Immune toxico-equivalence testing of nano-biopharmaceuticals: Animal models

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Health impact of immune toxicity

Adverse Drug Events

2,2 millions /year, USA, 5-6th cause of death

Immune toxicity

20 ± 5% (~440,000/ year)

Allergy vs. Pseudoallergy

≈ 77% of adverse drug effects are non-IgE mediated, hypersensitivity reactions = pseudoallergy) (~340,000/ year)

Extra health care expenses

≈ > hundreds of millions / year

Interactions between nanoparticles and the immune system

Immune effects on nanoparticles		Nanoparticle effects on the immune system	
Effect	**Consequence**	**Effect**	**Consequence**
• binding	• interference with the pharmacological effect • alteration of PK • toxicity	Activation of inflammatory cells	inflammatory response
• destruction		Activation of T and B cells	***immunogenicity***
• cellular uptake		Activation of allergy mediating cells	***infusion = hypersensitivity reaction***
		Suppression of immune cells	immune suppression

Significance and difficulty of toxico-equivalence testing in case of generic nano-biopharmaceuticals

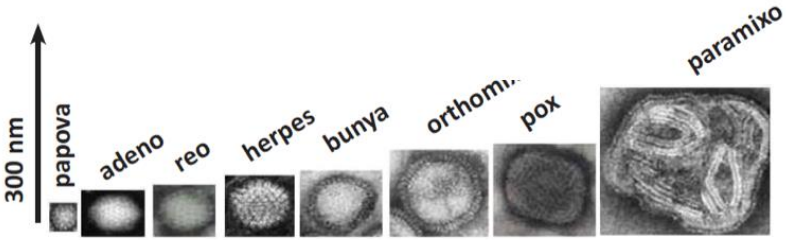
- The immune toxicity of nano-biopharmaceuticals is an inherent feature of these drugs, it is frequent and occasionally fatal.
- Generic drugs cannot be more toxic than the originator.
- There is no established, validated, predictive test for adverse immune effects.
- In lack of appropriate preclinical test, there is a risk that generic nanomedicines and biologicals, as well as new drugs, severe immune toxicity will be discovered only in late-stage clinical trials.

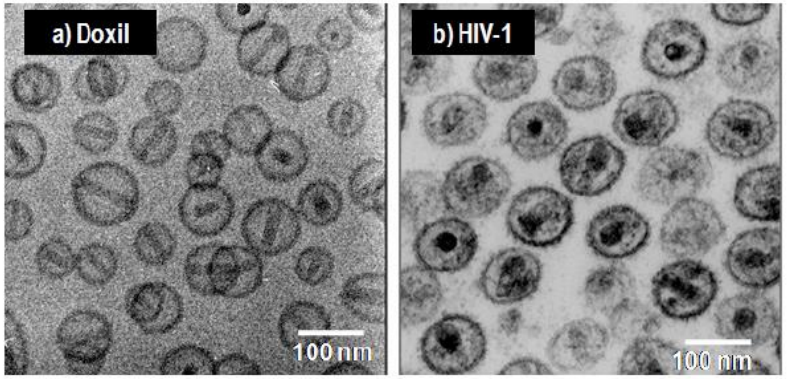
Rise of immune toxicity in case of nanomedicines: The dimension paradox

Adverse immune effects are caused not because nanodrugs are very small (which explains their unique physicochemical characteristics), but because they are *too large* compared to traditional small-molecule drugs.

Nanomedicines: nm range, mostly 10 - 300 nm

Solid Nanoparticles	Drug-Polymer Conjugate	Polymeric Micelle	Functionalized Gold NP	Biomimetic NP
Ligand-Functionalized Nanoliposomes	Ultrasmall Silica Nanoparticle (C Dot)	Drug-Encapsulated Dendrimer	Drug-Loaded NMOFs	Polymer-Polypeptide Conjugate
GRAS-Stabilized Nanocrystal	Silica Gold Nanoshell	Functionalized Nanodiamonds	Polymeric Nanoparticle	Phospholipid-Coated Magnetic NP
Dextran-Coated USPION	Self-Assembling Peptides	Drug-Loaded Bioinspired Bile Micelle	Drug-Loaded Chitosan-PEG Coated Nanogel	Drug-Loaded Nanoliposome
Nanonized API	Peptide-siRNA Liposome	Stealth Pegylated Nanoliposome	Functionalized Drug Magnetic NP	Nanogel
Peptide f-CNTs	C_{60} Buckminsterfullerene	Enzyme Nanocarrier	Functionalized Solid NP	Aptamers





Significance of infusion reactions

- **Clinical** (depends on risk vs. benefit)
  - Cancer, systemic fungal infections – *minor*
  - Cardiovascular application, large phospholipid doses, time limited administration *absolute critical*
  - All aplications - May contribute to immunogenicity
    - change pharmacokinetics, compromise efficacy *critical*

- **Nano-pharma industry** - *increasingly critical*
  - Rare, but serious –occasionally deadly- anaphylactic reactions may surface only in phase III-IV postmarket surveillance;
    - *can be fatal (in cardiac patients)*
    - *cannot be predicted by standard allergy tests*
    - *may lead to drug withdrawal*
  - Regulatory authorities increasingly demand experimental verification of short- and longterm complement tolerance

Significance of infusion reactions

nature nanotechnology

PERSPECTIVE

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Roadmap and strategy for overcoming infusion reactions to nanomedicines

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Infusion reactions (IRs) are complex, immune-mediated side effects that mainly occur within minutes to hours of receiving a therapeutic dose of intravenously administered pharmaceutical products. These products are diverse and include both traditional pharmaceuticals (for example biological agents and small molecules) and new ones (for example nanotechnology-based products). Although IRs are not unique to nanomedicines, they represent a hurdle for the translation of nanotechnology-based drug products. This Perspective offers a big picture of the pharmaceutical field and examines current understanding of mechanisms responsible for IRs to nanomedicines. We outline outstanding questions, review currently available experimental evidence to provide some answers and highlight the gaps. We review advantages and limitations of the in vitro tests and animal models used for studying IRs to nanomedicines. Finally, we propose a roadmap to improve current understanding, and we recommend a strategy for overcoming the problem.

Symptoms of infusion reactions

Cardiovascular	Broncho-pulmonary	Hematological	Mucocutaneous	Gastro-intestinal	Neuro-psycho-somatic	Systemic
Angioedema	Apnea	Granulopenia	Cyanosis	Bloating	Back pain	Chills
Arrhythmia	Bronchospasm	Leukopenia	Erythema	Cramping	Chest pain	Diaphoresis
Cardiogenic shock	Coughing	Lymphopenia	Flushing	Diarrhea	Chest tightness	Feeling of warmth
Edema	Dyspnea	Rebound leukocytosis	Nasal congestion	Metallic taste	Confusion	Fever
Hypertension	Hoarseness	Rebound granulocytosis	Rash	Nausea	Dizziness	Loss of consciousness
Hypotension	Hyperventilation	Thrombocytopenia	Rhinitis	Vomiting	Feeling of imminent death	Rigors
Hypoxia	Laryngospasm		Swelling		Fright	Sweating
Myocardial infarction	Respiratory distress		Tearing		Headache	Wheezing
Tachycardia	Shortness of breath		Urticaria		Panic	
Ventricular fibrillation	Sneezing					
Syncope	Stridor					

Note: The most dangerous for life are shown in bold.

