Preclinical immunogenicity testing

Christian Ross, Lisbeth Bjerring Jensen, Inger Mollerup

Immunogenicity studies in the preclinical phase

Scientific background

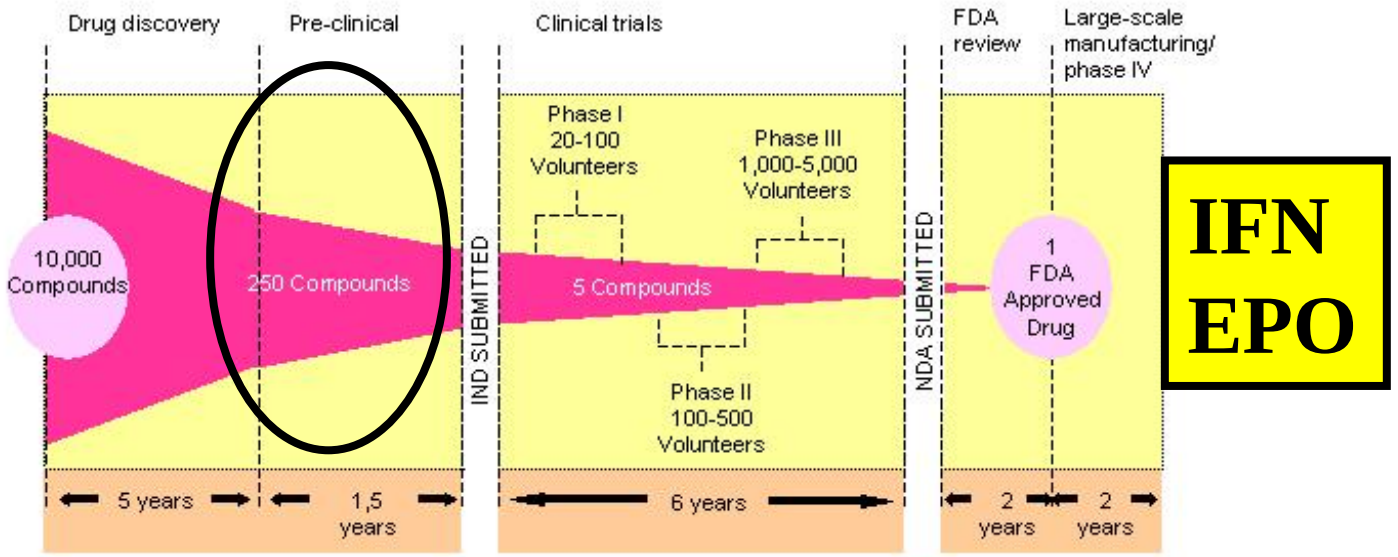
Risk based approach - planning of the preclinical immunogenicity program

Current aspects of preclinical immunogenicity program

Predictive value of preclinical immunogenicity testing ?

