Improving long-acting delivery

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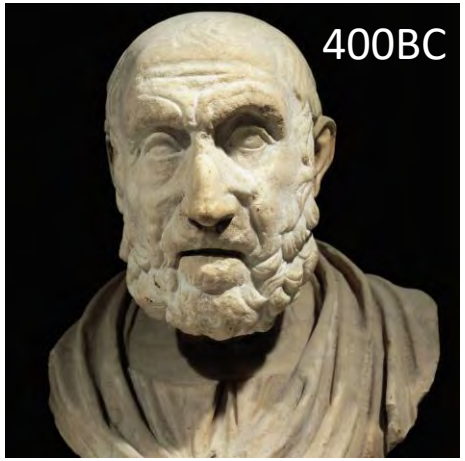
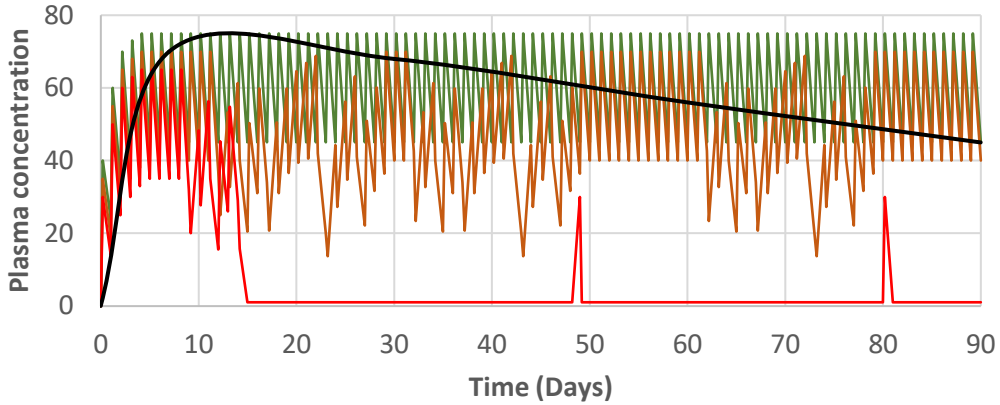
Adherence, Retention, Completion: The ARC of benefit for long-acting drug delivery



"Keep a watch also on the faults of the patients, which often make them lie about the taking of things prescribed"

"What they have done never results in a confession, but the blame is thrown upon the physician."

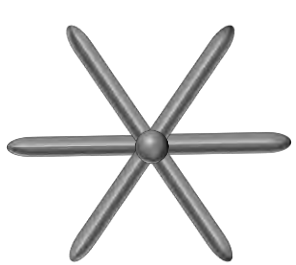


- Oral delivery of medicines places success of therapy in the hands of the patient
- Long-acting drug delivery has the potential to be transformative for patient management:
  - Issues of non-adherence are partially or entirely mitigated.
  - Problems with retention in therapy programmes are removed for some indications.
  - For indications within the range of the duration of exposure, completion may be achievable from a single visit.

Cabenuva (cabotegravir and rilpivirine)

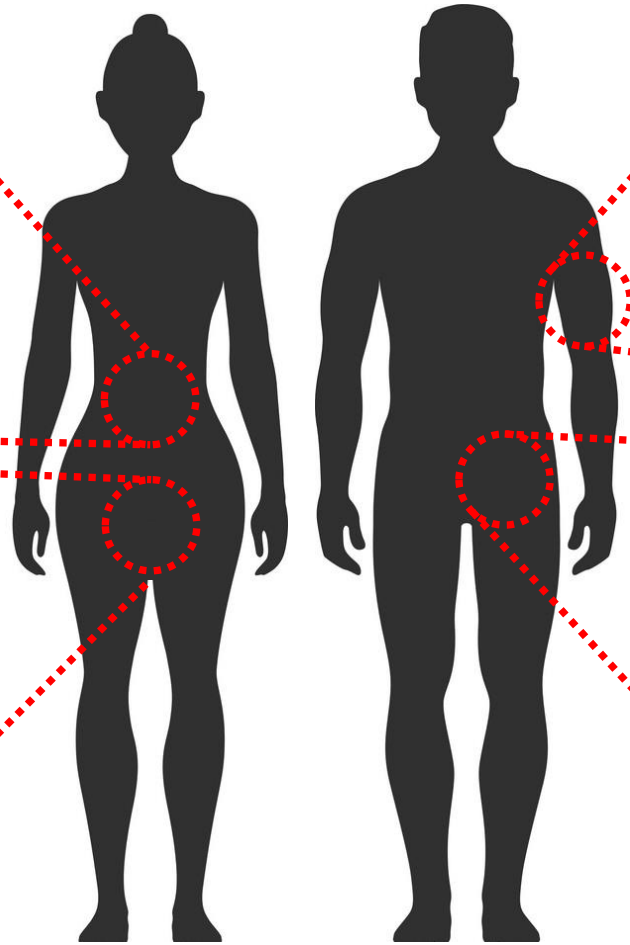
- Monthly Cabenuva is non-inferior to standard of care (daily oral 3-drug regimen) in maintaining viral suppression based upon two 48-week phase III trials (ATLAS and FLAIR trials).
- **ATLAS -** 308 patients in the treatment arm; 5 participants (1.6%) in the cabotegravir/rilpivirine arm and 3 (1.0%) in the control arm had viral load >50 c/mL at 48 weeks.
- **FLAIR -** 283 patients in the treatment arm; 6 participants (2.1%) in the cabotegravir/rilpivirine arm and 7 (2.5%) in the control arm had viral load >50 c/mL at 48 weeks.
- Generally well tolerated; E.g in ATLAS low rates of SAEs (4.2%) and AE (3.2%) withdrawals; 83% reported ISR (21% of injections), most (98.5%) were mild or moderate lasting an average of 3 days and only 4 (1.3% caused withdrawal).
- FDA declined approval in December 2019 related to chemistry, manufacturing and controls (CMC) process. Resubmitted mid-2020, and decision pending in early 2021.
- Health Canada approved Cabenuva in March 2020.
- EMA recommended marketing authorisation for Rekambys (rilpivirine) and Vocabria (cabotegravir) injections in December 2020.

What are the long-acting technologies?

