Improving long-acting delivery

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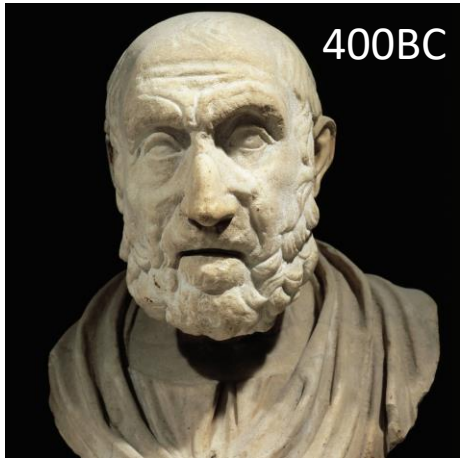
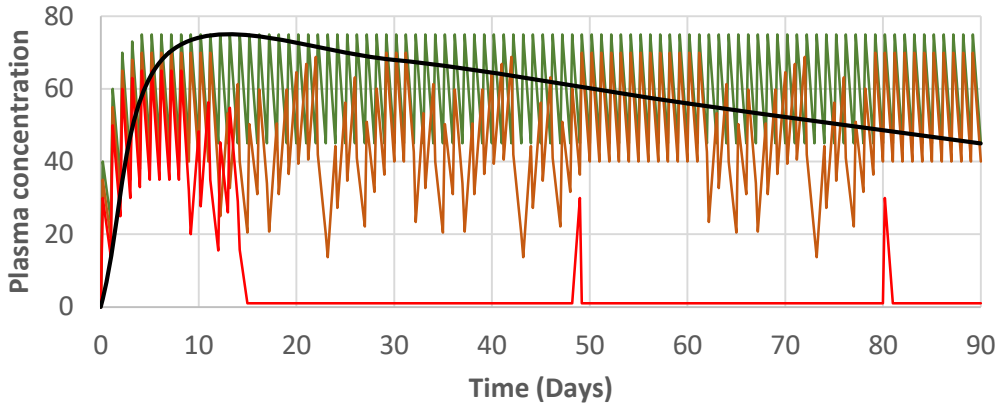
Adherence, Retention, Completion: The ARC of benefit for long-acting drug delivery



"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."

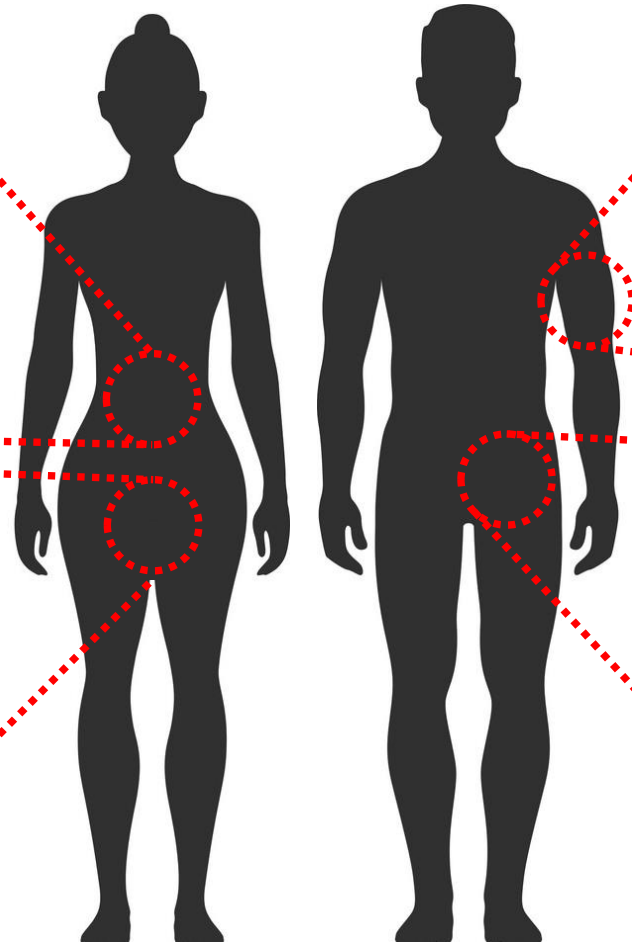


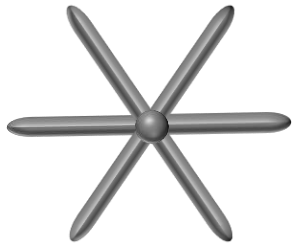
- Oral delivery of medicines places success of therapy in the hands of the patient
- Long-acting drug delivery has the potential to be transformative for patient management:
  - Issues of non-adherence are partially or entirely mitigated.
  - Problems with retention in therapy programmes are removed 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 on 21st December 2019 but this was related to chemistry, manufacturing and controls (CMC) process and not safety.

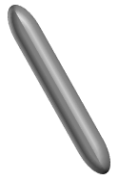
What are the long-acting technologies?



