnachie LA, et al. (2020) Novel drug combination nanoparticles exhibit enhanced plasma exposure and dose-responsive effects on eliminating breast cancer lung metastasis. PLoSONE 15(3): e0228557. https://doi.org/10.1371/journal.pone.0228557 **

Early diagnosis along with new drugs targeted to cancer receptors and immunocheckpoints have improved breast cancer survival. However, full remission remains elusive for metastatic breast cancer due to dose-limiting toxicities of heavily used, highly potent drug combinations such as gemcitabine and paclitaxel. Therefore, novel strategies that lower the effective dose and improve safety margins could enhance the effect of these drug combinations. To this end, we developed and evaluated a novel drug combination of gemcitabine and paclitaxel (GT). Leveraging a simple and scalable drug-combination nanoparticle platform (DcNP), we successfully prepared an injectable GT combination in DcNP (GT DcNP). Compared to a Cremophor EL/ethanol assisted drug suspension in buffer (CrEL), GT DcNP exhibits about 56-fold and 8.6-fold increases in plasma drug exposure (area under the curve, AUC) and apparent half-life of gemcitabine respectively, and a 2.9-fold increase of AUC for paclitaxel. Using 4T1 as a syngeneic model for breast cancer metastasis, we found that a single GT (20/2 mg/kg) dose in DcNP nearly eliminated colonization in the lungs. This effect was not achievable by a CrEL drug combination at a 5-fold higher dose (i.e., 100/10 mg/kg GT). A dose-response study indicates that GT DcNP provided a therapeutic index of ~15.8. Collectively, these data suggest that GT DcNP could be effective against advancing metastatic breast cancer with a margin of safety. As the DcNP formulation is intentionally designed to be simple, scalable, and long-acting, it

may be suitable for clinical development to find effective treatment against metastatic breast cancer.

** Koehn, Josefina; Iwamoto, Jennifer F.a; Kraft, John C.a; McConnachie, Lisa A.a; Collier, Ann C.b,c; Ho, Rodney J.Y.a,c,d Extended cell and plasma drug levels after one dose of a three-in-one nanosuspension containing lopinavir, efavirenz, and tenofovir in nonhuman primates AIDS: November 13, 2018 - Volume 32 - Issue 17 - p 2463-2467 doi: 10.1097/QAD.0000000000001969 **

Objective:

To characterize a drug-combination nanoparticle (DcNP) containing water-insoluble lopinavir (LPV) and efavirenz (EFV), and water-soluble tenofovir (TFV), for its potential as a long-acting combination HIV treatment.

Design:

Three HIV drugs (LPV, EFV, TFV) with well established efficacy and safety were coformulated into a single DcNP suspension. Two macaques were administered one subcutaneous injection and drug concentrations in plasma and mononuclear cells (in peripheral blood and lymph nodes) were analyzed over 2 weeks. Pharmacokinetic parameters and cell-to-plasma relationships of LPV, EFV, and TFV were determined.

Results:

This three-in-one nanoformulation provided extended concentrations of all drugs in lymph node cells that were 57- to 228-fold higher than those in plasma. Levels of all three drugs in peripheral blood mononuclear cells persisted for 2 weeks at levels equal to or higher than those in plasma.

Conclusion:

With long-acting characteristics and higher drug penetration/persistence in cells, this three-in-one DcNP may enhance therapeutic efficacy of these well studied HIV drugs due to colocalization and targeting of this three-drug combination to HIV host cells.

** Yu Gao, John C. Kraft, Danni Yu, Rodney J.Y. Ho, Recent developments of nanotherapeutics for targeted and long-acting, combination HIV chemotherapy, European Journal of Pharmaceutics and Biopharmaceutics, Volume 138, 2019, Pages 75-91, ISSN 0939-6411, https://doi.org/10.1016/j.ejpb.2018.04.014. **

Combination antiretroviral therapy (cART) given orally has transformed HIV from a terminal illness to a manageable chronic disease. Yet despite the recent development of newer and more potent drugs for cART and suppression of virus in blood to undetectable levels, residual virus remains in tissues. Upon stopping cART, virus rebounds and progresses to AIDS. Current oral cART regimens have several drawbacks including (1) challenges in patient adherence due to pill fatigue or side-effects, (2) the requirement of life-long daily drug intake, and (3) limited penetration and retention in cells within lymph nodes. Appropriately designed injectable nano-drug combinations that are long-acting and retained in HIV susceptible cells within lymph nodes may address these challenges. While a number of nanomaterials have been investigated for delivery of HIV drugs and drug combinations, key challenges involve developing and scaling delivery systems that provide a drug combination targeted to HIV host cells and tissues where residual virus persists. With validation of the drug-insufficiency hypothesis in lymph nodes, progress has been made in the development of drug combination nanoparticles that are long-acting and targeted to lymph nodes and cells. Unique drug combination nanoparticles (DcNPs) composed of three HIV drugs—lopinavir, ritonavir, and tenofovir—have been shown to provide enhanced drug levels in lymph nodes; and elevated drug-combination levels in HIV-host cells in the blood and plasma for two weeks. This review summarizes the progress in the development of nanoparticle-based drug delivery systems for HIV therapy. It discusses how injectable nanocarriers may be designed to enable delivery of drug combinations