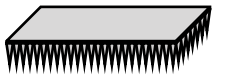


Gastric residence device

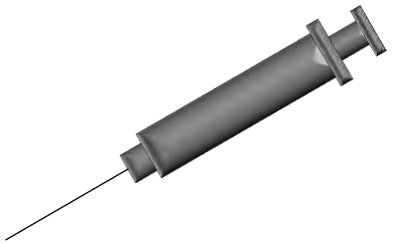
Vaginal ring



Implant



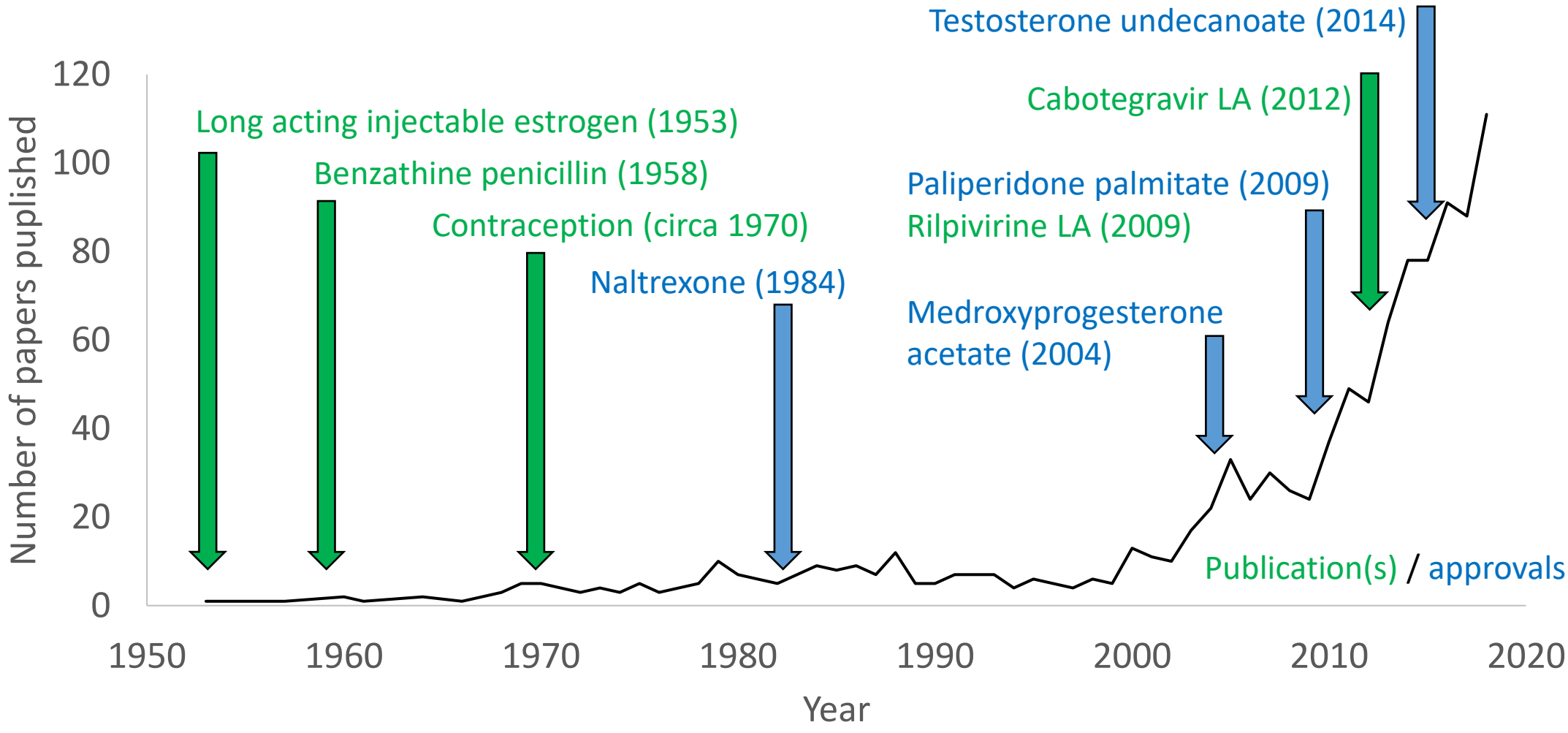
Microarray / microneedle patch (theoretical)



Injectable drug

Broadly neutralizing monoclonal antibodies

Long-acting injectables / parenterals: brief history

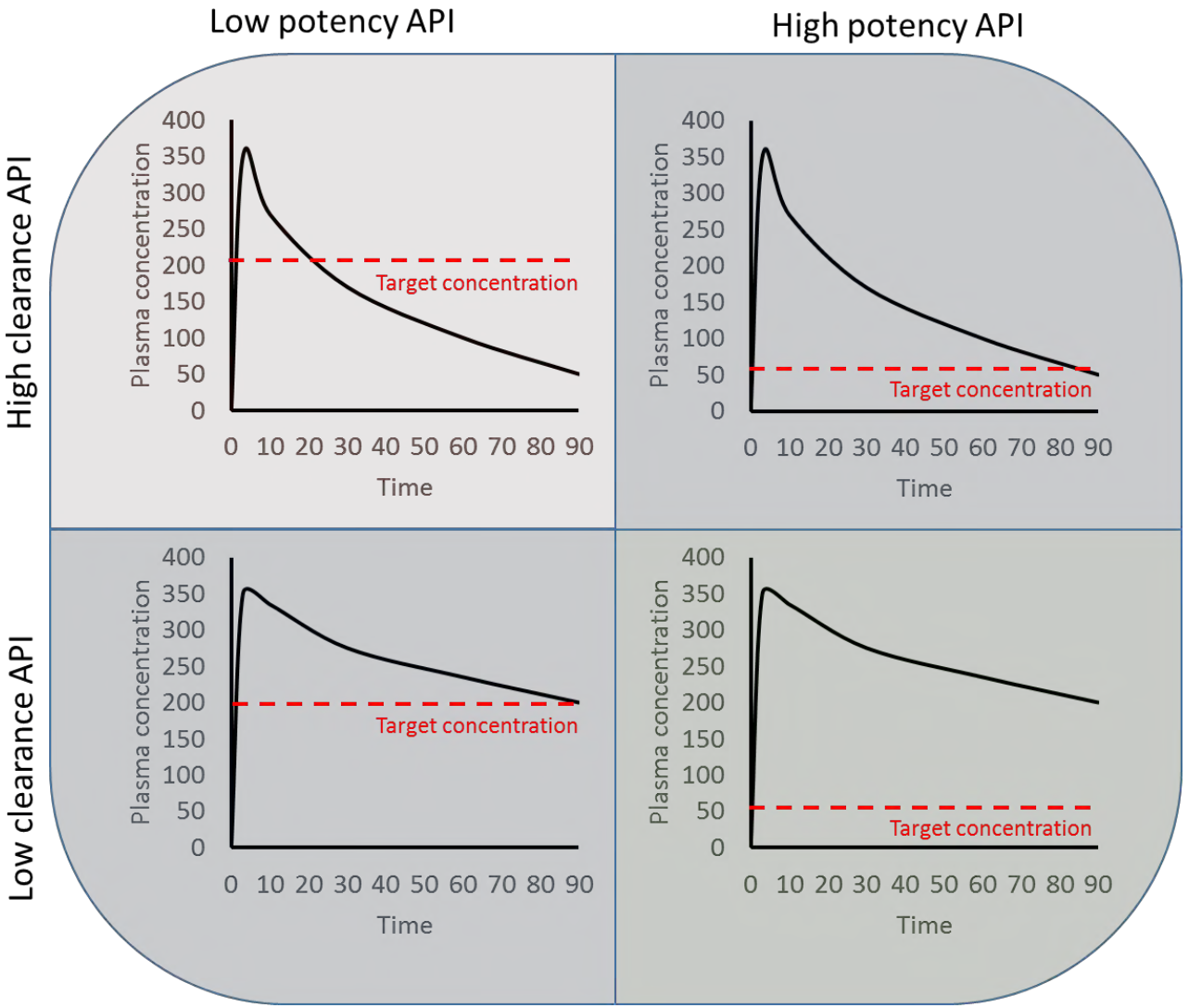


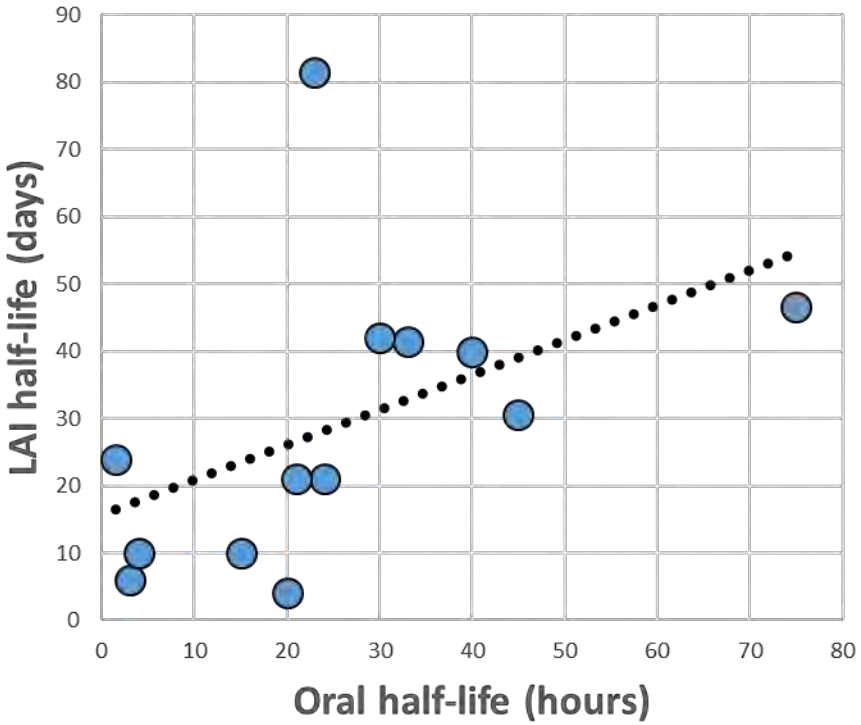
Using Pubmed search term: *"long acting injectable" OR "long acting parenteral" OR "long acting depot"*