Future aspects of preclinical immunogenicity testing

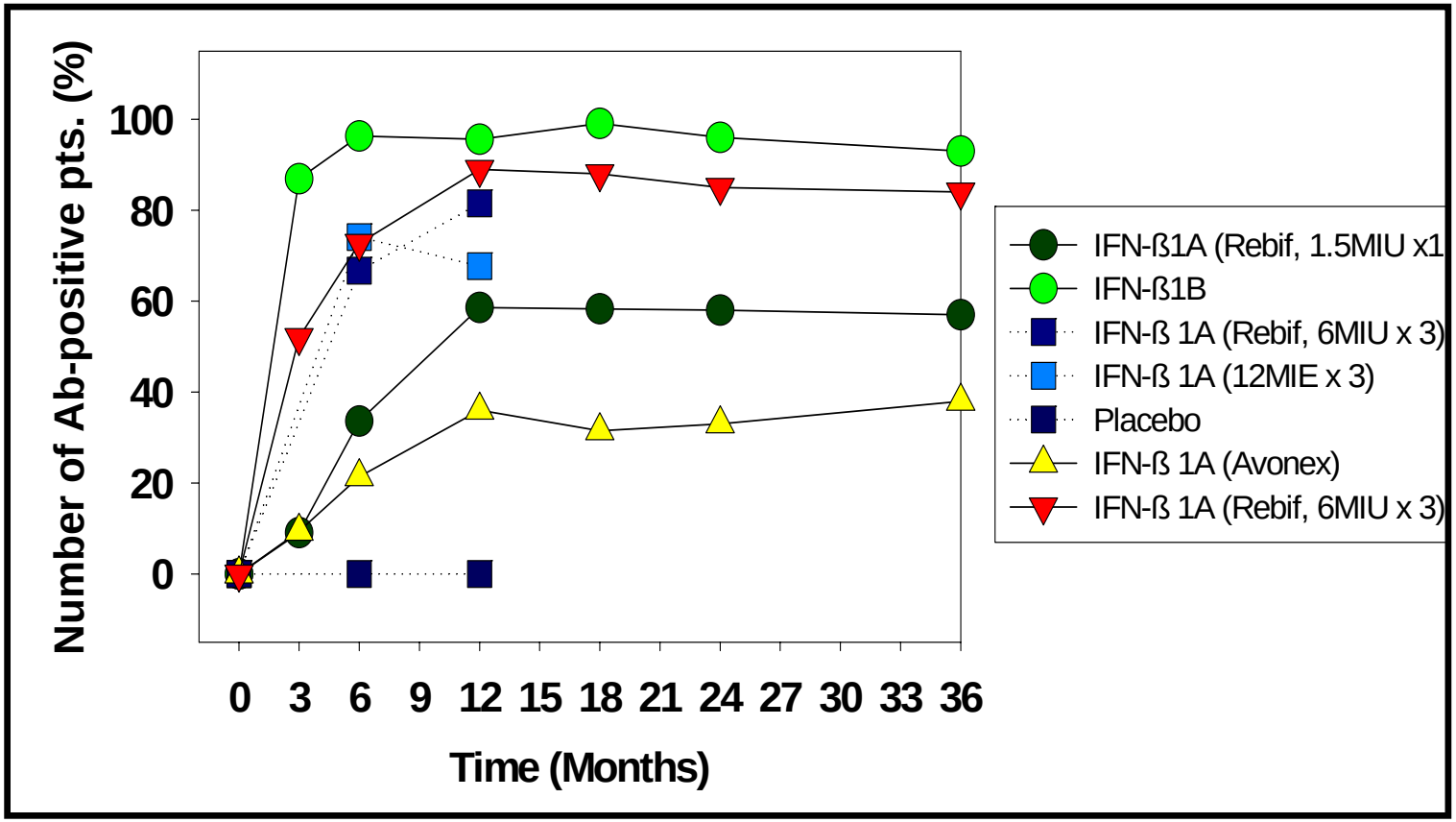
Attrition Rate for Biopharmaceutical Drug Development