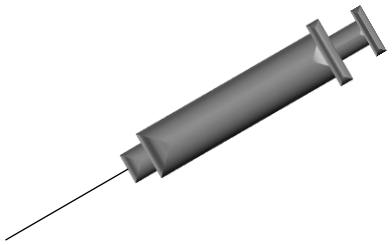


Gastric residence device

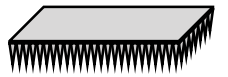
Vaginal ring



Implant



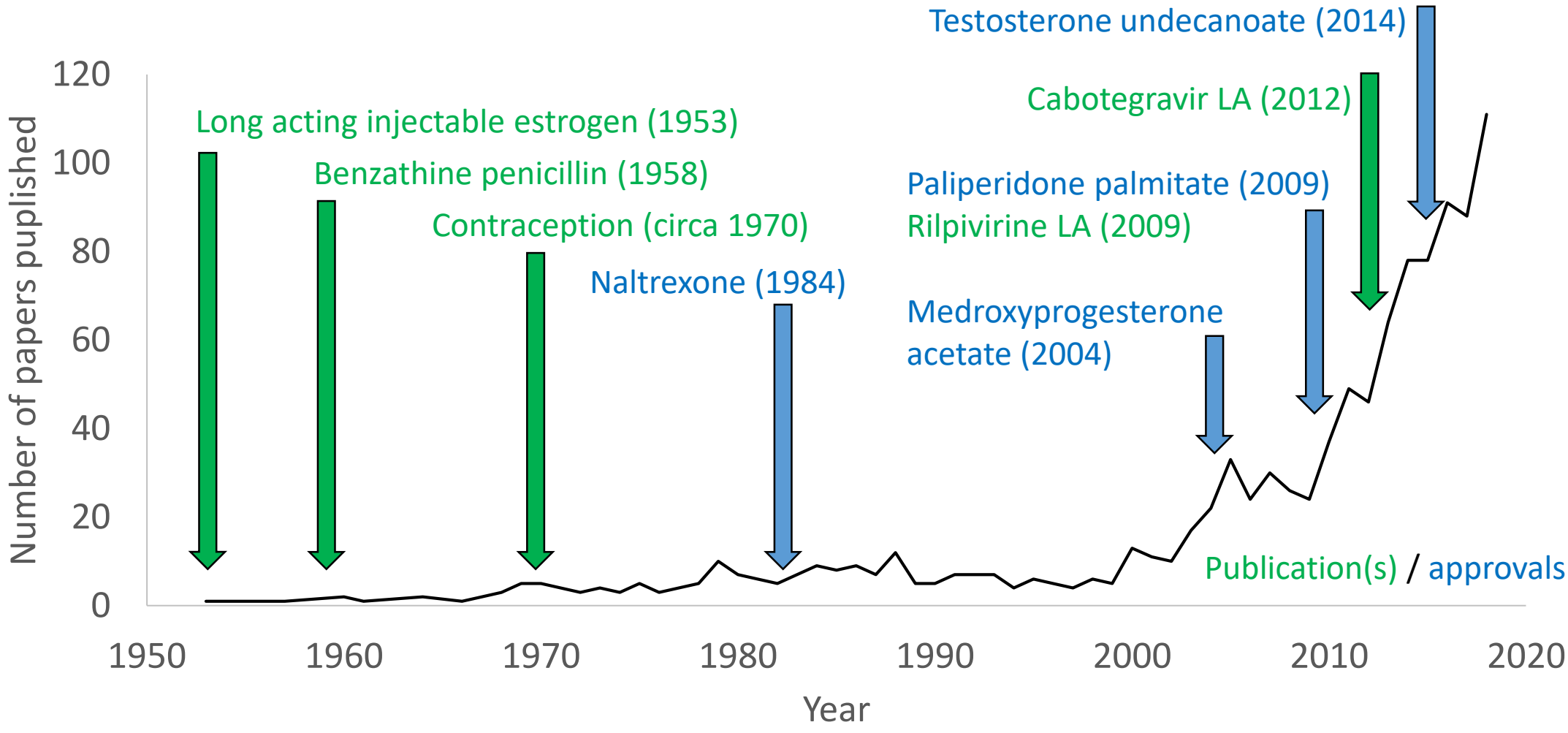
Injectable drug



Microarray / microneedle patch (theoretical)

Broadly neutralizing monoclonal antibodies

Long-acting injectables / parenterals: brief history

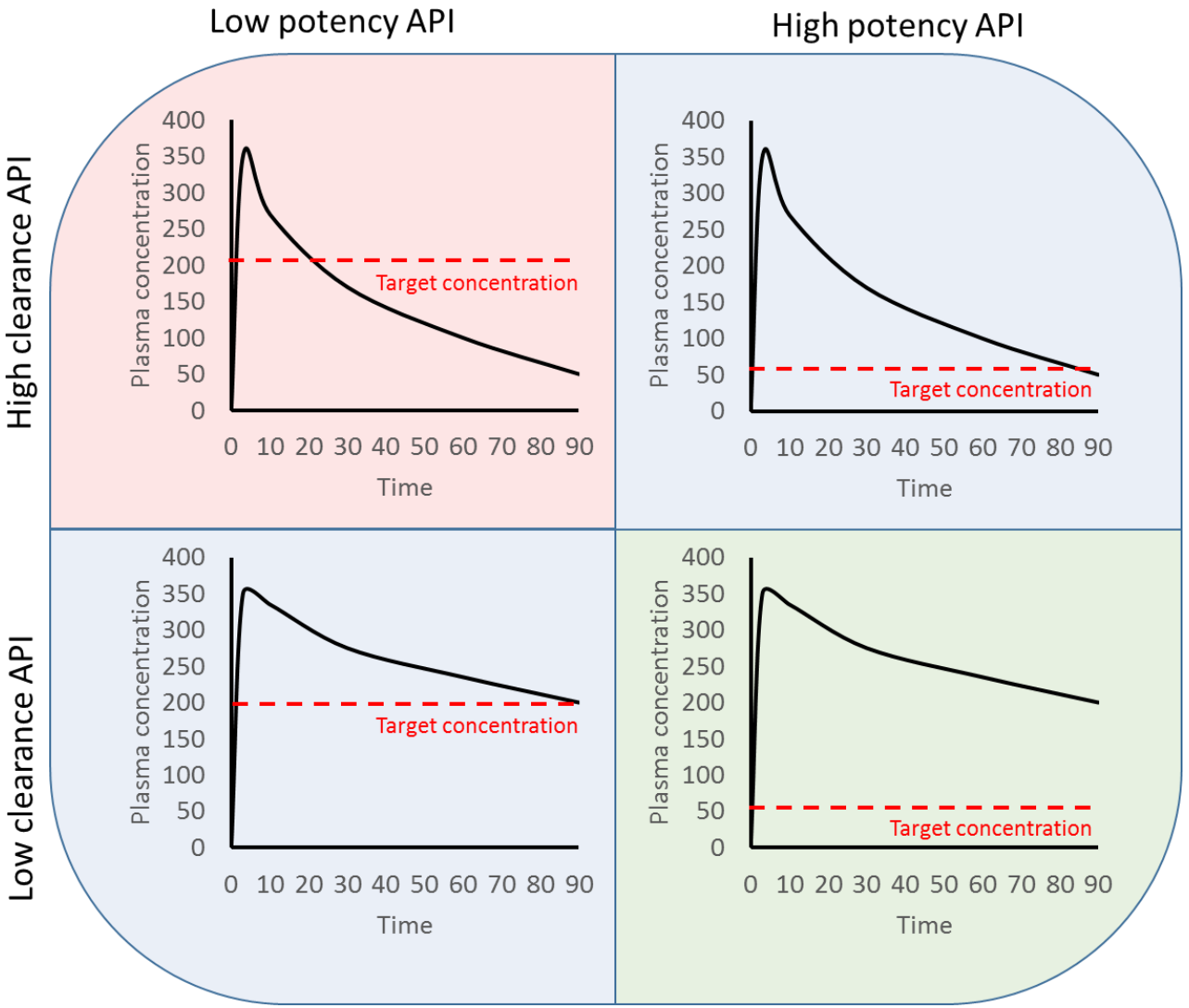


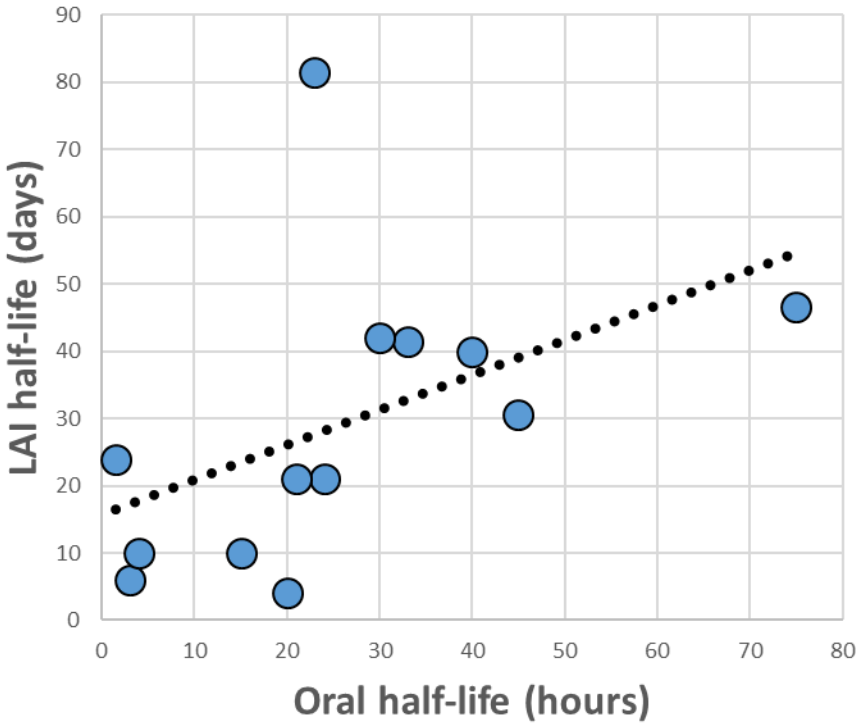
Using Pubmed search term: *"long acting injectable" OR "long acting parenteral" OR "long acting depot"*