Long-acting injectables: examples

	Duration (weeks)	Dose (mg)	Drug loading (mg /ml)	Formulation	Indication
Risperidone	2	120	12.5	Microspheres	Schizophrenia
Respiridone*	4	120	150	In situ forming gel	Schizophrenia
Naltrexone	4	380	95	Microspheres	Opioid addiction
Olanzapine pamoate	4	405	150	Dispersion	Schizophrenia
Haloperidol decanoate	4	300	100	Oil depot	Schizophrenia
Fluphenazine decanoate	4	100	25	Oil depot	Schizophrenia
Benzathine penicillin	4	1800	450	Dispersion	Rheumatic Fever
Leuprolide acetate	24	45	120	In situ forming gel	Androgen ablation
Leuprolide mesylate*	24	50	?	Dispersion	Androgen ablation
Aripiprazole lauroxil	8	675	280	Dispersion	Schizophrenia
Rilpivirine*	8	1200	300	Dispersion	HIV
Paliperidone Palmitate	12	525	150	Dispersion	Schizophrenia
Medroxyprogesterone acetate	13	150	150	Dispersion	Contraception
Cabotegravir*	12	400	200	Dispersion	HIV
Testosterone undecanoate	12	1000	250	Oil depot	Hypogonadism

High drug potency and long half-life underpins long-acting approaches

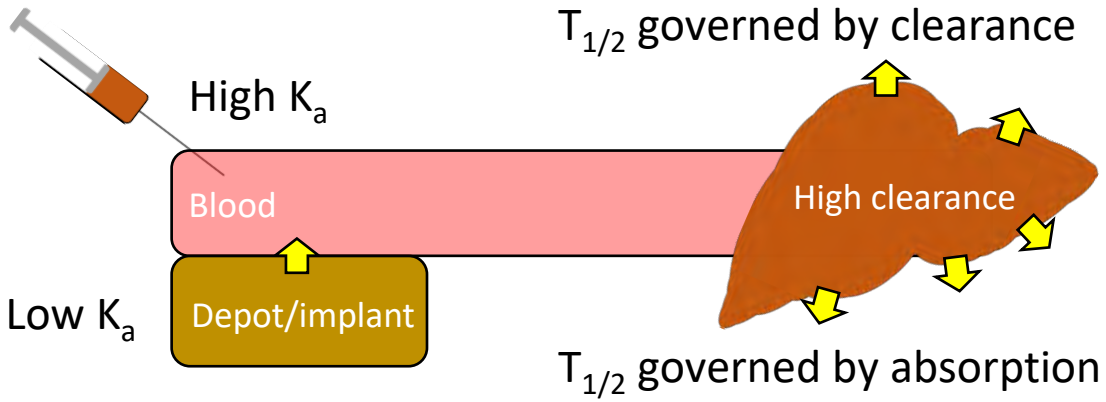


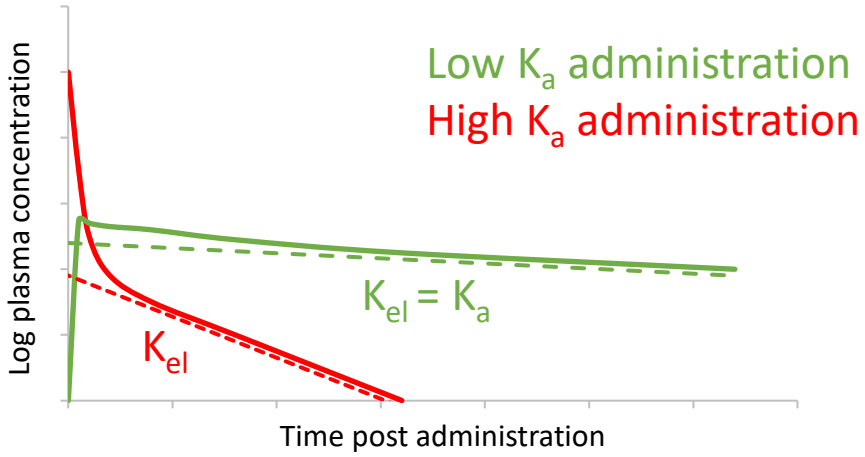


- Varying degree of half-life extension.
- Apparent relationship between oral and LAI half-life for existing medicines.
- **Caveat:** dose is also proportional to half-life for many LAI medicines.

Flip-flop pharmacokinetics underpins long-acting delivery

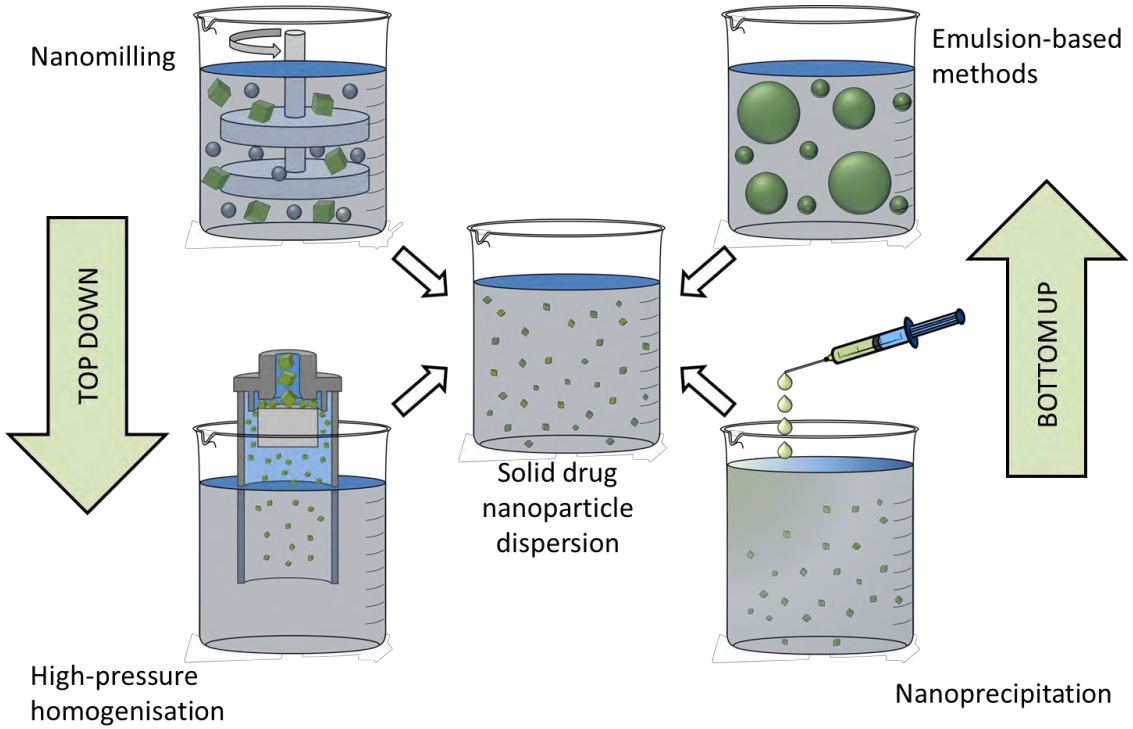
- Flip-flop pharmacokinetics occurs when the rate of absorption is slower than the rate of elimination.

