Engineering Nanomedical Systems

Lecture 9
Challenges of proper drug dosing with nanodelivery systems

James F. Leary, Ph.D.
SVM Endowed Professor of Nanomedicine
Professor of Basic Medical Sciences and Biomedical Engineering
Member: Purdue Cancer Center; Oncological Sciences Center; Bindley Biosciences Center; Birck Nanotechnology Center
Email: jfleary@purdue.edu

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9.1 Overview of drug dosing problem

9.1.1 Problems of scaling up doses from animal systems
9.1.2 Basing dosing on size, area, weight of recipient
9.1.3 Vast differences between adults in terms of genetics, metabolism
9.1.4 Dosing in children – children are NOT smaller adults!
9.1.5 Pharmacokinetics – drug distribution, metabolism, excretion, breakdown
9.1.6 Conventional dosing assumes drug goes everywhere in the body
9.1.7 Targeted therapies – a model for future nanomedical systems?
Comparing drug clearance in humans and other animals

Source: Wagima et al., 2004

MRT = mean residence time
9.1.3 Vast differences between adults in terms of genetics, metabolism

The volume of distribution of drugs changes in children with aging. These age-related changes are due to changes in body composition (especially the extracellular and total body water spaces) and plasma protein binding. Higher doses (per kg of body weight) of water-soluble drugs are required in younger children because a higher percentage of their body weight is water (see Fig. 1: Principles of Drug Treatment in Children: Changes in body proportions of body composition with growth and aging. ). Conversely, lower doses are required to avoid toxicity as children grow older because of the decline in water as a percentage of body weight. Source: http://www.merck.com/mmpe/sec19/ch270/ch270b.html
Pharmacokinetics – time profiles of cefodizime*

*Cefodizime is an antibiotic against salmonella

Figure 2. Predicted and observed concentration–time profiles of ceftizoxime after intravenous bolus administration of 500 mg (a), of cefodizime after intravenous bolus administration of 1000 mg (b), of cefotetan after intravenous bolus administration of 1000 mg (c), and of cefmenoxime after intravenous infusion of 1000 mg over 1 h (d). The solid line shows the concentration–time profile predicted from the normalized curve for dog and from the CL and Vdss predicted by eqs. 12 and 13. The broken line shows the concentration–time profile simulated from normalized curve for dog and from the observed CL and Vdss in human. Plots are the means and standard deviations of the observed data. Source: Wajima et al. 2004
Dedrick Plots to predict drug concentration-time profiles in humans

Dedrick plot using equivalent time, the concentration–time curve was transformed by dividing the concentration and time scales by dose per kg of BW (dose/BW) and BW$^{0.25}$ to superimpose concentration–time profiles for a variety of species. The transformed concentration ($C''$) and time ($t''$) are presented as follows.

$$C'' = \frac{C}{\text{Dose}/\text{BW}}$$  \hspace{1cm} (20)

$$t'' = \frac{t}{\text{BW}^{0.25}}$$  \hspace{1cm} (21)

The transformed curve using equivalent time is shown as follows.

$$C'' = \frac{A}{\text{Dose}/\text{BW}} \cdot \exp(-\alpha \cdot \text{BW}^{0.25} \cdot t'') + \frac{B}{\text{Dose}/\text{BW}} \cdot \exp(-\beta \cdot \text{BW}^{0.25} \cdot t'')$$  \hspace{1cm} (22)

The predicted concentration–time profile in humans after intravenous injection using the Dedrick plot approach (equivalent time) can be presented by eq. 23.

$$C = \frac{\text{Dose}_{\text{man}}/\text{BW}_{\text{man}}}{\text{Dose}_{\text{animal}}/\text{BW}_{\text{animal}}} \cdot A_{\text{animal}} \cdot \exp \left( -\alpha_{\text{animal}} \cdot \frac{\text{BW}_{\text{animal}}^{0.25}}{\text{BW}_{\text{man}}^{0.25}} \cdot t \right) + \frac{\text{Dose}_{\text{man}}/\text{BW}_{\text{man}}}{\text{Dose}_{\text{animal}}/\text{BW}_{\text{animal}}} \cdot B_{\text{animal}} \cdot \exp \left( -\beta_{\text{animal}} \cdot \frac{\text{BW}_{\text{animal}}^{0.25}}{\text{BW}_{\text{man}}^{0.25}} \cdot t \right)$$  \hspace{1cm} (23)