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

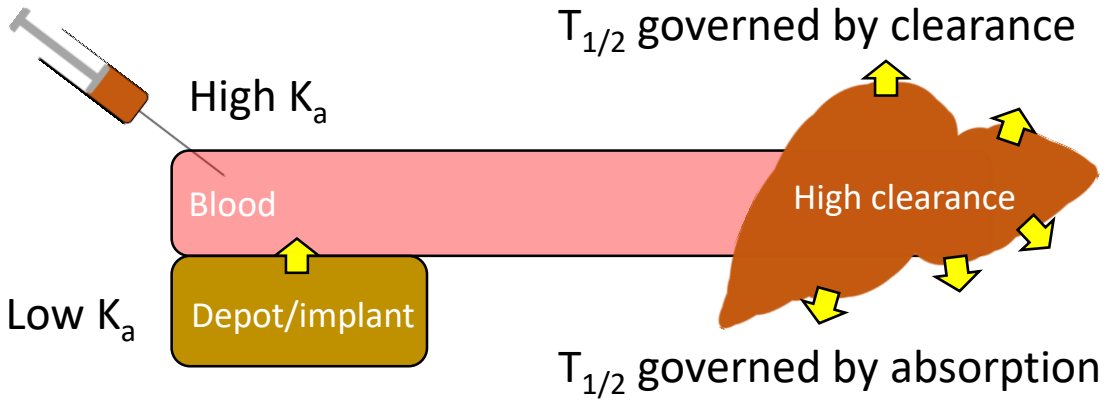


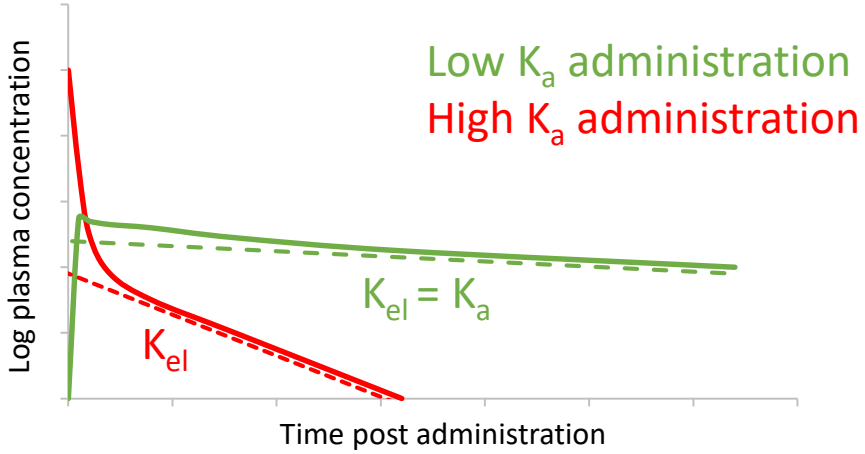


- Varying degree of half-life extension.
- Apparent relationship between oral and LAI half-life for existing medicines.
- **Caveat:** dose is also proportional to half-life for many LAI medicines.

Flip-flop pharmacokinetics underpins long-acting delivery

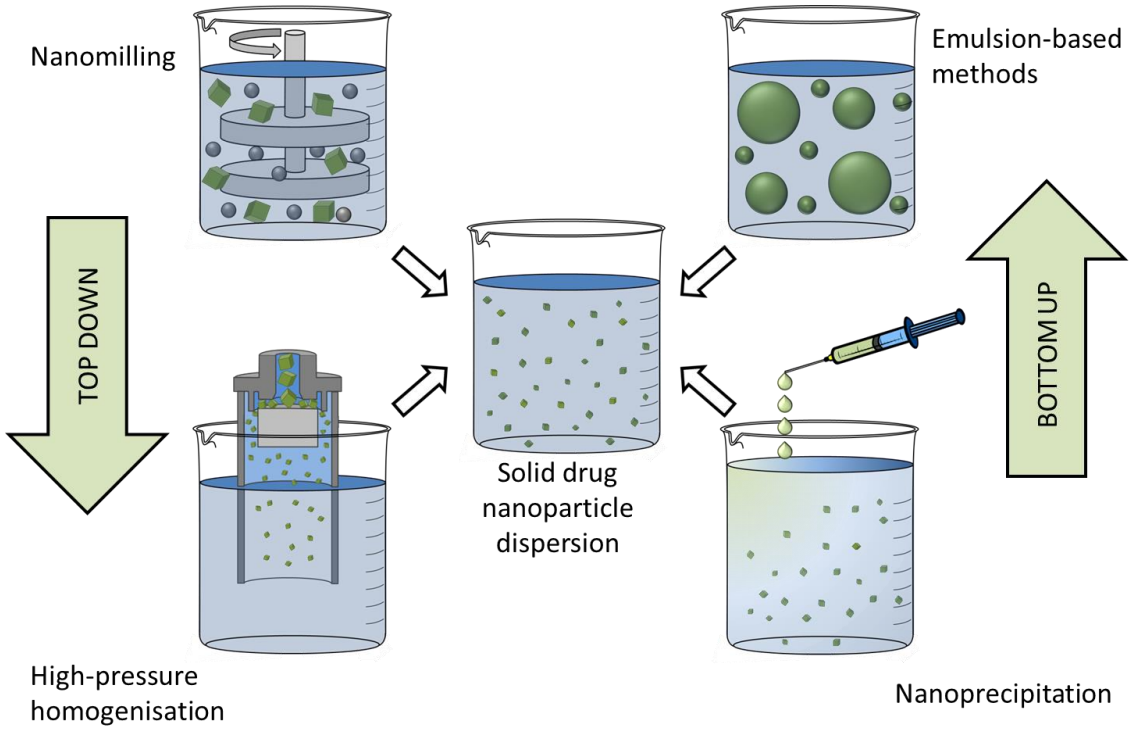
- Flip-flop pharmacokinetics occurs when the rate of absorption is slower than the rate of elimination.