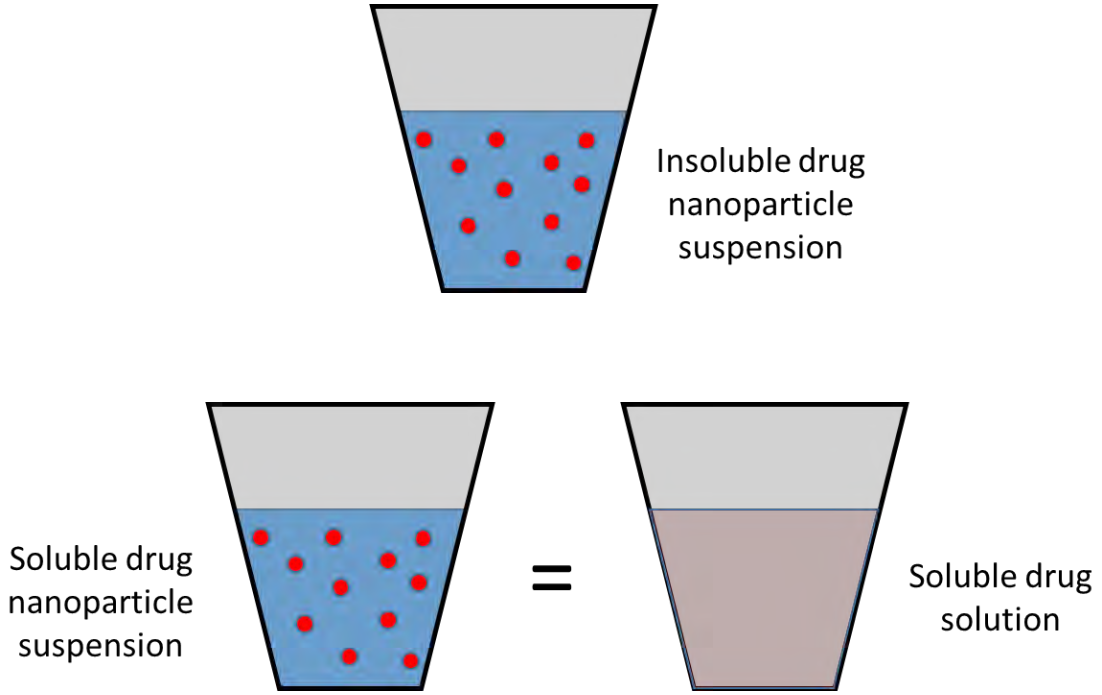




- Drug cannot be cleared until it is absorbed and as such the rate of elimination is determined by the rate of absorption.
- Flip-flop pharmacokinetics results in a longer apparent half-life for the same drug administered as slow versus immediate release formulations.

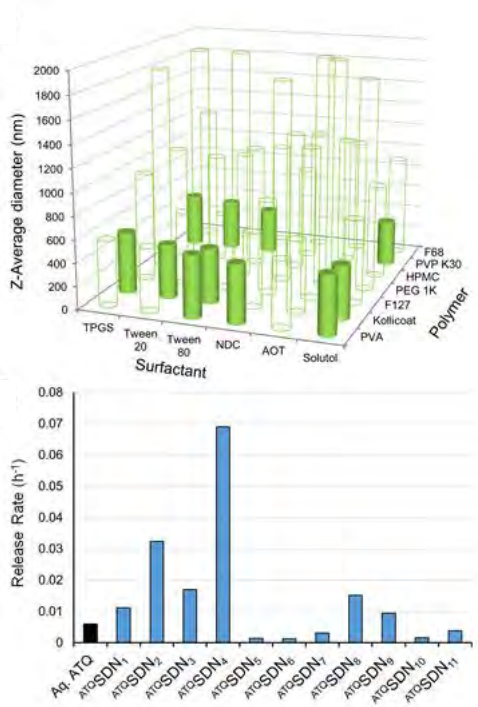
Aqueous suspensions yield the highest drug loading of all technologies and drug insolubility matters



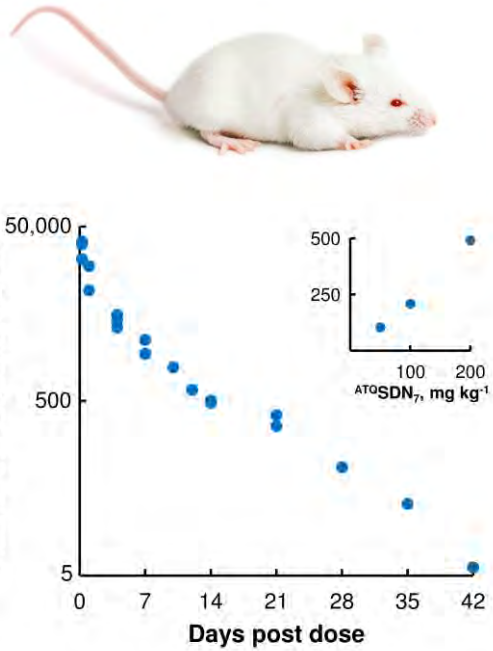


Long-acting injectables: Antimalarial prophylaxis

Library screening

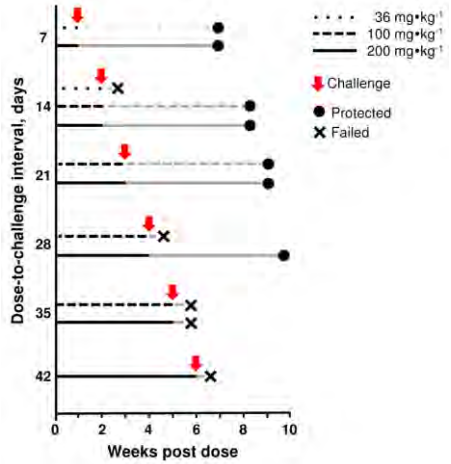


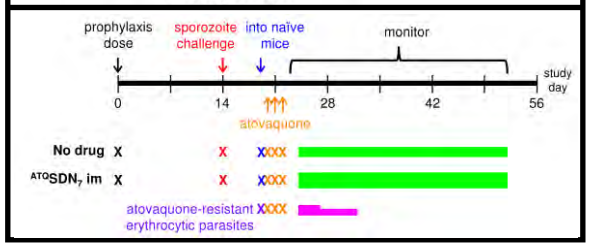
In vivo pharmacokinetics



In vivo pharmacodynamics

P. berghei ANKA-C57BL/6 mouse model





Atovaquone SDN formulation at 300mg/mL syringeable through a 23-gauge needle

Forward planning

- *GMP translation*
- *Depot site GLP tox*
- *Storage & stability*
- *Phase I/IIa healthy volunteer trial*

24-fold!