Dedrick plot to predict concentration-time profiles of drugs in human from animal data

Figure 3. The Dedrick Plot for (a) ceftizoxime, (b) cefodizime, (c) cefotetan, and (d) cefmenoxime. (Source: Wajima et al. 2004)
9.2 From the animal dosing to human clinical trials

9.2.1 Importance of picking an appropriate animal model system

9.2.2 Does drug dosing really scale?

9.2.3 The “human guinea pig” in human clinical trials and beyond!
9.3 Traditional drug dosing methods

9.3.1 Attempts to scale up on basis of area
9.3.2 Attempts to scale up on weight/volume
9.3.3 Attempts to use control engineering principles
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. The flow of drugs from/between compartments is usually modeled using a series of differential equations.

Source: Bailey & Haddad, 2005
9.4 Genetic responses to drug dosing

9.4.1 All humans are not genomically equivalent!
9.4.2 Predicting on basis of family tree responses
9.4.3 SNPs, chips, and beyond...predicting individual drug response
9.4.4 After the $???? individual genome scan...more closely tailored individual therapies
9.5 Dosing in the era of “directed therapies”

9.5.1 How directed therapies change the dosing equation

9.5.2 Current generation directed antibody therapies dosing

9.5.3 Next generation directed nanomedical systems dosing

N.B. Directed therapies are already FDA approved and being used. They represent the “almost nanomedicine” drugs. Many nanomedical strategies will use the targeting molecules and human experience of these drugs and then improve upon them by better protecting the body from anti-targeted therapy side effects and improving delivery of therapeutics.
9.6 Most directed therapies are “nonlinear” processes!

This means that small changes in input (amount of targeted therapy molecules) can result in potentially VERY large changes in output (therapeutic response)! Some of these therapies can also trigger the immune response or cellular responses and then have those processes greatly amplify the overall response, sometimes in unpredictable ways from individual-to-individual.
# Some “Directed Therapies”

FDA-approved monoclonal antibodies for cancer treatment

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

Source: http://www.mayoclinic.com/health/monoclonal-antibody/CA00082
Naming conventions for monoclonal antibodies are made up of three parts as defined by the World Health Organization.

<table>
<thead>
<tr>
<th>Target site of antibody</th>
<th>Source of antibody</th>
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<tbody>
<tr>
<td>o(s)</td>
<td>bone</td>
</tr>
<tr>
<td>vi(r)</td>
<td>viral</td>
</tr>
<tr>
<td>ba(c)</td>
<td>bacterial</td>
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<tr>
<td>li(m)</td>
<td>immune</td>
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<tr>
<td>le(s)</td>
<td>infectious lesions</td>
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<tr>
<td>ci(r)</td>
<td>cardiovascular</td>
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<tr>
<td>mo(l)</td>
<td>musculoskeletal</td>
</tr>
<tr>
<td>ki(n)</td>
<td>interleukin as target</td>
</tr>
<tr>
<td>co(l)</td>
<td>colonic tumour</td>
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<tr>
<td>me(l)</td>
<td>melanoma</td>
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<tr>
<td>ma(r)</td>
<td>mammary tumour</td>
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<tr>
<td>go(t)</td>
<td>testicular tumour</td>
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<tr>
<td>go(v)</td>
<td>ovarian tumour</td>
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<tr>
<td>pr(o)</td>
<td>prostrate tumour</td>
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<tr>
<td>tu(m)</td>
<td>misc tumour</td>
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<tr>
<td>neu(r)</td>
<td>nervous system</td>
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<tr>
<td>tox(a)</td>
<td>toxin as target</td>
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<td>fu(ng)</td>
<td>fungal</td>
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<td>u</td>
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<td>e</td>
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<td>i</td>
<td>primate</td>
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<tr>
<td>xi</td>
<td>chimeric</td>
</tr>
<tr>
<td>zu</td>
<td>humanized</td>
</tr>
<tr>
<td>axo</td>
<td>rat/murine hybrid</td>
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</tbody>
</table>

For example, Rituximab is made up of RI the unique name, TU(m) the target (misc tumour), and XI the source (chimeric) and MAB=monoclonal antibody.

