Pharmacokinetic and Pharmacodynamic Considerations in the Development of Macromolecules

Pamela D. Garzone, Ph.D.

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OUTLINE OF LECTURE TOPICS

- Macromolecules
- Interspecies Scaling
- Pharmacokinetic Characteristics
  - Scientific Issues
- Pharmacodynamics
- Monoclonal Antibodies

REPRESENTATIVE MARKETED MACROMOLECULES

Macromolecule	Trade Name
Erythropoietin	Epogen (Amgen)
Growth Hormone	Nutropin (Genentech)
G-CSF	Neupogen (Amgen)
IL-2	Proleukin (Chiron)
IL-11	Neumega (GI)
Factor IX	BeneFIX (GI)
rt-PA	Alteplase (Genentech)

APPROVED MONOCLONAL ANTIBODIES

Name	Approval	Indication
Avastin **Bevacizumab**	Feb, 2004	First line (with 5-FU) in metastatic colon CA
Erbitux **Cefuximab**	Feb, 2004	Alone or in combination in metastatic colon CA
Raptiva **Efalizumab**	Oct, 2003	Moderate to severe psoriasis
Xolair **Omalizumab**	June, 2003	Asthma
Humira **Adalimumab**	Dec, 2002	Prophylaxis of acute organ rejection
Campath **Alemtuzumab**	May, 2001	Second line treatment of β-cell CLL in patients

ASSAYS FOR MACROMOLECULES

- Immunoassays
  - ELISA (Enzyme-Linked Immuno-sorbent Assay)
  - RIA (Radioimmunoassay)
  - IRMA (Immunoradiometric Assay)
  - RRA (Radioreceptor Assay)

INTERSPECIES SCALING OF MACROMOLECULES

Factors to Consider

- Species specificity
- Glycosylation and sialation
- Binding proteins
- Size, shape and charge
- Relative abundance of tissue receptors

ALLOMETRIC EQUATIONS FOR SOME MACROMOLECULES

Macromolecule	Allometric Equations V_1	CL
Factor IX	$87\ W^{1.26}$	$14\ W^{0.68}$
Factor VIII	$44\ W^{1.04}$	$10\ W^{0.69}$
IL-12	$65\ W^{0.85}$	$8\ W^{0.62}$
GH	$68\ W^{0.83}$	$7\ W^{0.71}$
rt-PA	$91\ W^{0.93}$	$17\ W^{0.84}$

INITIAL COMPARTMENT VOLUME PREDICTED BY ALLOMETRIC SCALING COMPARED WITH OBSERVED V_1

Macromolecule	Human Parameter: V_1 Predicted (mL)	Observed (mL)
FIX	18,380	10,150
Factor VIII	3,617	3,030
IL-12	2,406	3,360
GH	2,243	2,432
rt-PA	5,814	4,450

ELIMINATION CLEARANCE PREDICTED BY ALLOMETRIC SCALING COMPARED WITH OBSERVED CL

Macromolecule	Human Parameter: Cl Predicted (mL/hr)	Observed (mL/hr)
FIX	248	434
Factor VIII	195	174
IL-12	113	406
GH	148	175
rt-PA	646	620

ALLOMETRIC EQUATIONS for EGF Mab PK PARAMETERS

Parameter (Y)	Coefficient (*a*)	Exponent (*b*)	*r*
V_d (mL)	**219**	**0.84**	**0.92**
CL (mL/hr)	**4.07**	**0.85**	**0.94**

COMPARISON BETWEEN the PREDICTED EGF PK PARAMETERS and OBSERVED PK PARAMETERS

Parameter (Y)	Predicted PK Parameter Estimate	Observed PK Parameter in Cancer Patients
V_d (L/kg)	0.01	0.04
CL (mL/hr/kg)	0.22	0.98

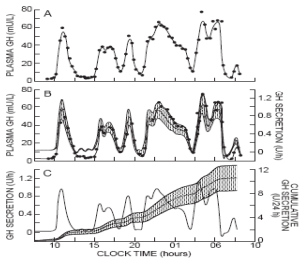
PHARMACOKINETIC CHARACTERISTIC OF MACROMOLECULES

- Endogenous concentrations
- Absorption
- Distribution
- Metabolism
- Elimination

THE PROBLEM OF ENDOGENOUS CONCENTRATIONS OF MACROMOLECULES

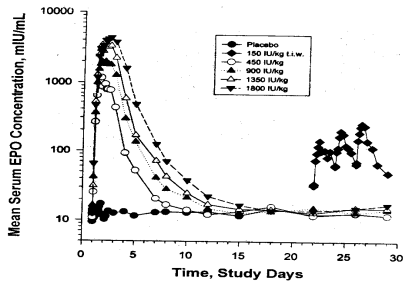
- Endogenous concentrations - What do you do with them?
- Two examples
  - Growth Hormone
  - Erythropoietin

Growth Hormone



Albertsson-Wikland K, et al. Am J Physiol 1989;257:E809-14.)