that are long-lasting and target-selective in physiological contexts (in vivo) to provide safe and effective use. Consistent drug combination exposure in the sites of residual HIV in tissues and cells may overcome drug insufficiency observed in patients on oral cART.

Keywords: Nanomedicine; Long-acting; Targeted; Drug combination; HIV/AIDS

** Yu, J., Mu, Q., Perazzolo, S. et al. Novel Long-Acting Drug Combination Nanoparticles Composed of Gemcitabine and Paclitaxel Enhance Localization of Both Drugs in Metastatic Breast Cancer Nodules. Pharm Res 37, 197 (2020). https://doi.org/10.1007/s11095-020-02888-8 **

Purpose

To develop drug-combination nanoparticles (DcNPs) composed of hydrophilic gemcitabine (G) and hydrophobic paclitaxel (T) and deliver both drugs to metastatic cancer cells.

Methods

GT DcNPs were evaluated based on particle size and drug association efficiency (AE%). The effect of DcNP on GT plasma time-course and tissue distribution was characterized in mice and a pharmacokinetic model was developed. A GT distribution study into cancer nodules (derived from 4 T1 cells) was performed.

Results

An optimized GT DcNP composition (d = 59.2 nm ±9.2 nm) was found to be suitable

for IV formulation. Plasma exposure of G and T were enhanced 61-fold and 3.8-fold when given in DcNP form compared to the conventional formulation, respectively. Mechanism based pharmacokinetic modeling and simulation show that both G and T remain highly associated to DcNPs in vivo (G: 98%, T:75%). GT DcNPs have minimal distribution to healthy organs with selective distribution and retention in tumor burdened tissue. Tumor bearing lungs had a 5-fold higher tissue-to-plasma ratio of gemcitabine in GT DcNPs compared to healthy lungs.

Conclusions

DcNPs can deliver hydrophilic G and hydrophobic T together to cancer nodules and produce long acting exposure, likely due to stable GT association to DcNPs in vivo.

** Kraft, John C.a; McConnachie, Lisa A.a; Koehn, Josefina; Kinman, Lorena; Collins, Carola; Shen, Danny D.a; Collier, Ann C.b,c; Ho, Rodney J.Y.a,c,d Long-acting combination anti-HIV drug suspension enhances and sustains higher drug levels in lymph node cells than in blood cells and plasma, AIDS: March 27, 2017 - Volume 31 - Issue 6 - p 765-770 doi: 10.1097/QAD.0000000000001405 **

Objective:

The aim of the present study was to determine whether a combination of anti-HIV drugs – tenofovir (TFV), lopinavir (LPV) and ritonavir (RTV) – in a lipid-stabilized nanosuspension (called TLC-ART101) could enhance and sustain intracellular drug levels and exposures in lymph node and blood cells above those in plasma.

Design:

Four macaques were given a single dose of TLC-ART101 subcutaneously. Drug

concentrations in plasma and mononuclear cells of the blood (PBMCs) and lymph nodes (LNMCs) were analysed using a validated combination LC-MS/MS assay.

Results:

For the two active drugs (TFV, LPV), plasma and PBMC intracellular drug levels persisted for over 2 weeks; PBMC drug exposures were three- to four-fold higher than those in plasma. Apparent terminal half-lives (t1/2) of TFV and LPV were 65.3 and 476.9 h in plasma, and 169.1 and 151.2 h in PBMCs. At 24 and 192 h, TFV and LPV drug levels in LNMCs were up to 79-fold higher than those in PBMCs. Analysis of PBMC intracellular TFV and its active metabolite TFV-diphosphate (TFV-DP) indicated that intracellular exposures of total TFV and TFV-DP were markedly higher and persisted longer than in humans and macaques dosed with oral TFV prodrugs, tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF).

