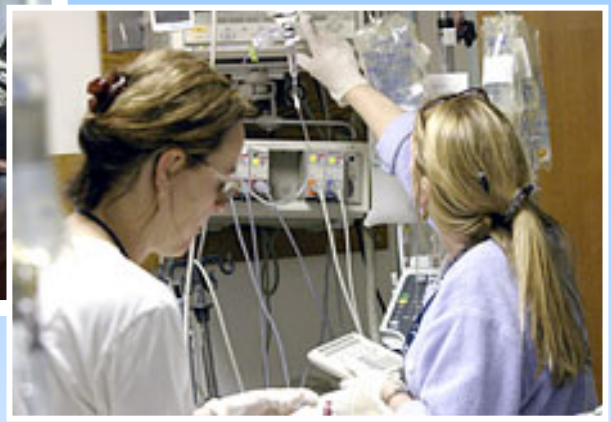

TGN1412: What happened?

Ganesh Suntharalingam, FRCA

Director of Intensive Care, NWLHT
Honorary Clinical Senior Lecturer,
Anaesthetics, Imperial College London
Northwick Park & St. Mark's site

Nicki Panoskaltsis, MD PhD

Director of R&D, NWLHT
Senior Lecturer, Haematology
Imperial College London
Northwick Park & St. Mark's site

Imperial College London

The North West London Hospitals NHS Trust

Disclaimer

- No involvement in trial conduct, and no affiliation to:
  - Trial sponsor (TeGenero AG, Germany)
  - Contract Research Organisation (PAREXEL International, USA)
  - Investigating regulatory authorities (MHRA, ESG)

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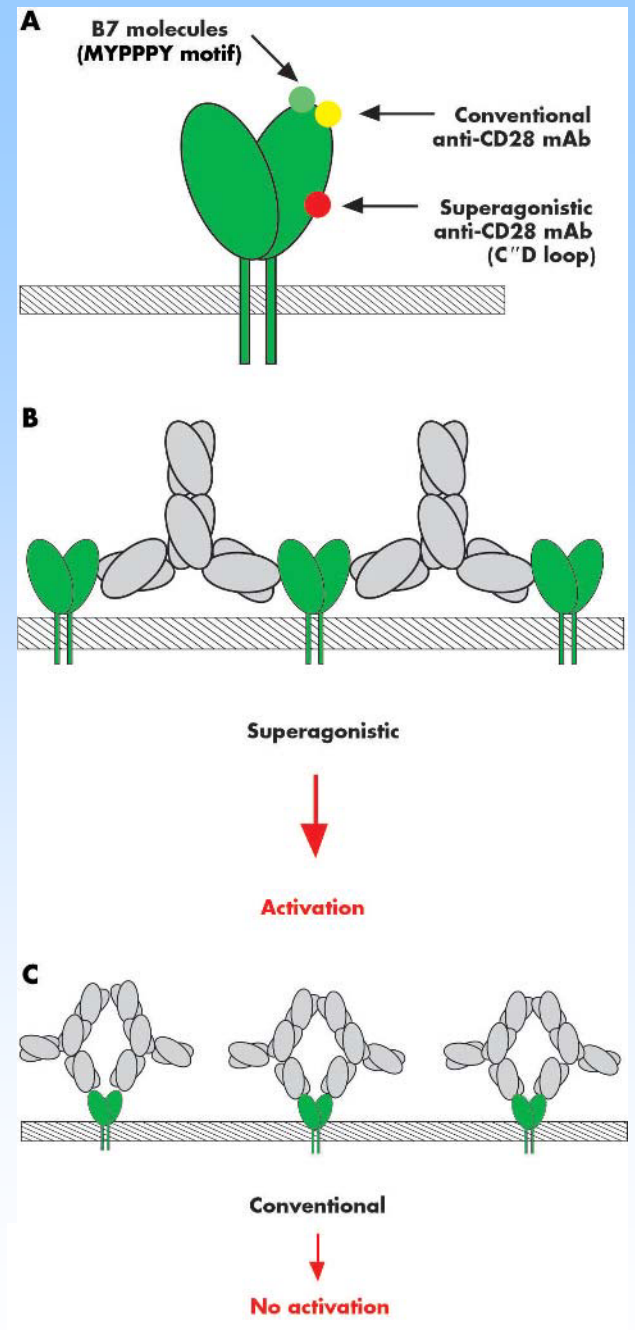

TGN1412

- Humanized $IgG_4\kappa$ mAb
- anti-CD28 superagonist

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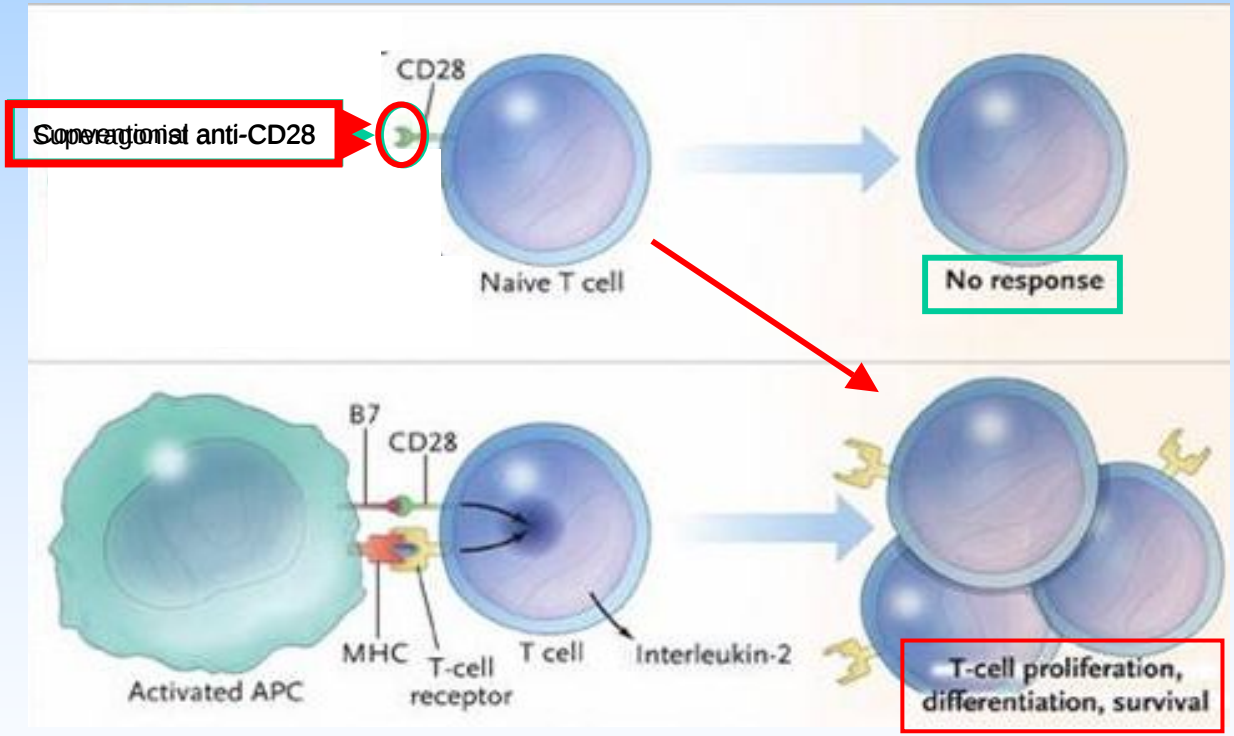
Beyersdorf et al, *Ann Rheum Dis* 2005

TGN 1412

- Humanised superagonist anti-CD28 monoclonal antibody (TeGenero AG)



Sharpe AK *et al.* N Engl J Med 2006;355:973-975

- March 13th 2006 clinical trial

  - FIM study
  - 8 healthy male volunteers
  - randomised
  - placebo-controlled (6 study, 2 placebo)
  - double-blinded
  - dose-escalation study (1st dose 0.1 mg/kg @ 2mg/min)