ERYTHROPOIETIN

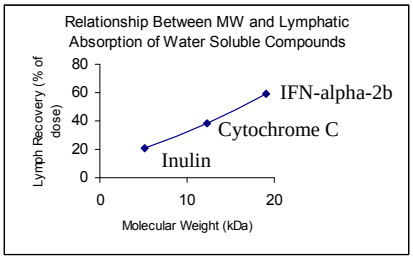


Cheung et al CPT 1998; 64:412-423

ABSORPTION OF MACROMOLECULES

- Flip-flop model
- Site of administration

RELATIONSHIP BETWEEN MW AND LYHMPHATIC ABSORPTION OF WATER SOLUBLE COMPOUNDS

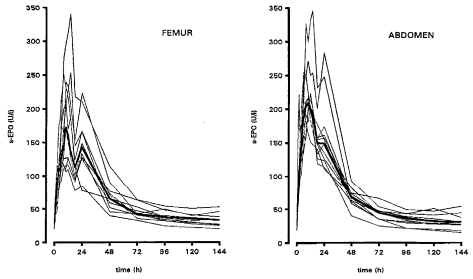


Supersaxo A et al. Pharm Res 1990; 7:167-169

COMPARISON OF ABSORPTION AND ELIMINATION RATE CONSTANTS

Macromolecule	Route of Administration	K_a (hr^{-1})	K_e (hr^{-1})
GH	SC	0.23 ± 0.04	0.43 ± 0.05
	IV		2.58
IFN-α-2b	SC	0.24	0.13
	IV		0.42
Erythropoietin	SC	0.0403 ± 0.002	0.206 ± 0.004
	IV		0.077

SITE OF INJECTION EFFECTS ON EPO ABSORPTION



Jensen JD et al Eur J Clin Pharmacol 1994; 46:333-337

DISTRIBUTION OF MACROMOLECULES

- Volume of Distribution
- Binding Proteins

DISTRIBUTION VOLUMES OF REPRESENTATIVE MACROMOLECULES

Macromolecule	MW (kDa)	V_1 (mL/kg)	V_{ss} (mL/kg)
Inulin	5.2	55	164
Factor IX	57	136*	271*
IL-2	15.5	60	112
IL-12	53	52	59
G-CSF	20	44	60
rt-PA	65	59	106

* Calculated from literature

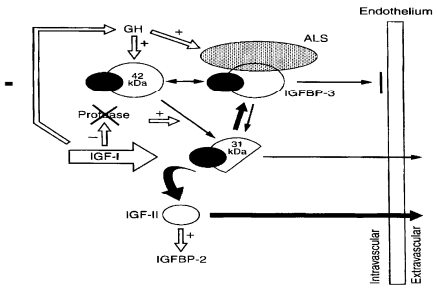
PHARMACOKINETICS of MARKETED MONOCLONAL ANTIBODIES

Mabs	Molecular Weight (kD)	$T_{1/2}$[a] (Days)	V_1[a] (L)	Vss[a]
Avastin	149	13-15	3	3.5-4.5 L
Erbitux	152	ND[b]	2.7-3.4	2-3 L/m^2
Raptiva	150	6-7.5[c]	NR[d]	9 L[e]
Humira	148	12-18	3	5 L
Campath	150	1-14[f]	NR[d]	7-28 L

EFFECTS & RELEVANCE OF MACROMOLECULE BINDING TO α_2-MACROGLOBULIN

Macromolecule	Effect	Relevance
NGF		Assay inteference
IL-1	Regulation of proliferation of thymocytes	Regulatory protein
IL-2	Impaired proliferation of T-cells	Inactivation
TGF_β	Growth of kidney fibroblasts	Clearance

HYPOTHETICAL MODEL of the BINDING EFFECTS of IGF-1



METABOLIC EFFECTS OF MACROMOLECULES

- Effects on P450s

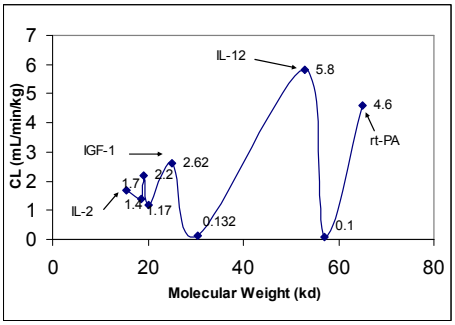
EFFECTS OF MACROMOLECULES ON P450 CYP ENZYMES