Drugs causing infusion reactions

Liposomal drugs	Micelle-solubilized drugs	Antibodies	PEGylated proteins	Contrast media	Enzymes/proteins/ peptides	Miscellaneous
Abelcet	**Cyclosporine**	Avastin	Adagen	Diatrizoate	Abbokinase	ACE inhibitors
AmBisome	Elitec	Campath	Neulasta	Iodipamide	ACH	AR blockers
Amphotec/ Amphocyl	Etoposide	Erbitux	Oncaspar, Pegaspargas	Iodixanol	Actimmune	Aspirin
DaunoXome	Fasturec	Herceptin		Iohexol	Activase	Cancidas
Doxil, Caelyx	**Taxol**	**Infliximab**		Iopamidol	Aldurazyme	Copaxone
Myocet	**Taxotere**	Muronomab		Iopromide	Avonex	Corticosteroids
Visudyne	Vumon	Mylotarg		Iothalamate	Fasturtec	Cyclofloxacin
		Remicade		Ioversol	Neulasta	Eloxatin
		Rituxan		Ioxaglate	Neupogen	Intralipid
		Vectibix		Ioxilan	Plenaxis	Opiates
		Xolair		Magnevist	protamine	Orencia
				Metrizamide	Urokinase	Salicilates
				SonoVue	Zevalin	Vancomycin

Table 1 | Selected examples of nanotechnology-based drug products known to induce IR

Brand name (manufacturer)	Active ingredient	Indication	Type of particle (size)	Symptoms
Doxil, Caelyx (Johnson & Johnson)	Doxorubicin	Ovarian cancer, Kaposi sarcoma, myeloma	Liposomes (80–100 nm)	Flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, hypotension
Myocet (Elan)	Doxorubicin	Multiplex	Liposomes	Flushing, dyspnoea, fever, facial swelling, headache, back pain, chills, tightness in the chest and throat, hypotension
Abelcet (Elan, Enzon)	Amphotericin B	Fungal infections	Solid microparticles (1.6–11 mm)	Shortness of breath, change in blood pressure
Ambisome (Gilead, Fujisawa)	Amphotericin B	Fungal infections	Liposomes (45–80 nm)	Chills, rigors, fever, nausea, vomiting, cardiorespiratory events
Amphotec, Amphocyl (Elan)	Amphotericin B	Fungal infections	Disk-shaped solid nanoparticles (115 nm)	Hypotension, tachycardia, bronchospasm, dyspnoea, hypoxia, hyperventilation
DaunoXome (Gilead)	Daunorubicin	Kaposi sarcoma	Liposomes (45 nm)	Back pain, flushing, chest tightness
Visudyne (Novartis)	Verteporfin	Age-related macular degeneration	Multilamellar liposomes (multimicrometre)	Chest pain, syncope, sweating, dizziness, rash, dyspnoea, flushing, changes in blood pressure and heart rate, back pain
Onivyde (Merrimack Pharmaceuticals)	Irinotecan	Metastatic pancreatic adenocarcinoma progressing after gemcitabine-based therapy	Liposomes	Rash, urticaria, periorbital oedema (pruritus)
Vyxeos (Jazz Pharmaceuticals)	Daunorubicin and cytarabine	Newly diagnosed therapy-related acute myeloid leukaemia (AML) and AML with myelodysplasia-related changes	Liposomes	Dyspnoea, headaches, chills, rash, nausea, vomiting, oedema

Brand name (manufacturer)	Active ingredient	Indication	Micelle-forming excipient (size)	Symptoms
Fasturec, Elitec (Sanofi Aventis)	Rasburicase	Hyperuricaemia	Poloxamer-188 (~15 nm)	Anaphylaxis, bronchospasm, chest pain, diarrhoea, dyspnoea, fever, headache, hypotension, nausea, rash, rhinitis, urticaria, vomiting
Taxol (Bristol-Myers Squibb)	Paclitaxel	Cancer	Cremophor EL (8–20 nm)	Acute respiratory distress, anaphylaxis, angioedema, arrhythmias, bronchospasm, chills, dyspnoea, facial and upper thorax flushing, fever, rash, sudden death, tachycardia, urticaria, wheezing
Cyclosporine injection, USP (Draxis Pharma)	Cyclosporine	Immunosuppression	Cremophor EL (8–20 nm)	Acute respiratory distress, anaphylaxis, angioedema, arrhythmias, bronchospasm, chills, dyspnoea, facial and upper thorax flushing, fever, rash, sudden death, tachycardia, urticaria, wheezing
Vumon injection (Bristol-Myers Squibb)	Teniposide	Leukaemia	Cremophor EL (8–20 nm)	Acute respiratory distress, anaphylaxis, angioedema, arrhythmias, bronchospasm, chills, dyspnoea, facial and upper thorax flushing, fever, rash, sudden death, tachycardia, urticaria, wheezing
Etoposide (Gensia Sicor Pharmaceuticals)	Podophyllotoxin	Different cancers	Polysorbate 80 (8–16 nm)	Apnoea, back pain, bronchospasm, chills, coughing, cyanosis, diaphoresis, dyspnoea, fever, flushing, facial swelling, hyper or hypotension, laryngospasm, loss of consciousness, rash, tachycardia, tightness in throat, tongue swelling, urticaria
Taxotere (Sanofi-Aventis)	Docetaxel		Polysorbate 80 (8–16 nm)	Back pain, bronchospasm, chest tightness, chills, dyspnoea, erythema, fatal anaphylaxis, fever, flushing, generalized rash, hypotension

Table based on numerous studies reviewed in refs[90,97–99].

Table 2 | Selected examples of non-nanotechnology drug products known to induce infusion reactions

Brand name (manufacturer)	mAb, type (target antigen)	Indication	Incidence	Symptoms
Avastin (Genentech/Roche)	Bevacizumab, recombinant humanized IgG_1 (VEGF-A)	Combination chemotherapy of metastatic colon, lung, kidney cancer and glioblastoma	<3%; severe 0.2%	Chest pain, diaphoresis, headache, hypertension, neurologic signs and symptoms, oxygen desaturation, rigors, wheezing
Campath (Genzyme)	Alemtuzumab)–IH, recombinant, humanized IgG_1k (CD52 on T and B cells)	B-cell chronic lymphocytic leukaemia (B-CLL)	4–7%	Bronchospasm, chills, dyspnoea, emesis, fever, hypotension, nausea, pyrexia, rash, rigors, tachycardia, urticaria
Erbitux (Bristol-Myers Squibb, Eli Lilly)	Cetuximab, chimeric IgG_1k (human EGFR)	Metastatic colorectal cancer, head and neck cancer, squamous cell carcinomas	<3%; fatal < 0.1%	Anaphylaxis, angioedoema, bronchospasm, cardiac arrest, chills, dizziness, dyspnoea, fever, hoarseness, hypotension, pruritus, rash, rigor, stridor, urticaria, wheezing
Herceptin (Genentech)	Trastuzumab, humanized IgG_1k (human EGFR receptor 2, HER2/neu/ erbB2)	Metastatic breast and gastric cancer	<1%	Asthenia, bronchospasm, chills, death within hours, dizziness, dyspnoea, further pulmonary complications, headache, hypotension, hypoxia, nausea, pain, rash, severe hypotension, vomiting
Mylotarg (Pfizer/Wyeth Pharmaceuticals)	Gemtuzumab ozogamicin, recombinant humanized IgG_4k (CD33 on haematopoietic cells)	CD33 positive acute myeloid leukaemia in first relapse	<8%	Acute respiratory distress syndrome, anaphylaxis, dyspnoea, fatal anaphylaxis, hypotension, pulmonary oedema
Vectibix (Amgen)	Panitumumab, recombinant humanized IgG_2k (human EGFR)	KRAS+ metastatic colorectal carcinoma	1–4%	Anaphylactic reaction, bronchospasm, chills, fever, hypotension
Rituxan (Genentech)	Rituximab, chimeric IgG_1k (CD20 on B cells)	B-cell leukaemia, rheumatoid arthritis, and non-Hodgkin's B-cell lymphoma	>80%; severe <10%	Acute respiratory distress syndrome (ARDS), bronchospasm, cardiogenic shock, flushing, hypotension, hypoxia, itching, myocardial infarction, pain (at the site of the tumour), pulmonary infiltrates, runny nose, swelling of the tongue or throat, ventricular fibrillation, vomiting

Table based on numerous studies reviewed in refs[1,100].

