Assessment of serum protein binding to predict non-specific uptake in vivo

Created on: 20-07-2022 - Last modified on: 09-08-2022

Contact person

Sophie Hernot

Organisation

Name of the organisation Vrije Universiteit Brussel (VUB)

Department BEFY

Country Belgium

SCOPE OF THE METHOD

The Method relates to	Human health
The Method is situated in	Translational - Applied Research
Type of method	In vitro - Ex vivo
Specify the type of cells/tissues/organs	Serum

DESCRIPTION

Method keywords

Serum protein binding

hepatobiliary clearance

size-exclusion chromatography

Scientific area keywords

in vivo biodistribution

non-invasive imaging

pharmacokinetics

Method description

For therapeutic or reporter molecules to be effective for therapy or imaging applications, proper accumulation of the compounds in the tissue of interest is required, with minimal accumulation in undesired organs to avoid toxic side-effects and increase bioavailability. After initial *in vitro* screening on functionality and potency, a panel of preselected analogues are often evaluated *in vivo* for their pharmacokinetic profile to select a lead compound. This is most often assessed *in vivo* following administration of the compound using chromatography techniques or ELISA on collected tissues/organs, or non-invasive imaging. We propose to screen the compounds beforehand for non-specific protein binding in order to predict undesired background accumulation, in particular in the liver. As such, the number of compounds that need to be tested *in vivo* can be limited to the most promising ones.

Lab equipment

HPLC Fluorescent- or radiolabeled drug-analogue Serum

Method status

History of use

PROS, CONS & FUTURE POTENTIAL

Advantages

By screening beforehand a panel of drugs on their serum protein binding, the number of preselected molecules that need to be evaluated *in vivo* can be reduced as these will exhibit *in vivo* non-specific binding, in particular liver accumulation. Depending on the application, this can lead to undesired toxic side-effects and decrease the bioavailability of the drug.

Challenges

To differentiate the signal of the drug from the signal of the serum proteins, the drug needs to be labeled either with a fluorophore or a radioisotope. One should be aware that the modification of a drug can also impact the biodistribution profile. In particular, hydrophobic fluorescent dyes are known to exhibit non-specific protein binding. Moreover, one should be reminded that the *in vitro* assay is a static assay that does not necessarily reflect the dynamic process happening *in vivo* and that metabolization, clearance, compartimentalization etc is not taken into account. Moreover, this assay does not predict *in vivo* efficacy of the compounds.

Modifications

This method could be adapted to screen the binding of drugs to other types of proteins that can predict non-specific accumulation in certain undesired organs/tissues in the body.

Future & Other applications

This method could be used to screen additional types of drugs (small molecules, peptides, large antibodies) for their non-specific serum protein binding and as such predict their *in vivo* behavior. This will limit the number of compounds tested *in vivo*.

REFERENCES, ASSOCIATED DOCUMENTS AND OTHER INFORMATION

References

P. Debie, C. M. Huygen, B. De Sloovere, D.M. van Willigen, ? Mateusiak, N. B. Declerck, J. Bridoux, J. Puttemans, N. Devoogdt, F. W. B. van Leeuwen, S. Hernot. Design and preclinical evaluation of a single-label bimodal nanobody tracer for image-guided surgery. Biomolecules (2021) 11, 360. IF2020 4.879 doi.org/10.3390/biom11030360

D.A. Smith, L. Di & E.H. Kerns. The effect of plasma protein binding on in vivo efficacy: misconceptions in drug discovery. Nature Reviews Drug Discovery (2010) 9, 929–939

Additional publications upcoming

Associated documents

Protocol.docx

Coordinated by

sciensano

VUB

Financed by

Vlaanderen
verbeelding werkt

bruxelles environnement
leefmilieu brussel
.brussels