Macromolecule	Isoenzyme	Effects
IFN-γ	CYP2C11	Decreased mRNA and enzyme levels
IL-1	CYP2C11	Decreased mRNA and enzyme levels
	CYP 2D	Decreased mRNA and enzyme levels
IL-2	CYP2D1	Increased mRNA and enzyme levels
IL-6	CYP2C11	Decreased mRNA and enzyme levels
TNF	CYP2C11	Decreased enzyme levels

EXCRETION OF MACROMOLECULES

- Contributions of kidney and liver
- CHO vs E. Coli produced
- Receptor mediated clearance

RELATIONSHIP BETWEEN MOLECULAR WEIGHT AND ELIMINATION CLEARANCE



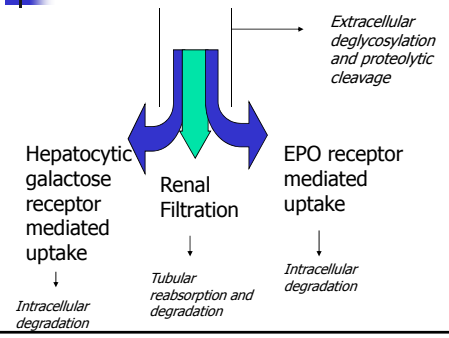
LIVER CELL SURFACE RECEPTORS FOR CLEARANCE OF CARBOHYDRATES & MONOSACCHARIDES

Specificity	Cell Type
Gal/Gal/NAc	Liver parencymal cells
Gal/GalNAc	Liver Kupffer and endothelial cells Peritoneal macrophages
Man/GlcNAc	Liver Kupffer and endothelial cells Peritoneal macrophages
Fuc	Liver Kupffer cells

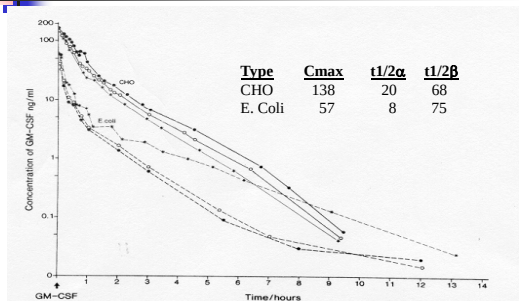
DIFFERENCES BETWEEN rhEPO AND NESP (NOVEL ERYTHROPOIESIS-STIMULATING PROTEIN)

- rhEPO
  - 165 normal amino acid sequence
  - Up to 40% carbohydrate
  - 3 N-linked sugar chains
  - Up to 14 sialic acids
  - 30.4 Kd
  - Plasma $T_{1/2}$= 4-8 hrs
- NESP
  - 5 amino acid exchanges
  - Up to 52% carbohydrate
  - 5 N-linked sugar chains
  - Up to 22 sialic acids
  - 38.5 Kd
  - Plasma $T_{1/2}$= 24 hrs

METABOLIC FATE OF EPO



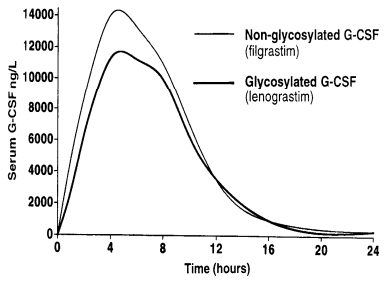
SERUM CONCENTRATION-TIME PROFILES FOR CHO VS. E. Coli PRODUCED GM-CSF



Type	Cmax	t1/2α	t1/2β
CHO	138	20	68
E. Coli	57	8	75

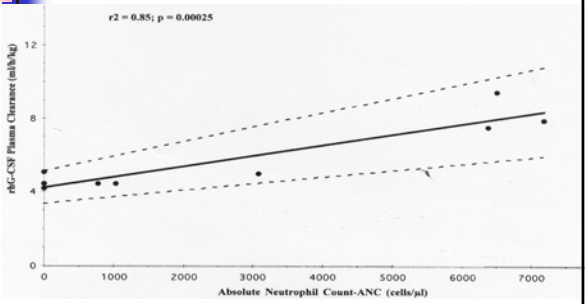
Mortensen HD et al. Eur J Haematol 1993; 50:32-36