Atovaquone plasma T½ in MICE = ~7 hours
Atovaquone LAI apparent T½ in MICE = 7 days

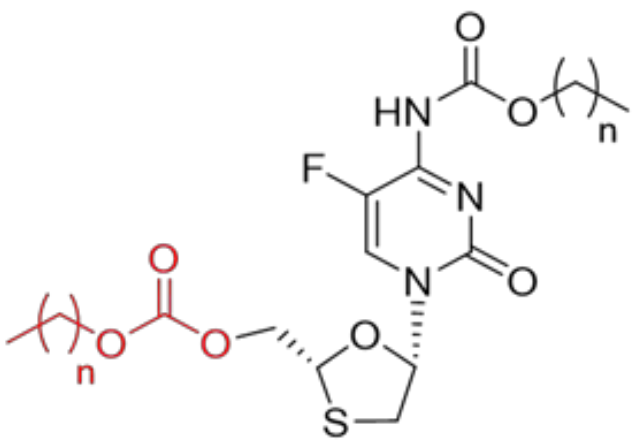
20-fold!

Atovaquone plasma T½ in HUMANS = up to 6 days
Atovaquone LAI plasma T½ in HUMANS = ????

???

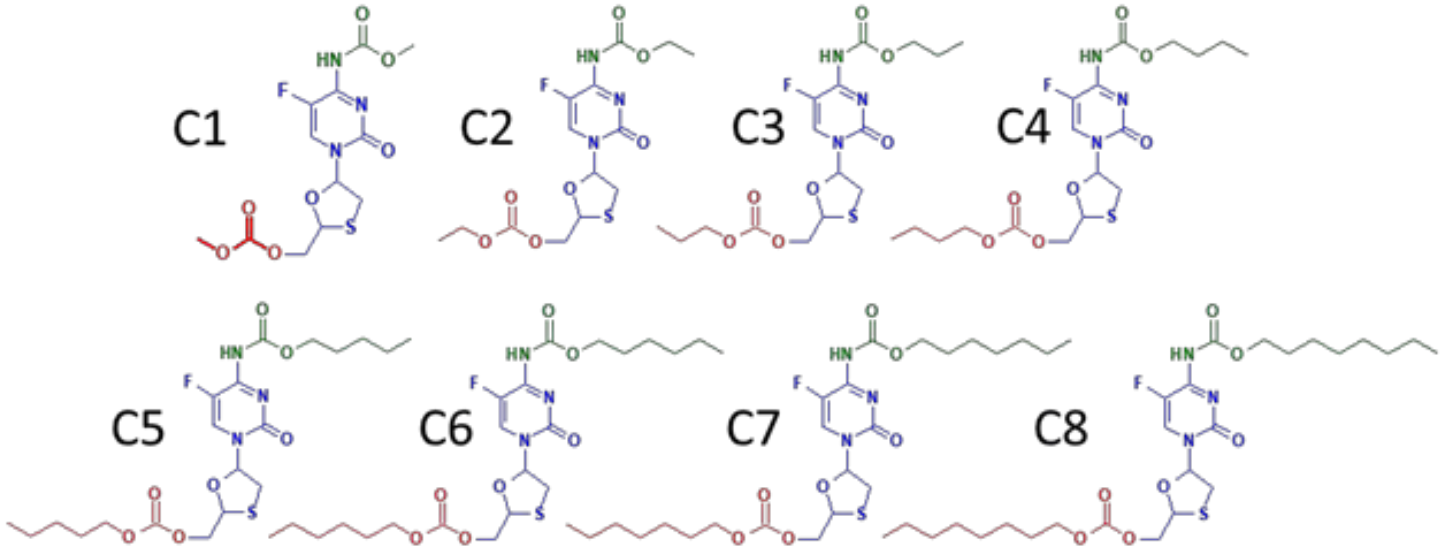
Bakshi *et al.* Long-acting injectable atovaquone nanomedicines for malaria prophylaxis. *Nat Commun.* **9**. 315 (2018)

Semi-solid emtricitabine prodrugs for long-acting injectable nanoparticles



FTC carbonate/carbamates

9-16: n = 0-7



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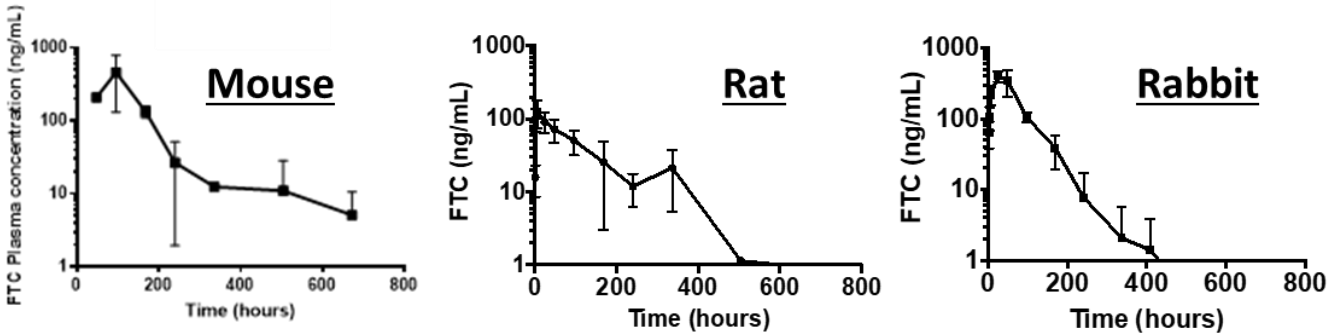
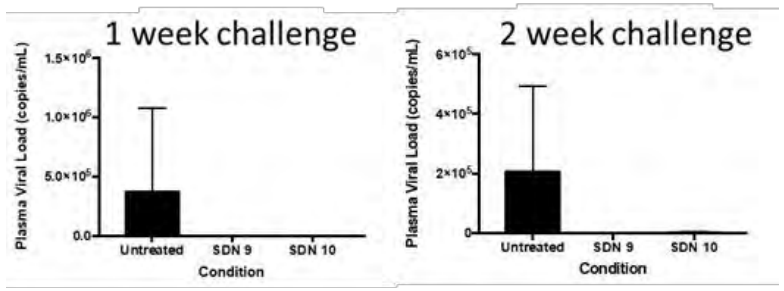
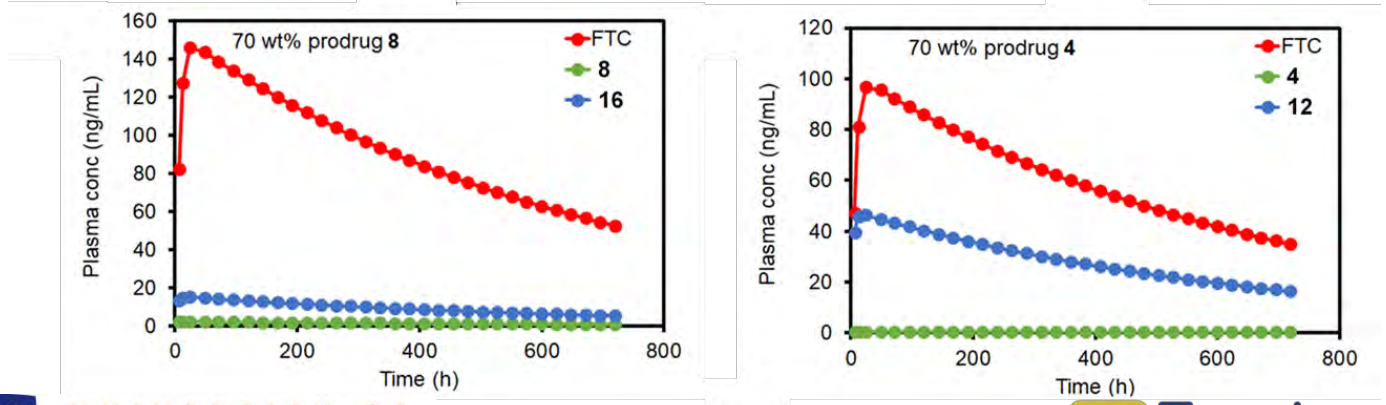
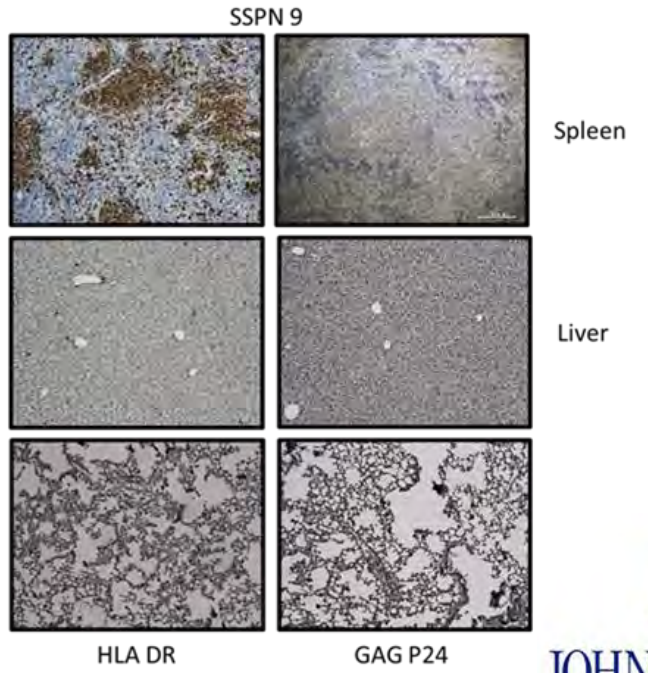
Towards LAI options for water soluble drugs (emtricitabine prodrugs)



