PURDUE UNIVERSITY

Weldon School of Biomedical Engineering

The Convergence of Differences, The Future of Excellence

BME 695N

Engineering Nanomedical Systems

Lecture 14

Challenges of proper drug dosing with nanodelivery systems

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I. Overview of drug dosing problem

A. Problems of scaling up doses from animal systems
B. Basing dosing on size, area, weight of recipient
C. Vast differences between adults in terms of genetics, metabolism
D. Dosing in children – children are NOT smaller adults!
E. Pharmacokinetics – drug distribution, metabolism, excretion, breakdown
F. Conventional dosing assumes drug goes everywhere in the body
G. Targeted therapies – a model for future nanomedical systems?

II. From the animal dosing to human clinical trials

A. Importance of picking an appropriate animal model system

B. Does drug dosing really scale?

C. The “human guinea pig” in clinical trials and beyond!

III. Traditional drug dosing methods

A. Attempts to scale up on basis of area

B. Attempts to scale up on weight/volume

C. Attempts to use control engineering principles

Control Theory for Drug Dosing

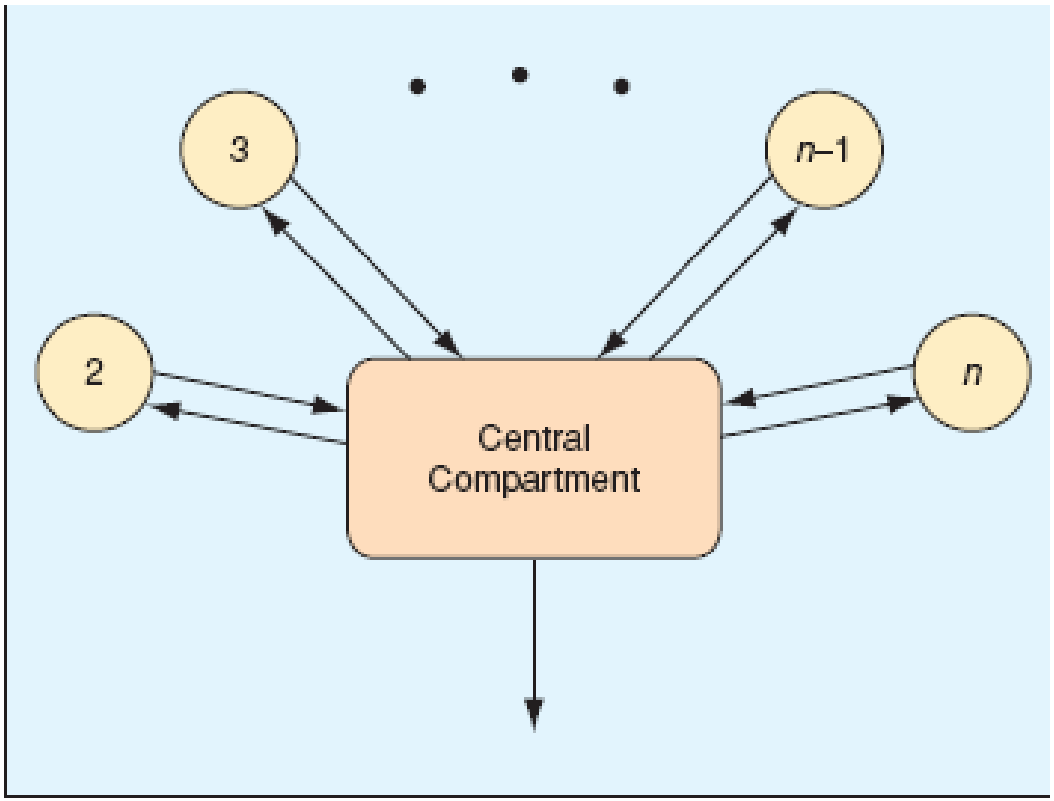


Figure 1. The n-compartment mammillary model. The central compartment, which is the site for drug administration, is generally thought to be comprised of the intravascular blood volume as well as highly perfused organs such as the heart, brain, kidney, and liver. The central compartment exchanges the drug with the peripheral compartments comprised of muscle, fat, and other organs and tissues of the body, which are metabolically inert as far as the drug is concerned.