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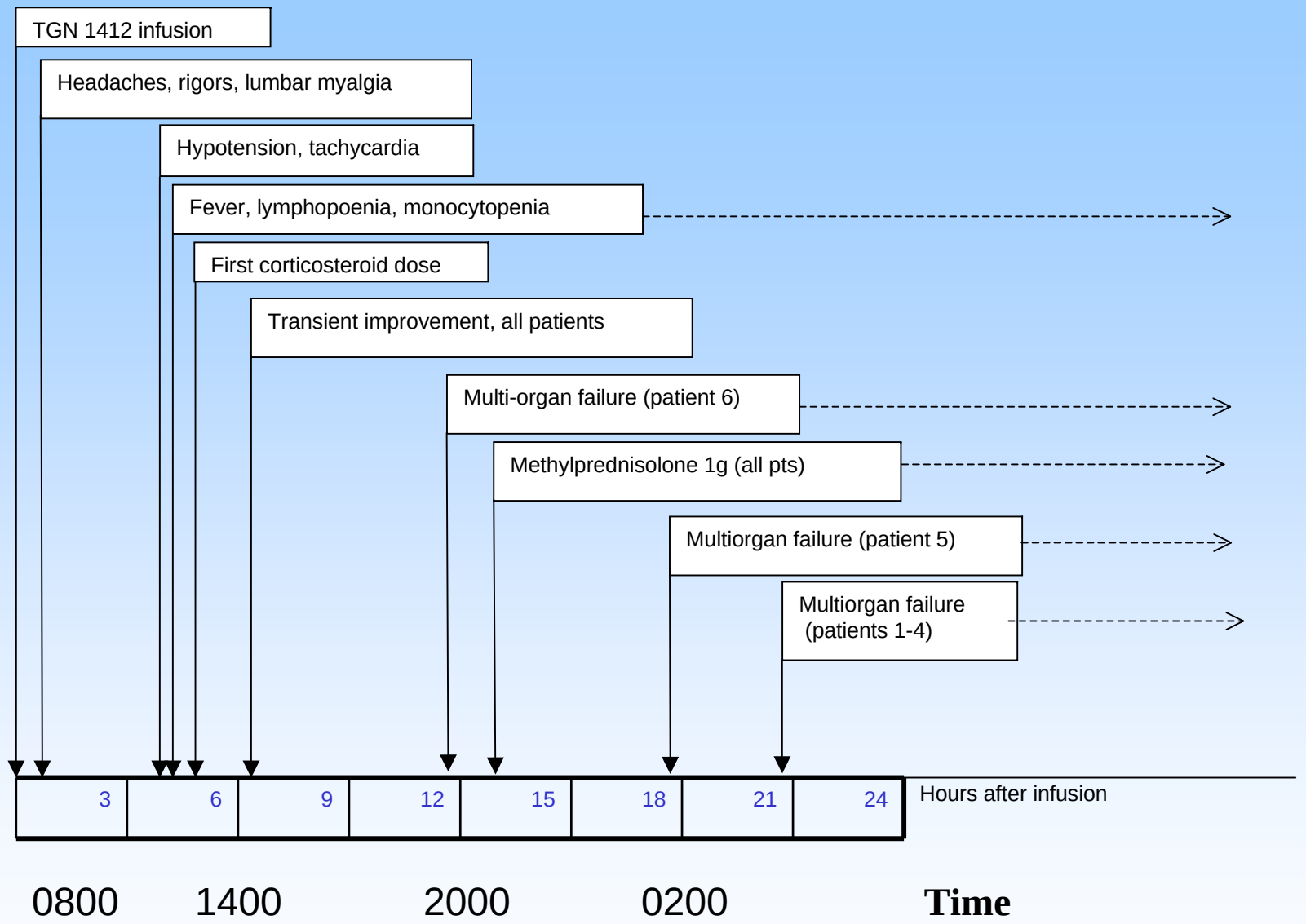

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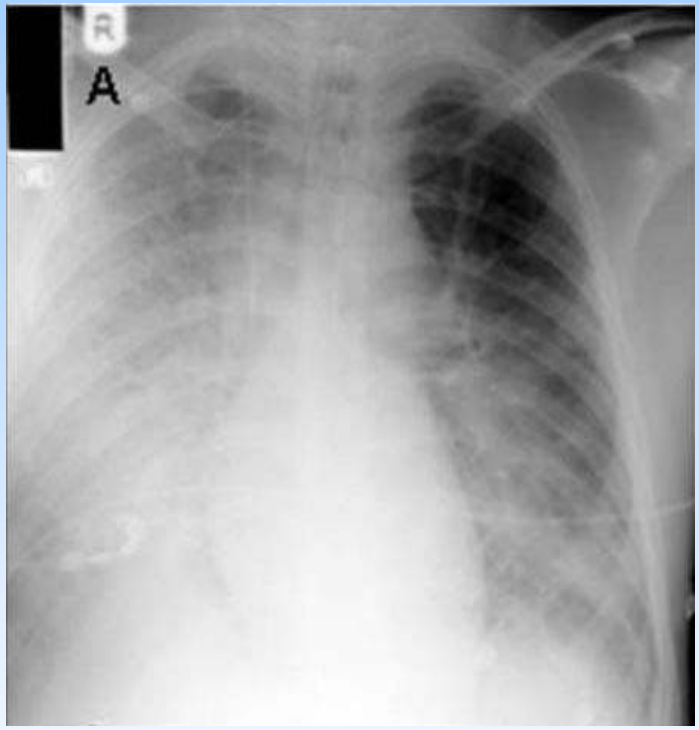
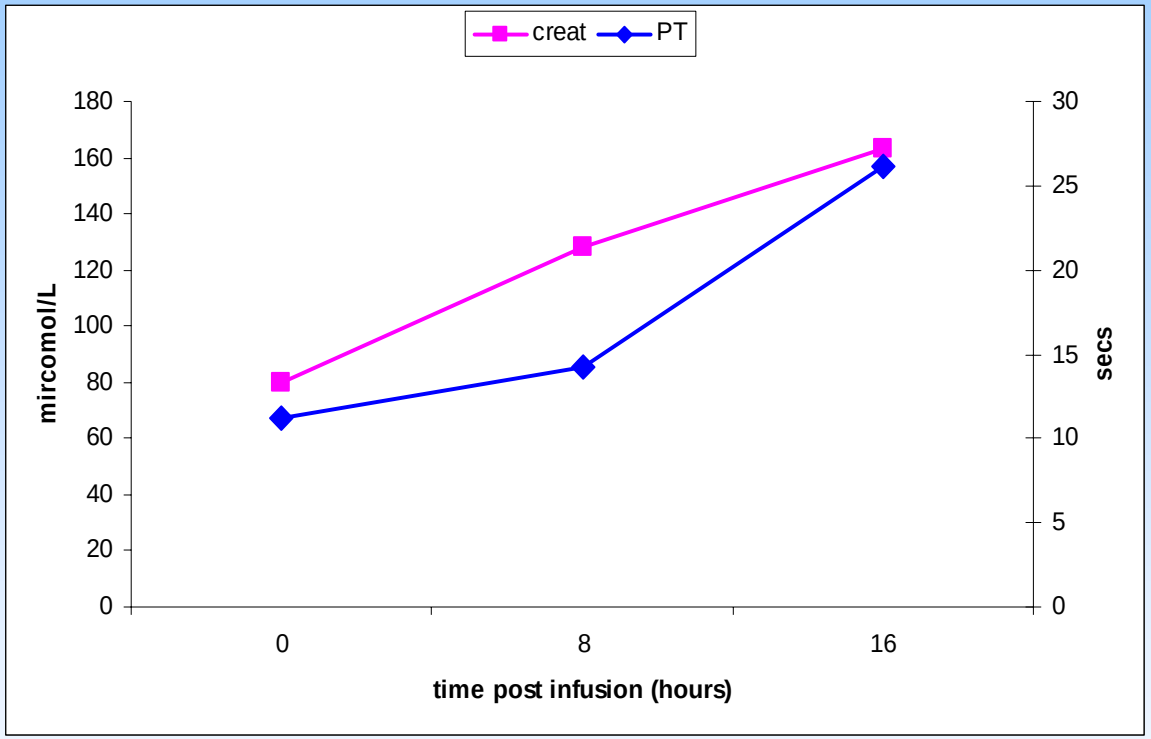
Clinical manifestation – sepsis-like organ failure pattern





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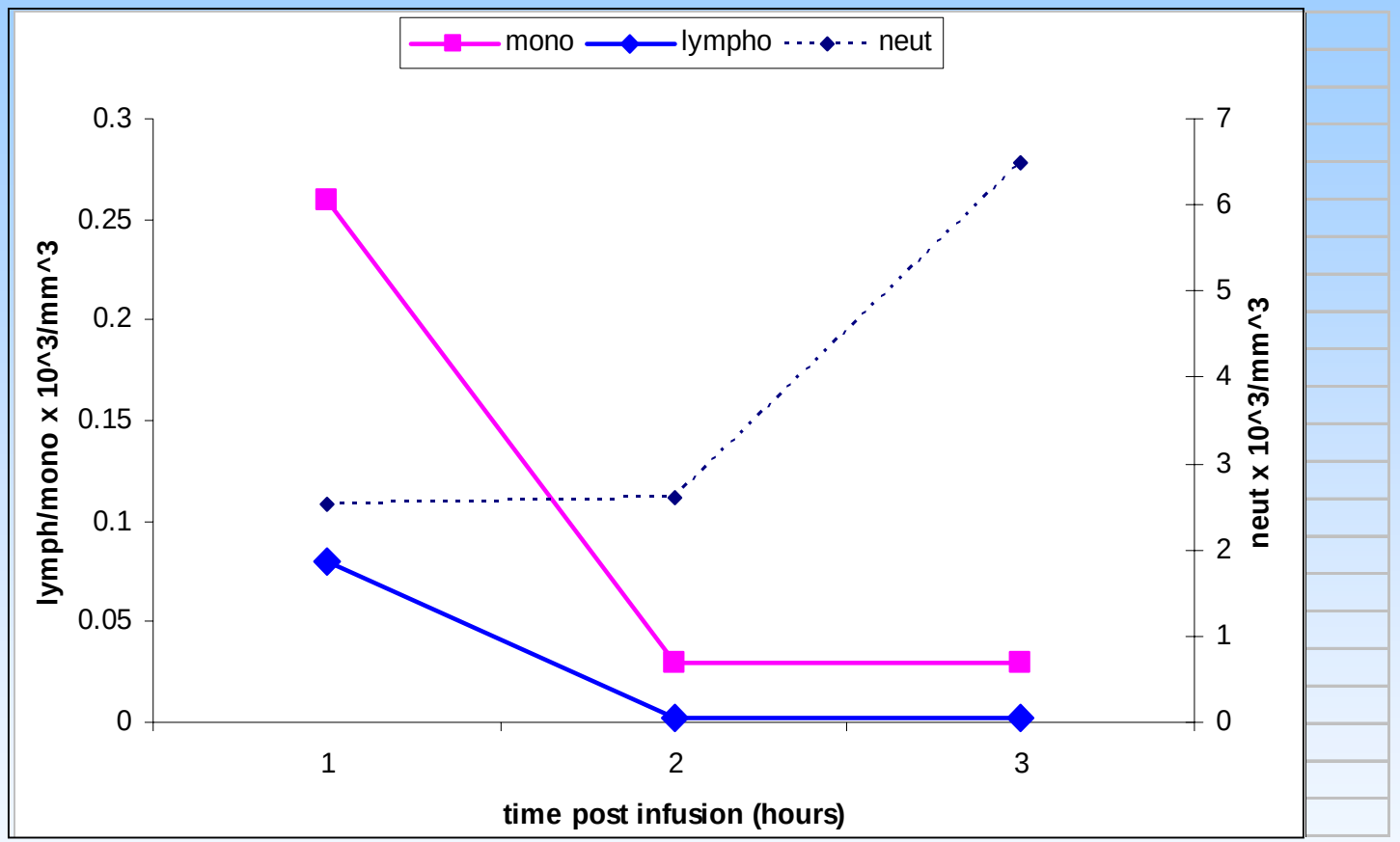

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Clinical management

- immune modulation
  - methylprednisolone 1g tds (→ tailing dose)
  - daclizumab (IL-2 receptor antagonist)

- organ support
  - haemodynamic resuscitation
  - aggressive lung support
  - high volume kidney support

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Key difficulties, decisions & ethics

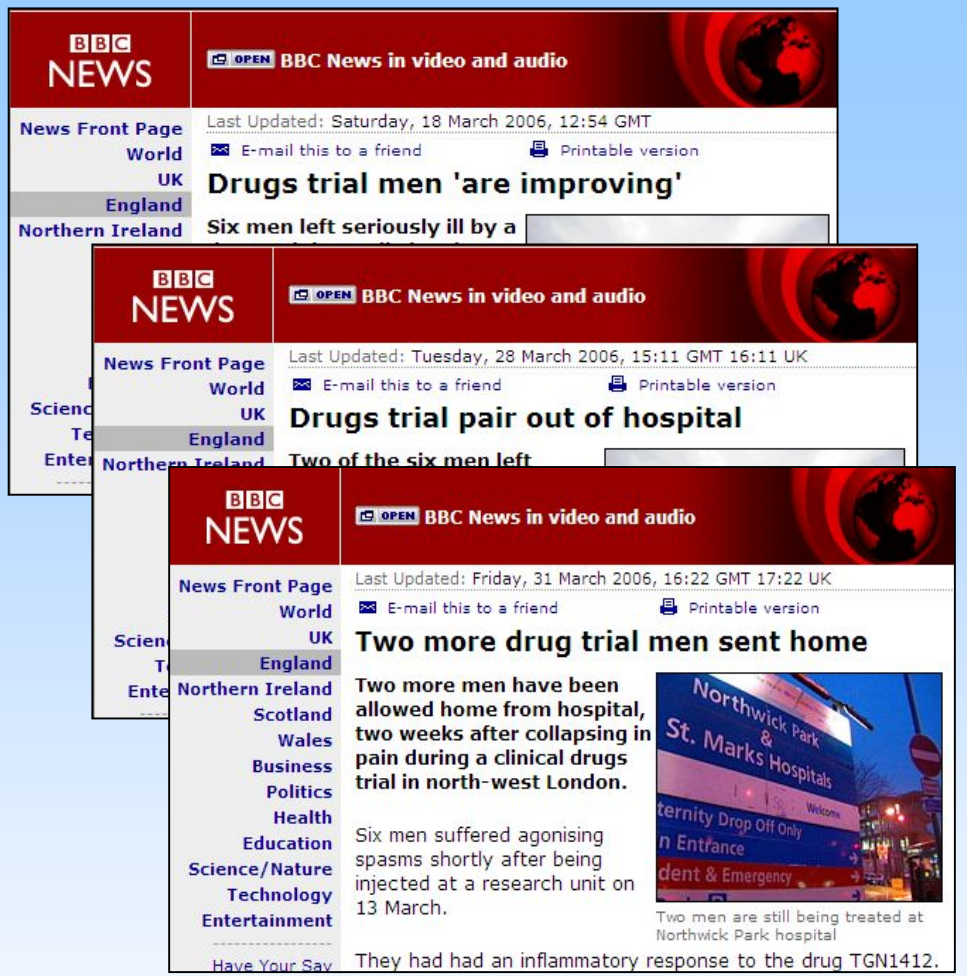
- Unpredictable effects
- Unpredictable severity
- Unknown kinetics in humans

→

- Admit as a cohort?
- Treat as a cohort ?
- Off-study → clinical investigations only

Outcome

- All six patients survived
- Full resolution of pulmonary injury and renal failure
- 1 pt peripheral necrosis
- Prolonged haematological/ immunological recovery



