RELEVANT CHALLENGES WITH IVRT WITH IRON-CARBOHYDRATE COMPLEXES: APPLICATION TO IVIVC MODELS

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DISCLOSURE

The presenter is an employee of Vifor Pharma. Views and opinions expressed are speaker's own and do not necessarily represent those of Vifor Pharma

OBJECTIVES

- Describe the development and engineering of intravenous (IV) iron-carbohydrate nanomedicines.
- Review the analytes that could be measured to support in-vitro release testing (IVRT).
- Discuss measurement of analytes in vivo that may support in vitro-to-in vivo correlation (IVIVC) model development for these complex drugs.
- Integrate in vitro and in vivo analyte profiles into a preliminary IVIVC model.
- Consider the caveats of IVIVC models in the context of remaining research gaps in understanding the uptake, biodegradation and mobilization of iron in the mononuclear phagocytic system.

IRON-CARBOHYDRATE NANOMEDICINES ALLOW FOR SAFE DELIVERY OF IRON INTRAVENOUSLY

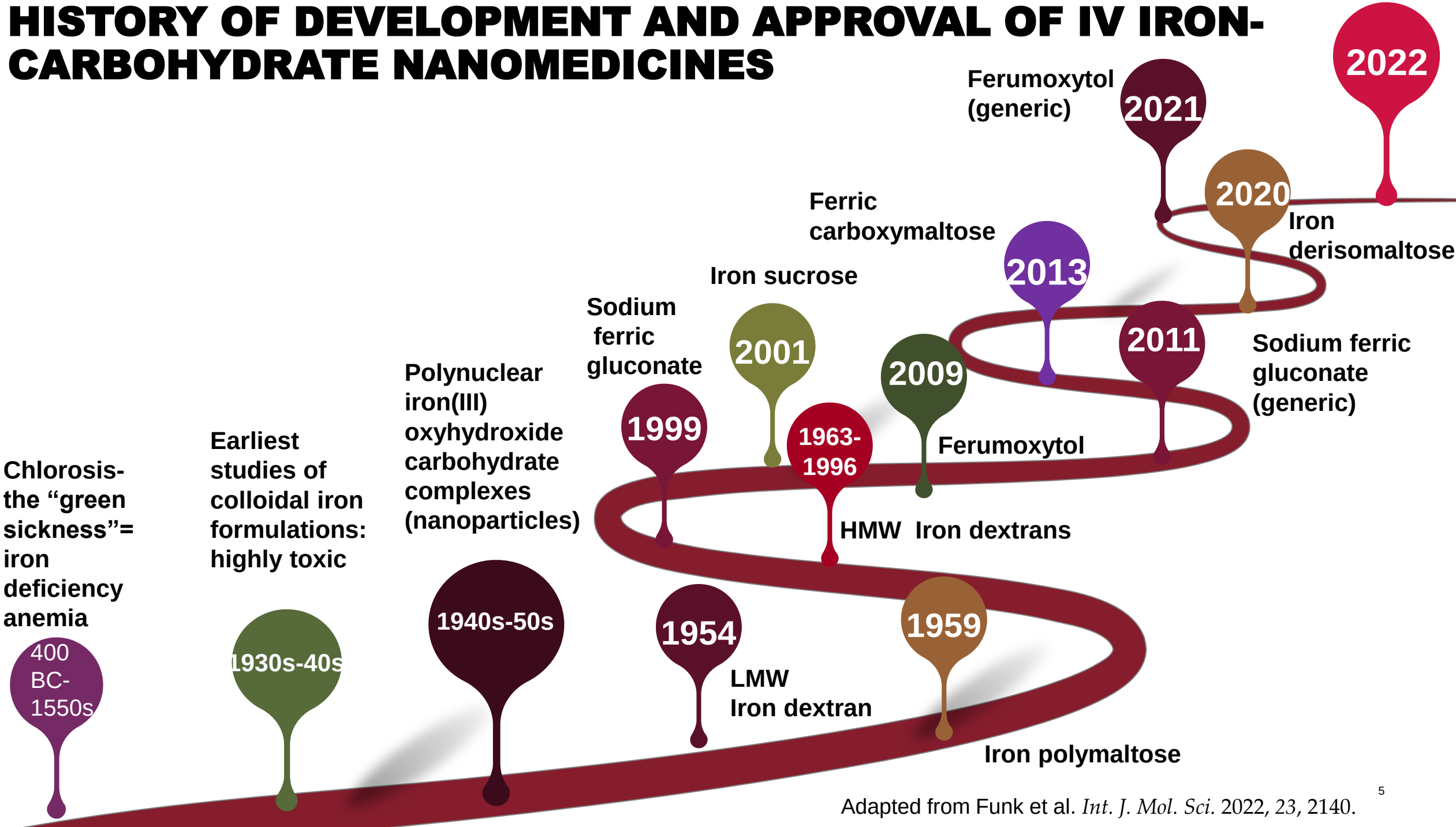
OBSERVATIONS ON THE EFFECT OF MASSIVE DOSES OF IRON GIVEN INTRAVENOUSLY TO PATIENTS WITH HYPOCHROMIC ANEMIA

By ANNE TOMPKINS GOETSCH, M.D., CARL V. MOORE, M.D., AND VIRGINIA MINNICH, M.S.