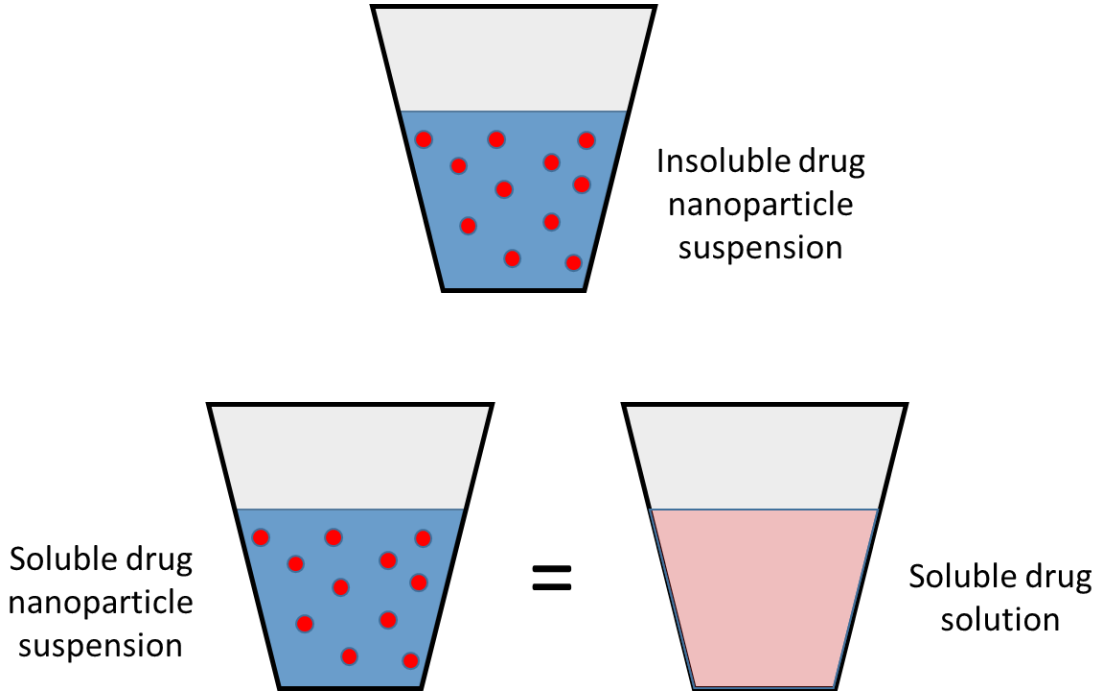




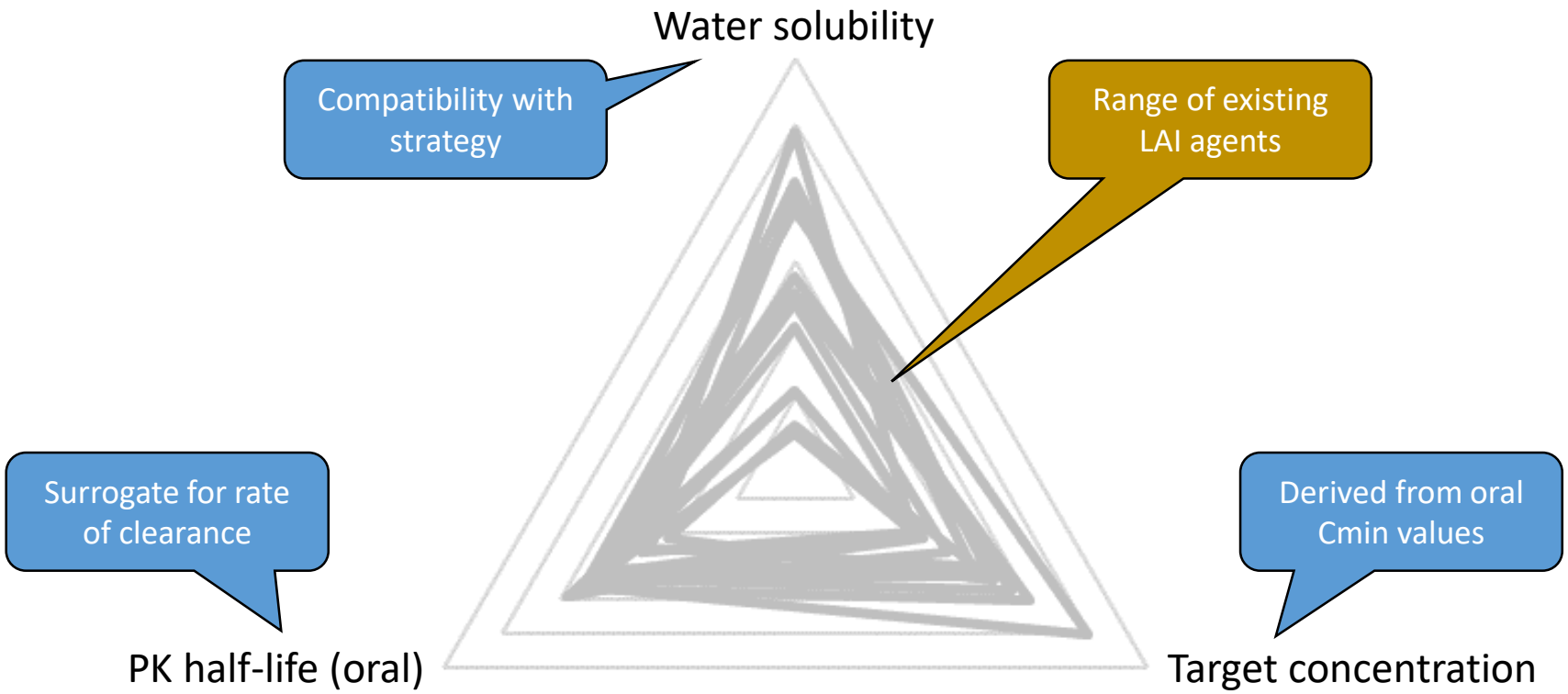
- Drug cannot be cleared until it is absorbed and as such the rate of elimination is determined by the rate of absorption.
- Flip-flop pharmacokinetics results in a longer apparent half-life for the same drug administered as slow versus immediate release formulations.

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

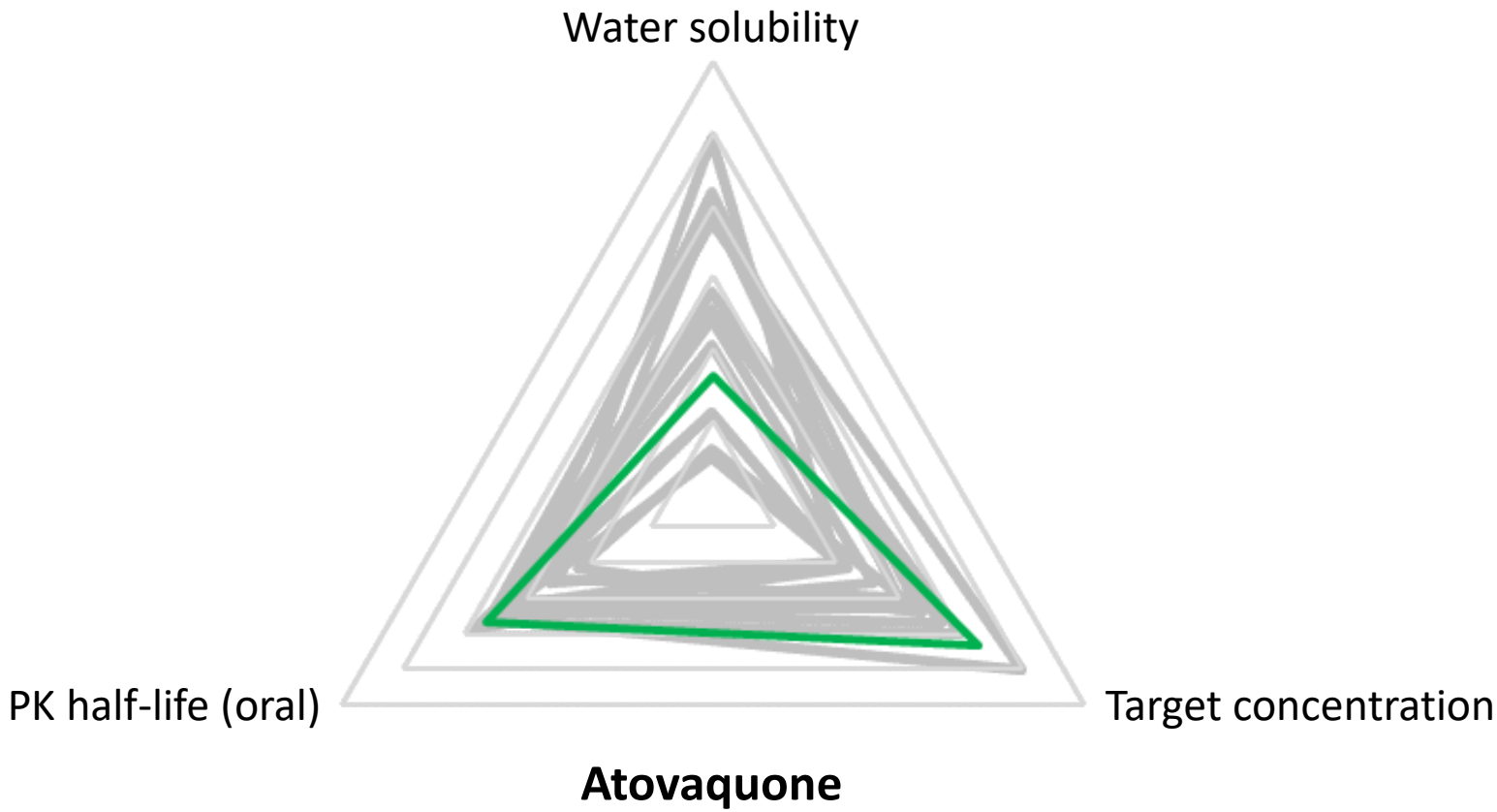




Summary of physiochemical and pharmacokinetic characteristics – informing choice of agent

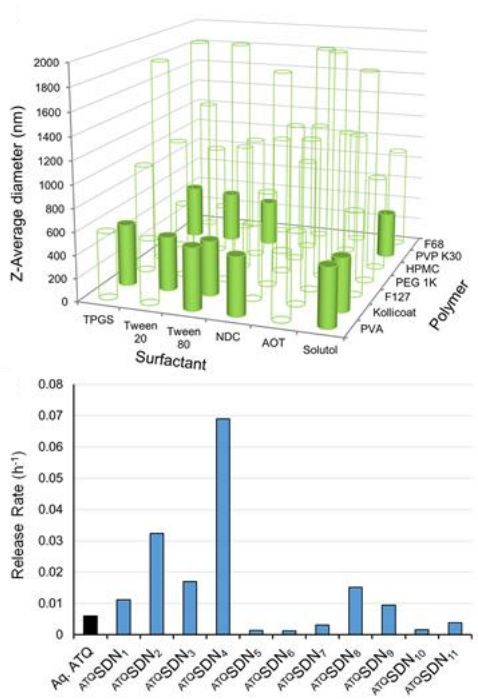


Preclinical development of a long-acting injectable atovaquone formulation for malaria prophylaxis

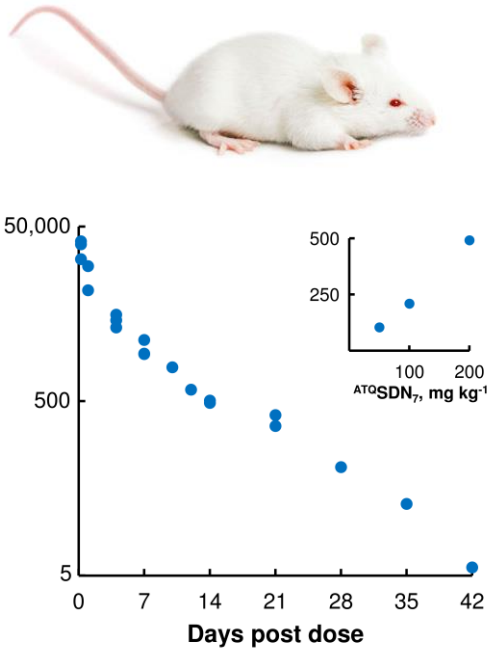


Long-acting injectables: Antimalarial prophylaxis

Library screening

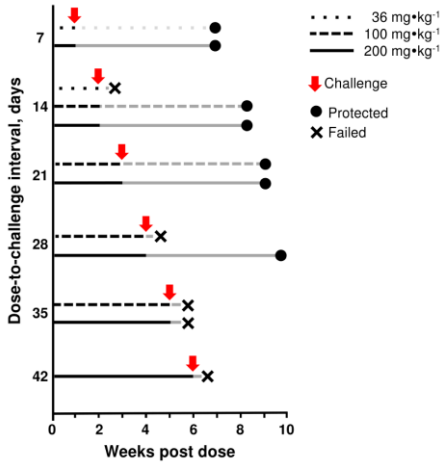


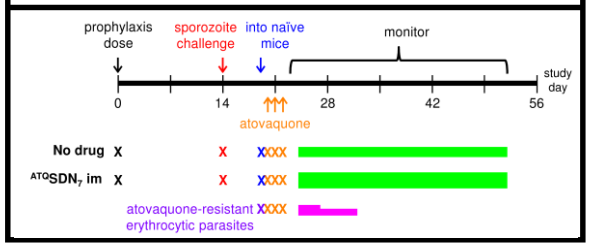
In vivo pharmacokinetics



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

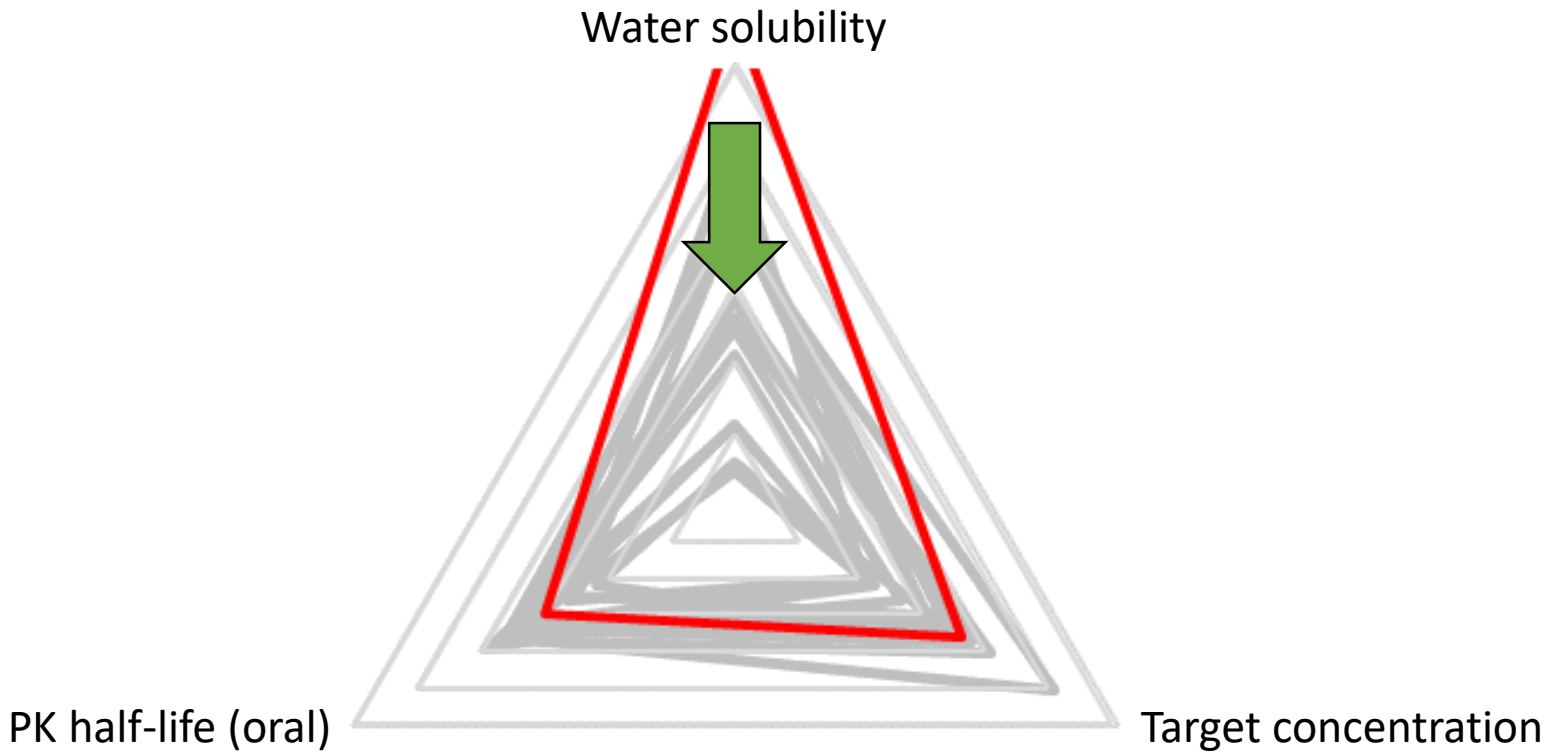
20-fold!