Table 4 | Available animal models

Animal species	Sensitivity to HSR	Advantages	Disadvantages
Mouse	Low	Simple and relatively cheap	Insensitive; not generally accepted for preclinical safety studies
Rat	Low	Simple and relatively cheap; generally accepted for preclinical safety studies	Insensitive
Rabbit	Medium-to-high	Simple and relatively cheap; generally accepted for pyrogen screening	Unknown relevance to IRs in human patients except for cytokine release in response to pyrogens
Pig	High	Reproduces clinical symptoms of human patients; consistent response between individual animals	Skills- and labour-intensive; not generally accepted for preclinical safety studies
Minipig	High	Reproduces clinical symptoms of human patients; consistent response between individual animals	Skills- and labour-intensive; not generally accepted for preclinical safety studies
Dog	High	Reproduces clinical symptoms of human patients; generally accepted for preclinical safety studies	High interanimal variability; expensive; ethical and logistic hurdles
Non-human primate	Medium-to-high	Reproduces clinical symptoms of human patients; generally accepted for preclinical safety studies	Expensive, ethical and logistic hurdles

Comparison of haemodynamic and other manifestations of HSRs in animal models. The summary is based on ref. [88].

Rise of immune toxicity in case of biologicals

- Non-self proteins are immunogenic, despite sequence identity/homology
- The therapeutic effects of antibodies (via binding to an antigen) may entail activation of both the humoral and cellular arms of immune response
  - Complement activation -> allergic, inflammatory and cytotoxic effects
  - Phagocyte activation -> inflammatory reaction, accelerated blood clearance (ABC)

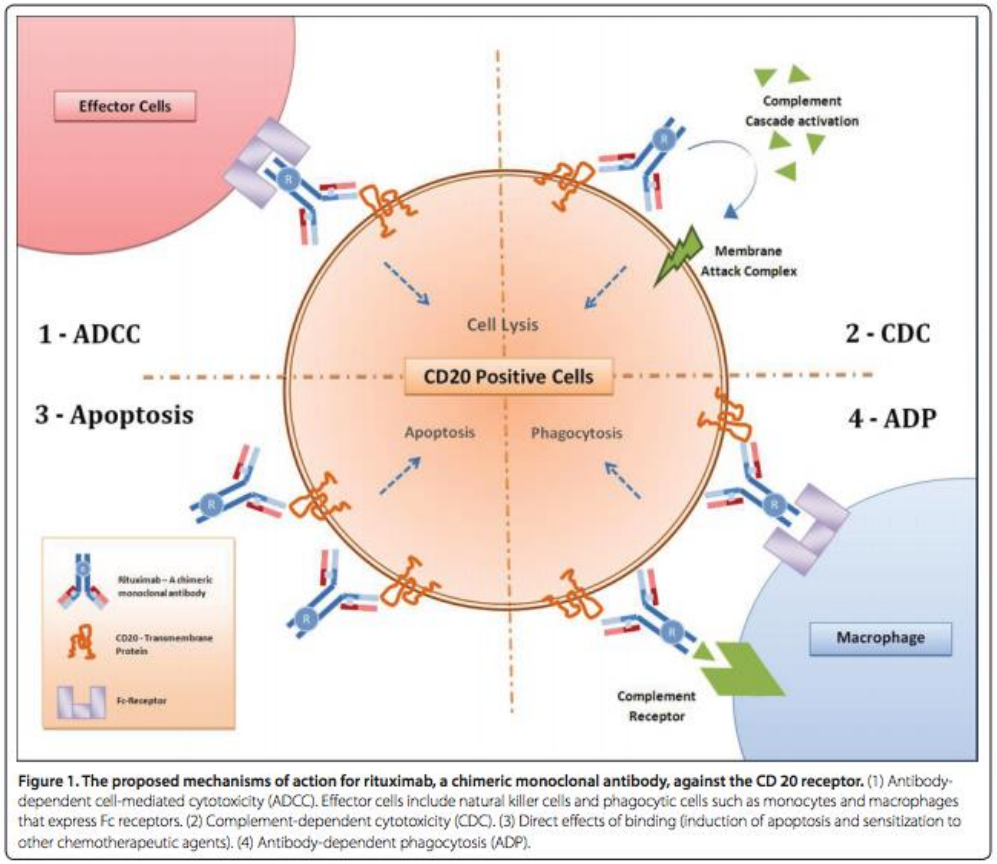


Figure 1. The proposed mechanisms of action for rituximab, a chimeric monoclonal antibody, against the CD 20 receptor. (1) Antibody-dependent cell-mediated cytotoxicity (ADCC). Effector cells include natural killer cells and phagocytic cells such as monocytes and macrophages that express Fc receptors. (2) Complement-dependent cytotoxicity (CDC). (3) Direct effects of binding (induction of apoptosis and sensitization to other chemotherapeutic agents). (4) Antibody-dependent phagocytosis (ADP).

Significance of immunogenicity

- **Clinical**
  - **Change of PK (ABC phenomenon) (murine models)**
  - **Cross reactions with native proteins (EPO)**
  - **Hypersensitivity reactions (pig model)**
- **Nano-pharma industry**
  - **Product failure - withdrawals**

Infusion reactions to Rituximab

- **Infusion reactions (34%), ascribed to either anaphylaxis or allergic reactions, were the most common SAEs associated with rituximab in 80% to 90% of randomized controlled trials. Grade 3 to 4 reactions (23%) were dose-dependent.**
- **The reported clinical features included fevers, chills, rigors, nausea, dizziness, pruritus, urticaria/rash, angioedema, laryngeal edema, sneezing, throat irritation/tightness, cough, hoarseness, bronchospasm, pulmonary infi ltrates, hypoxia, and acute respiratory insufficiency, with or without blood pressure changes or arrhythmias.**
- **Many reactions developed within 24 hours of the first infusion, were dose-dependent.**
- **80% of all fatal reactions (<1%) occurred with the first infusion.**
- **There are also isolated case reports of severe or fatal SIRS (systemic inflammatory response syndrome)-like reactions (or both) developing within 24 hours of infusing rituximab (cytokine release syndrome) that has been described after rituximab infusions in patients with high tumor-cell burden.**

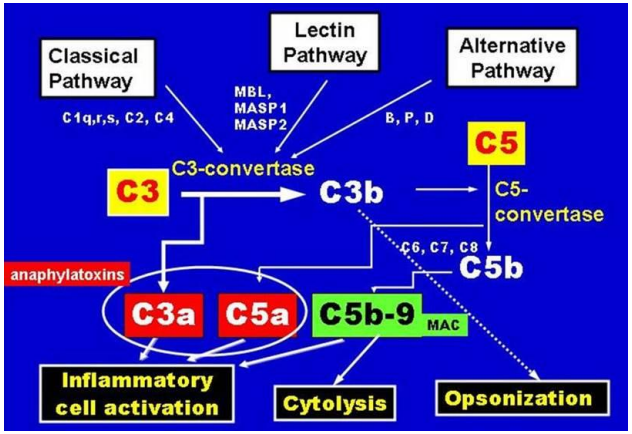
PEGylated nanopharmaceuticals with documented adverse immune effects

(immunogenicity ± HSRs)

Generic name	Trade name	API or Vehicle	Company
PEGylated liposomal doxorubicin	Doxil/Caelyx	liposome	ALZA/Janssen
Pegaspargase	Oncaspar	enzyme: asparaginase	Enzon
Pegfilgrastim	Neulasta	protein (GCSF)	Amgen
Pegaptanib	Macugen	aptamer (anti-VEGF)	Eye Tech/Pfizer
Mono-mPEG-epoetin-β	Mircera	protein (EPO)	Hoffmann-LaRoche
Certolizumab pegol	Cimzia	Fab of anti-TNF mAb	UCB, Inc., Smyrna
Pegvisomant	Somavert	peptid (somatotropin antagonist)	Pfizer
Pegloticase	Krystexxa	enzyme: urate oxidase	Horizon Pharma
Peginesatide	Omontys//Hematide	peptide (EPO-mimetic)	Affymax/Takeda
Pegnivacogin + Anivamersen	Revolixys kit	F-IXa blocker RNA aptamer + reverse agent	Regado/Tobira