PARENTERAL administration of iron is impractical, dangerous, and unnecessary as a therapeutic procedure.[1, 2]

Goetsch, A.T.; Moore, C.V.; Minnich, V. Observations on the effect of massive doses of iron given intravenously to patients with hypochromic anemia. *Blood* 1946:1,129–142.

HISTORY OF DEVELOPMENT AND APPROVAL OF IV IRON-CARBOHYDRATE NANOMEDICINES



Adapted from Funk et al. *Int. J. Mol. Sci.* 2022, *23*, 2140.

DIFFERENT IV IRON PRODUCTS HAVE DIFFERENT CARBOHYDRATE LIGANDS

IV iron products have distinct structures[1–4]

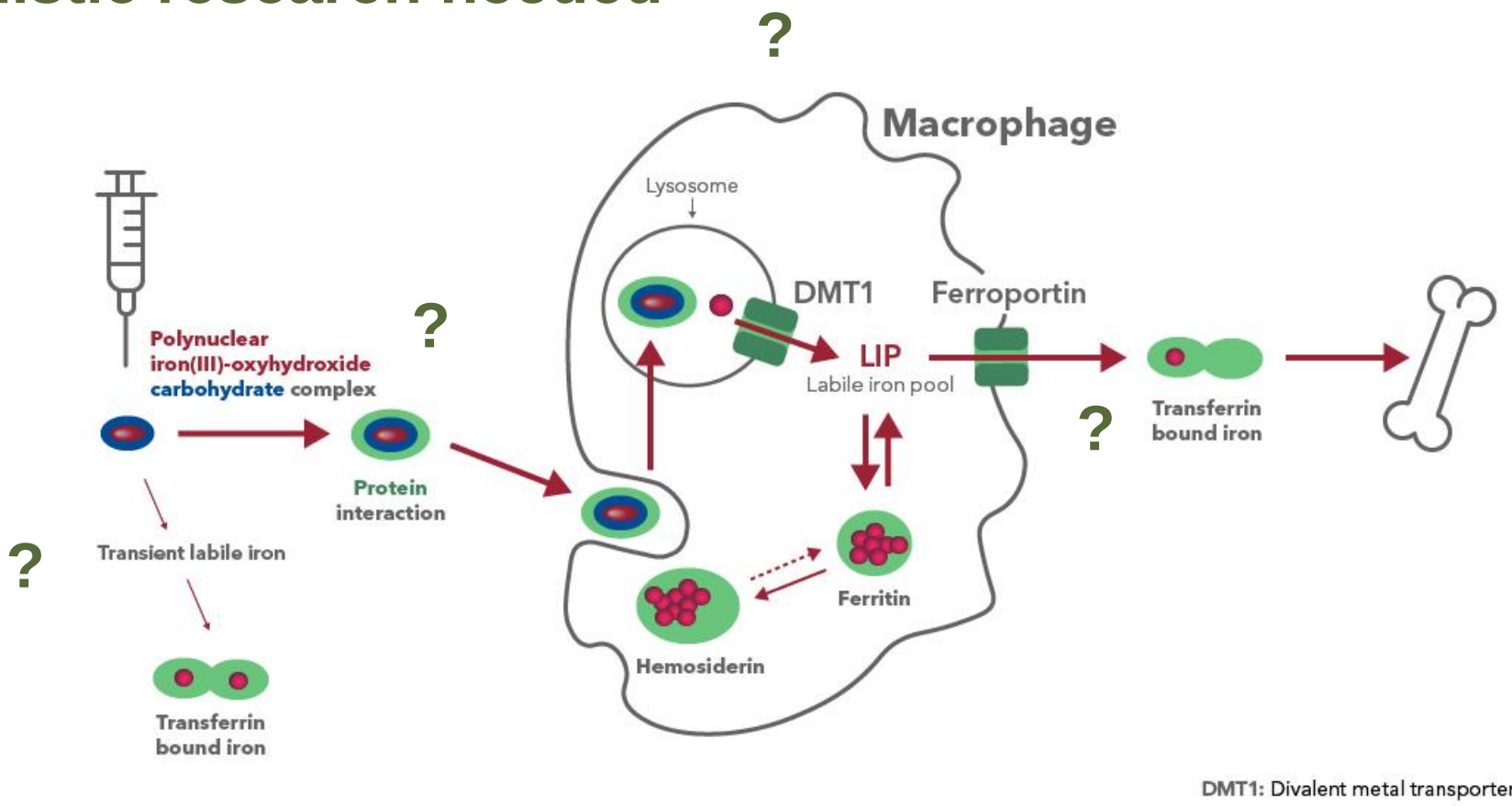
	Trade name[1–3]	Iron core	Carbohydrate	Pharmaceutical Ingredient[6–9]
Non-dextran-derived	Injectafer®	Akaganeite[1]	Carboxymaltose[1–3]	Ferric carboxymaltose[1–3]
	Ferrlecit®	Ferrihydrite/akagenite[4]	Gluconate[1–3]	Sodium ferric gluconate[1,2]
	Venofer®	Akaganeite[1]	Sucrose[1–3]	Iron sucrose[1–3]
Dextran-derived	CosmoFer®	Akaganeite[4]	Dextran[1–3]	LMW iron dextran[1–3]
	Feraheme®	Maghemite[1]	Polyglucose sorbitol carboxymethylether[1,2]	Ferumoxytol[1–3]
	Monofer/Monoferric®	Akaganeite[1]	Derisomaltose[2,5]	Iron isomaltoside 1000/[1,3] ferric derisomaltose[2,5]

