Stealth particles (continued)

Biology of vaccination

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**Last Time:**
carriers continued; avoiding the RES

**Today:**
polymer brush theory for protein resistant stealth particles
basic biology of primary immune responses and vaccination

**Reading:**
Plotkin and Orenstein, ‘The Immunology of Vaccination,’ from
*Vaccines* 3rd ed., pp. 28-39
Abbas et al. ‘General properties of immune responses,’ from
*Cellular and Molecular Immunology* 4th ed. Pp. 3-16

**Supplementary Reading:**

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**ANNOUNCEMENTS:**
Take-home exam 2 out today– due last day of class
‘stealth’ particles: avoiding the reticuloreendothelial system

- Eliminate protein binding to particles
- Macrophage receptors unable to bind...
- Enhanced solubility of proteins/stability of particles
Theory of protein-resistant surfaces

Protein modeled as an impenetrable sphere of radius $R$

Model parameters

$\sigma$

$L_0$

$Z$

$L_0$

$\sigma$
Attractive potential

$U_{\text{att}}(z)$

Repulsive potential

$U_{\text{rep}}(z)$
Total potential:

\[ U(z) \]

The graph shows the total potential \( U(z) \) as a function of \( z \) with various curves indicating different components such as \( U_{\text{att}} \), \( U_{\text{rep}} \), and \( U_{\text{total}} \).
Adsorption of small proteins

Langmuir binding model:
1) Proteins are dilute - do not interact with one another
2) Proteins bind to a finite number of unique surface sites
Achieving protein-resistant stealth particles

What condition for equilibrium primary protein adsorption resistance?
Adsorption of large vs. small proteins

Figure 2. Large proteins can approach the surface only by compressing the brush. The free energy penalty associated with the compression mechanism favors secondary adsorption at the outer edge of the brush.

Kinetic protein resistance: Depends on $L_0$ and $\sigma$, but $s,R$ dependence still dominates

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Comparison of theory with experiment

Surface plasmon resonance measurements:

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Please see: Figure 7 in Efremova, et al. "Measurements of Interbilayer Forces and Protein Adsorption on Uncharged Lipid Bilayers Displaying Poly(ethylene glycol) Chains."

Comparison of theory with experiment

Figure removed for copyright reasons. Please see: Figure 9 in Efremova, et al. "Measurements of Interbilayer Forces and Protein Adsorption on Uncharged Lipid Bilayers Displaying Poly(ethylene glycol) Chains." *Biochemistry* 39 (2000): 3441-51.

Figure removed for copyright reasons. Please see: Figure 9 in Efremova, et al. "Measurements of Interbilayer Forces and Protein Adsorption on Uncharged Lipid bilayers Displaying Poly(ethylene glycol) Chains." *Biochemistry* 39 (2000): 3441-51.
Additional benefits of PEGylated carriers: improved carrier stability

Liposomes:
Synthesis of ‘stealth’ particles

e.g. Pluronics:
- PEO
- PPO

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Example stealth particle results: PEGylated PLGA nanoparticles

Poly(vinyl alcohol): Adsorbs to surface of organic droplets to provide initial stability to forming spheres

Block copolymer localizes at organic/aq. solution interface

PEG = 5KDa, PLGA = 40 KDa

Fig. 1. Structure of the PEG–PLGA copolymer.
Block copolymer localization at aqueous/polymer interfaces

Fig. 1. Structure of the PEG–PLGA copolymer.

PEG = 5KDa, PLGA = 40 KDa
TEM of nanoparticles

Release properties of diblock particles

Increased t_{1/2} in blood:

Altered biodistribution:

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Please see: Figure 7 in Li, Y., et al. "PEGylated PLGA Nanoparticles as Protein Carriers: Synthesis, Preparation and Biodistribution in Rats." *Journal of Control Release* 71 (2001): 203-11.

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Clinically-approved stealth carriers

- **PEG-GCSF** (granulocyte colony stimulating factor, Amgen) 2002
  - Pegylated GCSF (cytokine)
  - Reduction of febrile neutropenia associated with chemotherapy
- **Pegademase** (Adagen) 1990
  - Pegylated adenosine deaminase (enzyme)
  - Treatment of severe combined immunodeficiency (SCID)- hereditary lack of adenosine deaminase
- **Pegaspargase** (Oncaspar)
  - Pegylated asparaginase (enzyme)
  - Treatment of leukemia
    - Leukaemic cells cannot synthesize asparagines; asparaginase kills cells by depleting extracellular sources of this amino acid
- **Pegylated IFN-α2a** (Pegasys) 2001
  - Treatment of hepatitis C
- **Doxil** (Alza) 1995-2003
  - Pegylated liposomes carrying anti-cancer drug doxorubicin
  - Improves treatment from daily 30min injections for 5 days every 3 weeks to once-a-month single injections
  - Approved for treatment of Karposi’s sarcoma, ovarian cancer, and breast cancer

Lecture 19 Spring 2006 16
Delivery into cells once the target tissue is reached:
Cell type-dependent endocytosis limits

Internalization of 200nm-diam particles by carcinoma cell line:

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Endpoint for most particles: endosomal compartments

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FOCUS TOPIC: INTEGRATING BIOLOGICAL KNOWLEDGE INTO BIOMATERIALS DESIGN FOR VACCINES

Basic Biology of Vaccination
KEY EFFECTORS OF ADAPTIVE IMMUNITY

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THE CLONAL IMMUNE SYSTEM

Physiology of the primary immune response

1) Attraction to sites of infection

2) Antigen loading and activation

3) Trafficking to lymph nodes

4) Activation of naïve T cells in the lymph nodes

1) Chemotaxis:
Migration ‘up’ concentration gradients of chemoattractant

Infection site

Infected cells
Biology of dendritic cells in T cell activation

Classical pathways of antigen processing and presentation:

- Classical Class I antigen loading pathway
- Exogenous ANTIGEN

CD4+ T cells

CD8+ T cells

Class II antigen loading pathway
Antigen is one of (at least) two signals that must be delivered by a vaccine.

- **MAXIMAL T CELL PROLIFERATION**
- **GENERATION OF FULL EFFECTOR FUNCTIONS**
- **GENERATION OF MEMORY T CELLS**

Signal 1 - antigen
Signal 2 - costimulation
B cell activation

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Induction of immunological memory (the basis of vaccination)

- Number of Pathogen-specific T cells
- Antibody titer
- Mean antibody affinities
OBJECTIVES OF VACCINATION

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Prophylactic vs. therapeutic immunization

Two situations where vaccination is of interest:

(1) Therapeutic vaccine:

(2) Prophylactic vaccine:
ROUTES OF IMMUNIZATION

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Further Reading


Further Reading