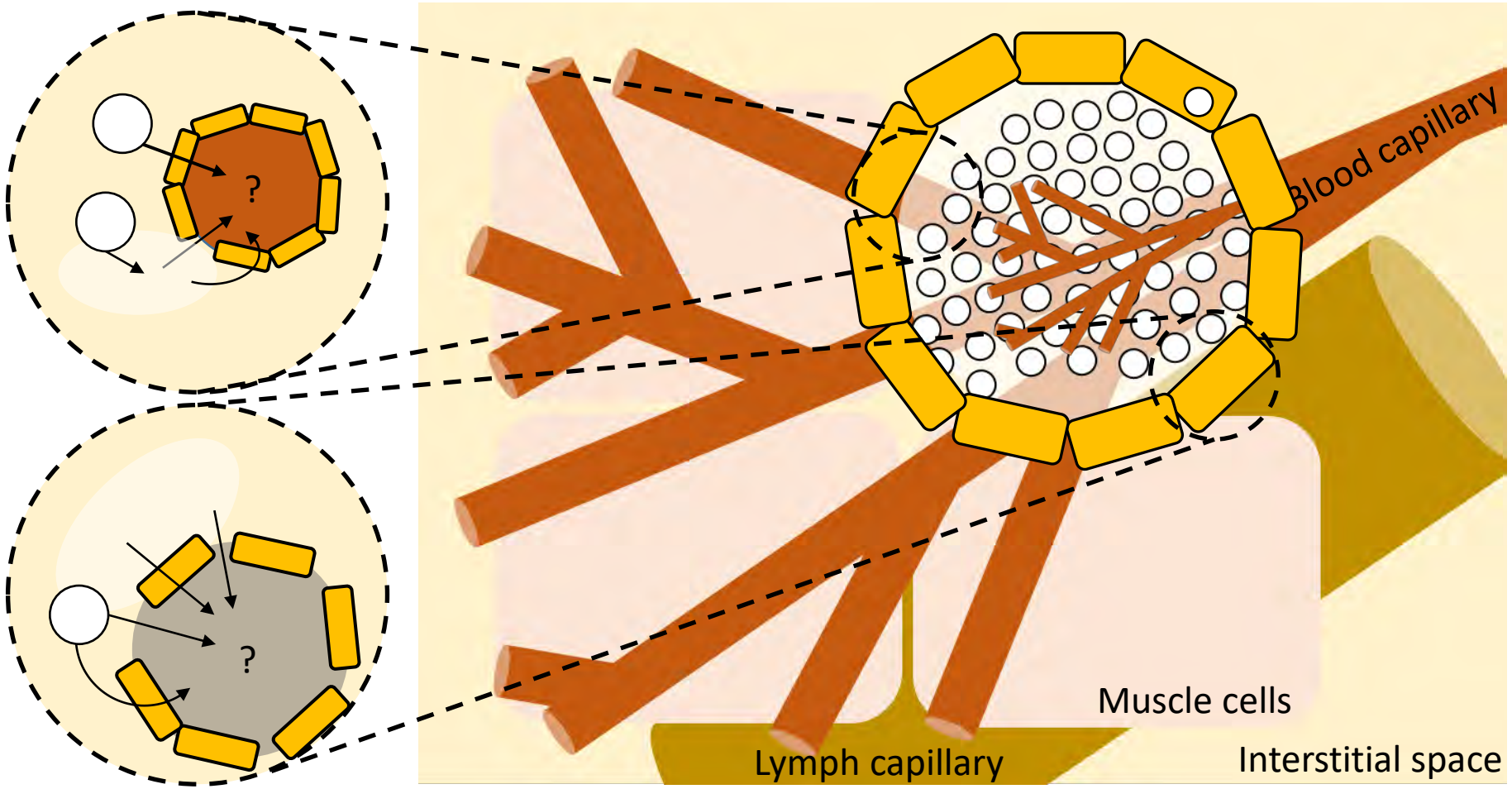


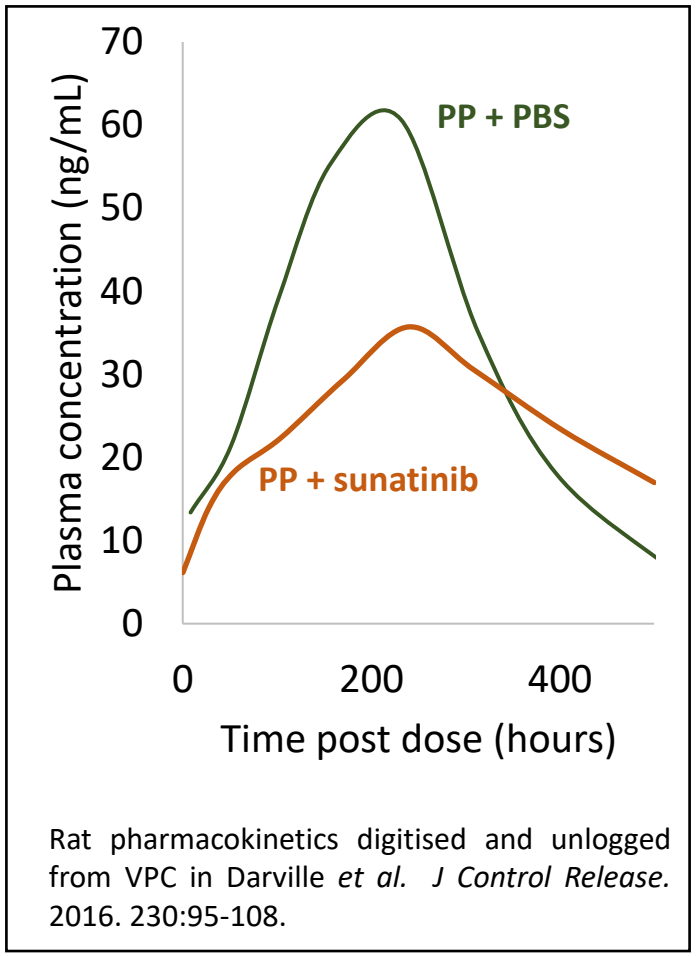
- 14 days exposure with apparent T½ almost 20-times higher (91.9 h) than previously described for orally-administered FTC in rats (4.8 h at 10 mg/kg; Nirogi et al, 2012).
- In humans, the FTC T½ is 10 h (FDA label) and species differences in renal clearance suggest exposures much longer than 14 days.





