Hemocompatibility of nanocarriers designed to transport biopharmaceutical drugs

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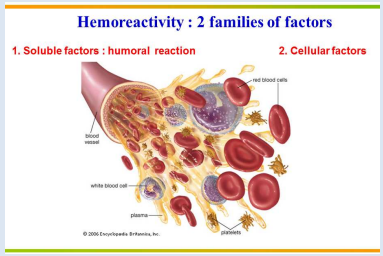
Introduction

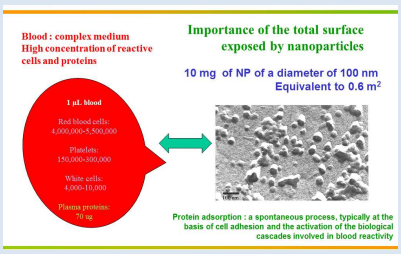
The optimization of nanoparticles (NP) for drug delivery, in particular to target the BBB, imposes to verify their hemocompatibility both for toxicological and efficiency of targeting perspectives. Indeed the large surface they are able to expose to the biological environment promotes their interaction with various biochemicals, in particular proteins which can after adsorption elicit the activation of biological cascades either responsible from NP clearance or/and harmful body reaction (inflammatory / coagulation).

In the frame of the European Integrated Project : "Nanobiopharmaceutics", we have the opportunity to compare the hemoreactivity of about 145 different NP samples differing in core and surface chemistry and classified according to their expected difference in hydrophobicity based on the nature of their core materials. According to this classification, PLGA nanoparticles, polyglycidol-polyethyethylene oxide nanoparticles, polyglycidol thyolated or polyacrylamide nanogels, and polyelectrolyte complexes either based on polyamidoamine or poly(N,N-dimethylamino-2-ethylmethacrylate) have been evaluated within a concentration ranging from 0.3 to 1000 µg/mL. These in vitro tests have been realized for screening purpose adopting normal human bloods and according to Iso 10993.

Hemoreactivity

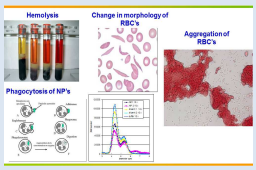
The main features of the elements involved in hemoreactivity



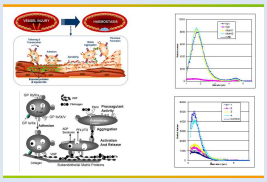


The main possible hemoreactions of the blood components

Erythrocytes

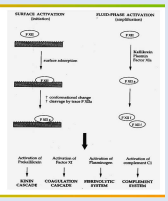


Platelets (aggregation – activation)

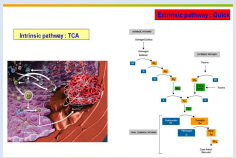


Solid phase activation of factor XII : Hageman factor

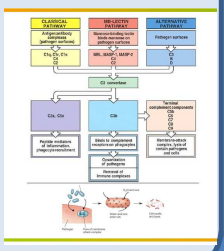
Factor XII : key element to initiate the activation of the 4 components of the inflammatory biological cascade



Coagulation



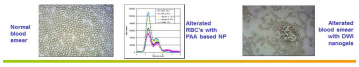
Complement activation



Cell reactivity

Cell reactivity : blood cells

Particle type	Concentration (µg/mL)	Tested	No	Slight	Moderate	Strong
Polyesters (PLGA) NP	100 - 1000	10	10			
Polyglycidol-co-polylactide NP	50 - 500	8	8			
Polyglycidol / PEG nanogels	100 - 1000	3	3			
Polyacrylamide based NP	1.25 - 800	30	16			14
Peptide	35 - 500	8	6			2
Carboxylated hyperbranched polyesters	10 - 100	1	1			
Self-assembly peptides	40 - 400	6	6			
Polyamidoamine based NP	8 - 80	1	1			
Poly(DMAEMA) based NP	60 - 600	8	6			2
	0.3 - 30	64	64			
Total		139	121	0	0	18