General Rules
1. The first part of the name is unique and does not hold any particular meaning.
2. The second part of the name is the target of the antibody. It may be two or three letters as shown in the table below. When the third part of the name (source) starts with a vowel then the second part has 3 letters.
3. The third part of the name is the source. This is the source of the antibody.

Source: [http://www.nhlcyberfamily.org/treatments/moab.htm](http://www.nhlcyberfamily.org/treatments/moab.htm)
Targeted Therapies – directly attack tumor cells

Some targeted therapies act by helping the immune system to destroy cancer cells.

**Rituximab (Rituxan®)** is a monoclonal antibody that is approved to treat certain types of **B-cell non-Hodgkin lymphoma**. It recognizes a molecule called CD20 that is found on B cells. When rituximab binds to these cells, it triggers an immune response that results in their destruction. Rituximab may also induce apoptosis. **Alemtuzumab (Campath®)** is approved to treat patients with B-cell **chronic lymphocytic leukemia**. It is a monoclonal antibody that is directed against CD52, a protein found on the surface of normal and malignant B and T cells and many other cells of the immune system. Binding of alemtuzumab to CD52 triggers an immune response that destroys the cells. **Ofatumumab (Arzerra®)** is approved for the treatment of some patients with chronic lymphocytic leukemia (CLL) that does not respond to treatment with fludarabine and alemtuzumab. This monoclonal antibody is directed against the B-cell CD20 cell surface antigen.

Targeted therapies – delivering toxic molecules directly to cells

Another class of targeted therapies includes monoclonal antibodies that deliver toxic molecules to cancer cells specifically.

**Tositumomab and 131I-tositumomab (Bexxar®)** is approved to treat certain types of B-cell non-Hodgkin lymphoma. It is a mixture of monoclonal antibodies that recognize the CD20 molecule. Some of the antibodies in the mixture are linked to a **radioactive** substance called **iodine-131**. The 131I-tositumomab component delivers radioactive energy to CD20-expressing B cells specifically, reducing collateral damage to normal cells of the type that is seen with traditional radiotherapy. In addition, the binding of tositumomab to the CD20-expressing B cells triggers the immune system to destroy these cells.

**Ibritumomab tiuxetan (Zevalin®)** is approved to treat some patients with B-cell non-Hodgkin lymphoma. It is a monoclonal antibody directed against CD20 that is linked to a molecule that can bind **radioisotopes** such as indium-111 or **yttrium-90**. The **radiolabeled** forms of Zevalin deliver a high **dose** of radioactivity to cells that express CD20.

**Denileukin diftitox (Ontak®)** is approved for the treatment of some patients with CTCL. Denileukin diftitox consists of **interleukin-2** (IL-2) protein sequences fused to diphtheria toxin. The drug binds to cell surface IL-2 receptors, which are found on certain immune cells and some cancer cells, directing the **cytotoxic** action of the diphtheria toxin to these cells.

Targeted Therapies - Signal Transduction inhibitors

Some targeted therapies block specific enzymes and growth factor receptors involved in cancer cell proliferation. These drugs are also called **signal transduction inhibitors**.

Imatinib mesylate (Gleevec®) is approved to treat gastrointestinal stromal tumor (a rare cancer of the gastrointestinal tract) and certain kinds of leukemia. It targets several members of a class of proteins called tyrosine kinase enzymes that participate in signal transduction.

Dasatinib (Sprycel®) is approved to treat some patients with CML or acute lymphoblastic leukemia. It is a small-molecule inhibitor of several tyrosine kinase enzymes.

Nilotinib (Tasigna®) is approved to treat some patients with CML. It is another small-molecule tyrosine kinase inhibitor.

Trastuzumab (Herceptin®) is approved for the treatment of certain types of breast cancer. It is a monoclonal antibody that binds to the human epidermal growth factor receptor 2 (HER-2). HER-2, a receptor with tyrosine kinase activity, is expressed at high levels in some breast cancers and also some other types of cancer.

Lapatinib (Tykerb®) is approved for the treatment of certain types of advanced or metastatic breast cancer. This small-molecule drug inhibits several tyrosine kinases, including the tyrosine kinase activity of HER-2. Lapatinib treatment prevents HER-2 signals from activating cell growth.