Challenges: Paucity of fundamental understanding





Rat pharmacokinetics digitised and unlogged from VPC in Darville *et al. J Control Release.* 2016. 230:95-108.

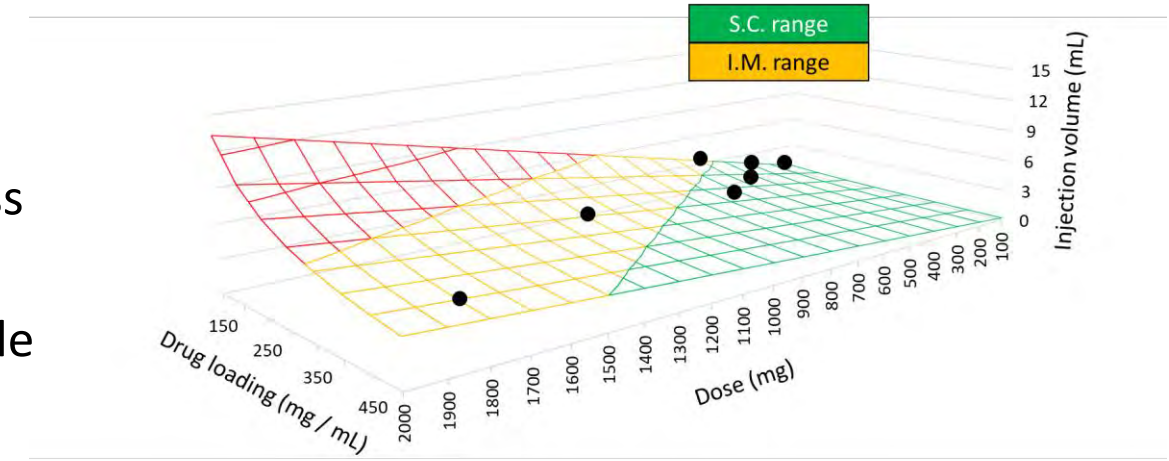
Darville, *et al.* J Pharm Sci, 103 (2014) 2072-2087.

Owen and Rannard. *Advanced Drug Delivery Reviews*. 2016

Challenges: We are constantly pushing against the challenge of depot /implant volume / size…

- Intramuscular administration has been the preferred route of administration for existing LAI approaches
  - Similar PK was observed for IM and SQ for rilpivirine LA
  - SQ offers opportunities for self-administration
- Generally, 4mL is the highest acceptable IM dose in humans (split over 2 x 2mL injections)
  - Lower volumes needed for SQ (2 x 1.5mL?)
- Formulations need to be “syringable” at high drug mass
- Drug to excipient ratio is a critical determinant for choice of approach (polymer carrier versus nanoparticle depot) and success of the option (volume of depot relative to the duration of exposure.
- **Critical to consider <u>all</u> the mass consequences**

LAI agent	Drug mass	Needle
Rilpivrine LAI	300mg/mL	1.5-inch 21-gauge
Cabotegravir LAI	200mg/mL	1.5-inch 25-gauge
Paliperidone palmitate	150mg/mL	1.5-inch 23-gauge



Challenges: PK is more variable and DDIs / pharmacogenetic issues don't go away…

Drug	Oral PK variability (AUC CV%)	LA PK variability (AUC CV%)
Paliperidone	35%	40%
Olanzapine	26%	50%
Medroxyprogesterone	52%	34%
Rilpivirine	39%	52%*
Cabotegravir	27%	39%

Owen and Rannard. *Advanced Drug Delivery Reviews*. 2016

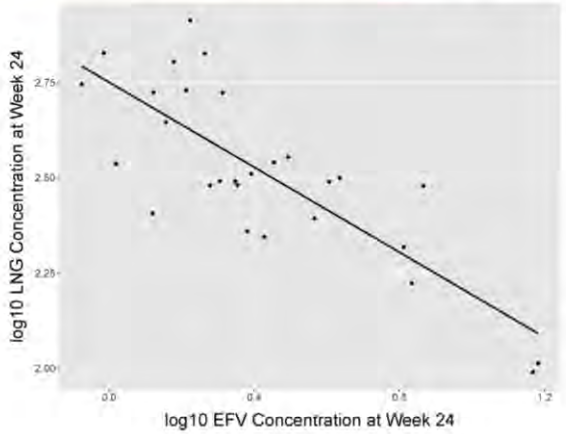
Effect of *CYP2B6* Metabolizer Status on Levonorgestrel Pharmacokinetics When Combined with Efavirenz-based Antiretroviral Therapy

Michelle Pham, Olive Mbabazi, Megan Neary, Shadia Nakalema, Kayla Campbell, Lauren Cirrincione, Anthony T. Podany, Marco Siccardi, Courtney V. Fletcher, Andrew Owen, Mohammed Lamorde, Kimberly K, Scarsi

EFV and LNG Week 24 Concentrations

β-coefficient	P-value
-0.56	3.37×10^{-7}

Higher EFV concentrations were correlated with lower LNG concentrations



LONGEVITY project

Developing the long acting pipeline to establish medicines for malaria, tuberculosis and hepatitis C virus with infrastructure for sustainable translational capacity.

The LONGEVITY project is designed to implement preclinical and clinical long-acting injectable product development for long-acting formulations for malaria and tuberculosis prevention, and a single-injection cure for hepatitis C by taking pre-existing oral medicines and repurposing them as injectable formulations administered far less frequently, and thereby reducing the effect that unsustainable oral regimens have on patients.

The University of Liverpool received funding from Unitaid to implement LONGEVITY

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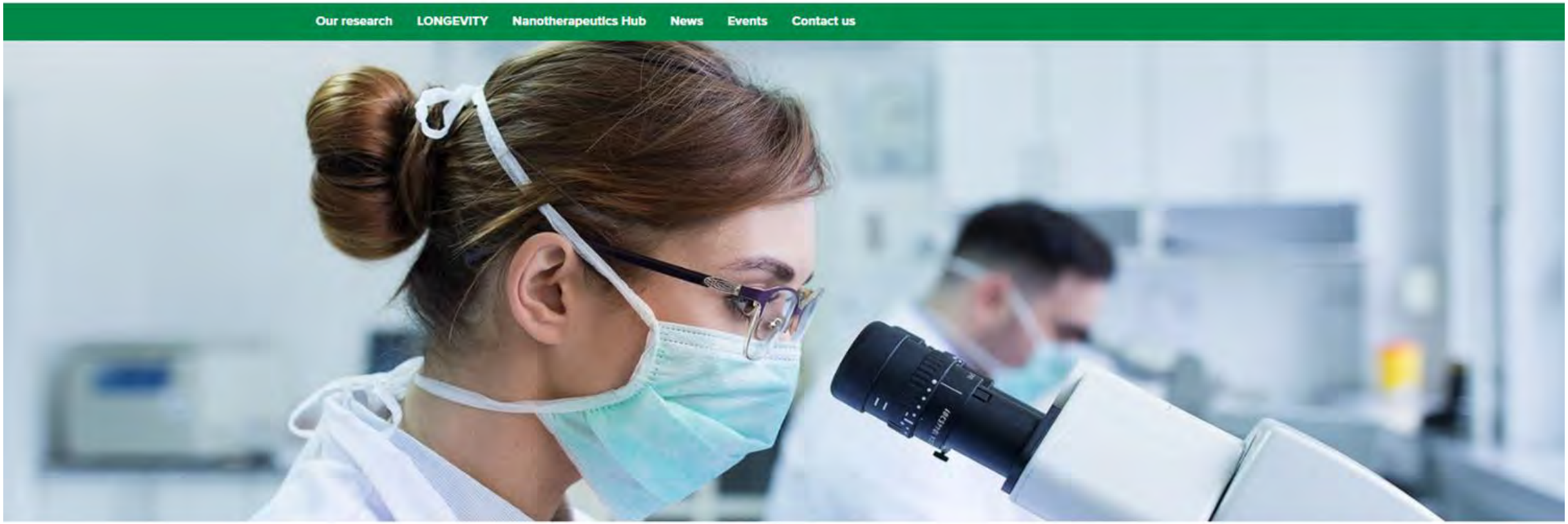
Useful links