Withdrawn from market

The CARPA concept of infusion reactions



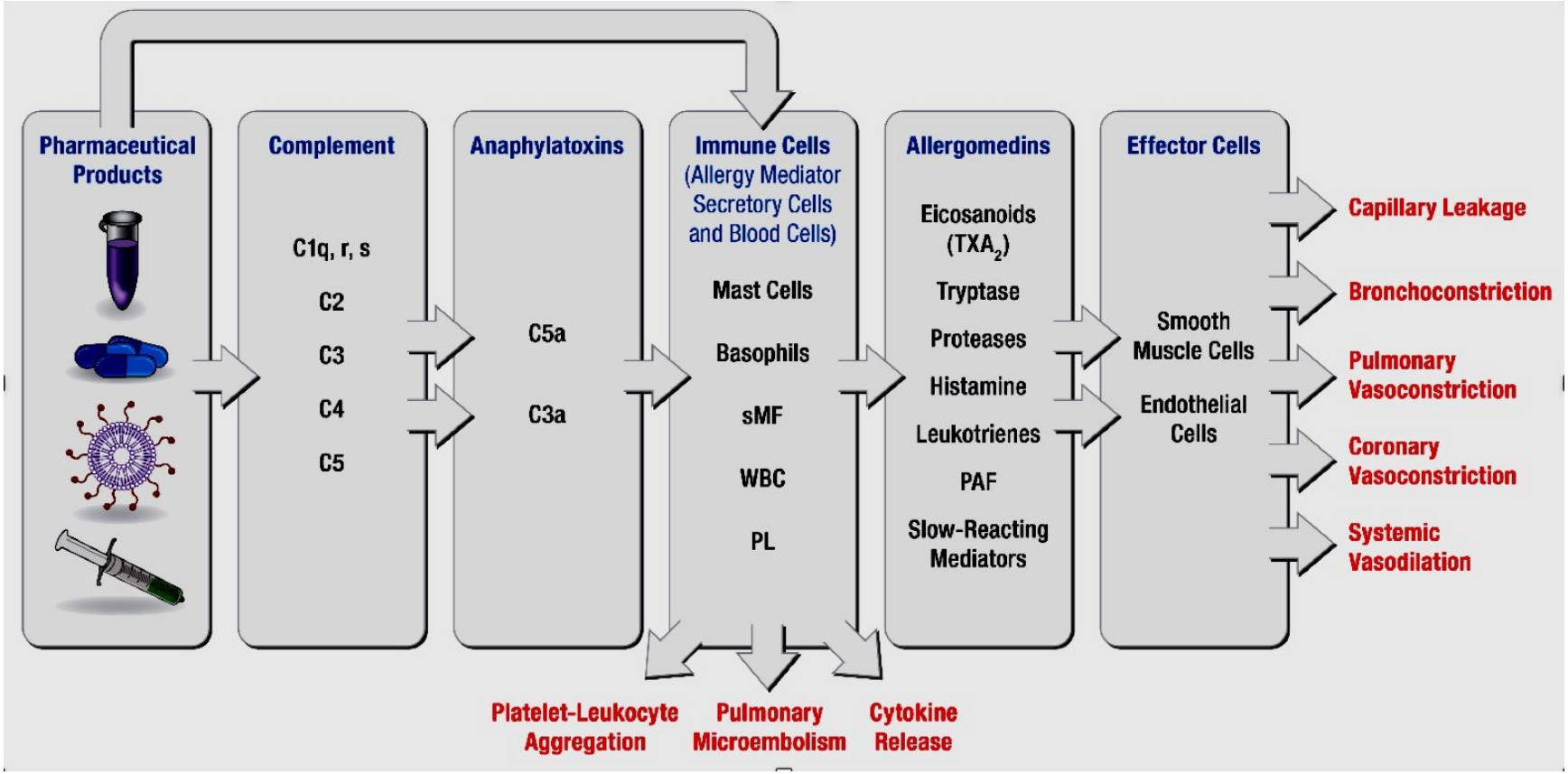
- A large fraction of acute hypersensitivity (infusion) reactions to I.V. drugs is caused by complement (C) activation, or at least C activation is a key contributor to these reactions.
- Many state-of-art anticancer and other nanomedicines and therapeutic antibodies have heightened risk to acivate C, and, hence, cause CARPA

Mild	Moderate	Severe
Nausea	Chest discomfort	Hypo/hypertension (>40 mm Hg)
Dizziness	Shortness of breath	Chest pain
Headache	Hypo/hypertension (>20 mm Hg)	Back pain
Flushing	Increased temperature	Increased temperature with rigors
Diaphoresis	Urticaria	Stridor
Palpitations		
No intervention needed	Intervention needed	Infusion needs to be abandoned

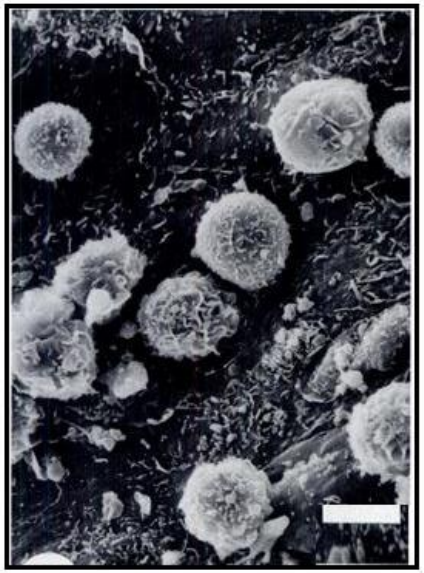
- Liposomal drugs
- Micellar drugs
- Biologicals with or without PEG
- Radiocontrast media
- Enzymes with or without PEG
- Miscellaneous small molecules

- first treatment (no prior exposure)
- milder or absent upon re-exposure
- spontaneous resolution
- pulmonary infiltration
- high reaction rate (2-10%) or higher

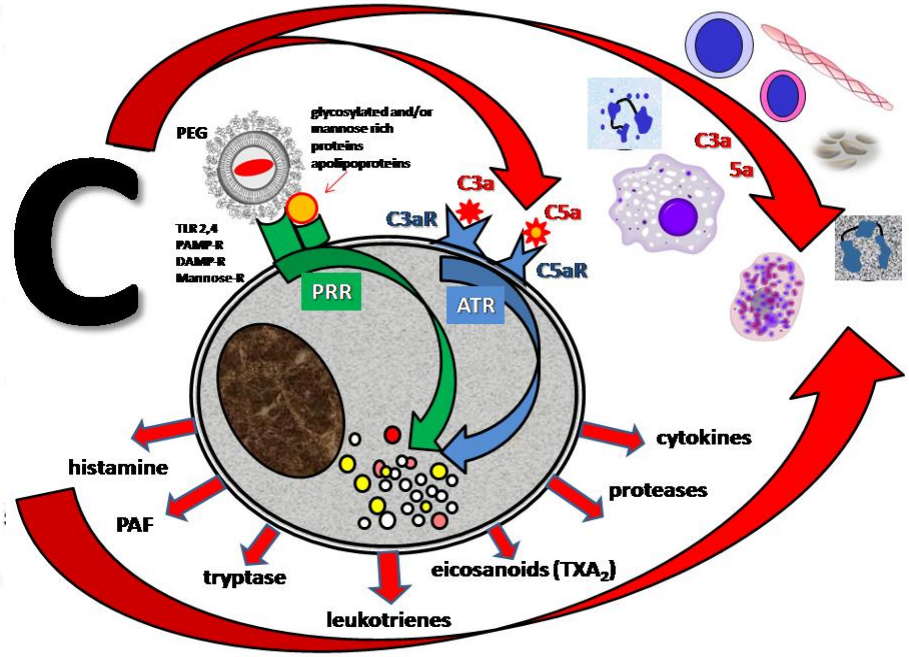
Multi-step comprehensive mechanism of infusion reactions