IV, intravenous.

1. Neiser S, *et al. Biometals* 2015;28:615–35;
2. Schaefer B, *et al. Mol Asp Med* 2020;doi:10.1016/j.mam.2020.100862;
3. Jahn MR, *et al. Eur J Pharm Biopharm* 2011;78:480–91;
4. Zou P, *et al. AAPS J* 2017;19:1359–76;
6. Flühmann B, *et al. Eur J Pharm Sci* 2019;128:73–80;
7. Astier A, *et al. Ann N Y Acad Sci* 2017;1407:50–62;
8. Mühlebach S and Flühmann B. *Advances in the Pharmaceutical Sciences Series*; Volume 20. 2015. Springer International Publishing; Switzerland;
9. Schellekens H, et al. *AAPS J* 2014;16:15–21.

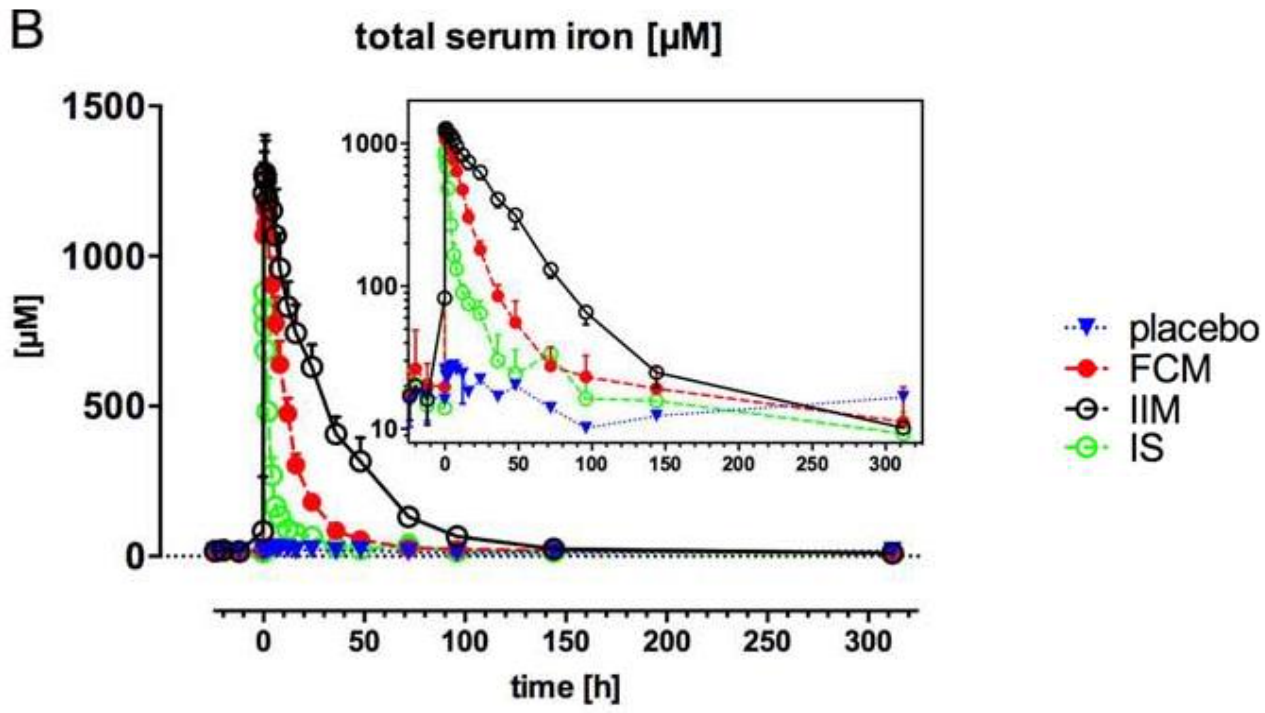
MANY AREAS OF IV IRON-CARBOHYDRATE NANOMEDICINE ADME NEED MORE MECHANISTIC RESEARCH