Source: Bailey & Haddad, 2005

IV. Genetic responses to drug dosing

A. All humans are not genomically equivalent!

B. Predicting on basis of family tree responses

C. SNPs, chips, and beyond…predicting individual drug response

D. After the $ 1000 individual genome scan…more closely tailored individual therapies

V. Dosing in the era of directed therapies

A. How directed therapies change the dosing equation

B. Current generation directed antibody therapies dosing

C. Next generation directed nanomedical systems dosing

VI. Most directed therapies are nonlinear processes

A. Current and pending FDA approved directed therapies

B. Some examples of how a few directed therapies work

1. Complement directed cytotoxicity
2. ADCC-mediated adaptive immunity switch
3. Antibody-directed enzyme producing therapy

Some “Directed Therapies”

FDA-approved monoclonal antibodies for cancer treatment

Name of drug	Type of cancer used to treat
Alemtuzumab (Campath)	Chronic lymphocytic leukemia
Bevacizumab (Avastin)	Colon cancer Lung cancer
Cetuximab (Erbitux)	Colon cancer Head and neck cancer
Gemtuzumab (Mylotarg)	Acute myelogenous leukemia
Ibritumomab (Zevalin)	Non-Hodgkin's lymphoma
Panitumumab (Vectibix)	Colon cancer
Rituximab (Rituxan)	Non-Hodgkin's lymphoma
Tositumomab (Bexxar)	Non-Hodgkin's lymphoma
Trastuzumab (Herceptin)	Breast cancer

Source: http://www.mayoclinic.com/health/monoclonal-antibody/CA00082

“Side Effects” of Directed Therapies

In general, the **more common side effects** caused by monoclonal antibody drugs include:

- Allergic reactions, such as hives or itching
- Flu-like symptoms, including chills, fatigue, fever and muscle aches and pains
- Low blood cell counts, which may lead to bleeding, fatigue and infection
- Nausea
- Diarrhea
- Skin rashes

Source: http://www.mayoclinic.com/health/monoclonal-antibody/CA00082

FDA Approved Monoclonal Antibodies for Directed Therapies Against Cancer

Table 1 Therapeutic mAbs approved for use in oncology

Generic name (trade name)	Origin	Isotype and format	Target	Indication	Year approved by FDA
Unconjugated mAbs					
Trastuzumab (Herceptin)	Humanized	Human IgG1	HER2/*neu*	Breast cancer	1998
Rituximab (Rituxan)	Murine-human chimeric	Human IgG1	CD20	Lymphoma	1997
Cetuximab (Erbitux)	Murine-human chimeric	Human IgG1	EGF receptor	Colorectal cancer	2004
Bevacizumab (Avastin)	Murine-human chimeric	Human IgG1	VEGF	Colorectal, lung cancers	2004
Alemtuzumab (Campath-1H)	Humanized	Human IgG1	CD52	Chronic lymphocytic leukemia	2001
Immunoconjugates					
Ibritumomab tiuxetan (Zevalin) together with rituximab	Murine	^{90}Y-radiolabeled murine IgG1	CD20	Lymphoma	2002
Tositumomab and ^{131}I tositumomab (Bexxar)	Murine	^{131}I-radioabeled murine IgG2a	CD20	Lymphoma	2003
Gemtuzumab (Myelotarg)	Human (drug derived from streptomycete)	Human IgG4 conjugated to calicheamicin	CD33	Acute myelogenous leukemia	2000

Source: Adams & Weiner, 2005

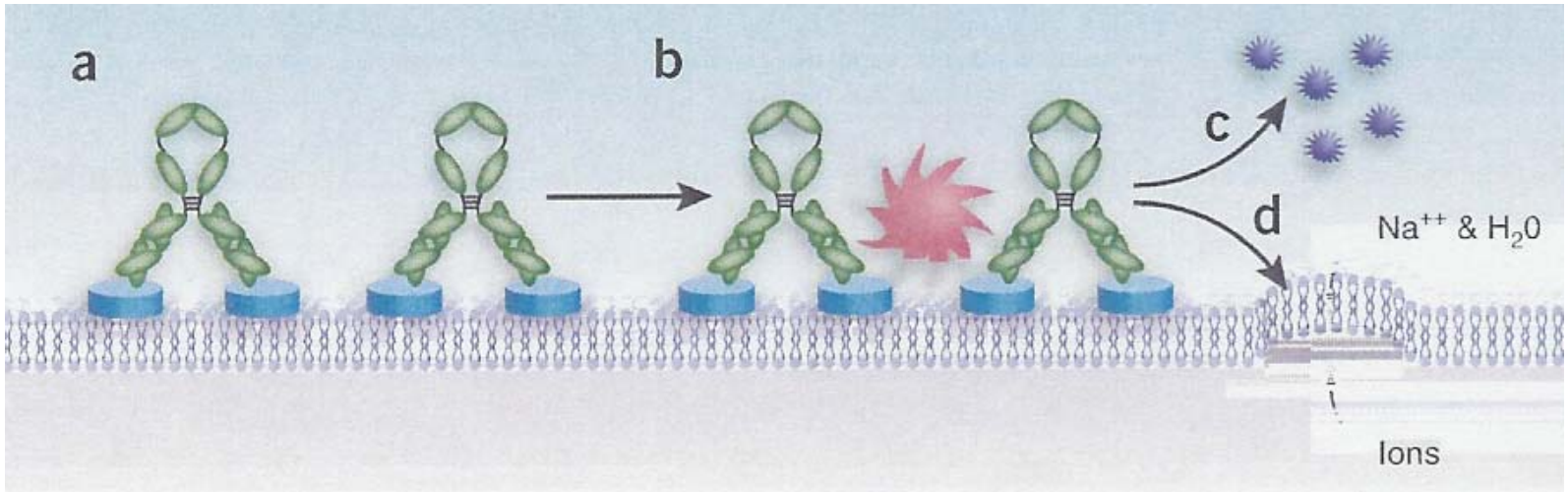
Not Yet Approved Monoclonal Antibodies for Possible Future Use against Cancer

Table 2 Selected novel (unapproved) mAbs in late-stage trials for cancer

Description	Target	Indication	Sponsor
Ch14.18. chimeric mAb	GD2	Neuroblastoma. Used in combination with chemotherapy radiotherapy and colony-stimulating factors	NCI
Rencarex (WX-9250; cG250) chimeric mAb	G250 antigen	Nonmetastatic kidney cancer. Used after surgery	Wilex
MDX-010 humanized mAb	CTLA-4	Melanoma. Used alone and in combination with gp100 peptide vaccine	Medarex
Panitumumab (ABX-EGF) human mAb	EGFR	Non–small cell lung cancer	Abgenix/ Immunex
Remitogen (Hu1D10) humanized mAb	MHC class II	Non-Hodgkin lymphoma	Protein Design Labs

Source: Adams & Weiner, 2005

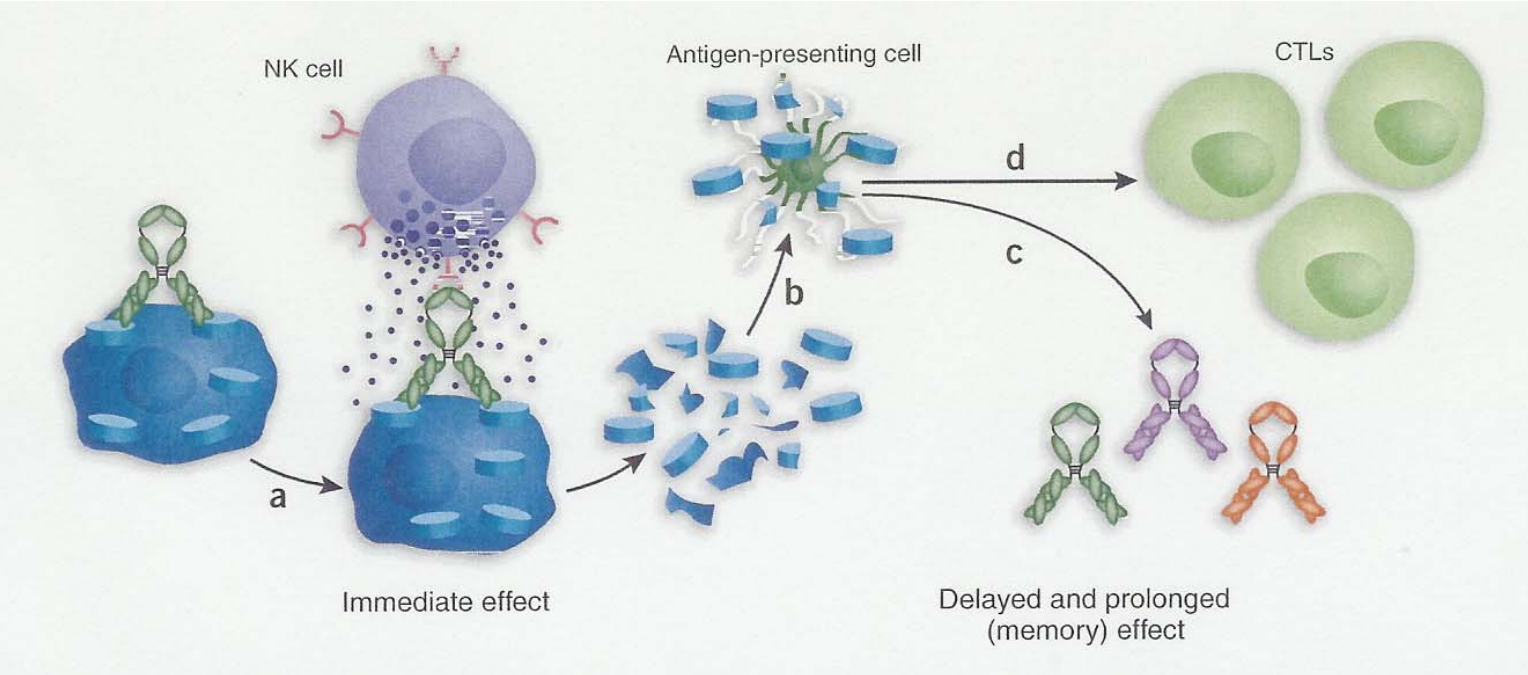
Complement-directed Cytotoxicity



Binding of antibodies on cell surface (a) exposes binding sites for proteins to initiate the complement cascade, (b) ultimately triggering release of chemotactic factors, (c) and the formation of the membrane attack complex, (d) which promotes cell lysis

Source: Adams & Weiner, 2005

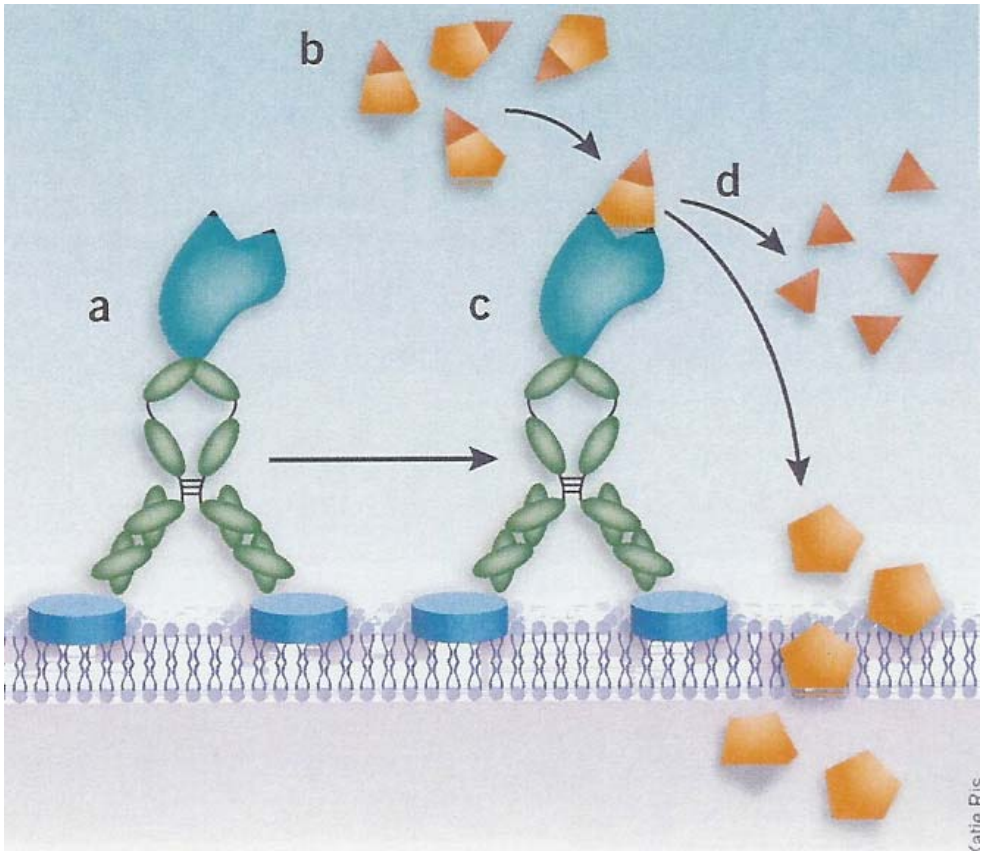
ADCC-Mediated Adaptive Immunity Switch



Antibodies bind to antigens on the tumor cell surface providing targets for FC-receptors on natural killer cells. Cross-linking of receptors triggers release of perforin and granzymes that lyse the tumor cells

Source: Adams & Weiner, 2005

Antibody –Directed Enzyme Producing Therapy



(a) The monoclonal antibody-enzyme conjugate binds to a tumor cell surface antigen, (b) prodrug is administered after clearance of unbound antibody, (c) where the prodrug is cleaved removing the inactivating sequence, and (d) releasing active forms of the drug locally.

Source: Adams & Weiner, 2005

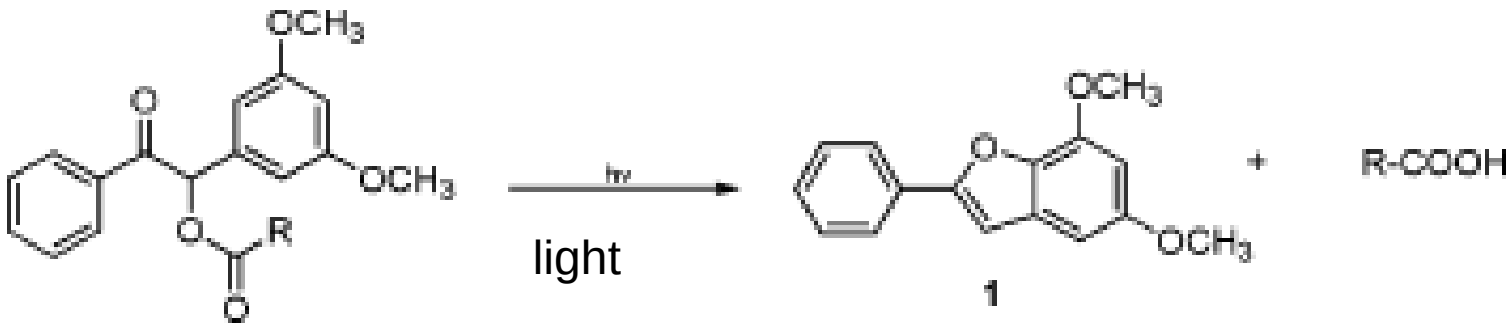
VII. Other ways of controlling dose locally

A. Magnetic field release of drugs

B. Light-triggered release of drugs

Light Triggered Dosing at the Molecule Scale

Scheme 1. Generalized Photochemical Reaction of 3,5-Dimethoxybenzoin Esters



Source: McCoy et al., Light-Triggered Molecule-Scale Drug Dosing Devices 2007.