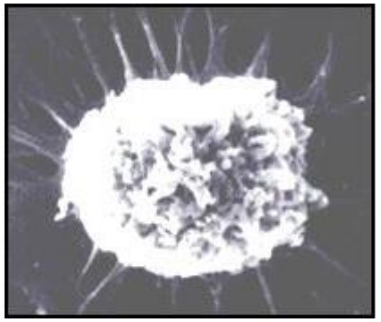


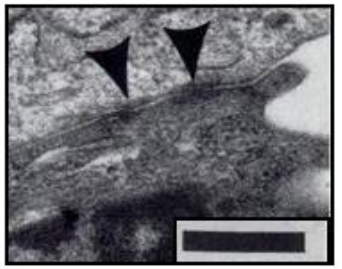
The double hit hypothes



PIM cells

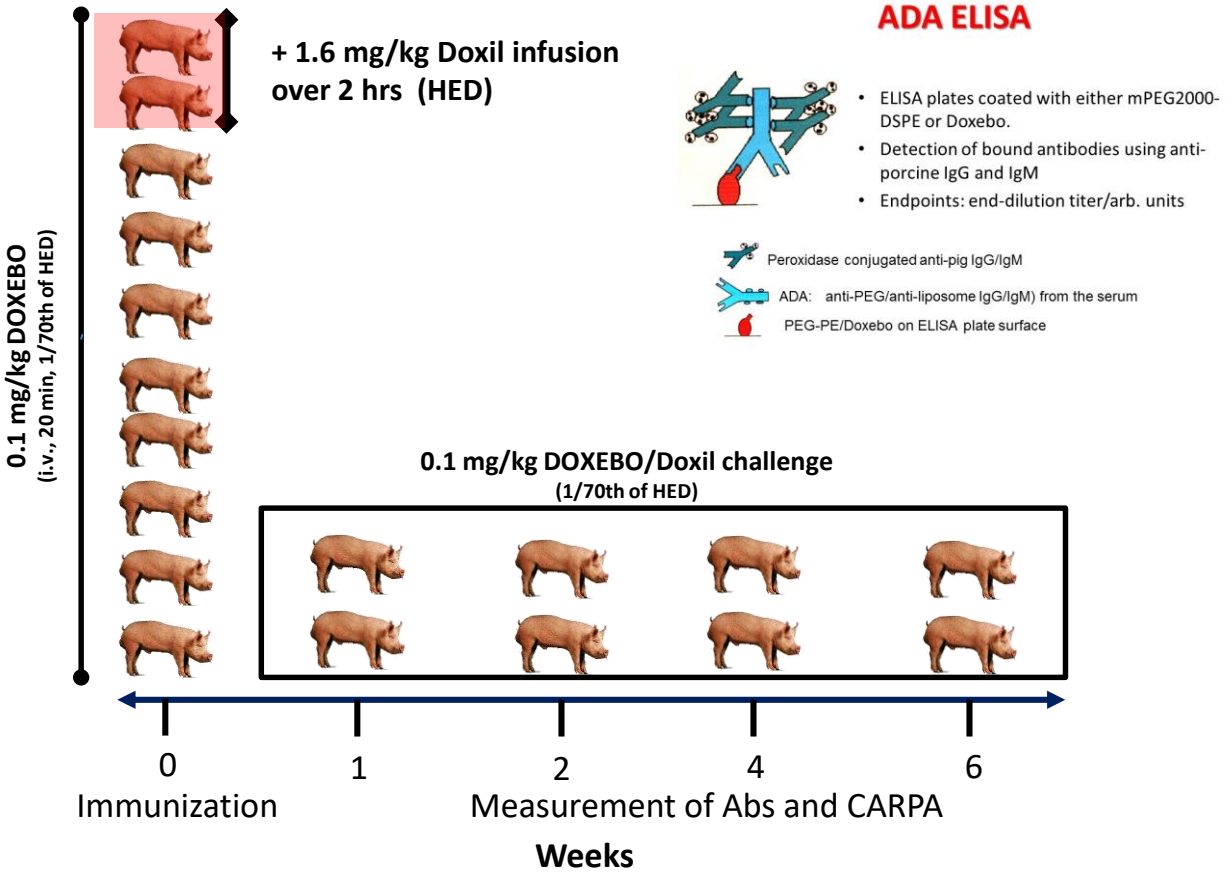






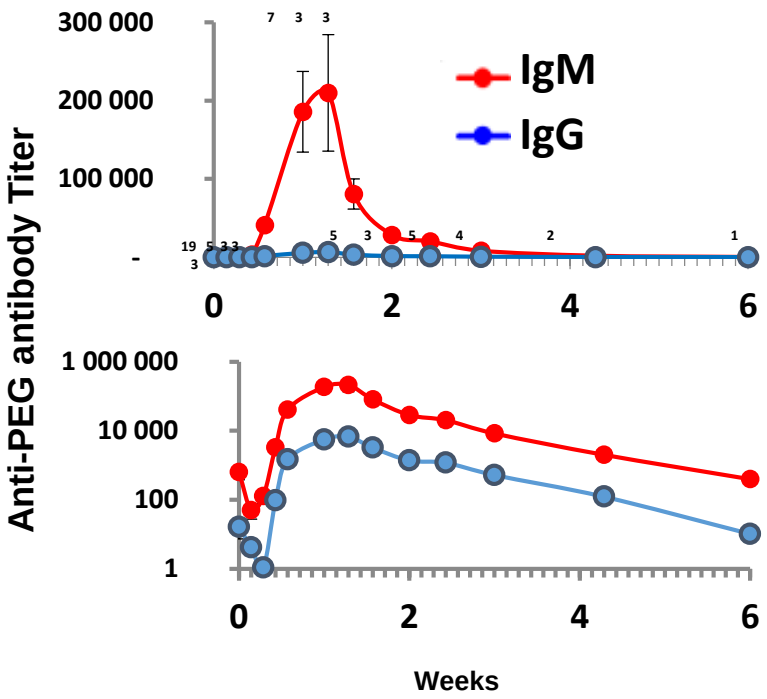
PIM cells

Immunization of pigs with PEGylated liposomes



Immunogenicity of PEGylated liposomes

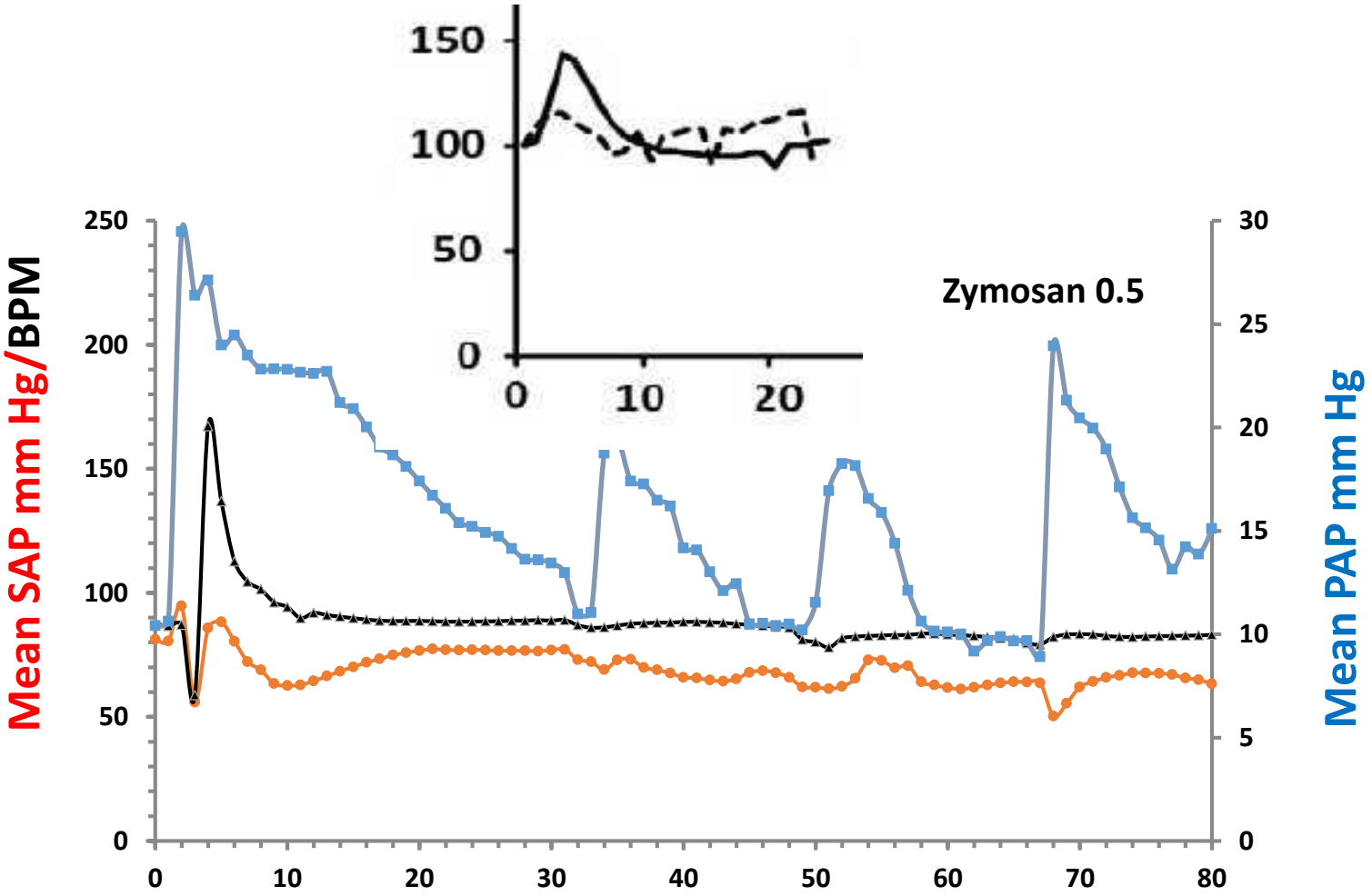
(anti-PEG-DSPE ADA)



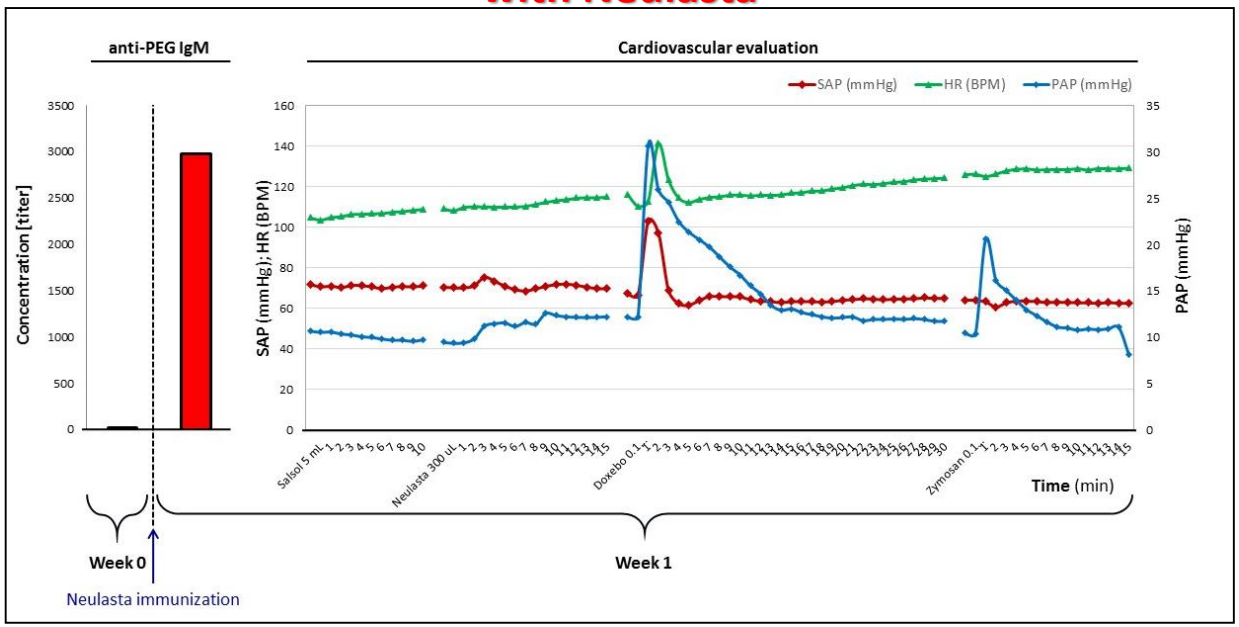
- PEGylated liposomes are ihighly immunogenic, leading to massive production of anti-PEG IgM and IgG antibodies
- IgM and IgG peak at day 8 ± 1
- Abs decline over 6 weeks
- IgM and IgG responses have the same kinetics
- IgM response >> IgG
- Initital titer is not zero => natural antibodies
- There is initial decrease at days 1 and 2 => Doxebo binds nAbs

Kinetics of Ab formation suggests T-cell independent B cell activation (so called type 2 immunogenicity).

Reactogenicity of PEGylated liposomes in immunized pigs



Reactogenicity of Liposopmes and Neulasta in pigs immunized with Neulasta

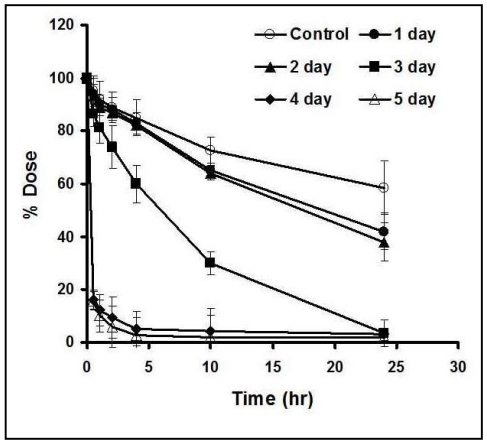


Immunization with neulasta produces IgM antibodies that cross-react with liposomes, causing amplified CARPA. However, Neulasta itself does not cause reaction.
-> CARPA depends on NP size????

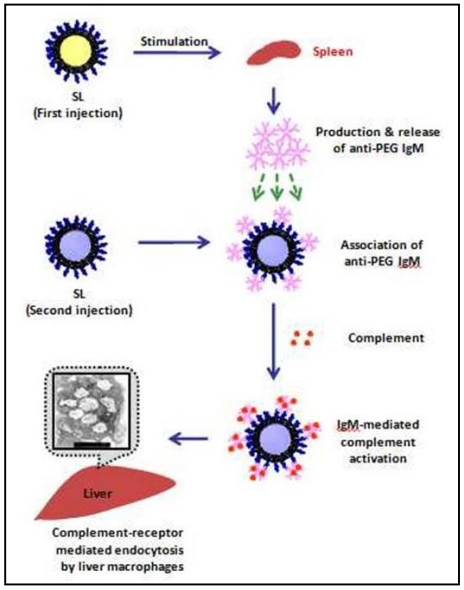
Prediction of immunogenicity

- In silico methods (antigen analysis)
- Antibody testing in human trials
  - tiered approach to verify individual biological effects of ADAs
- Animal models – none accepted
  - Preliminary evidence for the use of pigs in assessing type-2, T-independent immunogenicity of nanomedicines

Animal model of type-2 immunogenicity: Accelerated blood clearance (ABC) in rats



Accelerated blood clearance of a second dose of PEGylated liposomes. Rats were pretreated with PEGylated liposomes (0.001 μmol phospholipids/kg). Blood clearance of a second dose of radio-labeled PEGylated liposomes (5 μmol phospholipids/kg).