? = mechanistic research needed

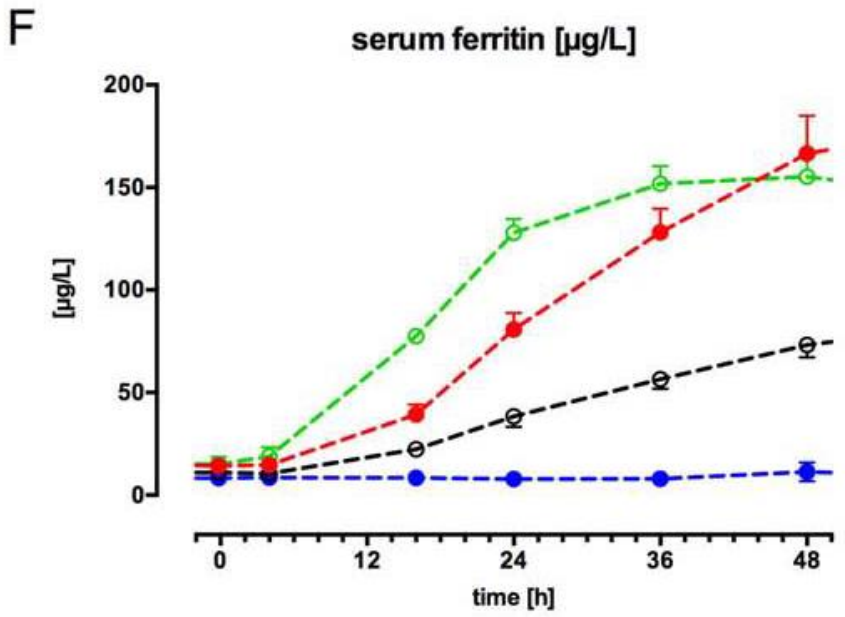


Adapted from Funk et al. *Int. J. Mol. Sci.* 2022, *23*, 2140.

EACH IV IRON-CARBOHYDRATE NANOMEDICINE HAS A UNIQUE PK/PD PROFILE



Pharmacokinetic Profiles



Pharmacodynamic Profiles

FCM=ferric carboxymaltose IIM-iron isomaltoside 1000 IS=iron sucrose

. Adapted from: Garbowski et al. Haematologica. 2021 Nov 1;106(11):2885-2896

CHALLENGES USING SERUM OR NON-TRANSFERRIN BOUND IRON AS A BE ENDPOINT FOR PK STUDIES

SERUM IRON

Serum iron measurement does not distinguish nanoparticle-bound (ie drug bound) iron from endogenous iron.[1]

The pharmacokinetic profile of serum iron < 24 hours is not reflective of actual tissue biodistribution.[2,3]

Iron-carbohydrate nanomedicines interfere with clinical iron assays, reducing the quantitative robustness.[2]

Short or sparse serum iron sampling may not capture the second phase of bioavailable iron after handling in the MPS.[2,3]

NON-TRANSFERRIN BOUND IRON (NTBI)

NTBI represents a very small, transient proportion of iron that is present after IV iron administration.[4]

The labile species of NTBI are hypothesized to potentially impact the safety profile of these drug products but does not impact efficacy.[4,5]