- AGILE Trial
- European Nanomedicine Characterisation Laboratory (EUNCL)
- Long-acting/extended release antiretroviral research resource programme (LEAP)
- British Society for Nanomedicine (BSN)

and then COVID-19 happened……

Centre of Excellence for Long-acting Therapeutics



University home > Centre of Excellence for Long-acting Therapeutics

Centre of Excellence for Long-acting Therapeutics

The Centre of Excellence in Long-acting Therapeutics (CELT) is a cross-faculty research initiative combining our world leading expertise in pharmacology and materials chemistry and working with international partners to disseminate research findings in long-acting medicine and change the global landscape of drug administration.

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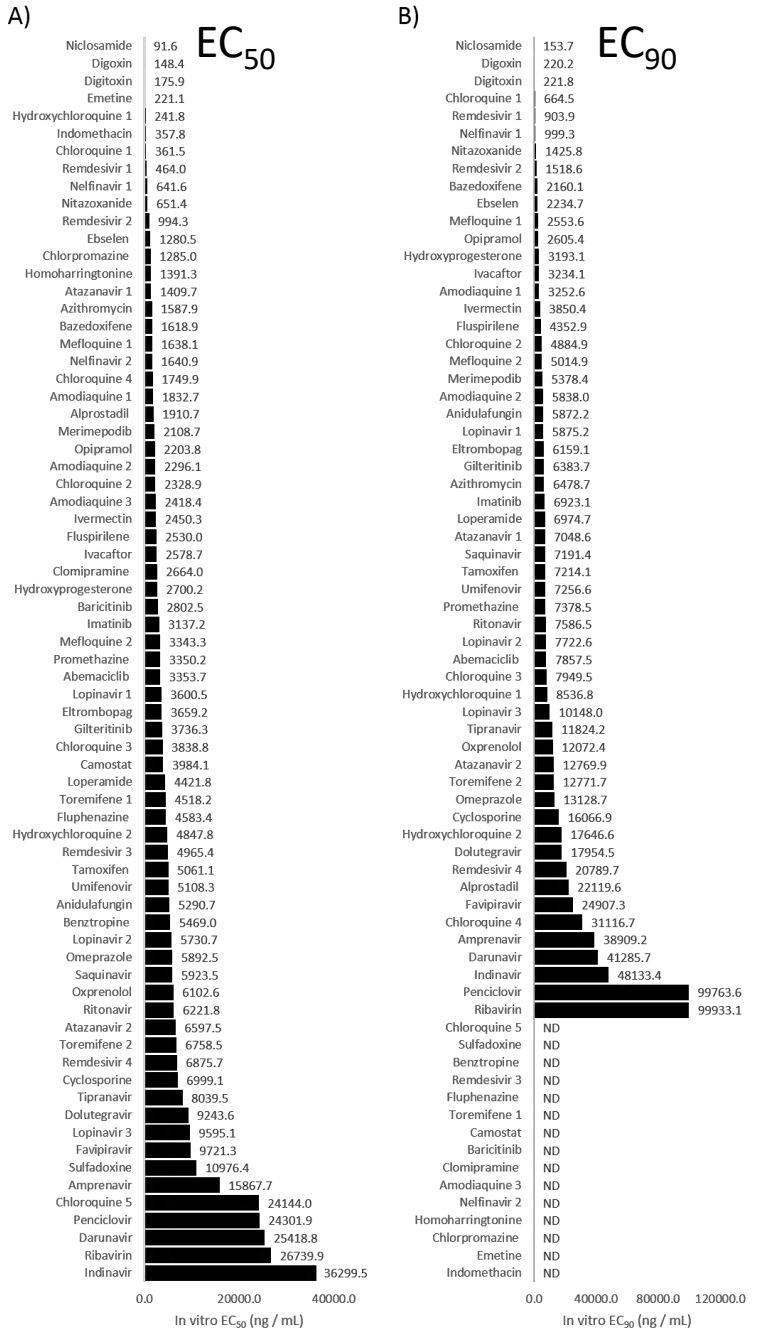
https://www.liverpool.ac.uk/centre-of-excellence-for-long-acting-therapeutics/

LAI for Covid-19

- LA medicines have putative application for treatment obviating the need for strict adherence.
- Opportunity for pre-exposure prophylaxis (PreP) to protect sectors of the population that may not benefit from the vaccines.
- For small molecules, low solubility drugs with high anti-SARS-CoV-2 potency are needed.
- Niclosamide is almost insoluble in water and is amongst the most potent agents for SARS-CoV-2 screened to date.
- Low solubility compromises oral bioavailability limiting application of current formulations for COVID-19.
- Under investigation separately for pulmonary delivery.



Arshad *et al*. 2020. *Clin Pharmacol Ther*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7280633/

Niclosamide supporting data and mechanism of action: SARS-CoV-2 and other viral diseases.

- Broad spectrum antiviral with potent *in vitro* activity against SARS-CoV-2, SARS-CoV, MERS-CoV, Zika, HCV, human adenovirus, influenza, and rhino virus (https://pubs.acs.org/doi/pdf/10.1021/acsinfecdis.0c00052).
- Mechanism of action against SARS-CoV-2 confirmed to be an entry inhibitor on 16th December 2020, blocking internalisation via clathrin and dynamin independent endocytic pathways (https://www.biorxiv.org/content/10.1101/2020.12.16.422529v1.full.pdf+html).
- Putative secondary mechanisms of action beyond direct antiviral activity through modulation of the innate antiviral response and pulmonary ion channel involved in bronchodilation (multiple reports).

Preclinical proof of concept in rats and planned SARS-CoV-2 infection studies.

- Preliminary studies in rats demonstrate exposures up to 28-days following intramuscular administration of injectable formulation.
- Dose linear between 50 – 200 mg/kg intramuscular administration to rats:

	Cmax (ng / mL)	Tmax (h)	Terminal $T_{1/2}$	CL (L/h/kg)	AUC (ng.h/mL)
NIC 50 mg/kg	1408.6	2.5	10	1.5	28,955
NIC 100 mg/kg	2041.3	2	8	1.7	55,734
NIC 200 mg/kg	3125.3	3	9	2.4	74,584

- Tolerability and sparse pharmacokinetic evaluation in Syrian Golden Hamster model underway over Christmas 2020.
- SARS-CoV-2 infection studies (treatment and prevention) to be initiated on January 24th 2021.
- Compatibility with manufacturing at CDMO already confirmed. Funding in place to engage with CDMO for GMP translation and storage / stability to support clinical batch manufacture.

Summary and conclusions

- Long-acting drug delivery holds enormous potential for overcoming issues related to medication adherence.
- So far has focused mainly on contraception, schizophrenia, androgen ablation and HIV but many other indications may benefit from the approach.
- Target exposure / potency, half-life and solubility (injectables) are critical to the success of the approach.
- Many technologies and modalities are being explored for long-acting delivery and each offer different opportunities and challenges.
- Universal challenges include depot volume / implant size, variability in exposure, drug-interactions, local administration-site safety - large knowledge gaps remain.
- Much to learn about what makes the ideal LAI agent but exciting opportunities for repurposing existing agents or for new chemical entities in development.

Acknowledgements

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