IFN
EPO

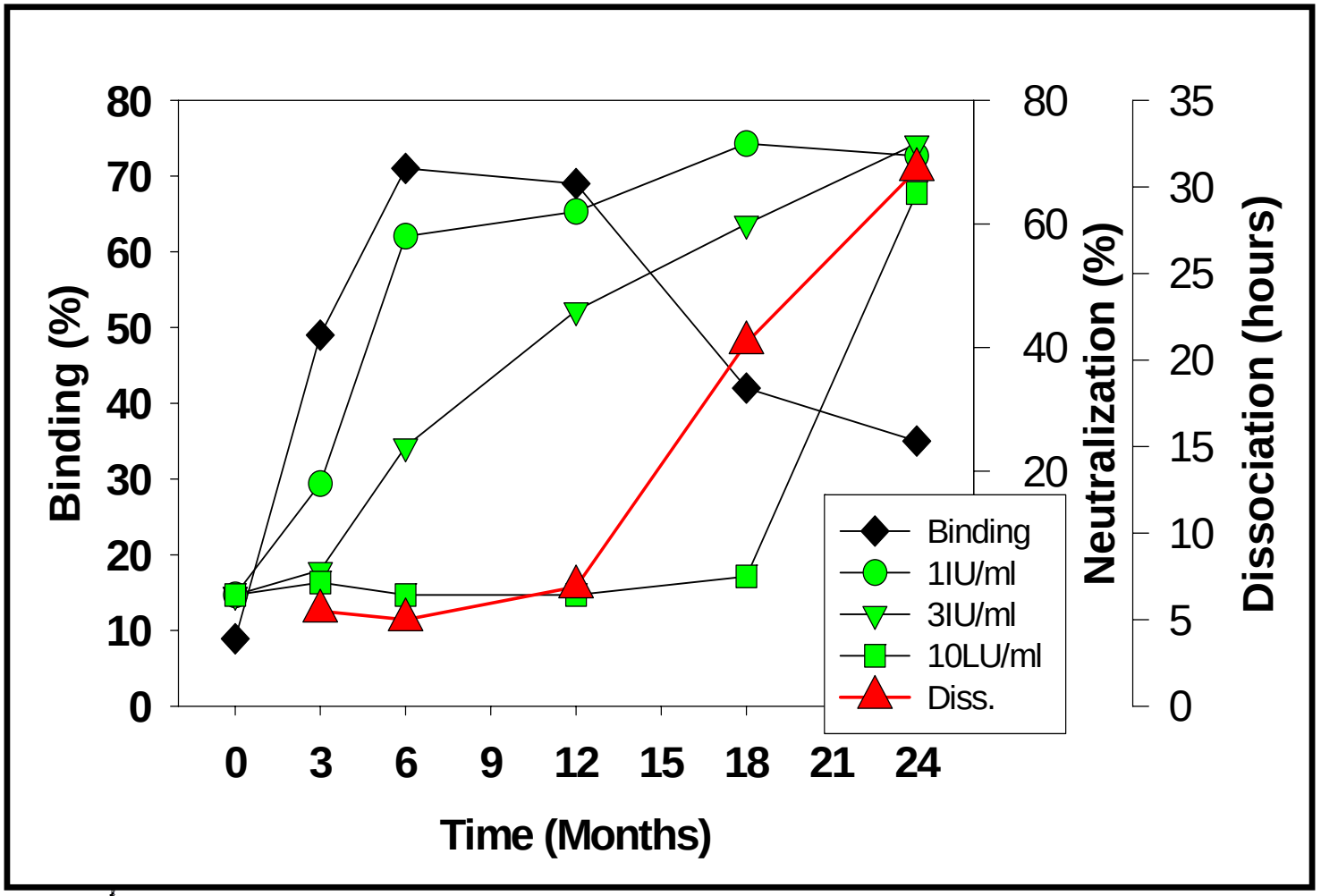
Quelle: Burrill Report Biotech 2006

Varying immunogenicity (bAb) of different IFN-beta preparations in MS



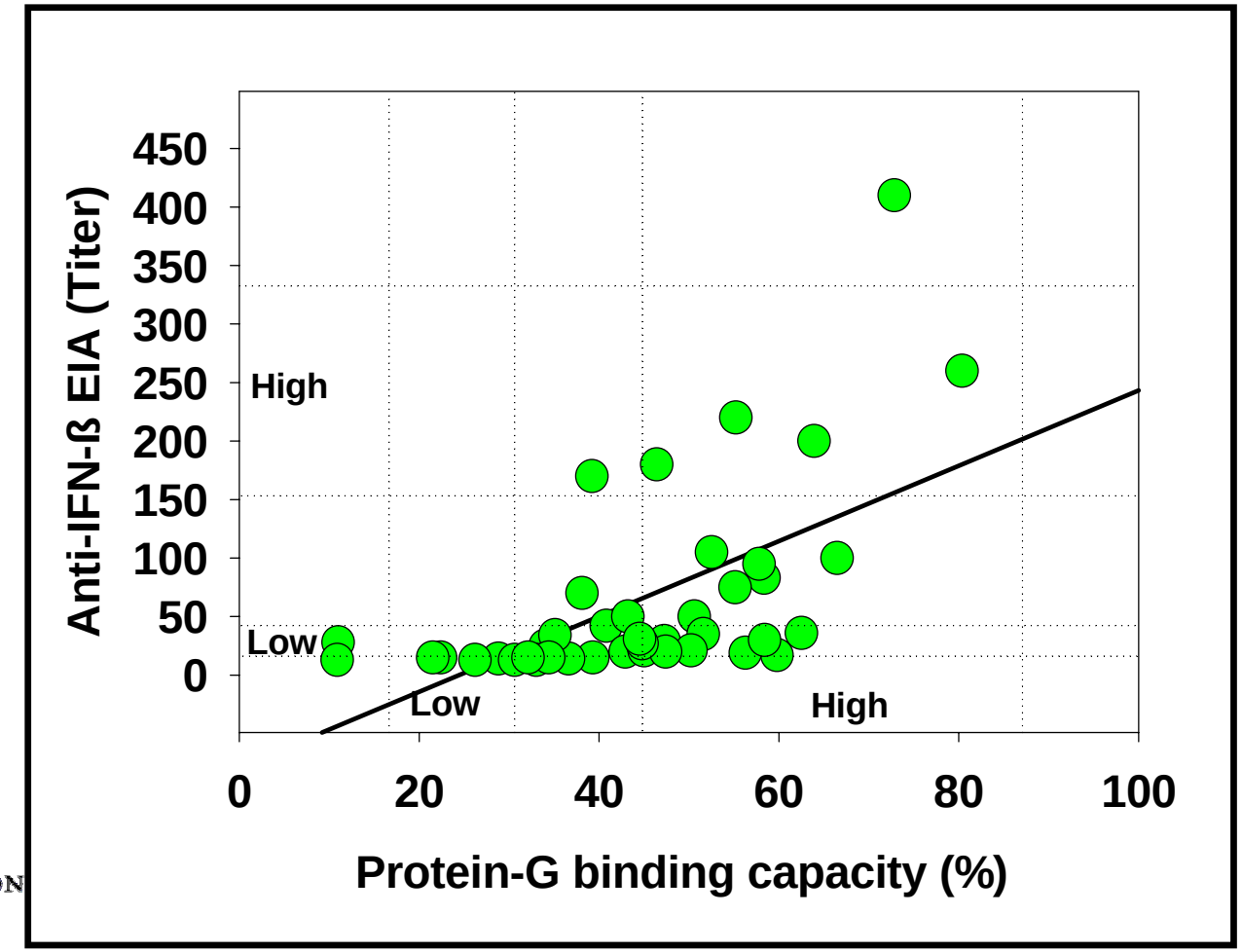
Ross et al

Binding and neutralizing antibodies over time



Ross et al

Significant variation between laboratories and assays



Ross et al

Fig. 1

Estimating the sensitivity and specificity of diagnostic tests[1]

Test results	True diagnosis 'gold standard': Disease present	Disease absent	
Positive	a True positive	b False positive	a + b
Negative	c False negative	d True negative	c + d
	a + c	b + d	

Sensitivity = a / (a + c)
Specificity = d / (b + d)