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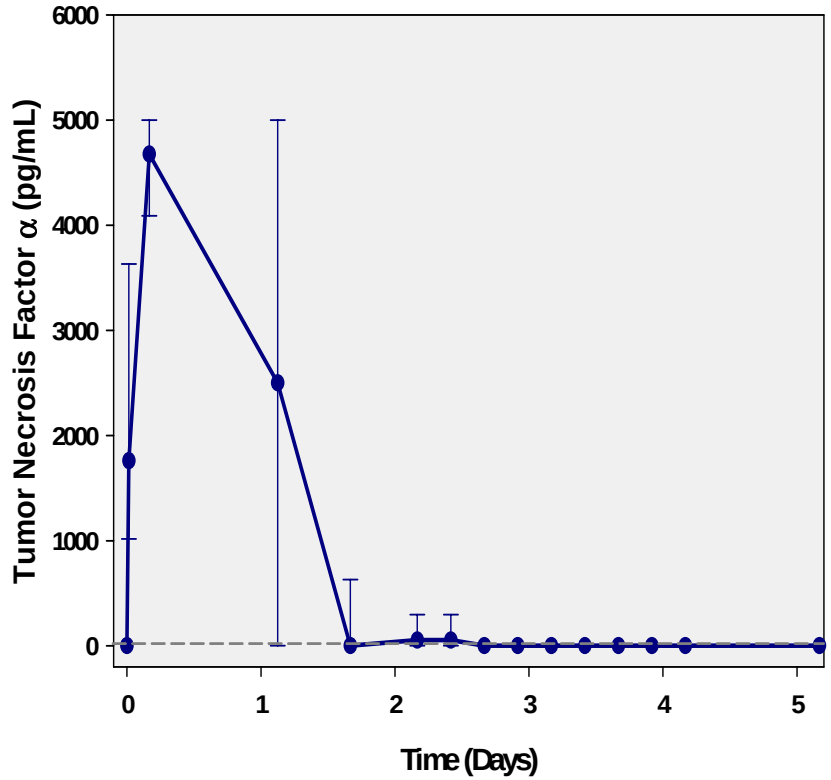
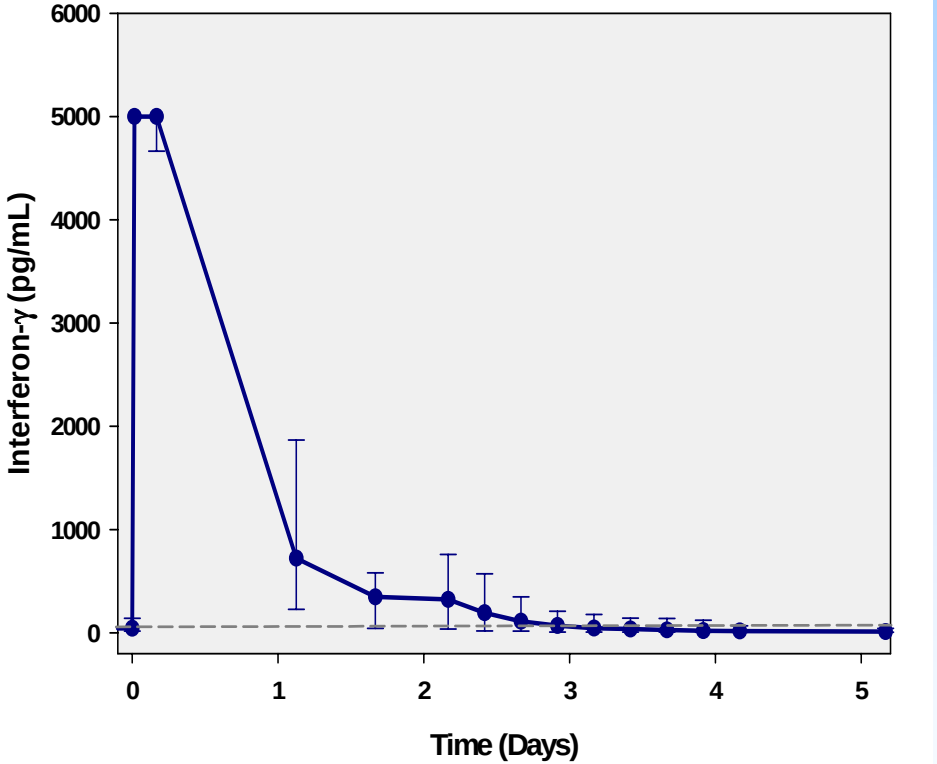
TNF-α and IFN-γ





N Engl J Med 2006;355:1018-28.

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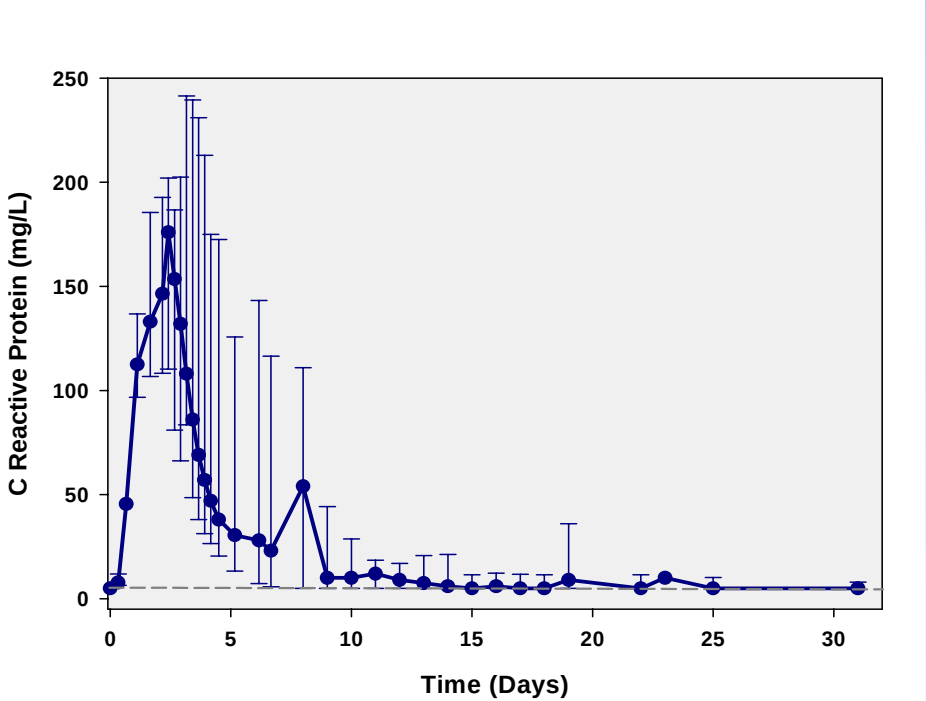
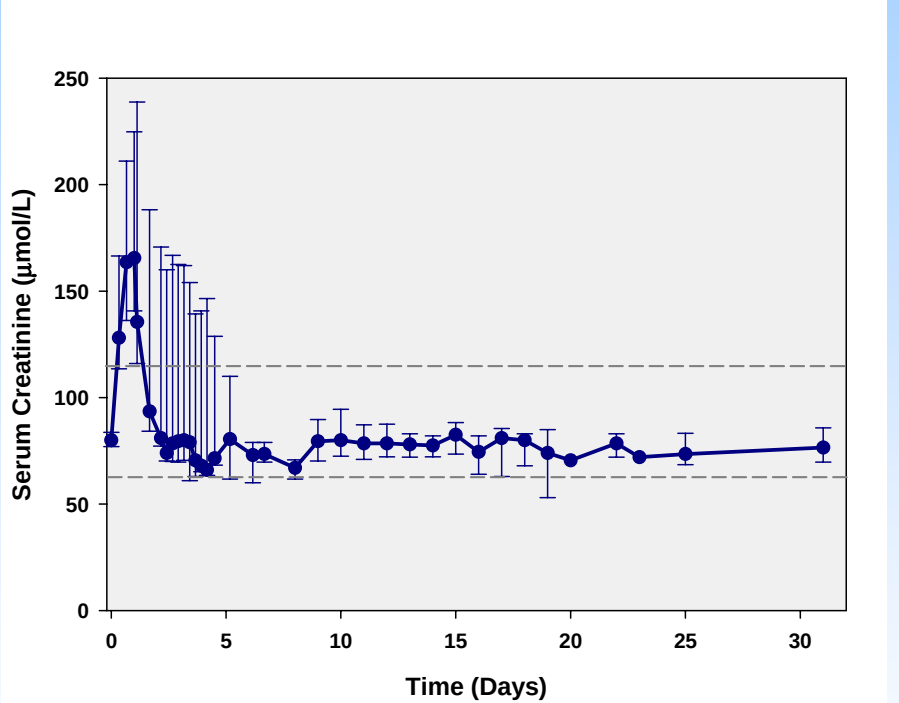
CRP



Creatinine



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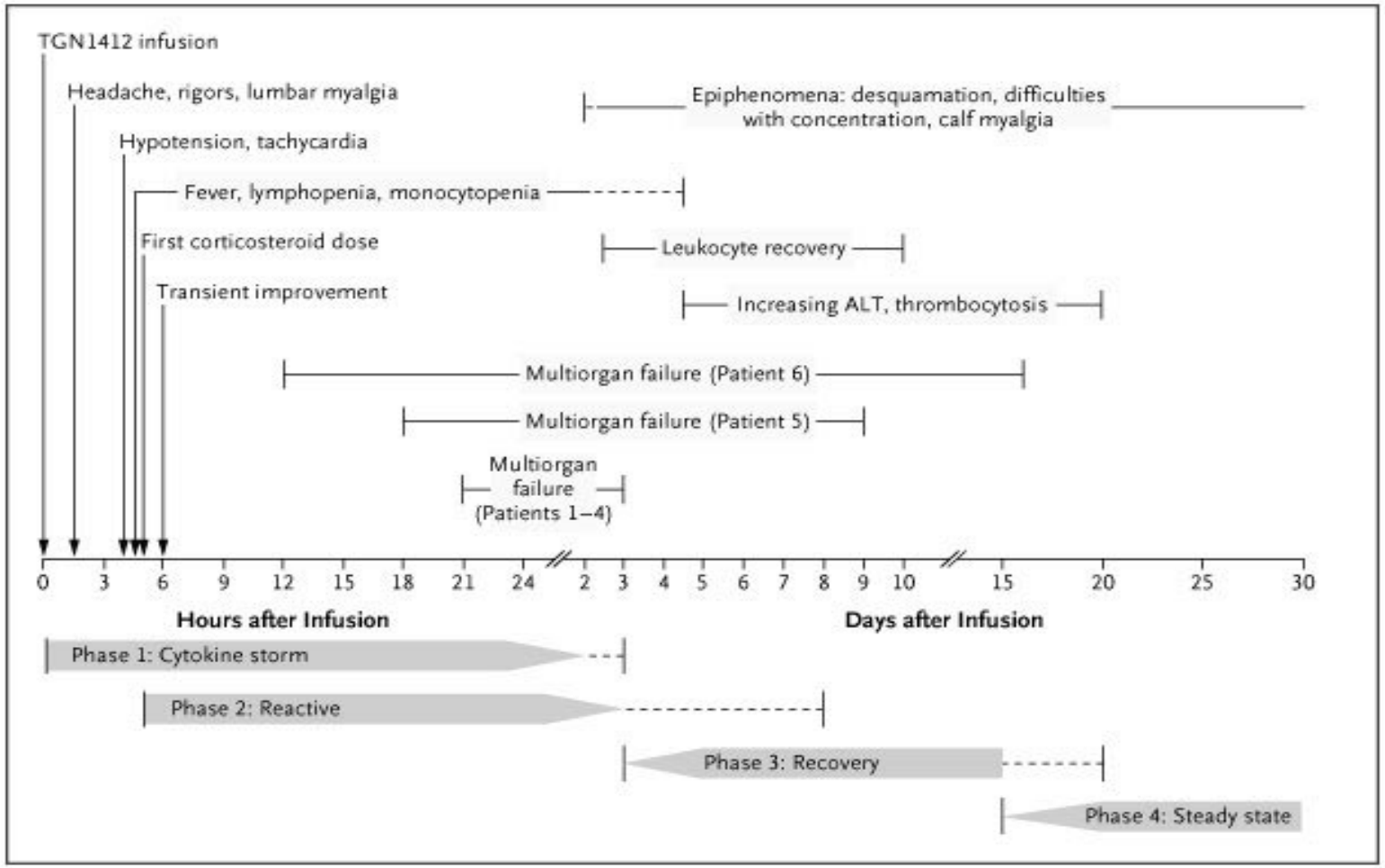

Suntharalingam G, Perry MR, Ward S *et al* N Engl J Med 2006;355:1018-28

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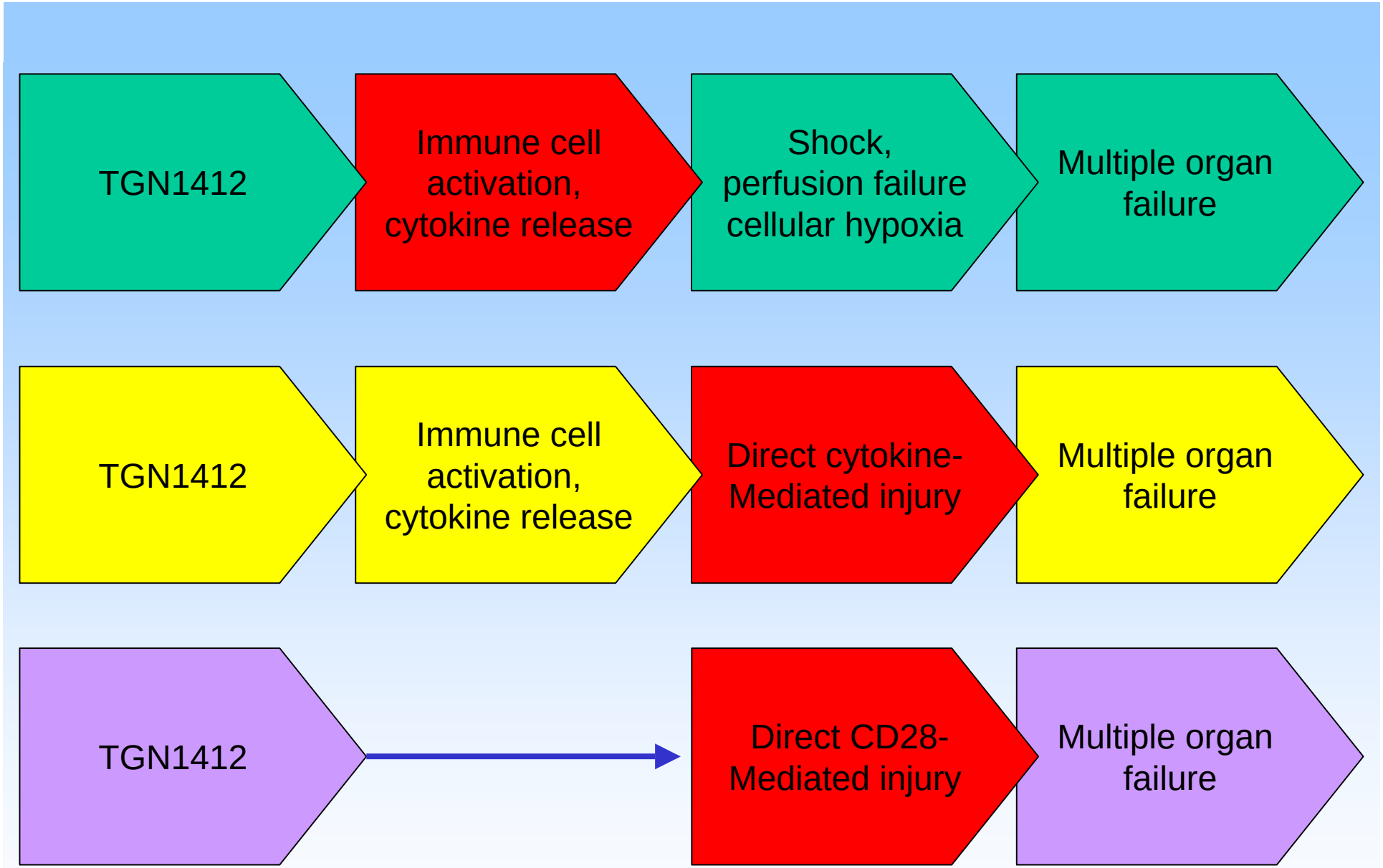

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Where does this leave us?

- MHRA Investigation (Metropolitan Police)
  - GCP: Parexel, Boehringer, TeGenero
    - Contractual irregularities, no 24 hour medical cover
  - GMP: Parexel
  - GLP: Preclinical studies
  - Product testing:
    - NIBSC, MHRA (UK): FCC, FDA (USA)
    - No errors in manufacture, formulation, dilution, administration
    - No bacterial, toxin, pyrogen contaminant
- Interim arrangements for novel biologic agents

ESG Terms of Reference

- Requirements in transition from pre-clinical to first-into-man studies
  - Biologicals with novel mechanism of action
  - New agents with a highly species-specific action
  - New drugs directed towards immune system targets
- Advice on the future authorisation of such trials

Lessons from TGN1412: Expert Scientific Group

- Final "Duff" Report – December, 2006

  Conclusion

  "…preclinical development studies that were performed with TGN1412 did not predict a safe dose for use in humans, even though current regulatory requirements were met."

- 22 Recommendations to improve safety of volunteers in first-in-man studies

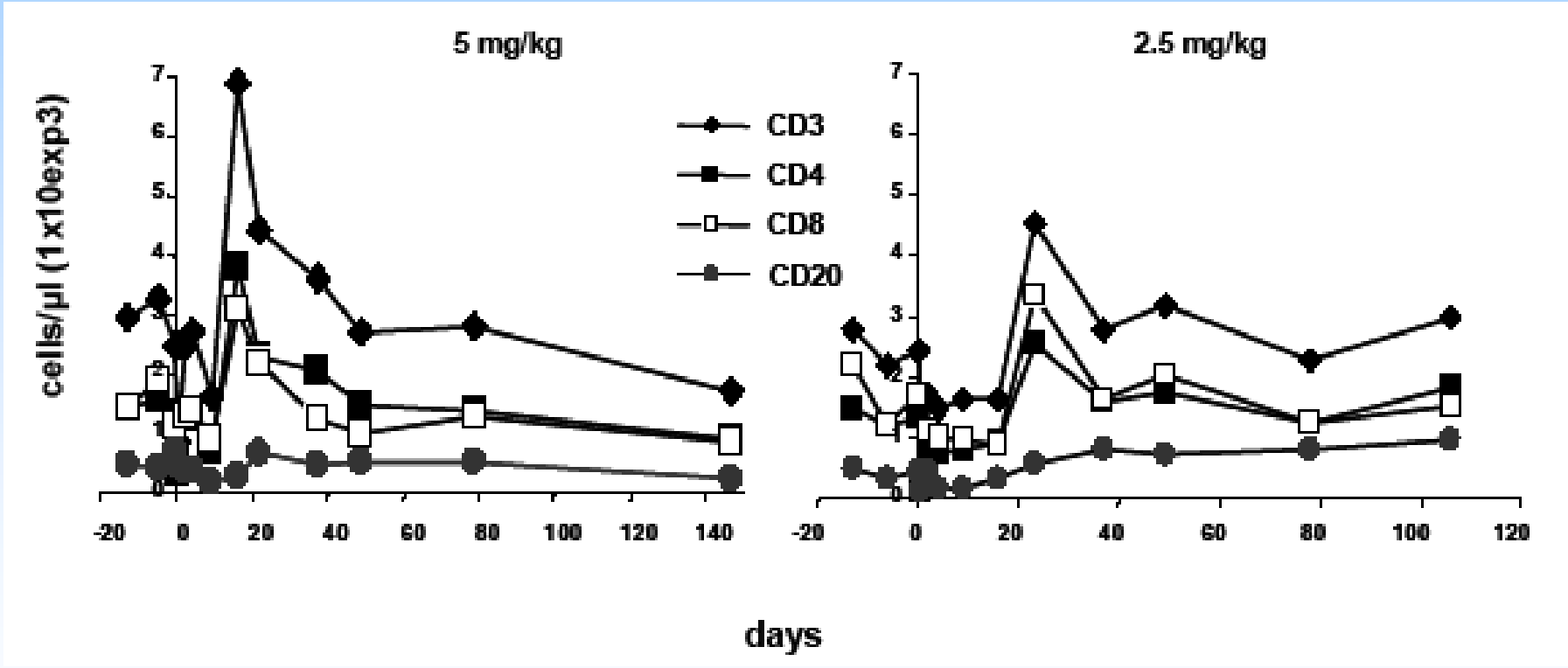
Recommendations (UK, EU, International): www.dh.gov.uk