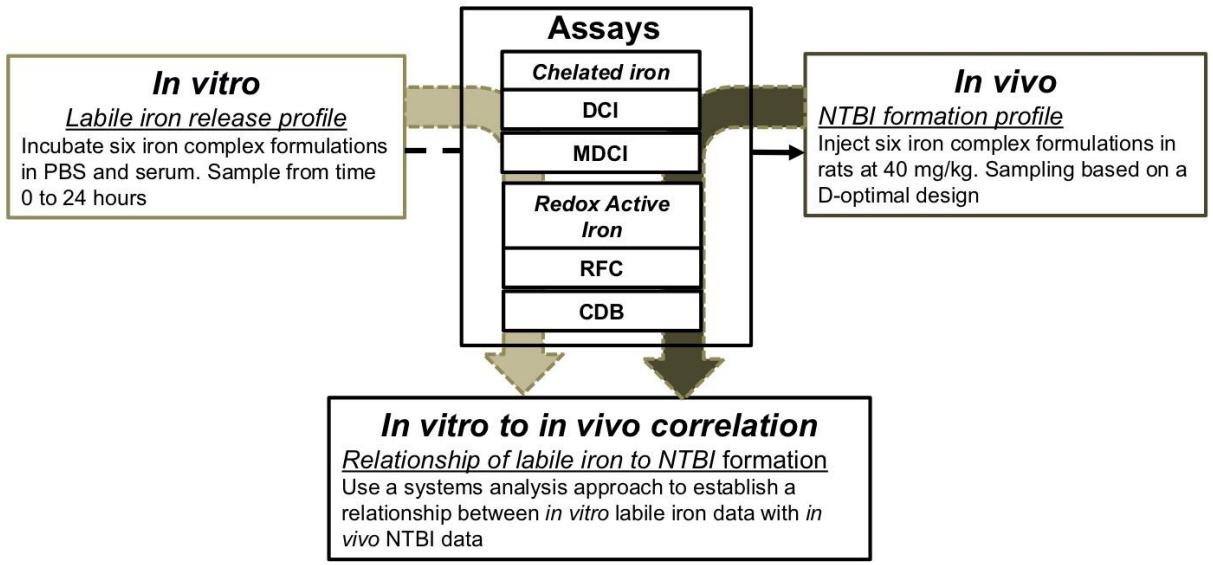
NTBI is comprised of multiple, dynamic species in equillibrium and there is not a universally accepted definition.[6]

NTBI is very difficult to measure and depends on assay type employed (capture vs. redox assay methodology).[3,7]

1. Barton Pai A et al. Clin Pharmacokinetic. 2015; 54(4):323-4
2. Funk F et al. Eur J Pharm Biopharm. 2022 May;174:56-76
3. Garbowski et al. Haematologica. 2021 Nov 1;106(11):2885-2896
4. Barton Pai A. et al. Clin Transl Sci. 2017 May;10(3):194-200
5. Barton Pai A. et al. Pharmacotherapy. 2007 Mar;27(3):343-50
6. Cabantchik IZ, Hershko C. Am J Hematol. 2022 Jan 1;97(1):7-9
7. De Swart L et al. Haematologica. 2016; 101(1):38-45

STUDY DESIGN

AN *IN VITRO-IN VIVO* CORRELATION MODEL TO PREDICT SERUM NON-TRANSFERRIN BOUND IRON FROM INTRAVENOUS IRON COMPOUNDS



Aims of the study:

In vitro studies

Aim 1. Physicochemical characterization

Aim 2. Evaluate labile iron release *in vitro*

In vivo studies

Aim 3. Pharmacokinetic study in preclinical species

Aim 4. Establish the relationship between *in vitro* labile iron data and *in vivo* NTBI data

Iron-carbohydrate nanomedicines tested: Venofer, Ferrlecit, sodium ferric gluconate complex (SFGC), INFeD, Feraheme, GEH121333 (pre-clinical test article)

FDA-1U01FD004889-01 (Barton Pai PI), Pai AB et al. *Clin Transl Sci* 2017 May;10(3):194-200, Pai AB et al. *Regul Toxicol Pharmacol*, 2018;97:17-23