SERUM CONCENTRATION-TIME PROFILES FOR NON-GLYCOSYLATED VS. GLYCOSYLATED G-CSF



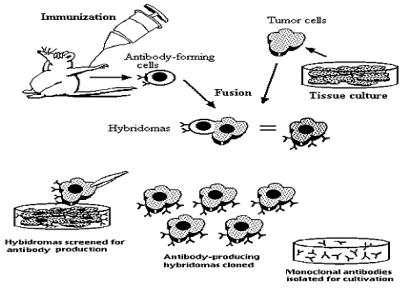
Watts et al. Br J Haematol 1997; 98:474-479

RELATIONSHIP BETWEEN G-CSF CLEARANCE AND ABSOLUTE NEUTROPHIL COUNT

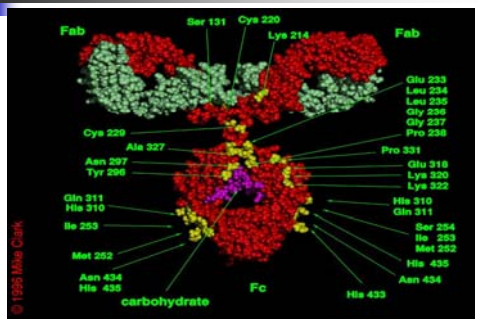


Ericson SG et al. Exper Hematol 1997; 25:1313-1325

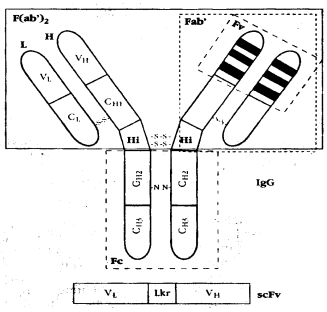
MONOCLONAL ANTIBODY PRODUCTION



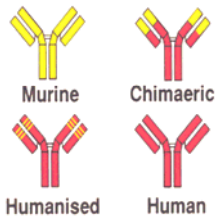
HUMAN IgG



IgG and SINGLE-CHAIN Fv



CONCEPT OF ANTIBODIES



PROPOSED HUMAN PLASMA CLEARANCE of DIFFERENT ANTIBODY MOLECULES

Antibody Molecule	Molecular Weight (kD)	Relative Plasma Clearance (Cl)
Native intact human IgG	150	≈ 21 days
Fully human/humanized	150	
Chimeric human-mouse IgG	150	
Whole mouse IgG	150	
F $(ab)_2$	110	
Fab'	50	
Single chain FV (scFV)	25	≈ 1 day

Advantages of mAbs

- High specificity
- Long half-life
- Improved benefit-risk ratio (in most therapeutic areas)

Risks of mAbs

- Immune reactions
  - Signs and symptoms
    - Infusion site reactions
    - Fever
    - Influenza syndrome
    - Acute anaphlaxis
    - Systemic inflammatory responses
- Infection
  - Reactivation of latent bacteria or virus

Risks of mAbs (continued)

- Platelet and thrombotic disorders
  - Thrombo- and hematopoietic toxicity
- Auto-immune disease
  - Cutaneous or systemic vasculitis
  - Nephritis
  - Colitis
- Cancer

Safety Related Regulatory Actions for Biologics[1]

- Between 1995 and June 2007, 174 biological products were approved
  - 67 obtained approval in both US and EU
- 82 safety related regulatory actions were issued for 41/174
  - 46 Dear Health Care Professional letter
  - 17 Direct Health Care Professional Communication
  - 19 Black Box warning

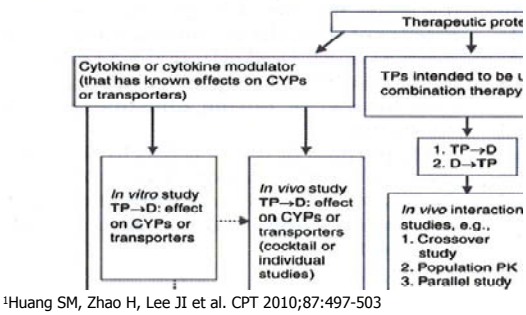
[1]GiezenTJ et al. JAMA 2008; 300:18787-1896

Drug Interactions

- Some of the principles in the recent draft guidance on drug interactions[1] can apply to biologics

[1]US FDA. Draft Guidance for Industry. Drug Interaction Studies-Study Design, Data Analysis and Implications for Dosing and Labeling.