**Source:** [http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted](http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted)
Targeted Therapies – More Signal Transduction inhibitors

Lapatinib (Tykerb®) is approved for the treatment of certain types of advanced or metastatic breast cancer. This small-molecule drug inhibits several tyrosine kinases, including the tyrosine kinase activity of HER-2. Lapatinib treatment prevents HER-2 signals from activating cell growth.

Gefitinib (Iressa®) is approved to treat patients with advanced non-small cell lung cancer. Its use is restricted to patients who, in the opinion of their treating physician, are currently benefiting, or have previously benefited, from gefitinib treatment. This small-molecule drug inhibits the tyrosine kinase activity of the epidermal growth factor receptor (EGFR), which is overproduced by many types of cancer cells.

Erlotinib (Tarceva®) is approved to treat metastatic non-small cell lung cancer and pancreatic cancer that cannot be removed by surgery or has metastasized. This small-molecule drug inhibits the tyrosine kinase activity of EGFR.

Cetuximab (Erbitux®) is a monoclonal antibody that is approved for treating some patients with squamous cell carcinoma of the head and neck or colorectal cancer. It binds to the external portion of EGFR, thereby preventing the receptor from being activated by growth signals, which may inhibit signal transduction and lead to anti-proliferative effects.

Panitumumab (Vectibix®) is approved to treat some patients with metastatic colon cancer. This monoclonal antibody attaches to EGFR and prevents it from sending growth signals.

Source: http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted
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Source: http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted
Targeted Therapies – More Signal Transduction inhibitors

Temsirelimus (Torisel®) is approved to treat patients with advanced renal cell carcinoma. This small-molecule drug is a specific inhibitor of a serine/threonine kinase called mTOR that is activated in tumor cells and stimulates their growth and proliferation.

Everolimus (Afinitor®) is approved to treat patients with advanced kidney cancer whose disease has progressed after treatment with other therapies. This small-molecule drug binds to a protein called immunophilin FK binding protein-12, forming a complex that in turn binds to and inhibits the mTOR kinase.

Source: http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted
Other targeted therapies modify the function of proteins that regulate gene expression and other cellular functions.

**Vorinostat (Zolinza®)** is approved for the treatment of CTCL that has persisted, progressed, or recurred during or after treatment with other medicines. This small-molecule drug inhibits the activity of a group of enzymes called histone deacetylases (HDACs), which remove small chemical groups called acetyl groups from many different proteins, including proteins that regulate gene expression. By altering the acetylation of these proteins, HDAC inhibitors can induce tumor cell differentiation, cell cycle arrest, and apoptosis.

**Romidepsin (Istodax®)** is approved for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy. This small-molecule drug inhibits members of one class of HDACs and induces tumor cell apoptosis.

More Targeted Therapies – modifying gene expression and cell function

**Bexarotene (Targretin®)** is approved for the treatment of some patients with CTCL. This drug belongs to a class of compounds called retinoids, which are chemically related to vitamin A. **Bexarotene** binds selectively to, and thereby activates, retinoid X receptors. Once activated, these nuclear proteins act in concert with retinoic acid receptors to regulate the expression of genes that control cell growth, differentiation, survival, and death.

**Alitretinoin (Panretin®)** is approved for the treatment of cutaneous lesions in patients with AIDS-related Kaposi sarcoma. This retinoid binds to both retinoic acid receptors and retinoid X receptors.

**Tretinoin (Vesanoid®)** is approved for the induction of remission in certain patients with acute promyelocytic leukemia. This retinoid binds to and thereby activates retinoic acid receptors.

Targeted Therapies – inducing apoptosis

Some targeted therapies induce cancer cells to undergo apoptosis (cell death).

**Bortezomib (Velcade®)** is approved to treat some patients with **multiple myeloma**. It is also approved for the treatment of some patients with **mantle cell lymphoma**. **Bortezomib** causes cancer cells to die by interfering with the action of a large cellular structure called the proteasome, which degrades proteins. Proteasomes control the degradation of many proteins that regulate cell proliferation. By blocking this process, bortezomib causes cancer cells to die. Normal cells are affected too, but to a lesser extent.

**Pralatrexate (Folotyn®)** is approved for the treatment of some patients with **peripheral T-cell lymphoma**. **Pralatrexate** is an **antifolate**, which is a type of molecule that interferes with **DNA** synthesis. Other antifolates, such as **methotrexate**, are not considered targeted therapies because they interfere with DNA synthesis in all dividing cells. However, pralatrexate appears to selectively accumulate in cells that express RFC-1, a protein that may be over-expressed by some cancer cells.