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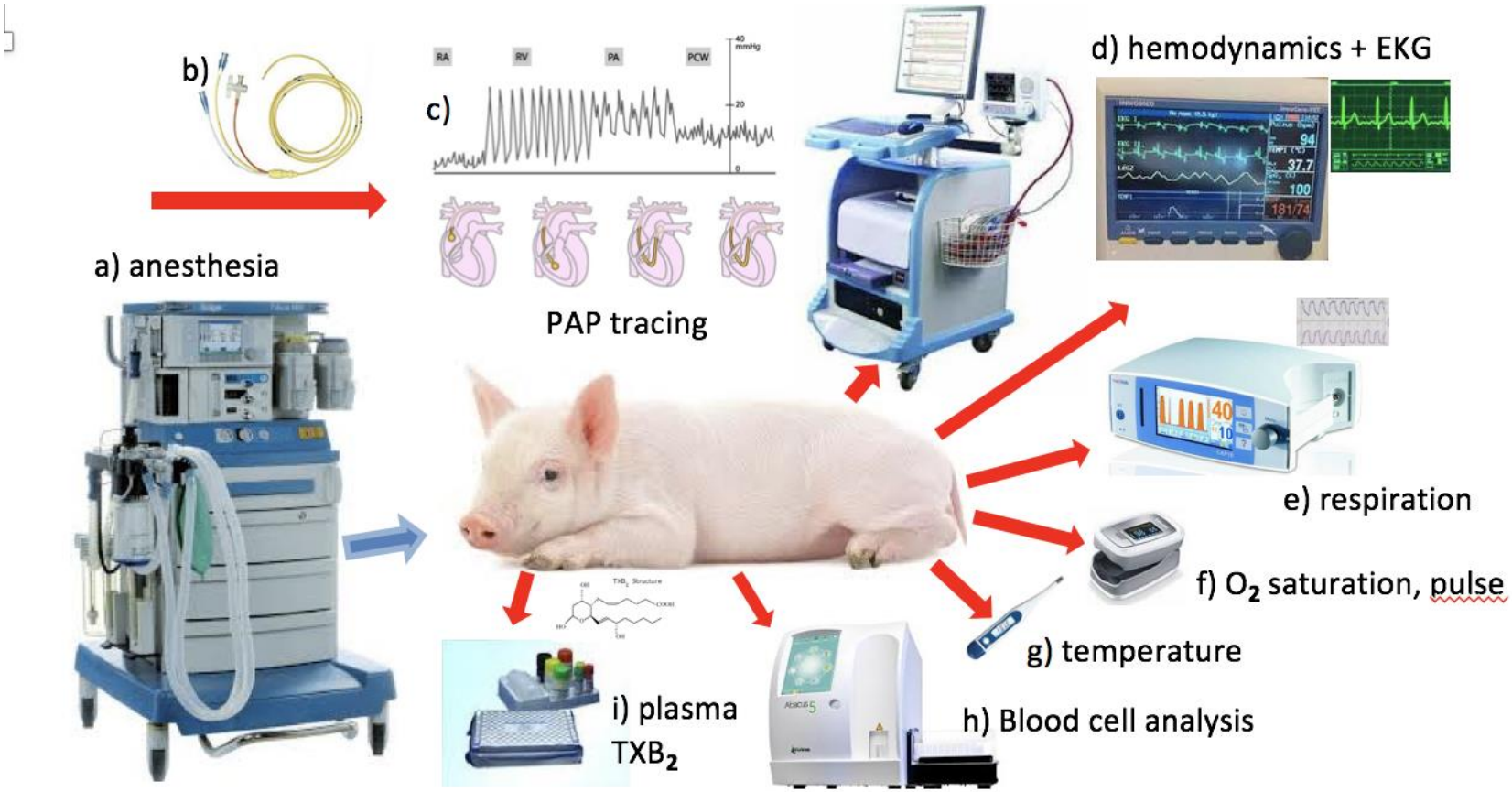
CARPA tests

- **In Vitro**
  - –Complement activation in human and animal serum
    - C5a
    - C3a
    - SC5b-9
    - C4d
    - Bb
    - CH50

- **In Vivo**
  - –Pig, dog, rat and mouse CARPA
  - –Hemodynamic analysis (SAP, PAP, CO, Hr)
  - –Cell counting (WBC, PLT)
  - –allergy mediators in blood
    - C3a, sC5b-9, C5a
    - histamine
    - thromboxane
    - PAF
    - LT4

Pigs provide a sensitive and highly reproducible *in vivo* model for the acute immune (anaphylactic) reactivity and immunogenicity of nanoparticles



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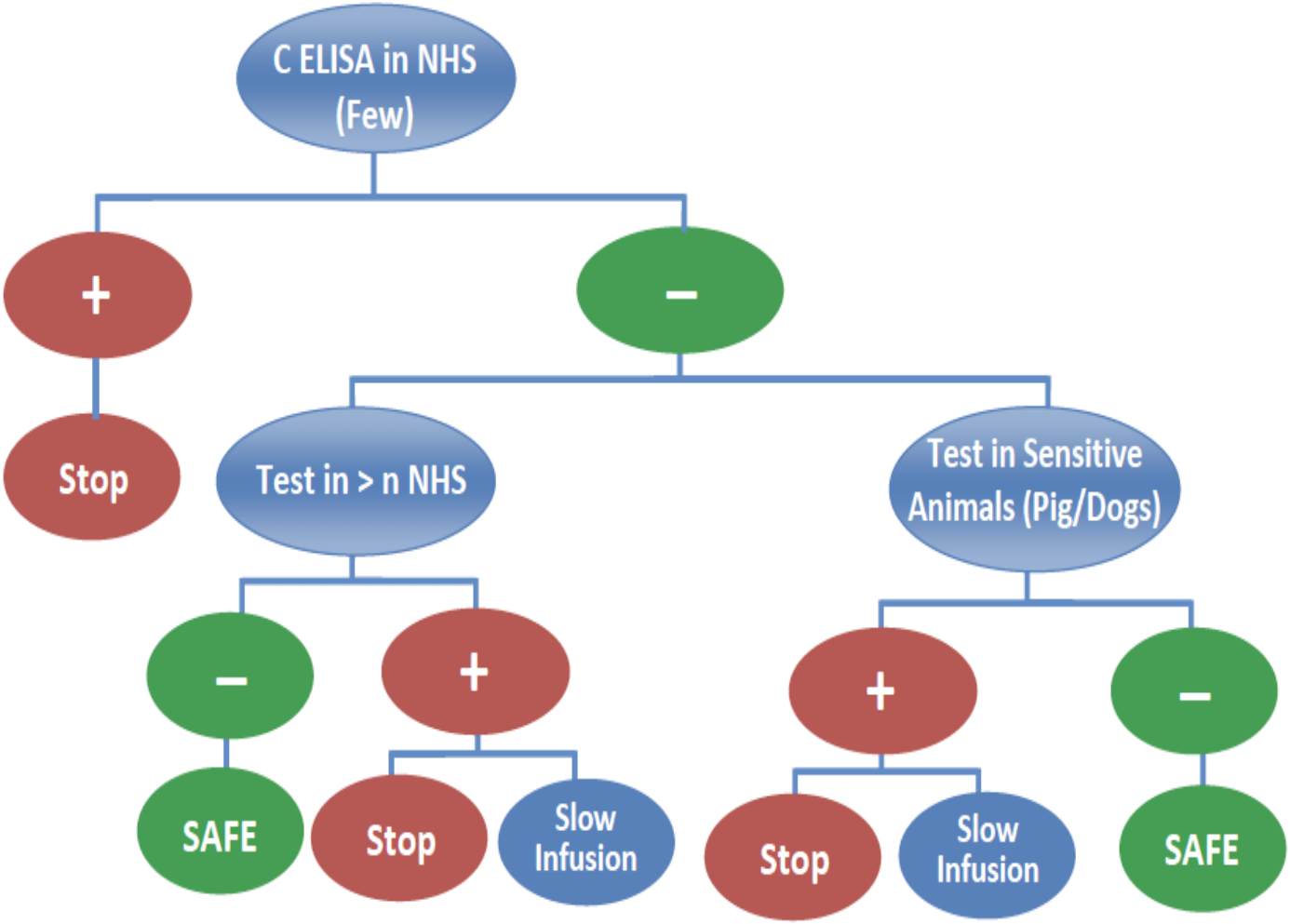
A decision tree for CARPA prediction



Conclusions

- **Infusion reactions remain an unsolved problem for many therapeutic or diagnostic nanomedicines.**
- **Current erxperimentally derived evidence is more in favor of a role of C activation in infusion reactions than its irrelevance.**
- **The porcine immune toxicity model is uniquely applicable for preclinical evaluation of the risk of acute hyper-reactivity and long-term immunogenicity of NP-based drugs and agents.**
- **The model, complemented with in vitro C assays, enables the prediction of CARPA and elaboration of safe administration protocols**