Cell reactivity : platelets

Particle type	Concentration (µg/mL)	Tested	No	Slight	Moderate	Strong
Liposomes	100 - 1000	10	10			
Polyesters (PLGA) NP	50 - 500	8	8			
Polyglycidol-co-polylactide NP	100 - 1000	3	3			
Polyglycidol / PEG nanogels	1.25 - 800	30	27		2	1
Polyacrylamide based NP	35 - 500	8	8			
Peptide	10 - 100	1	1			
Carboxylated hyperbranched polyesters	40 - 400	6	6			
Self-assembly peptides	8 - 80	1	1			
Polyamidoamine based NP	60 - 600	8	2	1	2	3
Poly(DMAEMA) based NP	0.3 - 30	64	2	12	50	4
Total		139	69	13	54	4

Humoral reaction

Coagulation : intrinsic pathway (TCA)

Particle type	Concentration (µg/mL)	Tested	Not Measured	No	Slight	Moderate	Strong
Liposomes	100 - 1000	10		2	4	4	
Polyesters (PLGA) NP	50 - 500	8	5	2	1		
Polyglycidol-co-polylactide NP	100 - 1000	3		3			
Polyglycidol / PEG nanogels	1.25 - 800	30	24	6			
Polyacrylamide based NP	35 - 500	8	2	4	2		
Peptide	10 - 100	1		0	1		
Carboxylated hyperbranched polyesters	40 - 400	6				6	
Self-assembly peptides	8 - 80	1		1			
Polyamidoamine based NP	60 - 600	8		2	2		4
Poly(DMAEMA) based NP	0.3 - 30	64	48	12	4		
Total		139		32	14	10	4

Coagulation : extrinsic pathway (Quick)

Particle type	Concentration (µg/mL)	Tested	Not Measured	No	Slight	Moderate	Strong
Liposomes	100 - 1000	10	2	8			
Polyesters (PLGA) NP	50 - 500	8	5	2	1		
Polyglycidol-co-polylactide NP	100 - 1000	3		3			
Polyglycidol / PEG nanogels	1.25 - 800	30	24	6			
Polyacrylamide based NP	35 - 500	8	2	6			
Peptide	10 - 100	1		0	1		
Carboxylated hyperbranched polyesters	40 - 400	6		6			
Self-assembly peptides	8 - 80	1			1		
Polyamidoamine based NP	60 - 600	8		4	4		
Poly(DMAEMA) based NP	0.3 - 30	64	48	12	4		
Total		139		47	11	0	0

Complement activation (C3a)

Concentration (µg/mL)	Concentration (µg/mL)	Tested	Not Measured	No	Slight	Moderate	Strong
Liposomes	100 - 1000	10				2	8
Polyesters (PLGA) NP	50 - 500	8				6	2
Polyglycidol-co-polylactide NP	100 - 1000	3			1	1	1
Polyglycidol / PEG nanogels	1.25 - 800	30	2	13		5	10
Polyacrylamide based NP	35 - 500	8		5	3		
Peptide	10 - 100	1			1		
Carboxylated hyperbranched polyesters	40 - 400	6		3	3		
Self-assembly peptides	8 - 80	1		1			
Polyamidoamine based NP	60 - 600	8		8			
Poly(DMAEMA) based NP	0.3 - 30	64	52	0	12		
Total	0	139		30	20	14	21

Conclusions

- Blood components : sensitive medium to the presence of NP's ; crucial parameter to take into consideration in the design of NP's for the future, in particular for BBB applications
- Some of the biological parameters (platelets, Intrinsic pathway of coagulation and C3a) are typically more reactive
- Useful correlations between NP's properties and blood reactivity can already be extracted from these data (additional information should be implemented to better understand these differences in hemoreactivity). A KEY result of Nanobiopharmaceutics regarding Nanotoxicological aspects.

Acknowledgement

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