*Source: http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted*
Targeted Therapies – blocking angiogenesis

Other targeted therapies block the growth of blood vessels to tumors (angiogenesis). To grow beyond a certain size, tumors must obtain a blood supply to get the oxygen and nutrients needed for continued growth. Treatments that interfere with angiogenesis may block tumor growth.

Bevacizumab (Avastin®) is a monoclonal antibody that is approved for the treatment of glioblastoma. It is also approved for some patients with non-small cell lung cancer, metastatic breast cancer, and metastatic colorectal cancer. Bevacizumab binds to the vascular endothelial growth factor (VEGF). This prevents VEGF from interacting with its receptors on endothelial cells, a step that is necessary for the initiation of new blood vessel growth.

Sorafenib (Nexavar®) is a small-molecule inhibitor of tyrosine kinases that is approved for the treatment of advanced renal cell carcinoma and some cases of hepatocellular carcinoma. One of the kinases that sorafenib inhibits is involved in the signaling pathway that is initiated when VEGF binds to its receptors. As a result, new blood vessel development is halted. Sorafenib also blocks an enzyme that is involved in cell growth and division.

Sunitinib (Sutent®) is another small-molecule tyrosine kinase inhibitor that is approved for the treatment of patients with metastatic renal cell carcinoma or gastrointestinal stromal tumor that is not responding to imatinib. It blocks kinases involved in VEGF signaling, thereby inhibiting angiogenesis and cell proliferation.

Source: http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted
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
Targeted nanomedical systems represent the next stage of directed therapies

- Addition of “stealth layers” can hide the treatment from the immune system preventing typical side effects such as directed-therapy caused neutropenia (death of neutrophils caused by ingestion of antibodies)
- Many patients do not have adequate immune system to interact efficiently with the directed therapy, so these nanomedical systems need not depend on a functioning immune system
- Patient immune systems can produce highly nonlinear, and sometimes dangerous and unpredictable responses that vary a great deal from individual-to-individual. Nanomedical approaches can avoid use of the immune system
- We can encapsulate therapies in side nanomedical devices that would not survive in the blood (e.g. ribozyme therapies)
9.7 Some other ways of controlling dose locally

9.7.1 Magnetic field release of drug

9.7.2 Light-triggered release of drugs
9.7.1 Magnetic field release of drugs

Source: Thomas et al. 2010
Figure 2. Cargo release using magnetic actuation. In (a), the MARS nanoparticles were continuously exposed to the magnetic field. The inset shows the data as a release profile. In (b), a sample was kept at 0 °C and exposed to pulses of the magnetic field. A single AC magnetic field exposure (b) exhibited ~40% cargo release after an initial 1 min pulse. Multiple pulses performed at 1, 3, 5, 7, and 9 min and then every 20 min for 270 min (9) enabled more dye release until all of the dye diffused out. A baseline (2) was obtained by monitoring the fluorescence with no pulses. The low temperature of the surrounding solution (0 °C) was maintained in order to observe the effects only from the magnetic field and not from heating of the surrounding solution.

Source: Thomas et al. 2010
Magnetically-controlled cell killing

Figure 3. Results of MDA-MB-231 exposure to the MARS. Panel (a) shows fluorescent microscope images (1, 3, and 5) and fluorescent images with differential interference contrast (2, 4, and 6). Color scheme: green, fluorescently labeled MARS; red, doxorubicin (DOX); yellow, merged green and red. MARS nanoparticles containing DOX were taken up into the cells, but before the AC field was applied, no drug release (images 1 and 2) and negligible cell death (~5%; panel (b), left bar) occurred. Images 3 and 4 show the effects of the magnetic field on MARS nanoparticles without DOX in the pores. Heating from the particles accounted for 16% of the cell killing [panel (b), middle bar]. Images 5 and 6 demonstrate DOX release after a 5 min AC field exposure, which caused 37% of the cell death [panel b, right bar]. The arrows in image 6 indicate the location of apoptotic cells.

Source: Thomas et al. 2010
9.7.2 Light Triggered Dosing at the Molecule Scale

9.7.2 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.

References


National Cancer Institute http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted