Does the active transport of albumin play a role on sorafenib distribution in human pulmonary artery endothelial cells?

G. Bonnefois[1], L. Payen[2], J.Guitton[1], G. Freyer[1], I. Rouvet[3], M. Tod[1,4]

(1)EA3738 Ciblage Thérapeutique en Oncologie, Faculté de Médecine Lyon-Sud, Oullins France; (2)Institut des Sciences Pharmaceutiques et Biologiques, Lyon France; (3)Centre de biotechnologie cellulaire, Centre de Biologie et de Pathologie Est - CHU Lyon, 69677 Bron, France; (4)Hospices Civils de Lyon, France.

Background

Albumin is able to penetrate into endothelial cells. Active influx is mediated by albondin [1], active efflux by FcRn [2]. The impact of intracellular albumin on intracellular drug concentration is unknown. PBPK models should take this into account.

Objective:

To study the impact of albumin transport on drug intracellular concentration in vitro. Probe: Sorafenib, an anti-angiogenic drug highly bound to albumin.

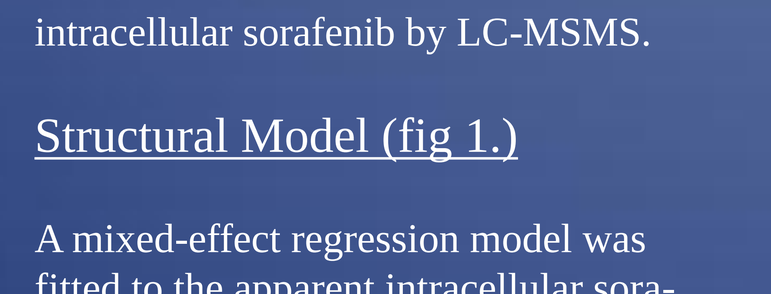
Material and Methods

Experimental design :

Cultures of human endothelial cells with different albumin and sorafenib concentrations. Measurement of intracellular sorafenib by LC-MSMS.

Structural Model (fig 1.)

A mixed-effect regression model was fitted to the apparent intracellular sora-fenib concentrations to estimate the parameters characterizing sorafenib and albumin penetration into cells (NONMEM 7).



Kd was measured by fluorescence quenching.

Different transports were considered :

- A passive diffusion : CLd
- An active transport :

If non linear : Vm and Km
If linear : CL_{AB} and CL_{BA}

The analytical process results in a factor of dilution (α) of the intracellular content.

Results

Table I. Parameter estimates with the final model

Parameter	Point Estimate (SE)
Kd (µM)	0.2 (fixed)
CL_{AB}/CL_{BA}	0.141 (0.040)
Median (α) Experiment 1, 2	163 (34) 338 (65)
CV(α)	0.62 (0.26)
CV(ε)	0.33 (0.04)

Intracellular concentration of albumin is 14 % of extracellular concentration.

Fig 2. Goodness-of-fit of the model

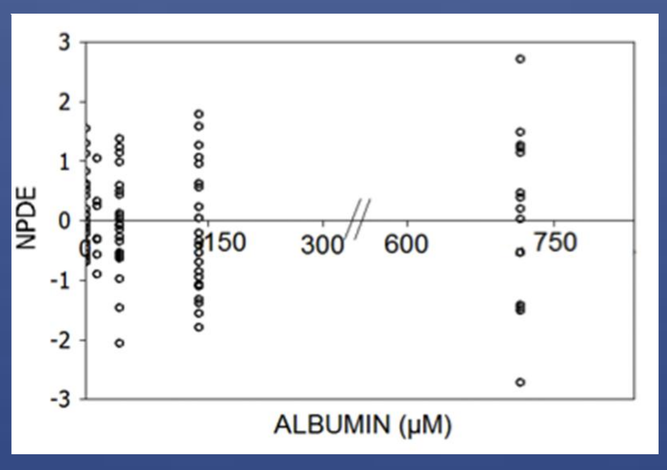


Fig 3. Individual predictions versus observed sorafenib concentrations

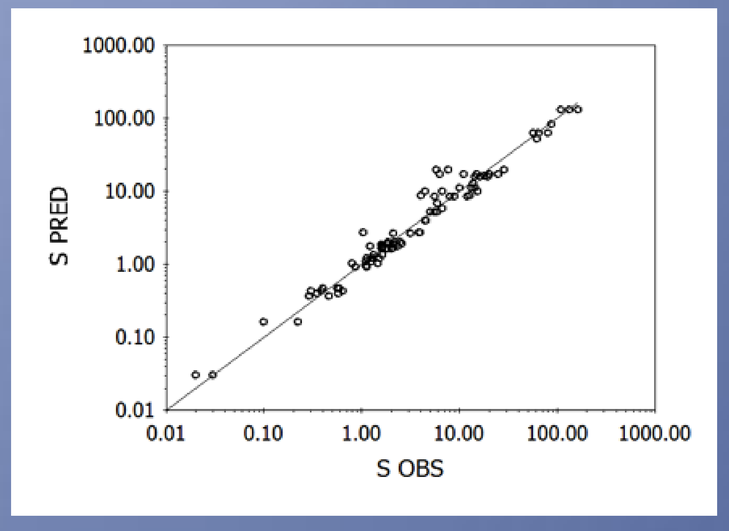
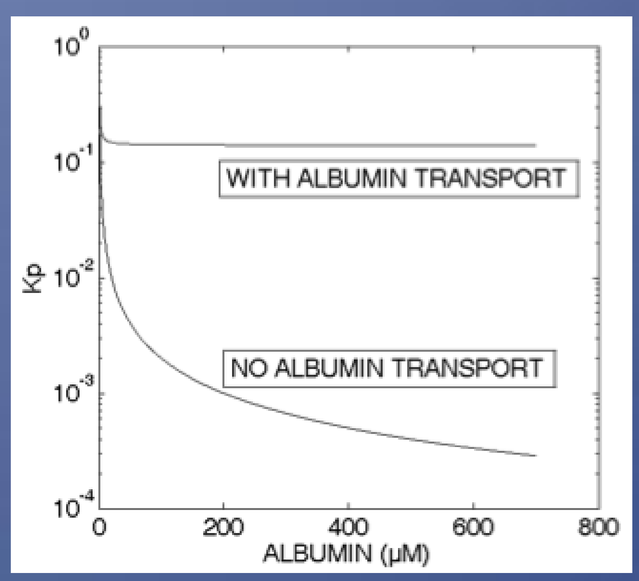


Fig 4. Impact of albumin transport on sorafenib coefficient of partition (Kp) into endothelial cells.



Conclusion

- Penetration of albumin was shown to behave as a linear process in our conditions.
- The Kp of sorafenib into endothelial cells was greatly increased by albumin transport, a fact that must be accounted for in mechanistic PBPK models.
- The impact of albumin transcytosis on intratumoral distribution of sorafenib remains to be studied.

References

1. John TA *et al.* *Am J Physiol Lung Cell Mol Physiol* 284(1):L187-96.
2. 2.Chaudhury C *et al.* (2003). *J Exp Med.* 197(3):315-22.