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



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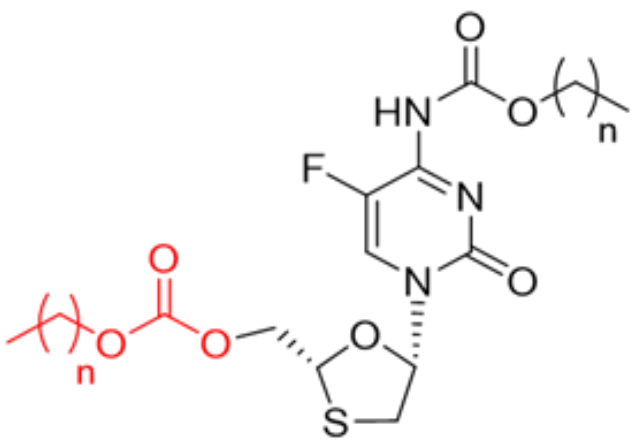
Tandem Nano Ltd

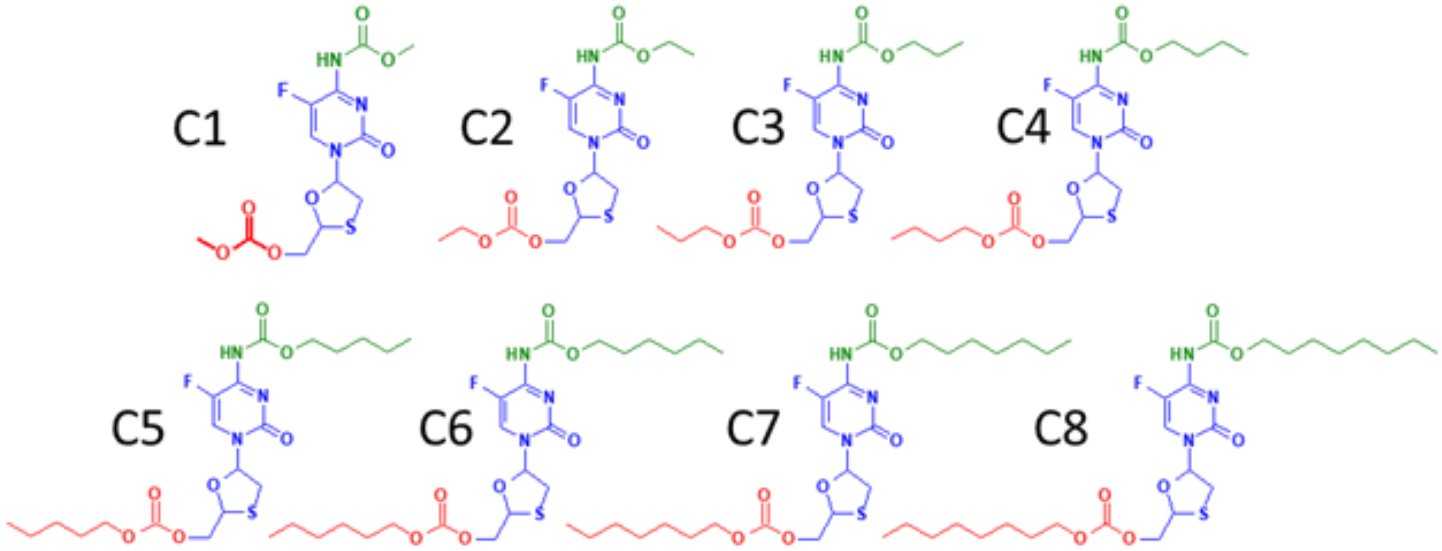
JOHNS HOPKINS MEDICINE

Semi-solid emtricitabine prodrugs for long-acting injectable nanoparticles



FTC carbonate/carbamates

9-16: n = 0-7



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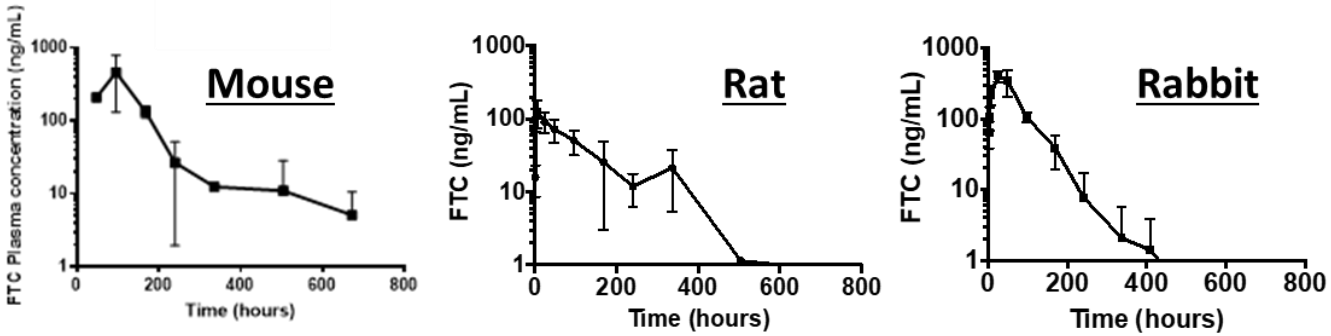
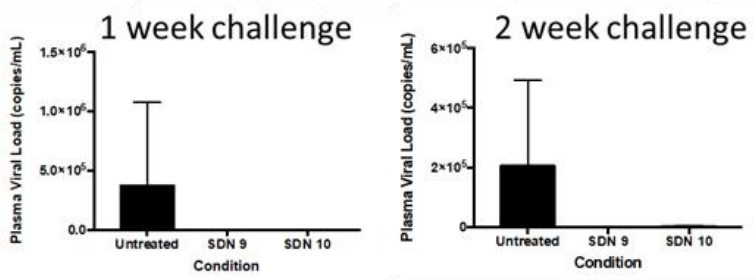
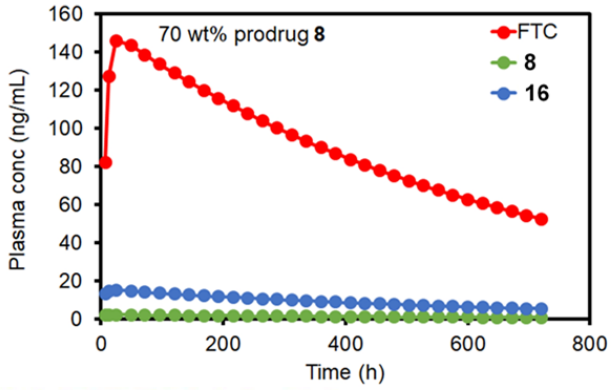
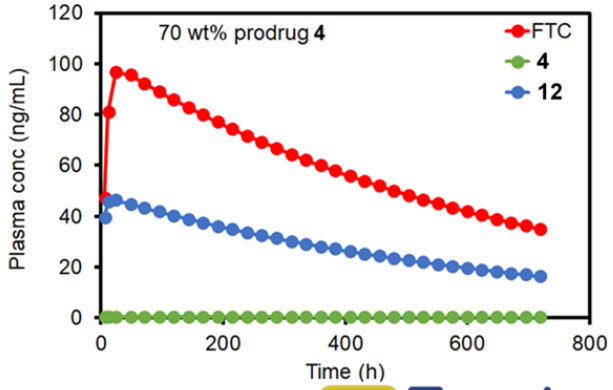
Towards LAI options for water soluble drugs (emtricitabine prodrugs)