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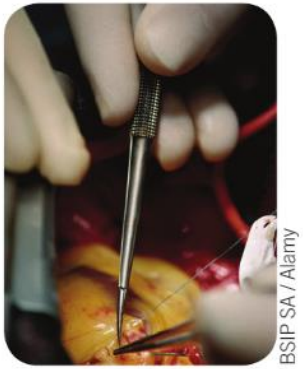
P 1060

in brief

Regado's aptamer lines up against anticoagulants

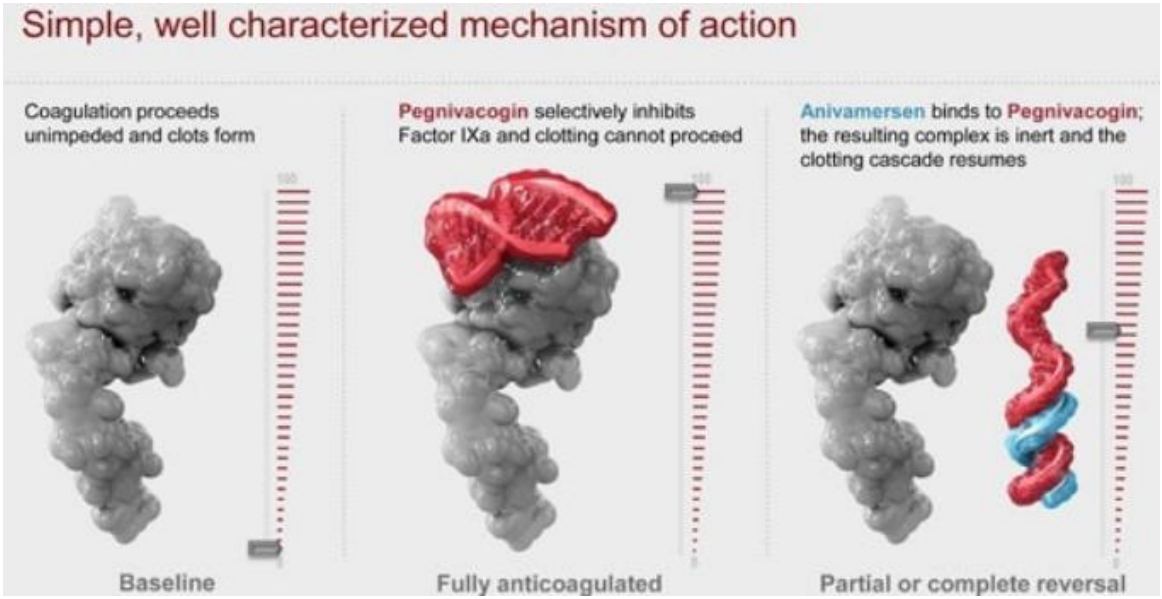


BSIP SA / Alamy

In September the first reversible antithrombotic drug entered phase 3 clinical trials in patients undergoing percutaneous coronary intervention (PCI). The REG1 anticoagulant system developed by Regado Biosciences, of Basking Ridge, New Jersey, is a two-component therapeutic consisting of a nucleic acid aptamer and its control agent. The combined drugs are pegnivacogin (RB006), a single-stranded 31-nucleotide aptamer that binds and inhibits Factor IXa, and a complementary 15-nucleotide control agent anivamersen (RB007). By adjusting the dose of anivamersen, physicians can release the therapeutic pegnivacogin from Factor IXa allowing coagulation activity to resume. Pegnivacogin is pegylated, with a half-life of more than 24 hours, whereas the control agent anivamersen is metabolized in a few minutes.

The educative story of PEGylated aptamer: Revolixys (against thrombosis)

Pegnivacogin (RB006):
An anticoagulant aptamer
31 nucleotides+40K-PEG t ½ >24 h
Specific for Factor IXa



Progress in understanding

1960s Coombs and Gell: Type I allergy
1980s Hugli: Anaphylatoxin release in blood => C activation
1990s Bradykinin release (contrast and dialyzis reactions)
2000s Complement activation-related pseudoallergy (CARPA)
2017-18 CARPA + CIPA (C activation-related/independent pseudoallergy)

CARPA

Hemodynamic Changes Induced by Liposomes and Liposome-Encapsulated Hemoglobin in Pigs

A Model for Pseudoallergic Cardiopulmonary Reactions to Liposomes: Role of Complement and Inhibition by Soluble CR1 and Anti-C5a Antibody

Janos Szebeni, MD, PhD; John L. Fontana, MD; Nabila M. Wassef, PhD; Paul D. Mongan, MD; David S. Morse, MD; David E. Dobbins, PhD; Gregory L. Stahl, PhD; Rolf Bünger, MD, PhD; Carl R. Alving, MD

Circulation, 99 (1999) 2302-2309.

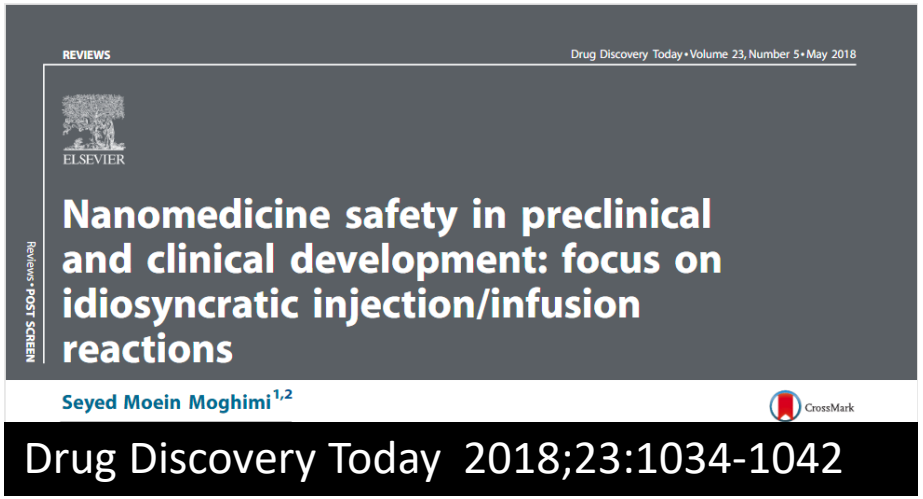
CIPA: Direct stimulation of allergy mediating cells

Bypassing adverse injection reactions to nanoparticles through shape modification and attachment to erythrocytes

Peter Pope Wibroe[1], Aaron C. Anselmo[2], Per H. Nilsson[3,4,5], Apoorva Sarode[2], Vivek Gupta[6], Rudolf Urbanics[7], Janos Szebeni[7], Alan Christy Hunter[8], Samir Mitragotri[2], Tom Eirik Mollnes[3,4,9,10,11] and Seyed Moein Moghimi[1,12,13]*

Nature Nanotech, 12 (2017) 589-594.

CIPA: Is there a role of complement activation?



Drug Discovery Today 2018;23:1034-1042

ELSEVIER

Drug Discovery Today 2018;23:487-492

feature

Mechanism of nanoparticle-induced hypersensitivity in pigs: complement or not complement?

János Szebeni[1,2], jszebeni@seroscience.com

Experimental and clinical evidence for complement activation having a causal role in hypersensitivity reactions (HSRs)

- **Animal studies**
  - Correlation between C activation by freactogenic drugs in vitro and hemodynamic and cardiopulmonary disturbance in pigs including systemic hypotension and pulmonary hypertension
  - Administration of human C5a causes cardiopulmonary and hemodynamic changes in pigs mimicking some of the hemodynamic abnormalities of human HSRs
  - Complement inhibitors sCR1 and IVIG inhibited the cardiopulmonary reaction of pigs to liposomes
- **Human studies**
  - Anaphylatoxins explain the symptoms
  - Correlation between C activation and HSRs to
    - HJSRTs to liposomal doxorubicin (Doxil)
    - HSRS to Rituximab
    - HSRs to Althesin
    - cardiac anaphylaxis
    - dialysis reactions
    - HSRs to intravenous iron.
    - radiocontrast agents

Mapping CARPA on the landscape of nanotoxicity