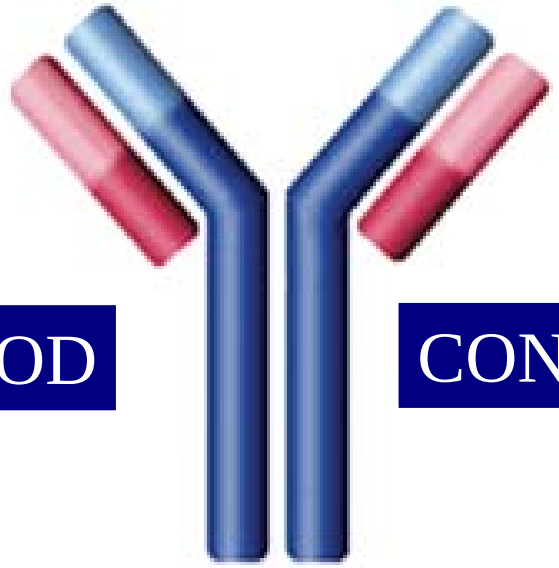
Positive predictive value = a / (a + b)
Negative predictive value = d / (c + d)

Positive likelihood ratio = $\frac{a / (a + c)}{b / (b + d)}$

Negative likelihood ratio = $\frac{c / (a + c)}{d / (b + d)}$

Planning of preclinical immunogenicity program

RISK BASED APPROACH



LIKELIHOOD

CONSEQUENCE

(for review, Shankar et al, Nature Biotechnology, 2007)

Assay development

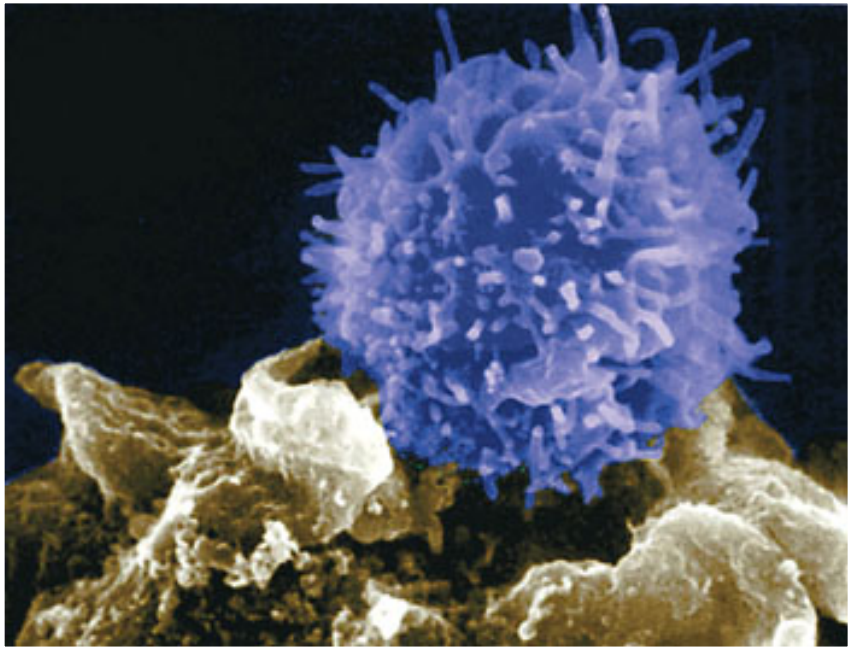
Screening assay
Confirmatory assay
Neutralizing/functional assay

Supporting exposure profile in preclinical animal studies
Preparation for clinical studies

Preclinical animal models

Insulin
Growth hormone
EPO
IFN

T-cell epitope models



Future recommendations

Validate correlation between preclinical analyses and clinical results including the ”Risk-based approach” to immunogenicity.

Guideline requirements should be based on validated analyses and data.

Active ongoing interaction between authoraties, pharmaceutical industry, international organizations and research institutions regarding immunogenicity. EIP.

Based on the unclear conclusions from present preclinical immunogenicity testing a full clinical program should **allways** be included in drug development

Preclinical immunogenicity testing does not yet show the clinical future in the crystal ball !