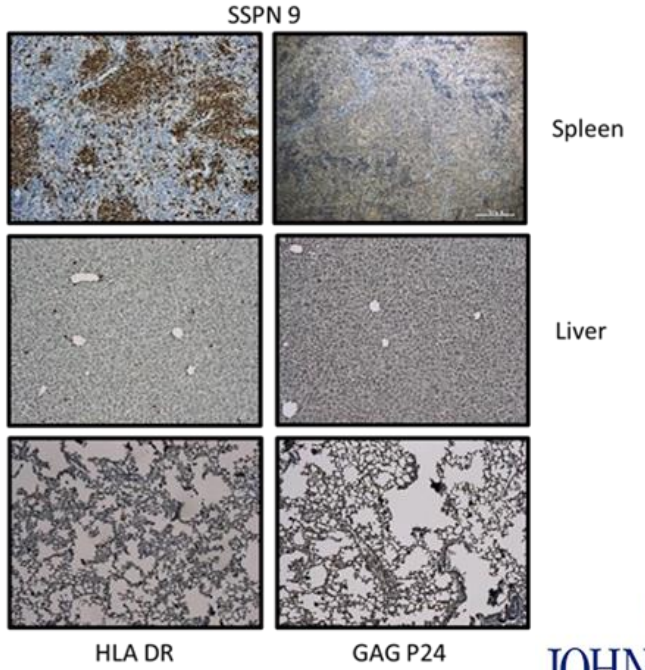




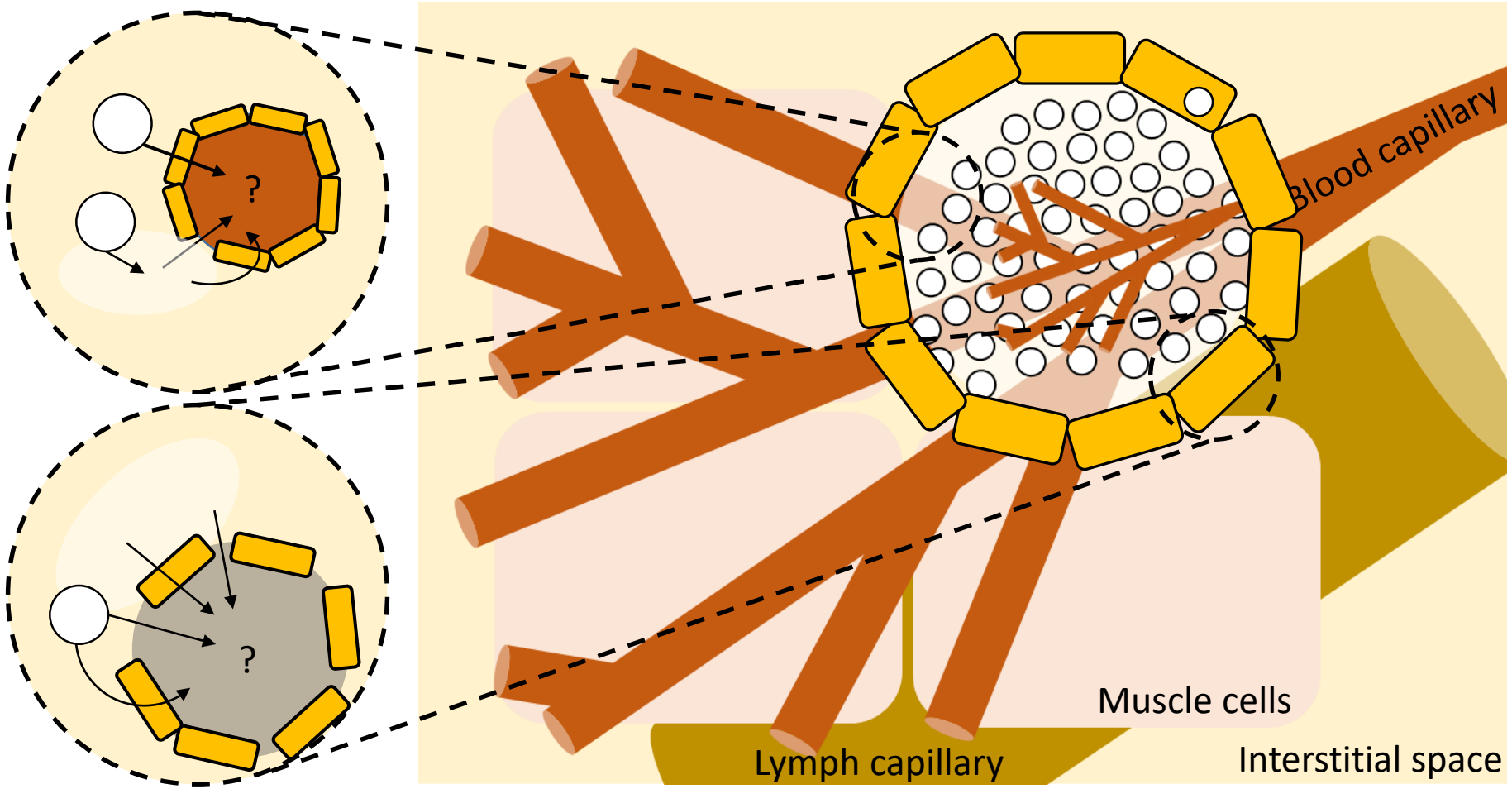
- 14 days exposure with apparent T½ almost 20-times higher (91.9 h) than previously described for orally-administered FTC in rats (4.8 h at 10 mg/kg; Nirogi et al, 2012).
- In humans, the FTC T½ is 10 h (FDA label) and species differences in renal clearance suggest exposures much longer than 14 days.