Conclusions:

A simple, scalable three-drug combination, lipid-stabilized nanosuspension exhibited persistent drug levels in cells of lymph nodes and the blood (HIV host cells) and in plasma. With appropriate dose adjustment, TLC-ART101 may be a useful HIV treatment with a potential to impact residual virus in lymph nodes.

** John C. Kraft, Piper M. Treuting & Rodney J. Y. Ho (2018) Indocyanine green nanoparticles undergo selective lymphatic uptake, distribution and retention and enable detailed mapping of lymph vessels, nodes and abnormalities Journal of Drug Targeting, 26:5-6, 494-504, DOI: 10.1080/1061186X.2018.1433681 **

The distributed network of lymph vessels and nodes in the body, with its complex architecture and physiology, presents a major challenge for whole-body lymphatic-

targeted drug delivery. To gather physiological and pathological information of the lymphatics, near-infrared (NIR) fluorescence imaging of NIR fluorophores is used in clinical practice due to its tissue-penetrating optical radiation (700–900 nm) that safely provides real-time high-resolution in vivo images. However, indocyanine green (ICG), a common clinical NIR fluorophore, is unstable in aqueous environments and under light exposure, and its poor lymphatic distribution and retention limits its use as a NIR lymphatic tracer. To address this, we investigated in mice the distribution pathways of a novel nanoparticle formulation that stabilises ICG and is optimised for lymphatic drug delivery. From the subcutaneous space, ICG particles provided selective lymphatic uptake, lymph vessel and node retention, and extensive first-pass lymphatic distribution of ICG, enabling 0.2 mm and 5–10 cell resolution of lymph vessels, and high signal-to-background ratios for lymphatic vessel and node networks. Soluble (free) ICG readily dissipated from lymph vessels local to the injection site and absorbed into the blood. These unique characteristics of ICG particles could enable mechanistic studies of the lymphatics and diagnosis of lymphatic abnormalities.

** Perazzolo S, Shireman LM, Shen DD, Ho RJY. Physiologically Based Pharmacokinetic Modeling of 3 HIV Drugs in Combination and the Role of Lymphatic System after Subcutaneous Dosing. Part 1: Model for the Free-drug Mixture. J Pharm Sci. 2021 Oct 18:S0022-3549(21)00547-5. doi: 10.1016/j.xphs.2021.10.007. Epub ahead of print. PMID: 34673093. **

Drug-combination nanoparticles (DcNP) is a nano-formulation of multiple HIV drugs in one injectable. DcNP demonstrated long-acting pharmacokinetics (PK) for all drugs in the blood and lymphatic system of nonhuman primates (NHP). Long-acting is due to stably circulating DcNP and a depot in the lymphatic system during subcutaneous absorption. Because the PK of each drug in DcNP evolves through two species, i.e., drugs that dissociate from DcNP and drugs retained in DcNP (Part 2, presented separately), we describe here a physiologically based PK model of the nanoparticle-free drugs featuring the role of the lymphatic system. The free drug model was built using subcutaneous injections of suspended lopinavir-ritonavir-tenofovir in NHP and

validated by external experiments. The model, for the first time, introduces the lymphatic network as part of a whole-body PBPK system and singles out major lymphatic regions: cervical, axillary, hilar, mesenteric, and inguinal nodes. Although the scope of the free-drug modeling was to support the construction of the nanoparticle model (Part 2), such a detailed/regionalized description of the lymphatic system and mononuclear cells represent an unprecedented level of prediction that renders the free drug model extendible to other small-drug molecules targeting the lymphatic system at both the regional and cellular level.

** Perazzolo S, Shen DD, Ho RJY. Physiologically Based Pharmacokinetic Modeling of 3 HIV Drugs in Combination and the Role of Lymphatic System after Subcutaneous Dosing. Part 2: Model for the Drug-combination Nanoparticles. J Pharm Sci. 2021 Oct 18:S0022-3549(21)00552-9. doi: 10.1016/j.xphs.2021.10.009. Epub ahead of print. PMID: 34673094. **

Drug-combination nanoparticles (DcNP) is a nano-formulation of multiple HIV drugs in one injectable. DcNP demonstrated long-acting pharmacokinetics (PK) for all drugs in the blood and lymphatic system of nonhuman primates (NHP). Long-acting is due to stably circulating DcNP and a depot in the lymphatic system during subcutaneous absorption. Because the PK of each drug in DcNP evolves through two species, i.e., drugs that dissociate from DcNP and drugs retained in DcNP (Part 2, presented separately), we describe here a physiologically based PK model of the nanoparticle-free drugs featuring the role of the lymphatic system. The free drug model was built using subcutaneous injections of suspended lopinavir-ritonavir-tenofovir in NHP and validated by external experiments. The model, for the first time, introduces the lymphatic network as part of a whole-body PBPK system and singles out major lymphatic regions: cervical, axillary, hilar, mesenteric, and inguinal nodes. Although the scope of the free-drug modeling was to support the construction of the nanoparticle model (Part 2), such a detailed/regionalized description of the lymphatic system and mononuclear cells represent an unprecedented level of prediction that renders the free drug model extendible to other small-drug molecules targeting the lymphatic system at both the regional and cellular level.