ASSAYS EVALUATED TO MEASURE LABILE IRON IN VITRO AND IN VIVO AT 0.952 MG FE/ML

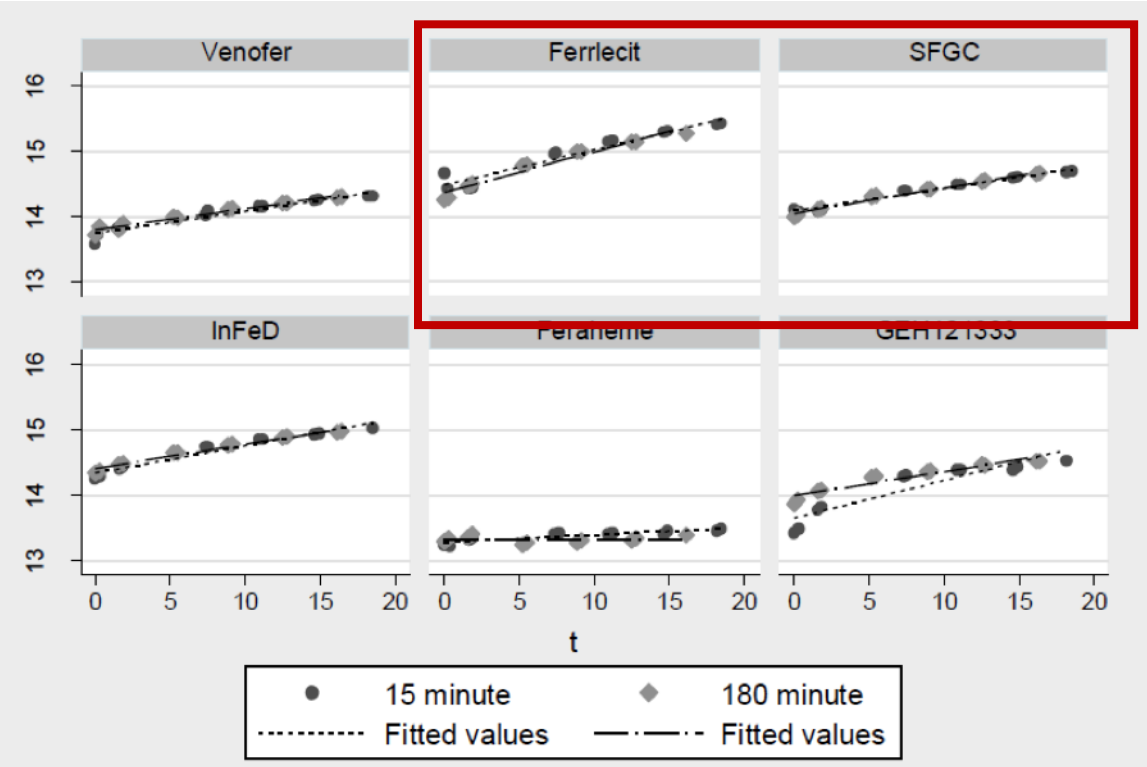
Labile Iron Assay	Assay Method	Approximate LOD	Practical limitations	In vitro limitations
Bleomycin detectable iron (BDI)	Redox active iron	10 µM Fe	Narrow assay dynamic range (10-100µM). Non-linear calibration response curve.	Apparent interference in the presence of agent complex.
Rhodamine fluorescence conversion	Redox active iron	30 µM Fe	Reaction product is very sensitive in ambient conditions and degrades rapidly.	No detectable signal in the presence of agents.
Directly chelatable iron: FL-DFO	Chelatable iron	2 µM Fe	Narrow assay dynamic range (~2-~60µM). Non-linear calibration response curve.	Reduced or abolished fluorescence in the presence of agents.
HPLC-DFO	Chelatable iron	20 µM Fe	None	Kinetic effect of DFO binding to labile iron

Pai AB. *Clin Transl Sci*. 2017 May;10(3):194-200

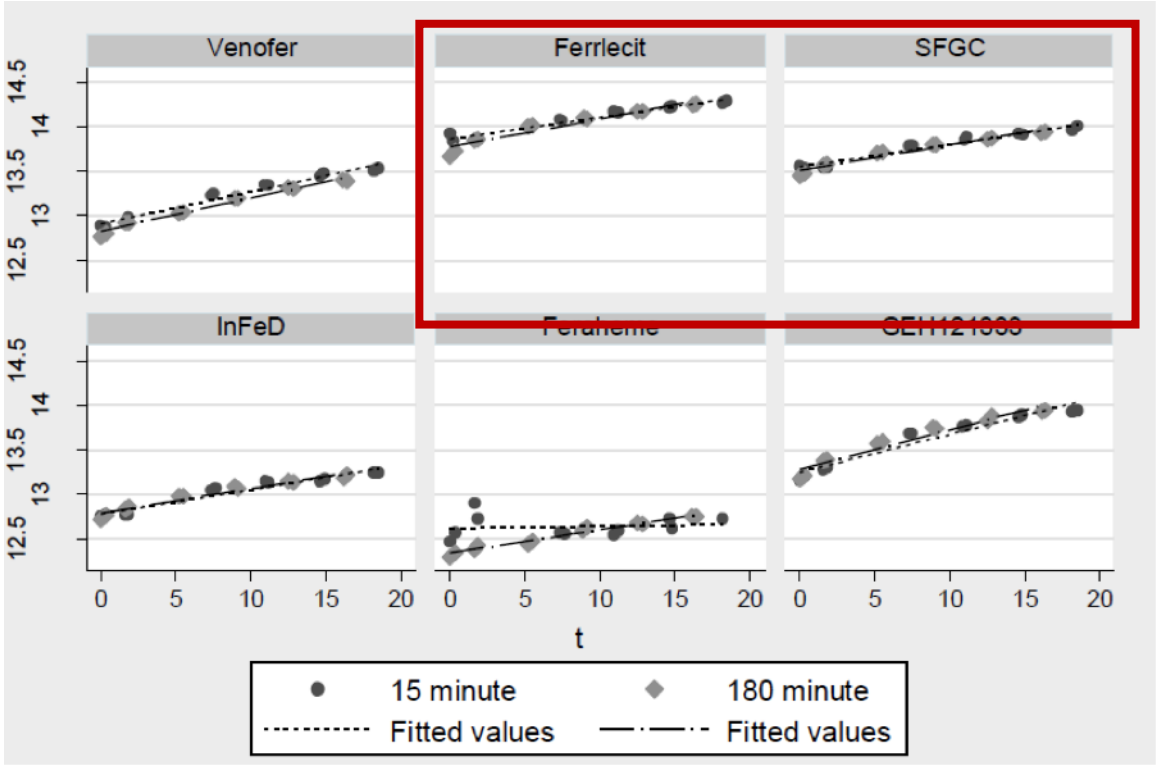
LOD=limit of detection, DFO=desferroximine