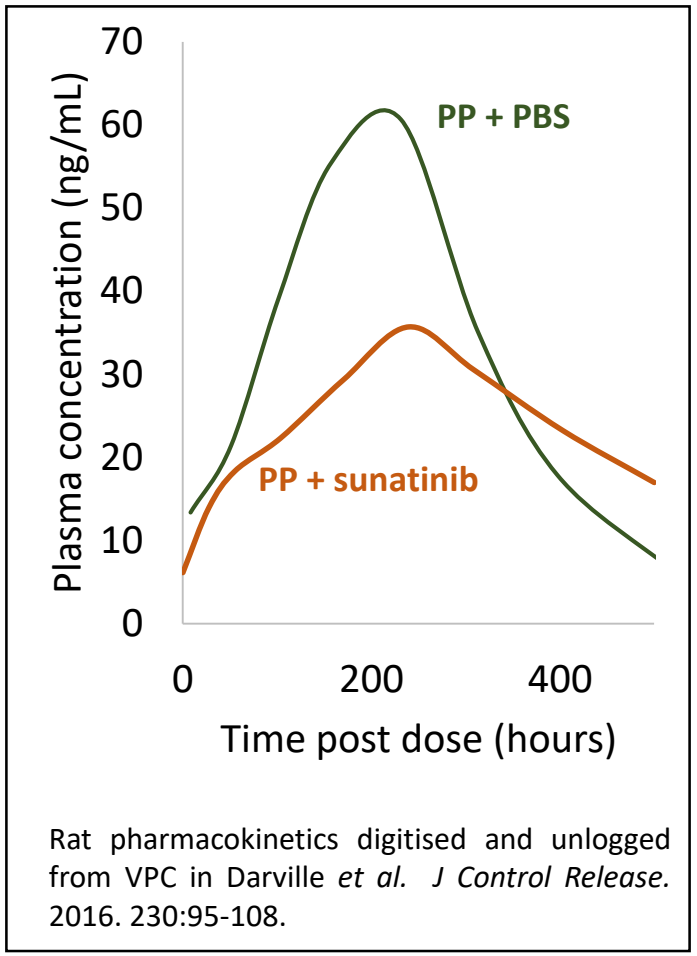






Challenges: Paucity of fundamental understanding





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

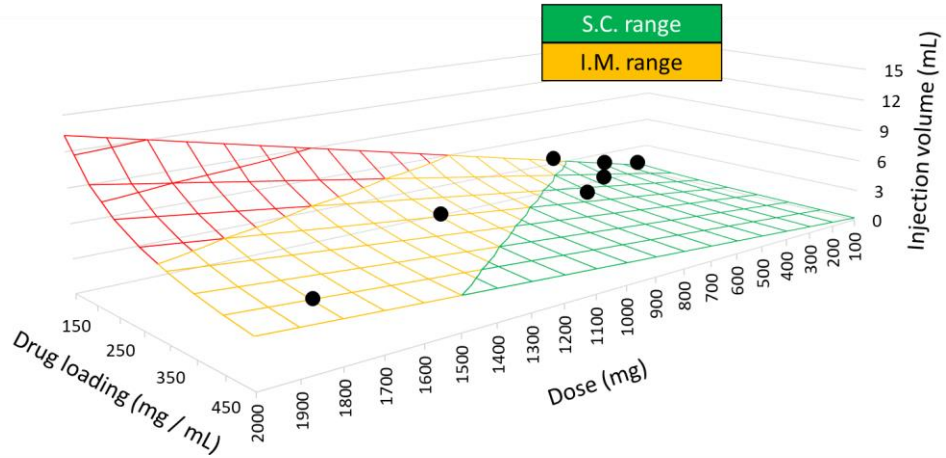
Darville, *et al.* J Pharm Sci, 103 (2014) 2072-2087.

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

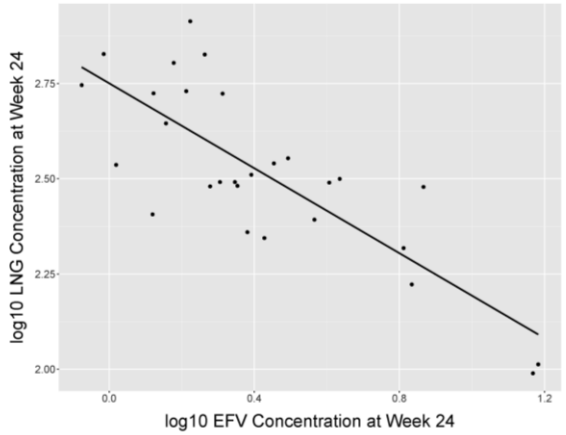
Effect of *CYP2B6* Metabolizer Status on Levonorgestrel Pharmacokinetics When Combined with Efavirenz-based Antiretroviral Therapy

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

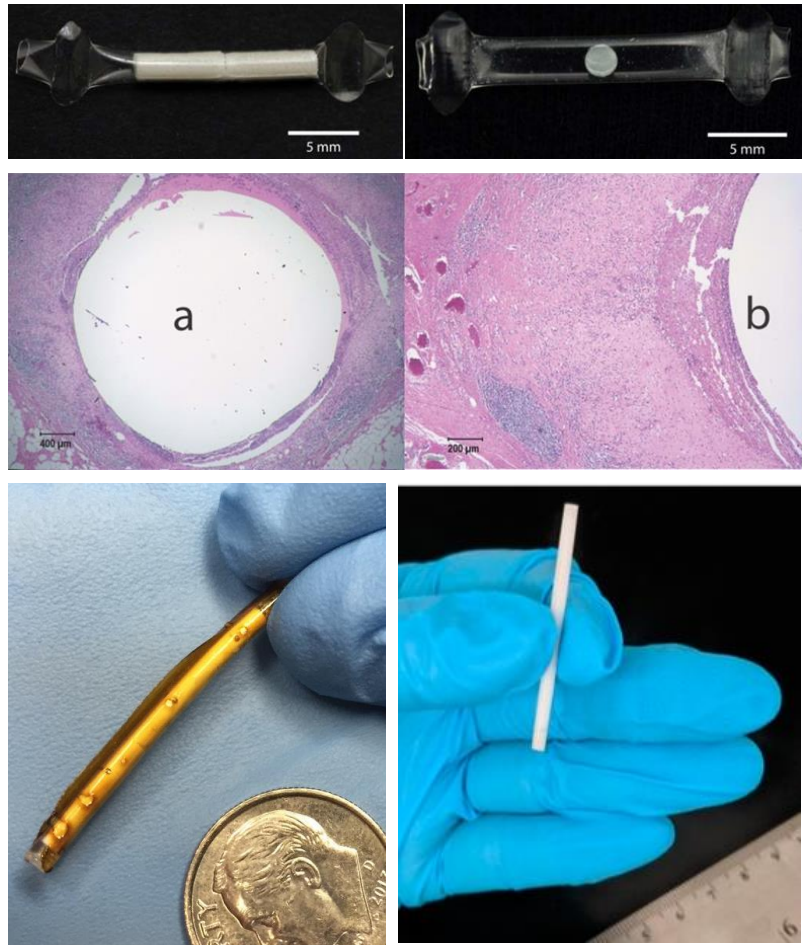
β-coefficient	P-value
-0.56	3.37×10^{-7}

Higher EFV concentrations were correlated with lower LNG concentrations



Challenges: new safety considerations need to be better understood…

- At least three different implant technologies with the ability to deliver TAF are under investigation globally.
- One of these (SLAP project) is a polyurethane implant loaded with TAF hemifumarate active for over 90 days *in vitro* and *in vivo*.[1]
- Histopathology revealed unexpected dose-dependent local inflammation up to severe necrosis around the active implants in rabbits and rhesus macaques.[1]
- However, two macaques exhibited pronounced inflammatory response to the placebo implant that at one month.[1]
- Responses may be different with silicone implants loaded with the TAF free base (Oak Crest)[2] or poly(ε-caprolactone) TAF implants (RTI).[3]
- **Clearly more to learn and further study is warranted.**



[1]Su et al. Antimicrob Agents Chemother. 2019 Dec 23. pii: AAC.01893-19. doi: 10.1128/AAC.01893-19. [Epub ahead of print]
[2]Gunawardana et al. Antimicrob Agents Chemother. 2015 Jul;59(7):3913-9. doi: 10.1128/AAC.00656-15.
[3]Johnson et al. Pharmaceutics. 2019 Jul 4;11(7). pii: E315. doi: 10.3390/pharmaceutics11070315.

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 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.

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