** A novel formulation enabled transformation of 3-HIV drugs tenofovir–lamivudine–dolutegravir from short-acting to long-acting all-in-one injectable. Perazzolo, Simonea; Stephen, Zachary R.a; Eguchi, Masaa; Xu, Xiaolina; Delle Fratte, Rachelea; Collier, Ann C.b; Melvin, Ann J.c; Ho, Rodney J.Y.a,d. AIDS 37(14):p 2131-2136, November 15, 2023. | DOI: 10.1097/QAD.0000000000003706
 https://journals.lww.com**

Objective:

To develop an injectable dosage form of the daily oral HIV drugs, tenofovir (T), lamivudine (L), and dolutegravir (D), creating a single, complete, all-in-one TLD 3-drug-combination that demonstrates long-acting pharmacokinetics.

Design:

Using drug-combination-nanoparticle (DcNP) technology to stabilize multiple HIV drugs, the 3-HIV drugs TLD, with disparate physical-chemical properties, are stabilized and assembled with lipid-excipients to form *TLD-in-DcNP*. *TLD-in-DcNP* is verified to be stable and suitable for subcutaneous administration. To characterize the plasma time-courses and PBMC concentrations for all 3 drugs, single subcutaneous injections of *TLD-in-DcNP* were given to nonhuman primates (NHP, *M. nemestrina*).

Results:

Following single-dose *TLD-in-DcNP*, all drugs exhibited long-acting profiles in NHP plasma with levels that persisted for 4 weeks above predicted viral-effective concentrations for TLD in combination. Times-to-peak were within 24 hr in all NHP for all drugs. Compared to a free-soluble TLD, *TLD-in-DcNP* provided exposure enhancement and extended duration 7.0-, 2.1-, and 20-fold as *AUC* boost and 10-, 8.3-, and 5.9-fold as half-life extension. Additionally, DcNP may provide more drug exposure in cells than plasma with PBMC-to-plasma drug ratios exceeding one, suggesting cell-targeted drug-combination delivery.

Conclusions:

This study confirms that TLD with disparate properties can be made stable by DcNP to enable TLD concentrations of 4 weeks in NHP. Study results highlighted the potential of *TLD-in-DcNP* as a convenient all-in-one, complete HIV long-acting product for clinical development.

Additional documents

- UW Program on Targeted Long-acting Combination Antiretroviral Therapy (TLC-ART)

Useful links

- TLC-ART website
- MPP and UW sign a licence for an investigational LA injectable drug combination candidate for HIV
- TLC-ART update on HIV Therapies at 2022 LEAP Conference

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

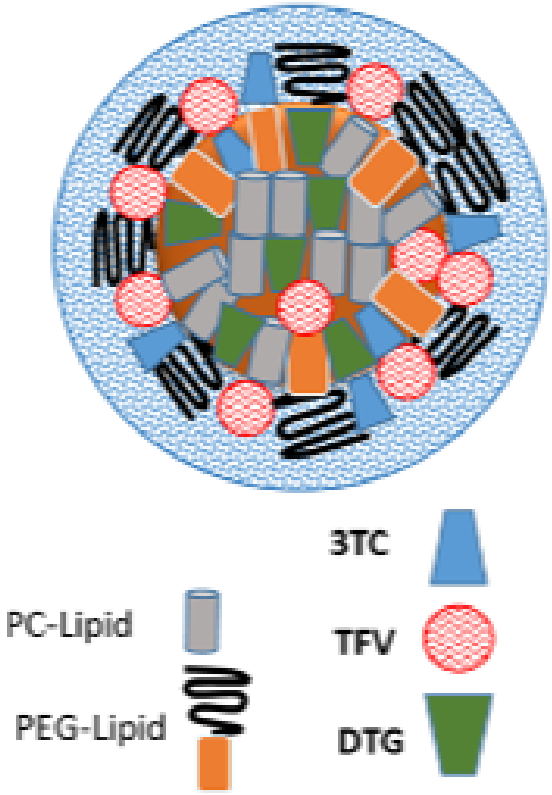
Work with MPP to expand access in LMICs

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



TLD nanoparticle

None