Types of DDI Studies Used During Drug Development of Biologics[1]



[1]Huang SM, Zhao H, Lee JI et al. CPT 2010;87:497-503

Points to Consider for DDIs of Biologics

- In vitro or in vivo animal studies have limited value in predicting clinical interactions
- Evaluating drug-drug interactions is particularly important when the therapeutic index is narrow
- Not all interactions between biologics and small molecule drugs are due to CYP or transporter modulation
- If the biologic is a cytokine modulator, there is compelling evidence that cytokine modulation affects the CYP 450 enzyme system

DESIGN OF ANTIBODIES

- Molecules that can be attached:
  - Enzymes
  - Toxins
  - Viruses
  - Cationic tails
  - Biosensors

CHARACTERISTICS THAT AFFECT THE PHARMACOKINETICS OF MACROMOLECULES

- Physical characteristics
- Post-translational modification
- Binding
- Route of administration
- Duration of administration
- Frequency of administration

PATIENT CHARACTERISTICS THAT AFFECT PHARMACOKINETICS OF MACROMOLECULES

- Age
- Gender
- Disease
- Concurrent drugs

EFFECTS OF GENDER ON GROWTH HORMONE PK/PD

- Daily rhGH dose/kg required to normalize IGF-1 response in GH deficient women is higher than in men
  - Estrogen replacement also significantly increases rhGH dose requirement

Drug-Drug Interactions


The Journal of Clinical Pharmacology
http://www.jclinpharm.org

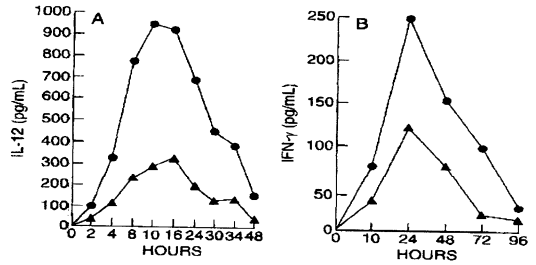
Drug Interaction Studies of Therapeutic Proteins or Monoclonal Antibodies
Iftekhar Mahmood and Martin David Green
J. Clin. Pharmacol. 2007; 47; 1540 originally published online Oct 25, 2007;
DOI: 10.1177/0091270007308616

The online version of this article can be found at:
http://www.jclinpharm.org/cgi/content/abstract/47/12/1540

PHARMACODYNAMICS OF MACROMOLECULES

- Important considerations
  - Regimen dependency
  - Endpoints
  - Models

REGIMEN DEPENDENCY OF IL-12 PHARMACOKINETICS AND IFN-γ STIMULATION

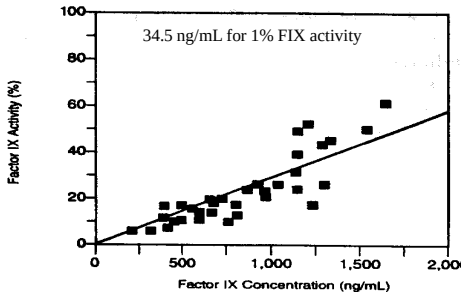


Motzer RJ et al. Clin Cancer Res 1998;4:1183-1191

PHARMACODYNAMIC ENDPOINTS

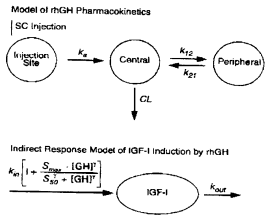
- Easy - replacement proteins
  - rFIX
- Difficult- casade of events
  - IGF-1

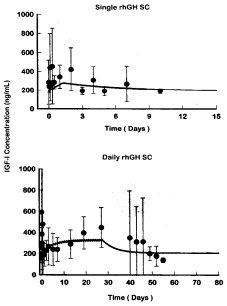
RELATIONSHIP BETWEEN rFIX CONCENTRATION AND ACTIVITY



Schaub et al. Seminars in Hematology 1998; 35:28-32

PK-PD MODEL OF rhGH WITH MEASURED VS. PREDICTED [IGF-1] AFTER SINGLE AND DAILY SC rhGH INJECTIONS





Sun YN et al. JPET 1999; 289:1523-1532

PHARMACODYNAMIC ENDPOINTS

Omalizumab: Free IgE levels
Clinical outcomes

Basiliximab: Soluble IL-2 receptor
CD25+ T lymphocytes ≦1%

Summary

- Use scientific judgement and good sense in the interpretation of PK/PD results with macromolecules
- Application of PK principles that have been developed work with macromolecules
- Difficult to select the most appropriate pharmacodynamic endpoint

Acknowledgements

- Genetic Institute
  - PK/PD Sciences
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- Dr. Juan Lertora