LABILE IRON RELEASE PROFILE OF IRON-CARBOHYDRATE NANOMEDICINES IN VITRO

IV iron-carbohydrate drug products diluted in 150mM saline



IV iron-carbohydrate drug products diluted in rat serum

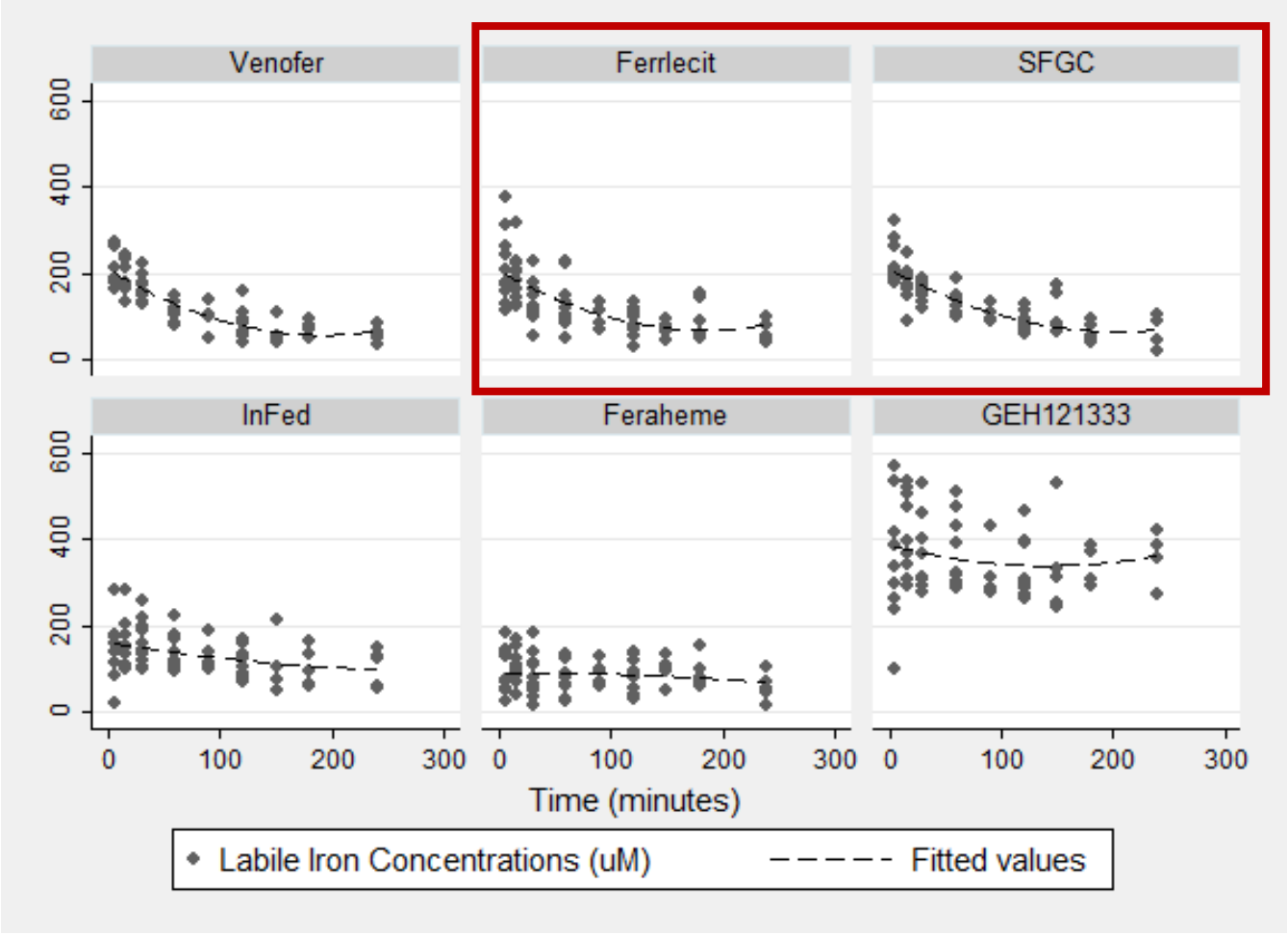


Natural log of the Fe-DFO peak area as a function of time following the addition of DFO

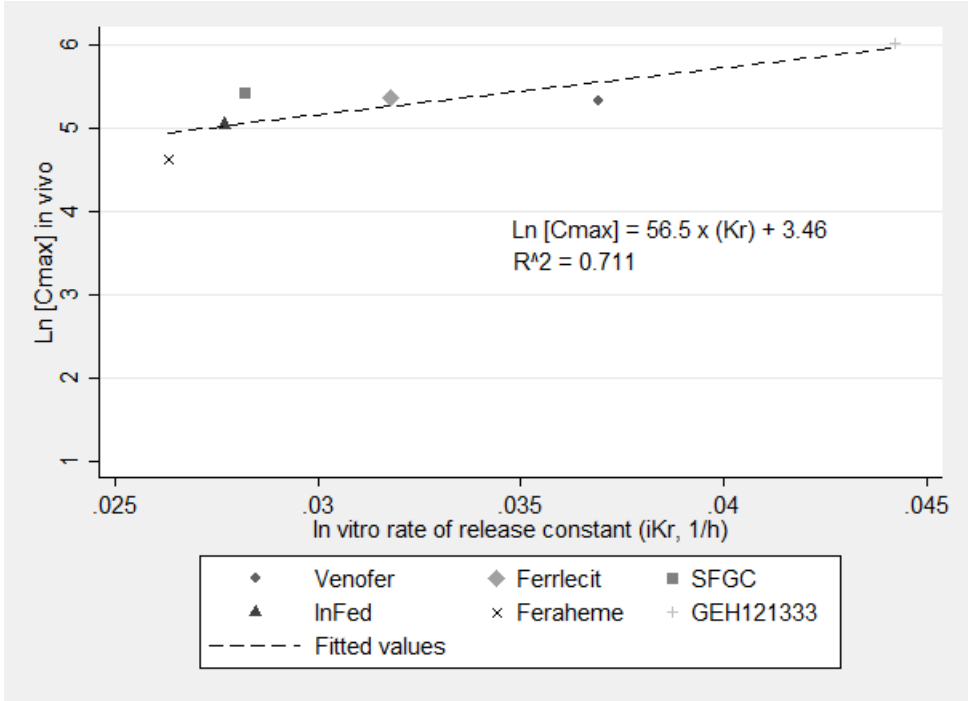
Pai AB et al. *Clin Transl Sci* 2017 May;10(3):194-200, Pai AB et al. *Regul Toxicol Pharmacol*, 2018;97:17-23

SERUM LABILE IRON PROFILES AFTER ADMINISTRATION OF INTRAVENOUS IRON-CARBOHYDRATE NANOMEDICINES IN VIVO

Scatter and fitted plots of serum labile iron after 40 mg Fe/kg IV in healthy male rats



Scatter and linear fit of observed mean natural logarithm labile iron in vitro release constant (Kr) to in vivo Cmax



Pai AB et al. *Clin Transl Sci*, 2017 May;10(3):194-200 , Pai AB et al. *Regul Toxicol Pharmacol*, 2018;97:17-23

SUMMARY

- Characterization of labile iron release from IV iron-carbohydrate nanomedicines in vitro and in vivo did not yield a point to point IVIVC.
- A correlation was observed (R^2 0.711) between the in vitro Kr to in vivo Cmax for labile iron.
- However, labile iron represents only a small, transient fraction of the iron that furnishes the pharmacologic effect.
- At nano-size range, drug products have specific, complex properties and in vivo behavior, which makes in vitro and computational models challenging.
- More research is needed to understand uptake, biodegradation and metabolic fate of IV iron-carbohydrate nanomedicines before potential computational and IVIVC models can be established.