1. Pre-clinical and early clinical development
2. The process of preparation and review of clinical trial applications, and early access to advice for both regulators and sponsors
3. Determining and administering the initial doses in man
4. The clinical environment for first-in-man studies
5. Developing the skills and training to meet future needs

Further testing at NIBSC:

Why was the cytokine storm not identified pre-clinically?

Rhesus monkeys: TGN1412 produced transient lymphocytosis at day16-23



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Cynomologus monkey + TGN1412:
Mean peak serum concentration of cytokines (2, 24 hrs)

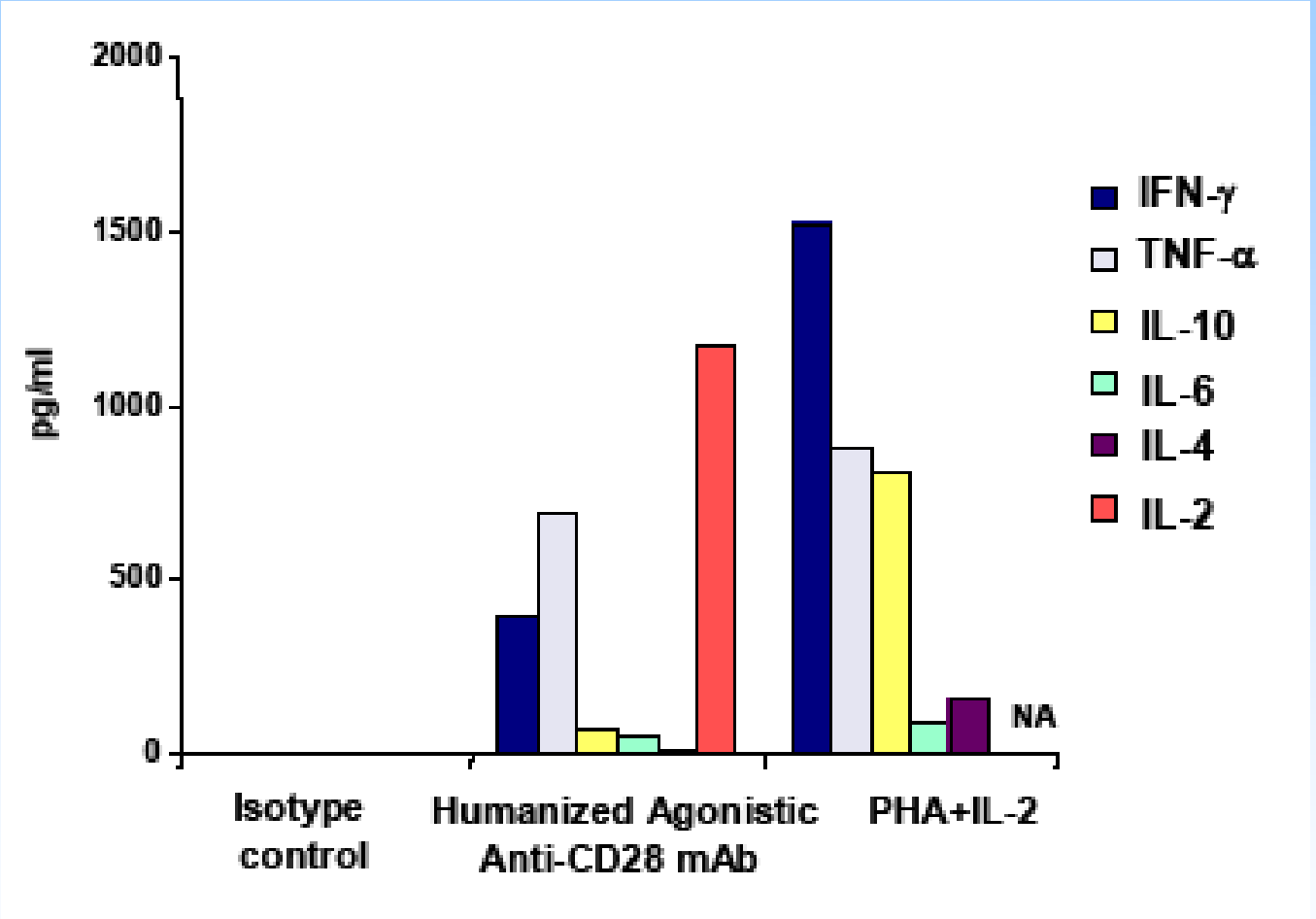
Cytokine	Mean peak cytokine level (range) in pg/ml		
	Control group (0 mg/kg)	Low dose group (5 mg/kg)	High dose group (50 mg/kg)
IL-2	37 (20-60)	25 (0-84)	100 (25-211)
IL-4	12 (0-18)	13 (8-18)	17 (0-40)
IL-5	6 (3-7)	49 (6-139)	107 (11-458)
IL-6	7 (0-22)	68 (32-101)	128 (24-390)
TFN-alpha	20 (11-26)	20 (15-27)	22 (19-26)
IFN-gamma	18 (0-35)	23 (19-32)	33 (17-93)

Preclinical Efficacy Studies – animal models of autoimmune disease

Animal Model	Species	Treatment	Dose	Disease score reduction	Observations	Ref.
Mycobacteria-induced adjuvant arthritis (preventive)	Rat	IV day -10 and 0 before onset of clinical signs	5 mg/kg 1 mg/kg	> 80% > 80%	Transient increase of CD25+CD4+ T cells (2-10x in LN and blood), reduction of cartilage destruction, inhibition of cell infiltration in bone.	(TGN01-NC-015, 2004)
Mycobacteria-induced adjuvant arthritis (early intervention)	Rat	IV day 3 and 6 after onset of clinical signs	5 mg/kg 1 mg/kg	> 80% > 80%		(TGN01-NC-015, 2004)
Mycobacteria-induced adjuvant arthritis (late intervention)	Rat	IV day 6 and 9 after onset of clinical signs	5 mg/kg 1 mg/kg	> 80% > 80%		(TGN01-NC-015, 2004)
Collagen-Induced Arthritis	Rat	IV, SC after onset of disease	0.03 to 3.0 mg/kg	no reduction	Aggravation of disease at highest dose, possibly due to enhanced B-cell mediated autoimmune response	(TGN01-NC-016, 2004)
Experimental Autoimmune Encephalomyelitis (EAE)	Rat	IV day 0 (prophylactic) and day 10 (disease onset)	0.03 to 1mg total dose	> 80%	Transient dose dependent expansion of regulatory T cells	(Beyersdorf, 2005)
Experimental Autoimmune Neuritis (EAN)	Rat	IP day -7	1mg total dose	> 50%	Reduced infiltration of the sciatic nerve in active EAN	(Schmidt et al., 2003)
Collagen-Induced Arthritis (CIA)	Rhesus monkey	IV prophylactic day -28, day 0	5 mg/kg 2.5 mg/kg	n.d.	Clinical response in 4/6 animals, delayed onset of disease, decrease in cartilage breakdown products	(TGN01-NC-017, 2004)

n.d. = not detected

Human B-CLL cells + TGN1412: Cytokine release into S/N after 48 hours



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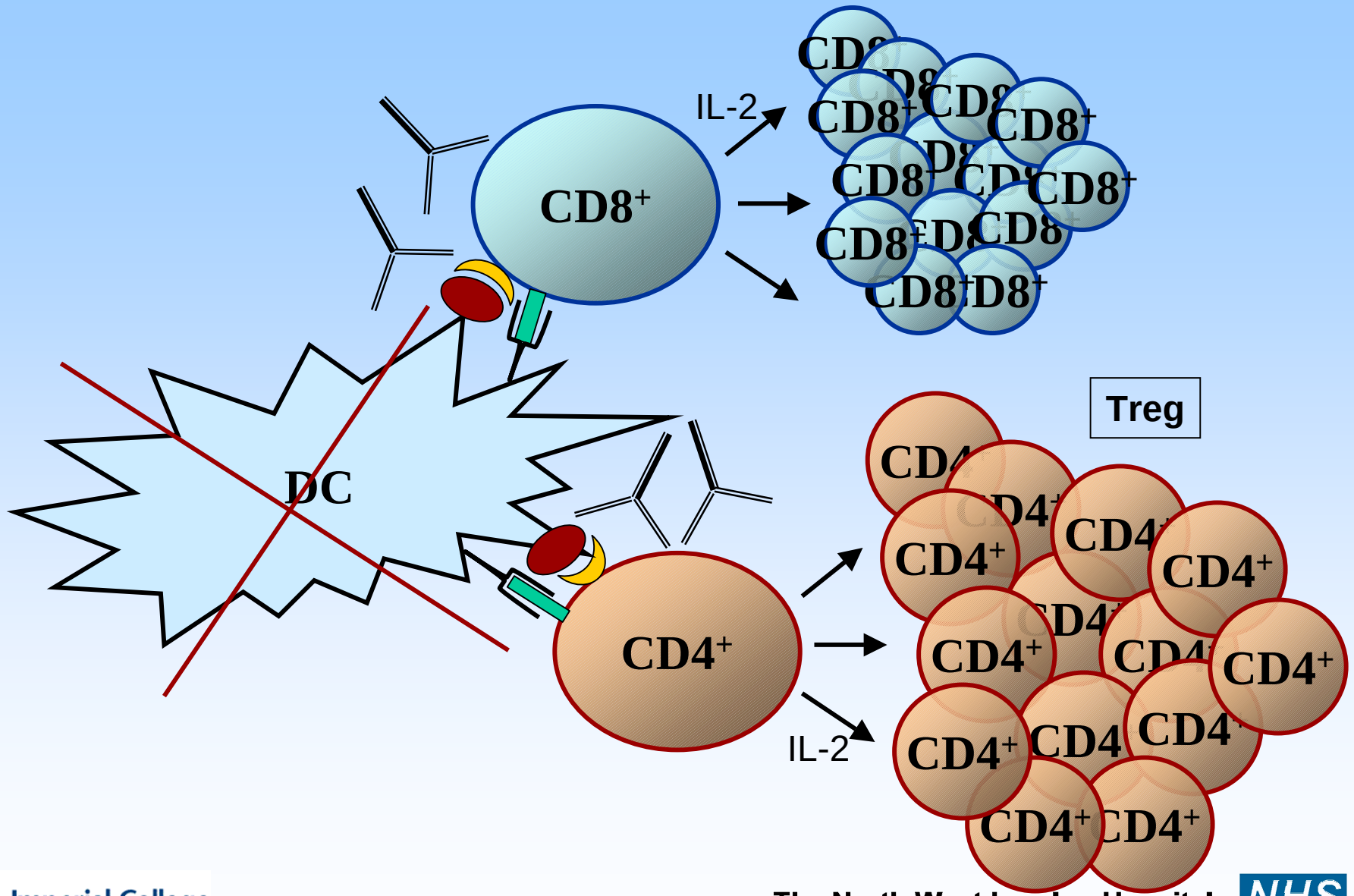
TGN1412: Preclinical data



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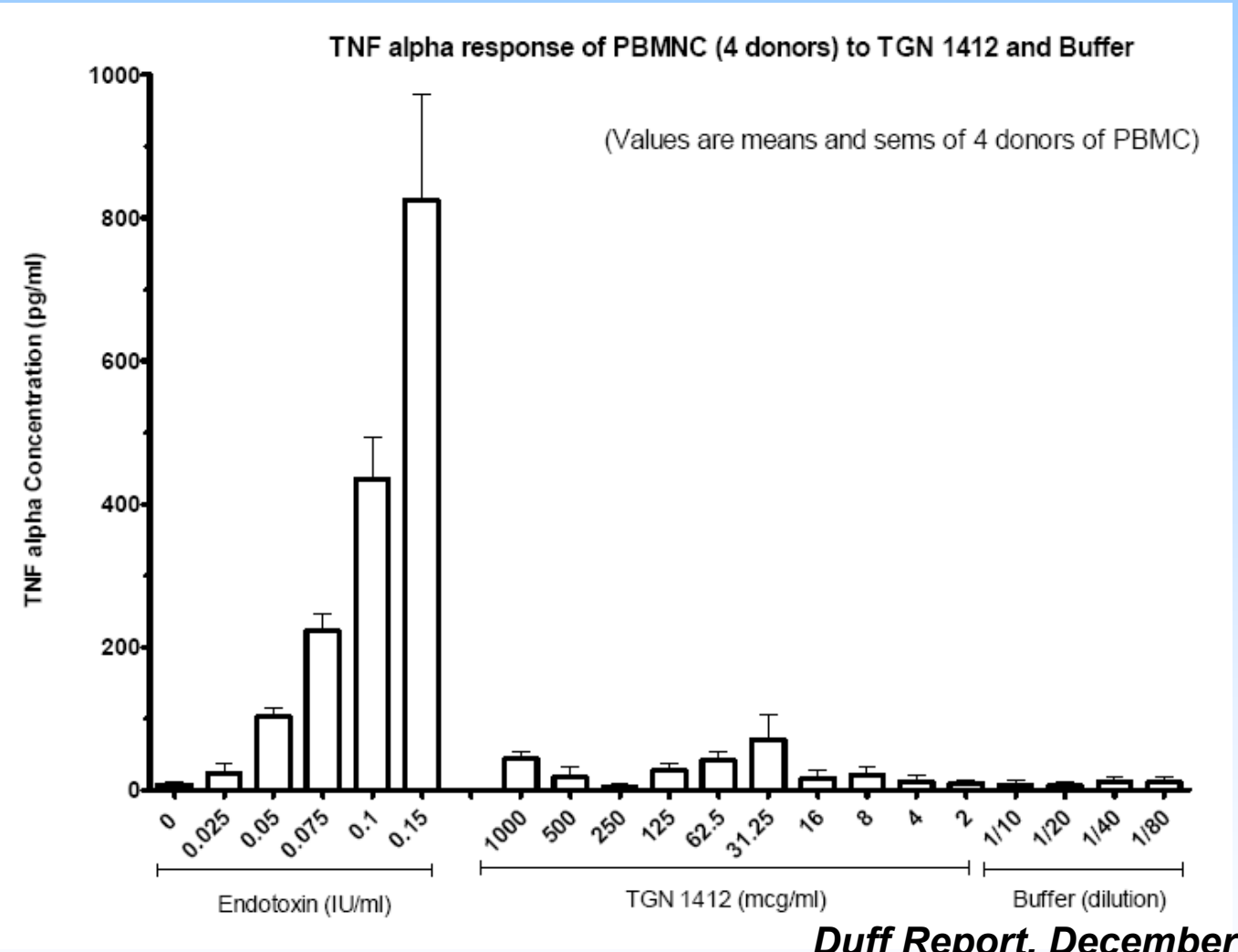
Healthy Human PBMNCs + TGN1412