Light Triggered Dosing at the Molecule Scale

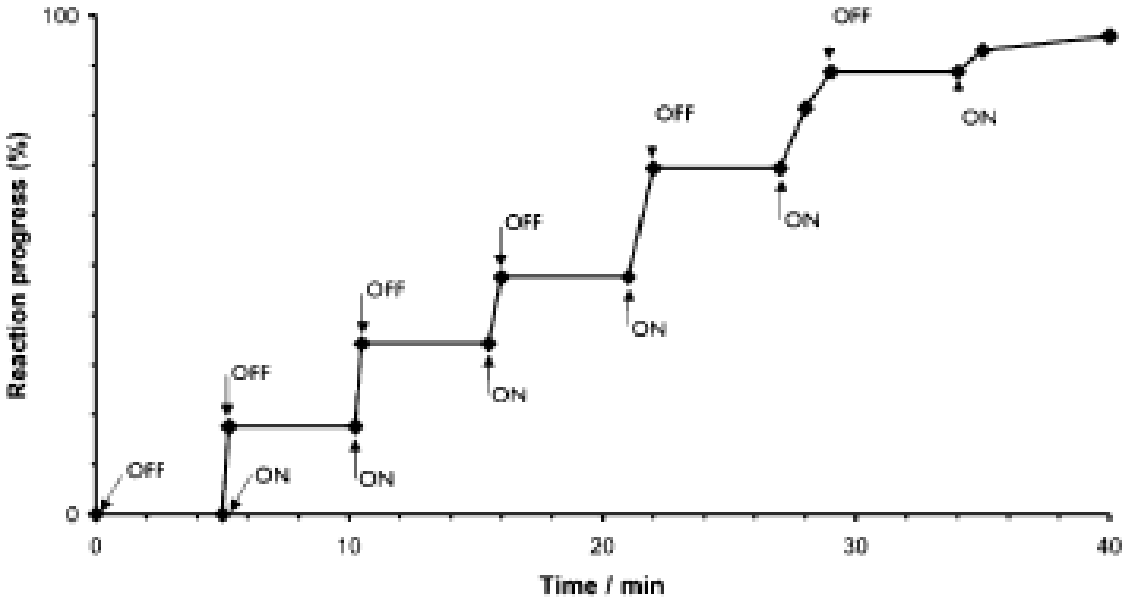


Figure 2. Progress of formation of ibuprofen and **1** from **2** in acetonitrile in light and dark conditions. "On" indicates the beginning of a period of light irradiation; "off" indicates the beginning of a period in dark conditions.

Source: McCoy et al., Light-Triggered Molecule-Scale Drug Dosing Devices 2007.

References

Adams, G.P., Weiner, L.M. Monoclonal Antibody Therapy of Cancer. Nature Biotechnology 23(9): 1147- 1157 (2005)

Bailey, J.M., Haddad, W.M. Paradiigms, Benefits,and Challenges: Drug Dosing Control in Clinical Pharmacology. IEEE Control Systems 35-51, April 2005

McCoy, C.P., Rooney, C., Edwards, C.R., Jones, D.S., Gorman, S.P. Light-Triggered Molecule-Scale Drug Dosing Devices. J. AM. CHEM. SOC. 2007, 129, 9572-9573

Miller, A.A Body Surface Area in Dosing Anticancer Agents: Scratch the Surface! Journal of the National Cancer Institute, Vol. 94, No. 24, December 18, 2002

Nigel Baber & Deborah Pritchard Dose estimation for children. *Br J Clin Pharmacol* 56 , 489–493 2003