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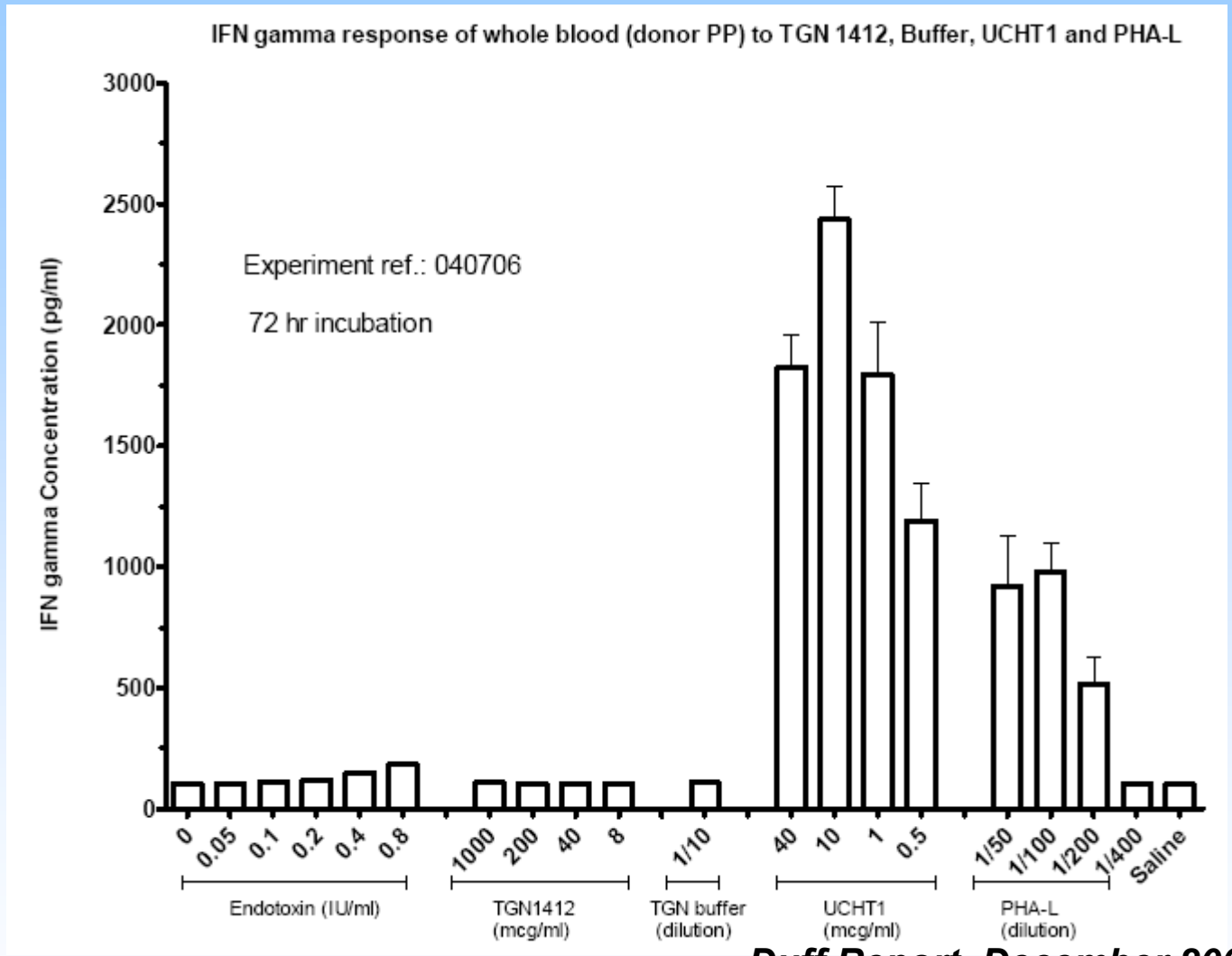
Healthy Human Whole Blood + TGN1412



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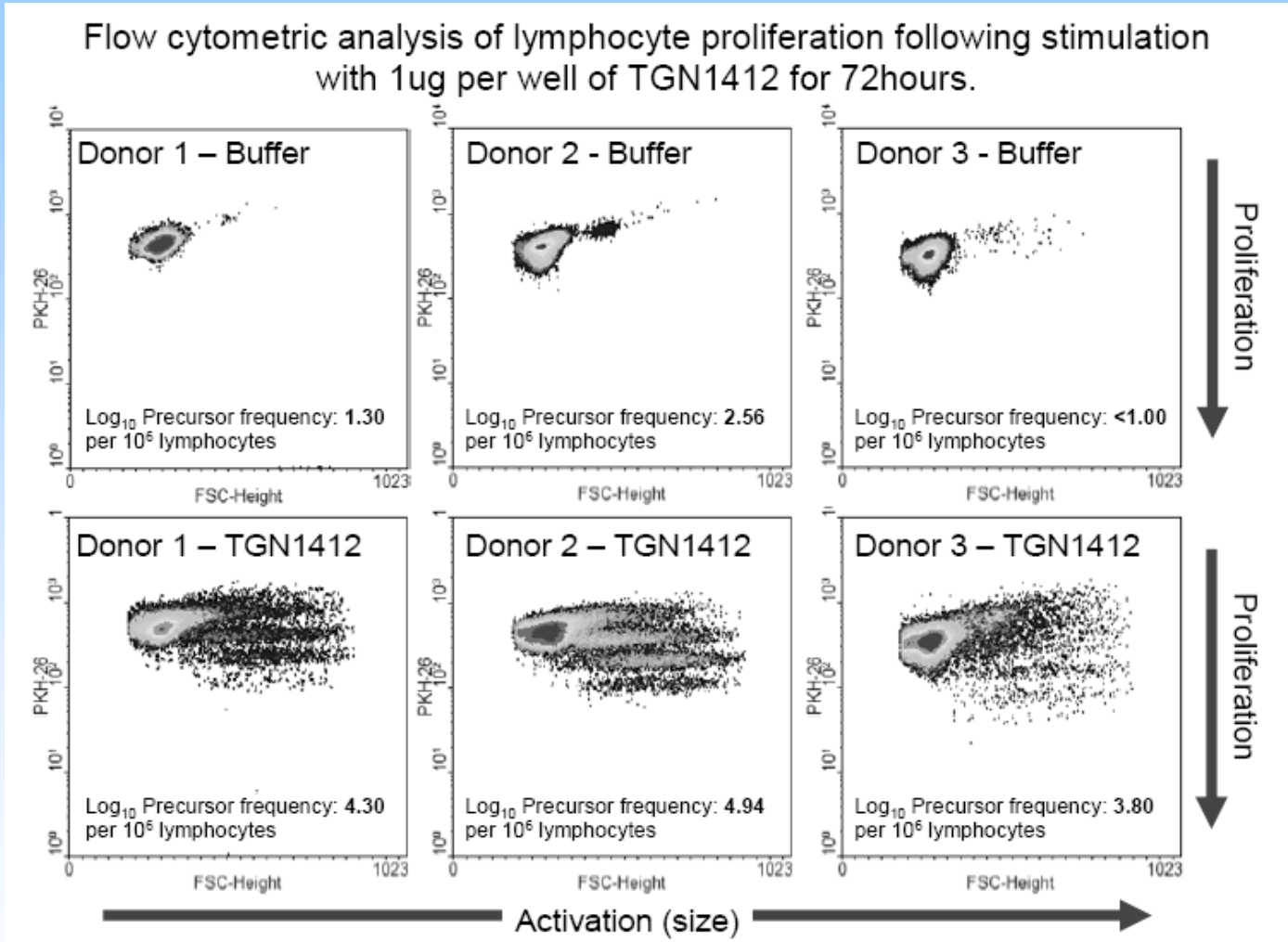
Immobilized TGN1412: Lymphocyte Proliferation



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In vitro Immobilized TGN1412

Summary of *in vitro* activation and proliferation responses of human and Cynomolgus macaque lymphocytes to immobilised TGN1412

	TGN1412 evoked activation	TGN1412 evoked proliferation	IL-2 evoked activation	IL-2 evoked proliferation	TGN1412+IL-2 evoked activation	TGN1412+IL-2 evoked proliferation
Human PBMC	++++	++++	–	–	Could not be tested*	Could not be tested*
Macaque PBMC	++	–	–	–	+++	+++

*: TGN1412 stimulates activation, IL-2 secretion and proliferation when given alone.

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Did pre- or post-clinical testing give insights?

NO…except for what did not happen

So what happened?
The data show:

- Early rise in TNF – prestored, non-Tcell
- Lung effects early - ?specific activation – first pass
- All volunteers had same response - unusual
- Early Immune recovery – similar in all volunteers despite “specific” treatments received

How do we prevent this from happening in the future?

We cannot, but…

1. **Be humble about the data** - Do not be lulled into a false sense of security with the science, *in vitro* and *in vivo* (especially with immune targets), and do not ignore data
2. **Prepare for the unexpected** - Careful "defensive" trial design in case unexpected occurs
3. **Think outside the box and use common sense** – what is different about this agent that might cause problems, organs/cells affected, & is the dosing specific for the agent?

How did we fail to protect the volunteers?

- Scientific rationale
- Pre-clinical testing
- Design of clinical trial
- Regulatory safe-checks
- Conduct of clinical trial
- Monitoring & follow-up of SAE

"Strategy on the pre-clinical development of a new medicine must be science-based, justified case-by-case by individuals with appropriate training."

Duff Report, 2006

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Acknowledgements

Authors

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- M. Brunner
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NHS Staff

Northwick Park & St. Mark's Hospital

Other London Hospitals

The Patients

Antigen Presentation Research Group
Imperial College London
Northwick Park & St. Mark's site

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